Glomerular Filtration 7.3

Learning Objectives

- Summarize the evidence that the renal corpuscle forms an ultrafiltrate
- List the three elementary processes found in the nephrons
- Define the clearance for any substance
- Calculate the GFR as the clearance of inulin and explain why the clearance of inulin is the GFR
- Calculate effective renal plasma flow from the clearance of PAH
- Describe what is meant by filtration fraction and give its normal range
- Describe the layers of the glomerular filtration barrier and how they provide a sequential size filter
- Define the sieving coefficient
- Write the Starling equation for the forces that produce the glomerular ultrafiltrate
- Provide approximate estimates of the components of the driving forces for ultrafiltration

MORPHOLOGICAL STUDIES FIRST LED TO THE IDEA OF GLOMERULAR FILTRATION

Unlike the description of the nephron given in Chapter 7.2, the cortex is actually a compact mass of coiled tubules that resembles a bag of worms. The blood vessels and tubules are jumbled together without the spaces between them as shown in Figure 7.2.4. Despite this confusion of tubules, early microscopists such as Malpighi, who published his findings in 1666, and Bowman, in 1842, recognized that each **renal corpuscle** (the glomerulus together with its Bowman's capsule) is connected to a single tubule. Bowman described the glomerular capillaries and found that their outer covering was continuous with the outer layer of the capsule and with the tubule. Thus any fluid formed in Bowman's space would drain down into the tubule. Bowman thought that the glomerulus secreted water that flushed away solutes secreted into the urine by the tubule cells. Bowman's contemporary, Ludwig, proposed that the glomerulus produced a protein-free ultrafiltrate. According to this view, reabsorption of water from the ultrafiltrate concentrated the waste products and reduced the volume of the urine. Although Ludwig's ideas substantially agree with the modern view, it is one thing to propose a mechanism and quite another to provide experimental evidence for it.

MICROPUNCTURE STUDIES SHOWED THAT THE FLUID IN BOWMAN'S SPACE IS AN ULTRAFILTRATE

A.N. Richards succeeded in removing samples of fluid from Bowman's space by using micropuncture techniques. Applying microchemical analysis to these samples, Richards and colleagues showed that the fluid was free of protein, but the concentrations of a variety of small molecular weight solutes such as creatinine, Cl^-, glucose, Pi, K^+, urea, and uric acid were the same in the Bowman's space fluid as they were in plasma. A filter removes suspended particles from a mixture. An ultrafilter removes not only the particulate matter but also removes colloidal materials such as proteins. Small molecular weight solutes, however, are not removed by an ultrafilter. Thus the fluid in Bowman's space had the composition of an ultrafiltrate. Richards accomplished this remarkable demonstration in the early 1920s. A diagram of the micropuncture technique along with the major features of the renal corpuscle is shown in Figure 7.3.1.

TUBULAR REABSORPTION EXPLAINS THE LACK OF NUTRIENTS IN THE FINAL URINE

The glomerular ultrafiltrate contains amino acids and glucose and a host of other materials in concentrations nearly identical to those in plasma. But substances such as glucose and amino acids are completely absent from the final urine. These two observations establish that some materials must be removed from the tubular fluid after formation of the ultrafiltrate and while the fluid travels down the nephron. The removal of materials from the tubular fluid is called **tubular reabsorption**. Reabsorbed materials move from the tubular fluid into the peritubular capillaries.

TUBULAR SECRETION ADDS MATERIAL TO THE ULTRAFILTRATE

Tubular secretion refers to a direction of movement of materials from the blood to the tubule lumen. Tubular reabsorption refers to the direction of movement in

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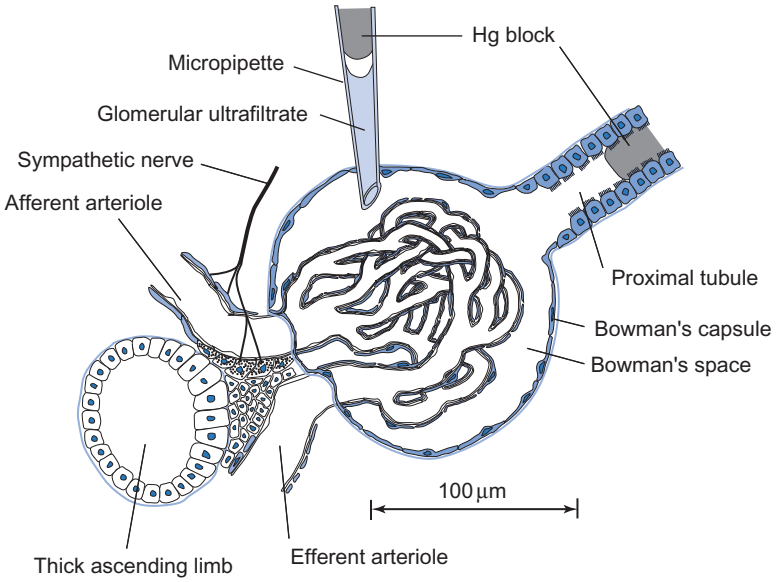

FIGURE 7.3.1 Micropuncture of the renal corpuscle. The renal corpuscle consists of the glomerulus, a tuft of capillaries between the afferent arteriole and the efferent arteriole, and its closely apposed Bowman's capsule. The outer fibrous layer of Bowman's capsule is continuous with the basement membrane of the proximal tubule. The flattened epithelial layer of Bowman's capsule is also continuous with the cuboidal epithelium of the proximal tubule. Micropuncture was accomplished by A.N. Richards in the 1920s by inserting a micropipette into Bowman's space and blocking the movement of fluid down the proximal tubule by inserting a plug of mercury. A second plug of Hg in the micropipette sealed the sample from air and thereby prevented evaporation of the tiny sample.

the opposite direction, from lumen to blood. Tubular secretion was demonstrated by showing that some materials show up in the urine in excess of what can be explained by filtration. This is a quantitative argument that depends on the rates of excretion and not the concentration in the urine because the concentrations of excreted materials depend on the reabsorption of water relative to the solute.

THE THREE ELEMENTARY NEPHRON PROCESSES ARE ULTRAFILTRATION, REABSORPTION, AND SECRETION

As outlined above, the first step in the formation of urine is the formation of an ultrafiltrate of plasma by the renal corpuscle. The fluid then flows down the nephron beginning with the proximal convoluted tubule, where water and solutes are either removed from the tubular fluid and returned to the blood (reabsorbed), or water and solutes are added to the tubular fluid from the blood (secretion). **Ultrafiltration**, **reabsorption**, and **secretion** constitute the three elementary functions of the nephron. The remainder of renal physiology is how these processes produce the final urine and how they are regulated to meet the demands of homeostasis.

THE CLEARANCE OF INULIN PROVIDES AN ESTIMATE OF THE GLOMERULAR FILTRATION RATE

In order to understand how the body regulates ultrafiltration, reabsorption, and secretion, we need to be able to quantify these processes. The clearance of inulin is an experimental measure of the rate of glomerular filtration. To see this, consider the simplified nephron shown in Figure 7.3.2. The nephron consists of a tube running from the renal corpuscle down into the duct of Bellini. At steady state, there is a constant throughput

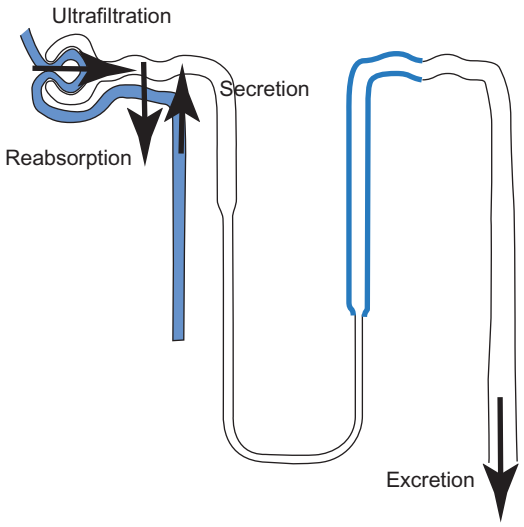

FIGURE 7.3.2 Schematic diagram of the nephron and the sources and sinks of materials across the tubule. At steady state for a material which is neither synthesized nor degraded by the nephron, the amount entering the tubule per unit time is the amount filtered + the amount secreted. During the same time, the amount leaving the tubule per unit time is the amount reabsorbed + the amount excreted.

of materials from the blood and into the urine, and the nephron is the agent of this throughput. However, the nephron itself, and the volume and contents of the tubular fluid, is constant. That is, the input of all materials into the tubular fluid is equal to the output of all materials at steady state:

$$\text{Input} = \text{output} \quad [7.3.1]$$

In this equation, we assume that the material is neither synthesized nor degraded by the tissue. The flow of material into the tubular fluid may occur at a number of sites in the nephron. These include glomerular filtration and secretion, denoted by the arrows leading into the tubule lumen in Figure 7.3.2. The output is the sum

of all the material excreted in the final urine and the material that is reabsorbed from the tubular fluid back into the blood. These are denoted by the arrows leading away from the tubule lumen in Figure 7.3.2. So we can write

[7.3.2] Amount filtered + amount secreted = amount excreted + amount reabsorbed

What this simple equation means is that if something shows up in the urine (the amount excreted), it had to come from someplace and that someplace is either the filtered plasma or secretion from plasma, or both. Conversely, if a substance is filtered but does not show up in the urine, or shows up less in the urine than in the filtrate, then it must have been reabsorbed. It is possible to deduce which of these events is occurring by looking at the rate of excretion of a substance as a function of its plasma concentration.

The amounts filtered, secreted, excreted, or reabsorbed in Eqn (7.3.2) refer to the amounts filtered, secreted, excreted, or reabsorbed *in some definite time interval*. We can divide both sides of Eqn (7.3.2) by the time interval over which the amounts are measured, to obtain

[7.3.3] Rate of filtration + rate of secretion = rate of excretion + rate of reabsorption

Inulin is a polymer of fructose derived from plants. It is small enough that it is freely filtered by the glomerulus, meaning that the concentration of inulin in the ultrafiltrate is the same as its concentration in the plasma. It is also neither secreted nor reabsorbed by the kidney tubules. Thus, in Eqn (7.3.3) the rate of secretion = 0 and the rate of reabsorption = 0, and Eqn (7.3.3) is rewritten as

Rate of inulin filtration = rate of inulin excretion

[7.3.4]

The amount of inulin that is filtered per unit time is given as $GFR \times UF_{inulin}$, where the GFR refers to the **glomerular filtration rate**, in units of volume per unit time, and UF_{inulin} refers to the concentration of inulin in the ultrafiltrate. Because inulin is freely filtered, the ultrafiltrate concentration is the same as its plasma concentration, denoted as P_{inulin}, so that the rate of filtration is $GFR \times P_{inulin}$. The amount of inulin excreted per unit time is the urinary inulin concentration times the rate of urine excretion, denoted here as Q_u. Thus Eqn (7.3.4) becomes

$$[7.3.5] \qquad GFR\, P_{inulin} = Q_u U_{inulin}$$

This equation is easily rearranged to solve for GFR:

$$[7.3.6] \qquad GFR = \frac{Q_u U_{inulin}}{P_{inulin}}$$

A typical value for the GFR for the two kidneys is 120 mL min^{-1}. This is the aggregate rate of formation of glomerular filtrate from all functional nephrons. Since there are about 1.3×10^6 nephrons in each kidney, the aggregate GFR is produced by a single nephron GFR that averages about 120 mL min^{-1}/2.6×10^6 nephrons $\approx 45 \times 10^{-9}$ L min^{-1} per nephron. This is an average value for the SNGFR, the single nephron GFR. Some nephrons may have greater SNGFR and some may have smaller SNGFR.

THE CLEARANCE OF PARA AMINO HIPPURIC ACID ALLOWS ESTIMATION OF RENAL PLASMA FLOW

Para amino hippuric acid, or PAH, is avidly secreted by the renal tubules so that nearly all of the blood that enters the kidneys is "cleared" of PAH and renal venous blood contains very little PAH. The amount of PAH appearing in the urine per unit time, then, is equal to the amount contained in the blood that perfuses the kidney per unit time. This conservation relation is written as

$$[7.3.7] \qquad ERPF P_{PAH} = Q_u U_{PAH}$$

where ERPF stands for the **effective renal plasma flow**, P_{PAH} is the plasma concentration of PAH, Q_u is the rate of urine formation, and U_{PAH} is the concentration of PAH in the urine. The left-hand side of this equation is the amount of PAH that enters the kidney per unit time, and the right-hand side is the amount of PAH that is excreted per unit time. This equation can be rewritten as

$$[7.3.8] \qquad ERPF = \frac{Q_u U_{PAH}}{P_{PAH}}$$

As in Eqn (7.3.6), the units of ERPF are in mL min^{-1}. A typical value for ERPF calculated from PAH excretion is about 600 mL min^{-1}. This calculation gives the ERPF because part of the blood plasma that supplies the kidneys goes to regions of the kidney that do not filter the blood or secrete materials from it into the nephrons. These regions include the adipose tissue and the renal capsule and the renal medulla. The true renal plasma flow (RPF) can be estimated by redefining the boundaries through which the flows of material occur, as shown in Figure 7.3.3. Here the input of PAH to the kidneys is the RPF times the renal arterial plasma [PAH]. The output includes two sinks: the urine and the venous blood. The conservation principle equates the input and the output to give

$$[7.3.9] \qquad RPF\, RA_{PAH} = RPF\, RV_{PAH} + Q_u U_{PAH}$$

where RA indicates the renal arterial plasma and RV denotes the renal venous plasma. Solving for RPF, we obtain:

$$[7.3.10] \qquad RPF = \frac{Q_u U_{PAH}}{RA_{PAH} - RV_{PAH}}$$

Equation (7.3.10) gives the true RPF. It differs from Eqn (7.3.8) in that the equation for ERPF requires that the renal venous plasma [PAH] is zero. Typically about 10% of the renal plasma supplies regions of the kidneys that do not actively secrete PAH. Thus the renal plasma flow is about 10% higher than the ERPF. RPF averages about 660 mL min^{-1}.

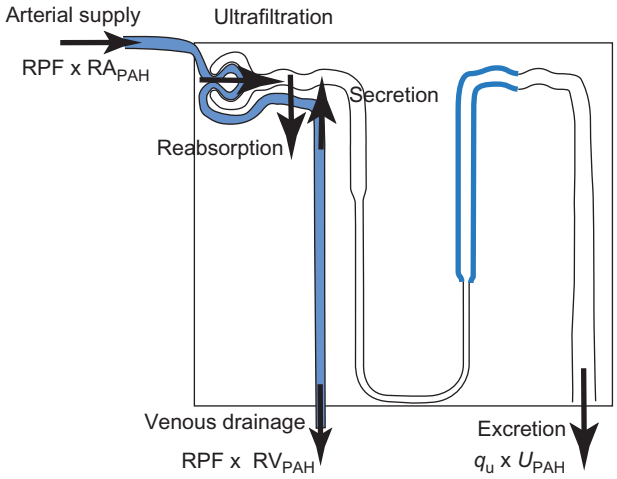

FIGURE 7.3.3 Estimation of the renal plasma flow from the renal handling of PAH. The boundaries of the system are expanded to include the vasculature. The balance of input and output refers to inputs and outputs across the boundaries of the system, and movement of materials inside the "box" do not enter into the conservation equation.

The plasma flow is related to the blood flow. The **hematocrit** is the fraction of blood volume occupied by the blood cells, mostly the erythrocytes (see Chapter 5.1). Typically this is about 0.45, meaning that 45% of the blood volume consists of the blood cells. This means that the plasma volume is the remaining volume or 55% of the blood volume. The plasma volume is thus $(1 - \text{Hct}) \times$ blood volume. Thus the effective renal blood flow and renal blood flow can be calculated from the effective renal plasma flow and renal plasma flow as

$$\text{ERBF} = \frac{\text{ERPF}}{1 - \text{Hct}} \qquad \text{RBF} = \frac{\text{RPF}}{1 - \text{Hct}} \qquad [7.3.11]$$

Using Hct = 0.45, the typically ERBF would be 600 mL min^{-1}/(1 − 0.45) = 1090 mL min^{-1}. The total renal blood flow would be given as RBF = 660 mL min^{-1}/(1−0.45) = 1200 mL min^{-1}. The typical cardiac output is about 5 L min^{-1}, so that the kidneys receive 1.2 L min^{-1}/5.0 L min^{-1} = 0.24. Thus nearly one-quarter of the cardiac output at rest is directed to the kidneys.

THE CLEARANCE OF A SUBSTANCE DEPENDS ON HOW IT IS HANDLED BY THE KIDNEY

Equations (7.3.6) and (7.3.8) both have the form

$$C_x = \frac{Q_u U_x}{P_x} \qquad [7.3.12]$$

where C_x is called the **clearance** of substance x. Q_u is the flow of urine, in mL min^{-1}; U_x is the concentration of substance x in the excreted urine; and P_x is the plasma concentration of substance x. The clearance of any substance x is a flow measured in mL min^{-1} but it represents a virtual flow, not a real flow. For example, the clearance of inulin is 120 mL min^{-1}, meaning that the amount of inulin that appears in the urine each minute is equal to the amount of inulin contained in 120 mL of plasma, and therefore 120 mL of plasma has been "cleared" of inulin in each minute. Similarly, when the clearance of PAH is 600 mL min^{-1}, it means that the amount of PAH in the urine is equal to the amount contained in 600 mL of plasma, and thus 600 mL of plasma has been "cleared" of PAH each minute. The interpretation given to the clearance of a substance depends on the way in which the nephron processes it. In the case of inulin, the clearance is equal to the GFR because inulin is freely filtered by the glomerulus, but it is neither secreted nor reabsorbed. The clearance of PAH equals the ERPF because blood that perfuses the tubules is completely cleared of PAH by secretion.

GLOMERULAR FILTRATION IS LIKE A LEAKY HOSE; ABOUT 20% OF THE PLASMA CONSTITUENTS END UP IN THE FILTRATE

The GFR is typically 120 mL min^{-1} and the ERPF is about 600 mL min^{-1}. Thus the kidney takes 600 mL min^{-1} of plasma and makes 120 mL min^{-1} of ultrafiltrate. The plasma flow through the aggregate efferent arterioles, then, should be about 480 mL min^{-1}. Thus the kidneys do not "clear" inulin from 120 mL of plasma per minute. Instead they incompletely clear the inulin from 600 mL min^{-1}. The amount of inulin that is filtered, and ultimately excreted, per minute is equal to that contained in 120 mL of plasma. In this sense, ultrafiltration "clears" 120 mL of plasma per minute. Thus glomerular filtration is like a leaky hose: most of the fluid passing through the afferent arteriole continues on through the efferent arteriole, with a relatively small fraction passing into the tubule lumen as an ultrafiltrate. This idea is expressed in the **filtration fraction**, defined as

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{RPF}} \qquad [7.3.13]$$

Since GFR ≈ 120 mL min^{-1} and RPF ≈ 660 mL min^{-1}, the filtration fraction is normally about 120/660 = 0.18.

MULTIPLE STRUCTURES CONTRIBUTE TO THE SELECTIVITY OF THE GLOMERULAR FILTRATE

The glomerular filtration barrier consists of a sandwich of three layers: the **endothelial cell layer** of the glomerular capillaries, a **basement membrane** consisting of a meshwork of fibers of the extracellular matrix, and a second cell layer provided by specialized cells called **podocytes.** Each of these layers contributes to the filtration barrier. Figure 7.3.4 shows these layers.

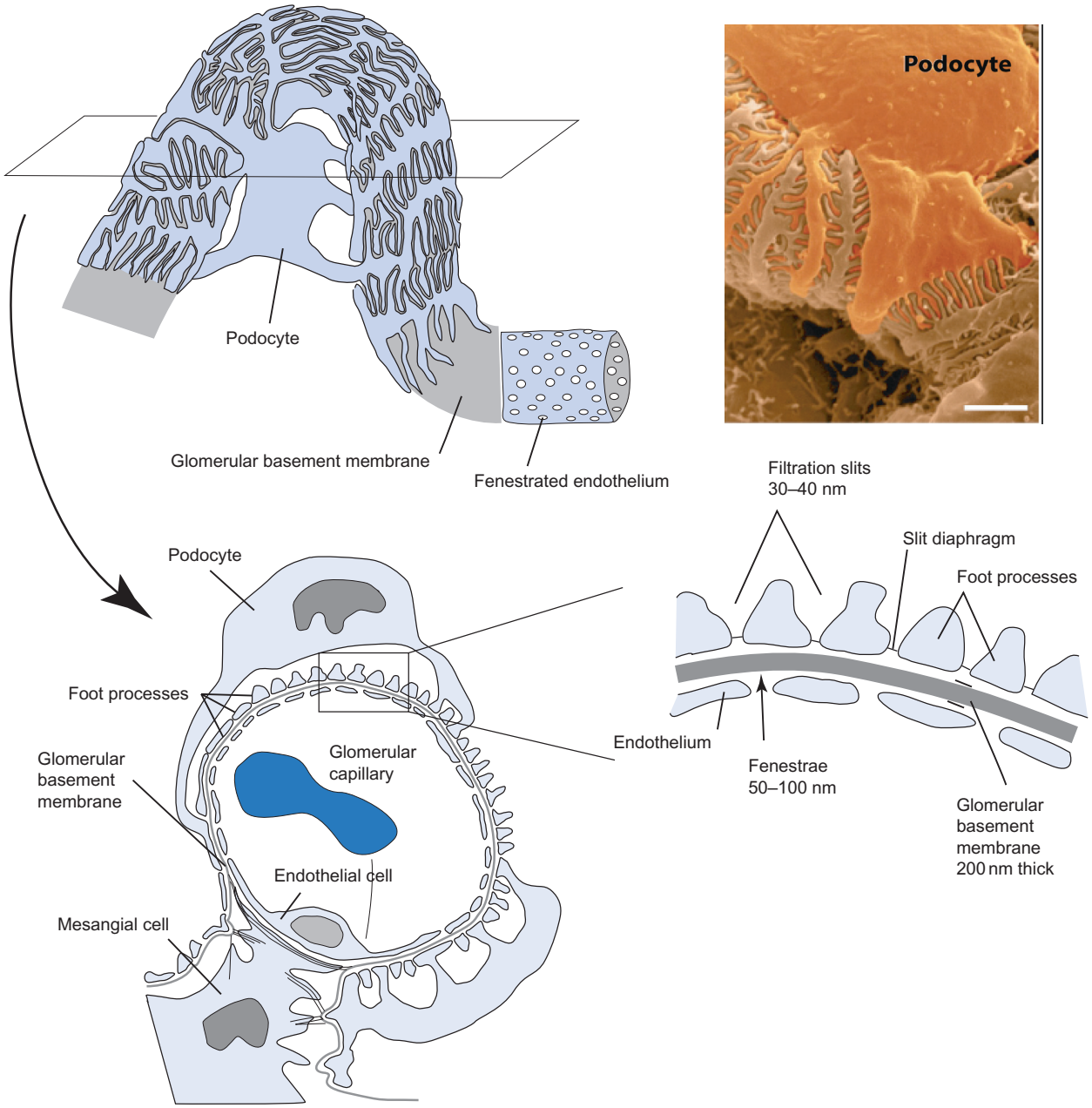

FIGURE 7.3.4 Structure of the glomerular filtration barrier. The ultrafiltration barrier consists of a fenestrated endothelial cell layer, a glomerular basement membrane (GBM), and a layer of glomerular podocytes. The endothelial cell is penetrated by a large number of fenestrae, or windows, about 50–100 nm in diameter. The endothelial cells lie along the glomerular basement membrane, which consists of a meshwork of fibers. This basement membrane presents part of the filtration barrier. Glomerular podocytes line the glomerular basement membrane on the side of the ultrafiltrate, in Bowman's space. These cells send out foot processes that interdigitate with other foot processes, thereby forming filtration slits, about 30–40 nm across. The glomerular epithelium slit diaphragms (GESD) link foot processes together. The slit diaphragms also provide a crucial filtration barrier to proteins 70 kDa and larger. At the right is a scanning EM in false color of a podocyte with interdigitating foot processes that effectively cover a glomerular capillary. *From R.P. Scott and S.E. Quaggin, The cell biology of renal filtration,* J. Cell Biol. ***209***:199–210 (2015).

THE ENDOTHELIAL CELL LAYER RETAINS THE CELLULAR ELEMENTS OF BLOOD

The endothelial cells that line the glomerular capillaries are specialized for their function. These capillaries are **fenestrated**. The root word for fenestra means "window." These capillaries are full of holes or windows that provide nearly no resistance to fluid flow but retain all of the blood cells and platelets. The fenestrae are typically about 50–100 nm in diameter. This distance is much larger than the width of most plasma proteins, suggesting that the fenestrae exclude the cells but all of the plasma solutes, including the plasma proteins, easily pass through this endothelial layer. The endothelial layer is specialized for filtration. Electron microscopy of rat glomeruli indicates that the fenestrae cover about 20% of the endothelial surface. This is a far greater area than the fenestrae that occur in other capillary beds, such as muscle.

Although the fenestrae seem too large to exclude proteins, evidence suggests that proteins are at least partially retained by the glomerular endothelial layer, due to the presence of the **glycocalyx**, a fibrous network of negatively charged glycoproteins on the surface of the endothelial cells. "Glycocalyx" derives from roots meaning "sweet husk." The glycocalyx in the glomerular capillaries is expanded to form the endothelial surface layer, ESL, more than 200 nm thick, that may form a restrictive barrier to protein filtration. The role of the ESL in protein restriction is controversial.

THE BASEMENT MEMBRANE EXCLUDES SOME PROTEINS

THE GLOMERULAR BASEMENT MEMBRANE IS A MESHWORK OF FIBERS INCLUDING TYPE IV COLLAGEN, LAMININ, NIDOGEN, AND PROTEOGLYCANS

The glomerular basement membrane derives from a fusion of the basement membranes of the glomerular endothelial cells and the podocytes. It consists of a meshwork of fibers. The human glomerular extracellular matrix contains some 144 different proteins. The most abundant of these includes **Type IV collagen**, **laminin**, nidogen, and proteoglycans, and is illustrated in Figure 7.3.5. Type IV collagen forms the basement membrane backbone. It consists of a protomer fiber made up of three α chains, each about 180 kDa. Six different genes encode for various α subunits of Type IV collagen. The Type IV collagen protomers self-associate to form a network that supports the basement membrane.

Laminin is the second most abundant basement membrane component. These large molecules (600−800 kDa) are heterotrimers of α, β, and γ chains. Currently recognized isoforms include five distinct α chains (α1−5), three isoforms of the β chains (β1−3), and two types of γ chains (γ1 and γ2). There are 30 possible combinations of these isoforms, but only 11 have been identified. They are named according to their α, β and γ components. In the adult, LM-521 predominates. The three subunits arrange themselves to produce a long arm and three short arms. In the presence of Ca^{2+}, laminin polymerizes into a hexagonal lattice by interactions between the short arms.

Nidogen, also known as entactin, is about 150 kDa and is shaped like a dumbbell, consisting of three globular domains connected by linker segments. Nidogen binds the γ1 chain of laminin, and it also binds type IV collagen and to another component of basement membranes, perlecan.

Proteoglycans have a protein core with attached chains of glycosaminoglycans. Heparan sulfate proteoglycans are the most abundant class in basement membranes. The negative charges of the heparan sulfate confer a net negative surface charge to the basement membrane. These proteoglycans include perlecan (see above) and agrin.

THE GLOMERULAR BASEMENT MEMBRANE FILTERS OUT SOME PROTEINS

Whether the glomerular basement membrane (GBM) or the glomerular slit diaphragms determine the selectivity of the glomerular filtration membrane has been debated for more than 30 years. Several kidney diseases that result in **glomerulonephritis** and consequent leakage of protein into the urine are caused by defects in basement membrane proteins. Mutations in COL4A3 and COL4A4 are examples. Mice deficient in the β2 component of laminin die shortly after birth due to massive **proteinuria**, loss of proteins in the urine.

THE SLIT MEMBRANE RETAINS PROTEINS 70 kDa OR LARGER

The slit diaphragms are specialized junctions between neighboring podocyte foot processes. They contain a variety of proteins including nephrin, podocin, CD2AP, α-actinin-4, and other key proteins associated with adherens junctions and tight junctions including ZO-1 (zona occludens-1), JAM-1 (junctional adhesion molecule 1), catenins, occludin. The exact disposition of these is not yet known, but a proposed structure is shown in Figure 7.3.5. Early experiments showed that proteins like horse radish peroxidase, with a molecular weight of 40 kDa, penetrate through the endothelial layer, basement membrane, and the slit pores to enter Bowman's space. Larger proteins such as myeloperoxidase, about 160 kDa, cross the endothelium and the basement membrane but pile up at the slit diaphragms. Other experiments with knock-outs of slit diaphragm proteins in mice suggest that the glomerular epithelial slit diaphragm is the crucial barrier to plasma proteins. According to this view, mutations of the glomerular basement proteins cause proteinuria by secondarily changing the slit diaphragms.

THE SIEVING COEFFICIENT DEPENDS MAINLY ON THE SLIT DIAPHRAGM

The local sieving coefficient of proteins or of any solute is defined as

$$\text{Sieving coefficient} = \Theta = \frac{C_B}{C_P} \qquad [7.3.14]$$

where C_B is the concentration of protein in Bowman's space and C_P is its concentration in the glomerular capillary plasma. Theoretical calculations of the sieving coefficient for membranes of different composition indicate that the slit diaphragm provides the filtration barrier to proteins (see Figure 7.3.6).

THE GLOMERULUS SELECTIVELY EXCLUDES PROTEINS BASED ON SIZE AND CHARGE

The negative charges on the proteins of the GBM and the slit diaphragm selectively restrain negatively charged proteins more than positively charged proteins.

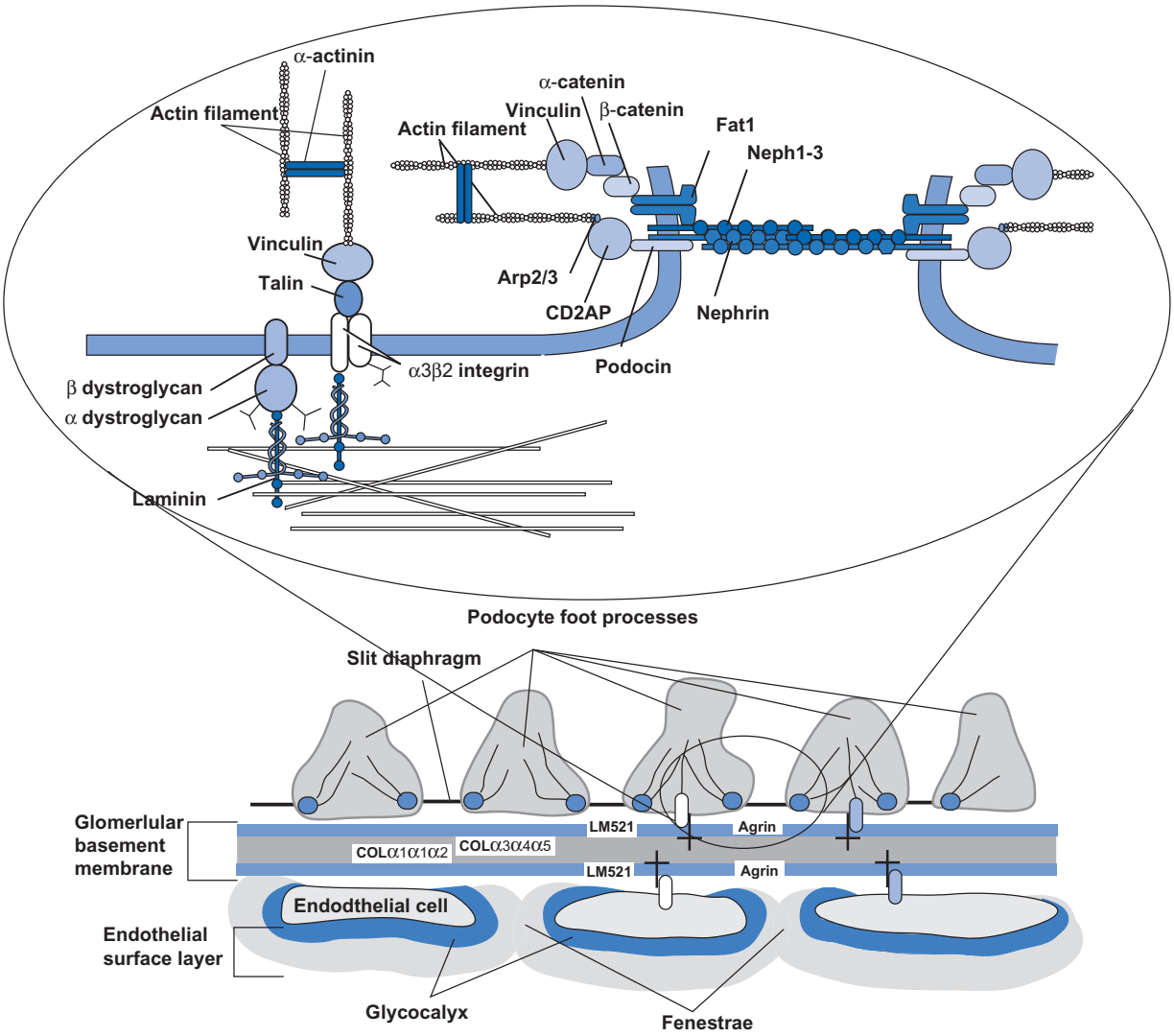

FIGURE 7.3.5 Molecular structure of the glomerular filtration barrier. The glomerular basement membrane is the fused basement membrane of both the endothelial cell layer and the podocyte cell layer. The endothelial cells have a glycocalyx coat that is extended to form the endothelial surface layer, over 200 nm thick. The charges in this layer may be important in restricting plasma protein filtration. The basement membrane is ordered, with a collagen core lined with layers relatively enriched in agrin, perlecan, and laminin 521. The collagen is mostly α3α4α5 type IV collagen, but the less abundant α1α1α2 type IV collagen is distributed more to the endothelium side. Both endothelial cells and foot processes anchor to the basement membrane through integrins and dystroglycans that bind laminin in the basement membrane. The slit diaphragms themselves contain specialized proteins including Nephrin and Neph1–3 and the cadherin Fat1. Podocin within the foot processes binds nephrin and CD2AP that links the slit diaphragm to the actin cytoskeleton. The slit diaphragms likely consist of mainly of cross-bound nephrin and neph1–3. Additional proteins, such as occludin, junctional adhesion molecule, and zona occludens-1, not shown, are also present in the foot processes.

The combined effects of protein size and charge on their sieving coefficient are shown in Figure 7.3.7.

THE STARLING FORCES DRIVE ULTRAFILTRATION

The forces that govern the formation of the glomerular ultrafiltrate are identical in form to those that govern exchange of material across any capillary in the body. The equation that describes the relationship between flow and forces across a porous membrane is

$$[7.3.15] \quad J_v = L_P\left[(P_L - P_R) - \left(\sum_i \sigma_i \pi_{i\,L} - \sum_i \sigma_i \pi_{i\,R}\right)\right]$$

where J_v is the volume flux; L_P is the hydraulic permeability; P_L and P_R are the hydrostatic pressures on the left and right sides of the membrane, respectively; σ_i is the reflection coefficient of the ith species; and π_{iL} and π_{iR} are the osmotic pressures contributed by the ith species on the left and right sides of the membrane, respectively. If we multiply both sides by the aggregate area of the glomeruli, we obtain

$$\begin{aligned} GFR = Q_v &= A\,L_v \\ &= A\,L_P\left[(P_L - P_R) - \left(\sum_i \sigma_i \pi_{i\,L} - \sum_i \sigma_i \pi_{i\,R}\right)\right] \end{aligned} \quad [7.3.16]$$

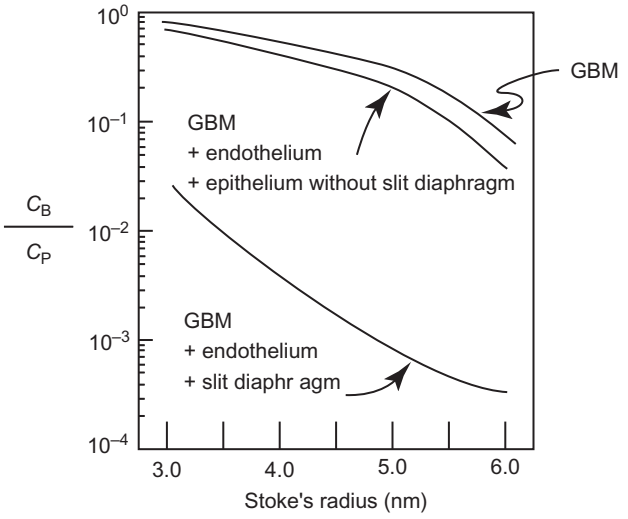

FIGURE 7.3.6 Results of theoretical calculations of the sieving coefficient as a function of molecular size for hypothetical membranes consisting of glomerular basement membrane alone (GBM); glomerular basement membrane plus the attached endothelial cell layer and podocyte epithelial cell layer, but without the slit diaphragms; the entire capillary wall consisting of endothelium, glomerular basement membrane, and podocytes with intact slit diaphragms. *Modified from A. Edwards, B.S. Daniels, and W.M. Deen, Ultrastructural model for size selectivity in glomerular filtration,* Am. J. Physiol. ***276****:F892—F902, 1999.*

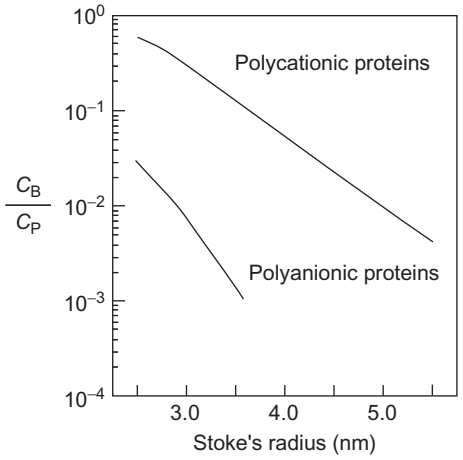

FIGURE 7.3.7 Effect of charge and size on the sieving coefficient of renal corpuscles *in vivo*. Values of the sieving coefficient were obtained by direct micropuncture or by urinary clearance corrected for tubular reabsorption. Note that cationic proteins (those with + net charge) are filtered far more easily than anionic proteins of the same size. The filterability of proteins diminishes precipitously with larger size. For reference, the Stokes radius for serum albumin is about 3.6 nm. *Modified from B.D. Myers, Determinants of the glomerular filtration of macromolecules, in S.G. Massry and R.J. Glassock, eds.,* Massry & Glassock's Textbook of Nephrology, *4th edition, Lippincott, Williams and Wilkins, Philadelphia, PA, 2001.*

We further simplify the equation by assuming that materials are either freely filtered or they are not filtered at all. If they are freely filtered, then $\sigma = 0$; if they are not filtered at all, then $\sigma = 1.0$. We identify the "left" side of the membrane with the capillary, and the "right" side with Bowman's space. Then Eqn (7.3.16) becomes

$$[7.3.17] \qquad GFR = K_f[(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$$

where K_f is the filtration coefficient; P_{GC} is the hydrostatic pressure within the glomerular capillaries; P_{BS} is the hydrostatic pressure within Bowman's space; and π stands for the total osmotic pressure contributed only by the proteins that are not filtered by the glomerulus. Recall that the osmotic pressure is the sum of all contributions to the osmotic pressure and that it is a property of the solution itself. Here we have partitioned the total osmotic pressure into the part contributed by the freely permeable solutes and the part contributed by the impermeant proteins. We have discarded the part contributed by freely permeable solutes because it makes no contribution to the *effective* osmotic pressure since $\sigma = 0$ for these solutes. The remaining part of the osmotic pressure, that part contributed by the proteins, is called the **colloid osmotic pressure** or the **oncotic pressure** (see Chapter 5.2). Because the protein content of the ultrafiltrate is near zero, $\pi_{BS} \approx 0$ and Eqn (7.3.17) is simplified further to

$$[7.3.18] \qquad GFR = K_f[P_{GC} - P_{BS} - \pi_{GC}]$$

Thus the driving force favoring glomerular filtration is the glomerular capillary hydrostatic pressure. The glomerular capillary is a high-pressure capillary, with hydrostatic pressures near 60 mmHg over its length. The formation of the glomerular filtrate is opposed by the pressure within Bowman's space, which is a fairly constant 20 mmHg. The oncotic pressure of the glomerular capillaries is not constant over their length because the blood is concentrated by removal of about 20% of its volume (the filtration fraction) as a protein-free filtrate. Thus the protein left behind is concentrated. The oncotic pressure is not linear with protein concentration but can be fit by a higher order polynomial (see Problem 15 of PS2.2). The oncotic pressure at the beginning of the glomerular capillary is about 25 mmHg. As the blood passes through the capillaries and protein-free filtrate is removed, the oncotic pressure climbs to 35 mmHg. The degree to which the blood is concentrated depends in part on its flow. Faster flowing blood has a lower filtration fraction because it is in the glomerular capillaries a shorter time. If the flow is sufficiently sluggish, **filtration equilibrium** can be reached. At this point, the net force for filtration becomes zero and no further filtration occurs. The balance of Starling forces is shown schematically in Figure 7.3.8.

Average values for the Starling forces are as follows:

$$P_{GC} = 60 \text{ mmHg}$$
$$P_{BS} = 20 \text{ mmHg}$$
$$\pi_{GC} = 30 \text{ mmHg}$$

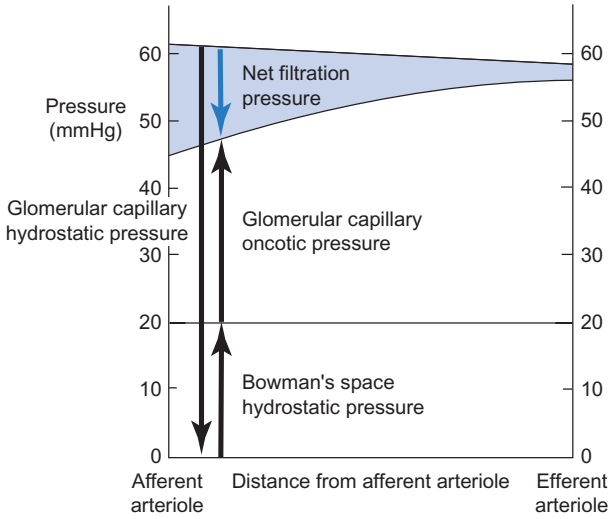

FIGURE 7.3.8 Starling forces as a function of distance from the afferent arteriole to the efferent arteriole. Glomerular capillary hydrostatic pressure is about 60 mmHg and declines only slightly through the glomerular capillary. Similarly, the hydrostatic pressure within Bowman's space is about 20 mmHg and is not different along the length of the capillary. The oncotic pressure of the glomerular capillary begins at about 25 mmHg and increases as protein-free filtrate is removed from the blood. At the efferent arteriole end of the glomerular capillary, the oncotic pressure increases to about 35 mmHg. These profiles in pressures depend on the flow of blood through the capillary. If flow is slower, the glomerular capillary oncotic pressure may rise further and the net filtration pressure will shrink to zero. At this point, the glomerular capillary reaches filtration equilibrium.

Insertion of these into Eqn (7.3.18) shows that the net driving force averages about 10 mmHg in favor of filtration.

WHY DOES THE GLOMERULAR FILTRATION BARRIER NOT CLOG?

How the glomerular filtration barrier provides both a size and charge selectivity, and the respective roles of the glomerular endothelial cell, the basement membrane, and the slit diaphragms have been intensely investigated and debated for over 50 years, and the issues are still not resolved. There are two major questions that need answering: (1) why doesn't the glomerular filtration barrier clog? And (2) why does the sieving coefficient for proteins increase when the glomerular filtration rate decreases? Hydraulic-driven filters invariably clog, and the solution is replacement of the filter or back-flushing the filter to remove the clogging material. The kidney cannot use either of these solutions. The most likely case is that the kidneys do not become clogged because the retained proteins diffuse back into the blood. If the major pathway for albumin across the glomerular filtration barrier is by diffusion, then reduction of filtration to zero would lead to diffusion equilibration across the barrier, or an increase in the sieving coefficient.

Clinical Applications: Nephrotic Syndrome

The nephrotic syndrome is a set of symptoms that include the following:

- protein in the urine;
- low blood protein levels;
- swelling or edema.

It may also include elevated levels of serum lipids, anemia, and vitamin D deficiency, all because of loss of plasma proteins into the urine. This can have multiple causes, but all involve defects in the glomerular barrier to proteins so that excess proteins are filtered and thereby excreted in the final urine. The three barriers were discussed in the text: the fenestrated endothelial cell layer, the GBM, and the podocyte and slit diaphragm.

Nephrotic syndrome can be primary or secondary. Primary causes are described by their histological changes: minimal change disease, focal segmented glomerulosclerosis, and membranous nephropathy. Secondary causes are described by their underlying cause, which include diabetes mellitus, sarcoidosis, hepatitis B, hepatitis C, bacterial infections, parasitic infections, and more.

All of the diseases are characterized by protein in the urine, at least 3.5 g per 24 h. The loss of protein can cause hypoalbuminemia, with resulting edema that may show as puffiness around the eyes, pitting edema in the legs, and pleural effusion. Loss of proteins stimulates liver synthesis, including lipoproteins. Because lipoprotein lipase levels fall, lipoprotein levels increase. Loss of vitamin D binding protein can lead to vitamin D deficiency diseases, with calcium malabsorption and bone disease.

Mutations of nephrin, a protein of the filtration slit, cause nephrotic syndrome. Mutations of podocin also cause nephrotic syndrome that is insensitive to steroid treatment. Podocin is an integral protein of the podocyte cell membrane that segregates into lipid rafts and is required to recruit nephrin into those rafts. Current thought is that podocin and nephrin form a signaling complex that activates protein kinases involved in glomerular structural integrity. These mutations cause minimal change diseases in which structural changes are evident only at the electron microscope level and not at the histological level. Until recently, these were part of the set of nephrotic syndrome called idiopathic nephrotic syndrome.

Membranous glomerulonephritis is one of the more common causes of nephrotic syndrome in adults. It is an inflammatory disease, believed to be caused by binding of antibodies to antigens in the GBM that triggers the formation of a membrane attack complex from complement (see Chapter 5.3). This triggers release of proteases and oxidants that damage the capillary walls, causing them to become leaky. Histology reveals thickened basement membranes.

Treatment depends on etiology. For all nephrotic syndromes, monitoring and maintaining normal fluid levels and distribution among the body compartments are the goal. This could include restriction of fluid intake, restriction of salt intake, regular monitoring of blood pressure and urine output, and the use of diuretics. Inflammatory causes of nephrotic syndrome are treated with immunosuppressants such as prednisolone and dietary modificaton.

SUMMARY

Glomerular filtration is the first step in the formation of urine. It was originally posited on morphological grounds and was established by micropuncture and microanalysis studies in the 1920s. The GFR can be estimated from the inulin clearance because inulin is neither secreted nor reabsorbed by the nephron. The ERPF can be estimated from the clearance of para amino hippuric acid because PAH is so avidly secreted by the nephrons. The clearance of any substance is calculated as

$$C_x = \frac{Q_u \times U_x}{P_x}$$

where C_x is the clearance, Q_u is the urine flow rate, in mL min^{-1}, U_x is the urinary concentration of x, and P_x is the plasma concentration of x. Clearance has the units of mL min^{-1} and its interpretation depends on the way in which the nephrons handle substance x. The RPF is about 660 mL min^{-1}, whereas the GFR is about 120 mL min^{-1}. The filtration fraction, GFR/RPF, is about 0.2.

The rapid filtration of large volumes of fluid is accomplished by the specialized structures of the glomerulus and Bowman's capsule. The filtration barrier consists of the capillary endothelial cell, basement membrane, and podocytes of Bowman's capsule. The endothelial cells are highly fenestrated. These openings increase the area available for filtration but retain the cellular elements of blood. The basement membrane restricts filtration of larger molecular weight proteins. Slit diaphragms appear in the openings between podocyte foot processes. These may form the final filtration barrier to proteins like plasma albumin. The sieving coefficient is given as

$$\Theta = \frac{C_B}{C_P}$$

the ratio of concentration of material in Bowman's space to its concentration in plasma. For most small molecular weight materials, $\Theta = 1.0$.

The forces producing the ultrafiltrate are the same as those that govern exchange across any capillaries. The net force is the balance between hydrostatic and osmotic pressures within the glomerular capillary and the fluid in Bowman's space. The glomerular capillary is specialized in that its filtration coefficient is large and its major driving force, the hydrostatic pressure within the glomerular capillary, is high.

REVIEW QUESTIONS

1. What is the sieving coefficient for small molecular weight solutes such as amino acids, glucose, and electrolytes?
2. What characteristics of molecules determine their sieving coefficient?
3. Why is the clearance of inulin equal to the GFR, whereas the clearance of PAH is equal to the ERPF?
4. What is the main force favoring formation of the glomerular ultrafiltrate?
5. What are the main forces opposing the formation of the glomerular ultrafiltrate?
6. What layers constitute the glomerular filtration apparatus and what specializations allow them to produce a rapid ultrafiltrate that excludes most plasma proteins?