5.10 The Microcirculation and Solute Exchange

Learning Objectives

- List three different types of capillaries and where they are typically found
- Describe the various routes of transfer of materials across the capillary wall
- List those determinants of transfer that increase passive transport
- Describe what is meant by flow-limited and diffusion-limited transport
- Define solute extraction
- Describe vasomotion
- Write the Starling equation that describes volume transfer across the capillaries
- Define the filtration coefficient
- Define colloid osmotic pressure and estimate it from the protein concentration
- Describe the function of the lymph

THE EXCHANGE VESSELS INCLUDE CAPILLARIES, TERMINAL ARTERIOLES, AND VENULES

Direct exchange of materials between the cells and the external environment is impractical because the diffusion distance is too large. The diffusion distance is effectively shortened by convection, the movement of materials by bulk transport, through the circulatory system. The final perfusion of tissues is through the **microcirculation**, which closely apposes nearly all cells of the body. The arteries branch extensively, and each generation of branches increases the number of vessels, decreases their caliber, but increases the overall cross-sectional area, so that flow slows with each succeeding branch. The last arteries branch to form **first-order arterioles**, which finally branch to form **terminal arterioles**, which then form **capillaries**. The capillaries are tiny vessels 4–8 μm wide that extend for 0.5–1 mm (500–1000 μm). These are invisible to the naked eye. In 1628, Harvey postulated their existence to explain the circulation of the blood, and Malpighi first observed them in frog lungs in 1661. These small channels coalesce to form **venules**, vessels some 15 μm wide that contain pericytes but no smooth muscle. These smallest venules unite to form progressively larger venules and eventually small and then larger veins. Smooth muscles are present in the walls of the veins when their width exceeds 30–50 μm. A schematic of this branching is shown in Figure 5.10.1. Exchange occurs across vessels on both sides of the capillary bed—some oxygen diffuses across the arteriolar walls and some fluid flows across the walls of pericytic venules, but the **major site of material exchange occurs across the capillary walls**.

ULTRASTRUCTURAL STUDIES REVEAL THREE DISTINCT TYPES OF CAPILLARIES

There are three distinct types of capillaries:

A. Continuous capillaries
B. Fenestrated capillaries
C. Discontinuous capillaries.

The overall ultrastructural appearance of these capillaries is shown schematically in Figure 5.10.2.

Continuous capillaries are the most abundant, being present in muscle, skin, lung, fat, connective tissue, and nervous tissue. This type of capillary consists of a

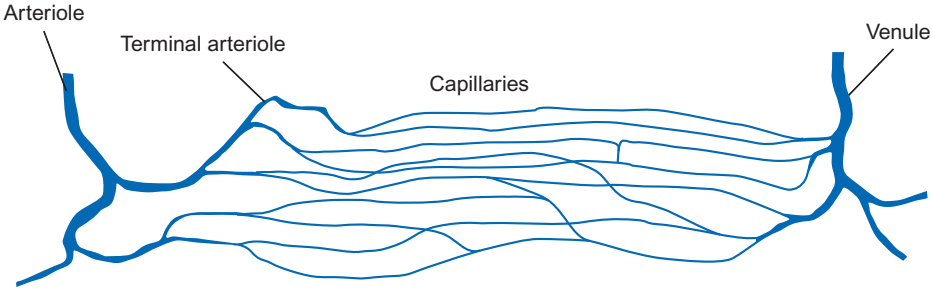

FIGURE 5.10.1 Schematic drawing of an arteriole giving rise to a capillary bed perfusing a tissue (cells not shown). The capillaries may branch extensively within the tissue. In some tissues, particularly the skin, arteriovenous anastomoses may directly link the arterioles to the venules, allowing blood flow to bypass the capillary bed.

© 2012 Elsevier Inc. All rights reserved.
DOI: http://dx.doi.org/10.1016/B978-0-12-800883-6.00055-0

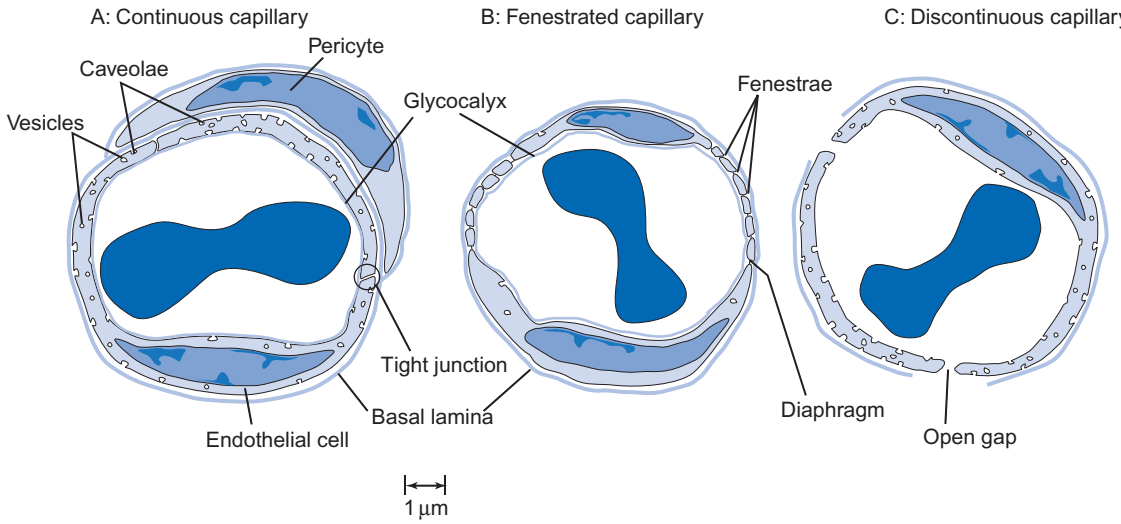

FIGURE 5.10.2 Types of capillaries. See text for their description.

continuous barrier of 1–3 endothelial cells with a continuous basement membrane. Its wall is only one cell thick—the endothelial cell—the distance separating plasma and interstitial fluid is only about 0.5 μm. **Pericytes** partially cover the outside of the capillary and may help direct the formation and proper structure of capillaries. A glycocalyx (literally "sweet husk") covers the inner surface of the endothelial cells. The negative charge on the glycocalyx repels the negatively charged plasma proteins and helps retain these in the plasma. Neighboring endothelial cells join at **tight junctions**. Despite their name, fluid can pass through these so-called tight junctions where **junctional strands** incompletely seal the junction. Both the inner and outer surface of these capillaries bind fluid-filled vesicles about 70 nm in diameter. At the surfaces, the vesicles fuse with the endothelial cell membrane, forming a narrower neck about 20–30 nm across. Thus, at the surface, these vesicles form flask-shaped vesicles called **caveolae**. The protein **caveolin** stabilizes the cytoplasmic face of these vesicles, and the vesicular membrane itself contains receptors for a variety of plasma materials such as albumin, insulin, transferrin, and ceruloplasmin. Electron micrographs show free-floating vesicles that are closely apposed to these caveolae. Serial sections show that these vesicles connect with others. These vesicles allow transport of macromolecules into the cell **(endocytosis)** or across it **(transcytosis)**.

Fenestrated capillaries have "windows" for solute and fluid exchange. These capillaries are found in tissues that specialize in fluid exchange—such as the kidney, intestinal mucosa, exocrine glands, choroid plexus, and ciliary body of the eye. The **fenestrae** or gaps are about 50–60 nm wide. In most tissues, a thin diaphragm bridges the gap.

Discontinuous capillaries are also called **sinusoidal** capillaries. They are present in organs that require transfer of proteins or cells across the capillary wall. Discontinuous capillaries possess large gaps in the endothelial cell lining—over 100 nm—and gaps in the basement membrane. Both large proteins and cells can leave the capillaries through these gaps. These types of capillaries are found in: the liver, where many plasma proteins are synthesized and placed into the plasma; the spleen, which destroys worn erythrocytes; and the bone marrow, which makes erythrocytes and therefore must be able to get the erythrocytes into the capillaries.

CAPILLARY EXCHANGE USES PASSIVE MECHANISMS

Capillary exchange occurs through three mechanisms:

A. Passive diffusion
B. Bulk flow of fluid
C. Transcytosis.

The routes used for these mechanisms are shown schematically in Figure 5.10.3. The capillary presents a series of permeability barriers beginning with the innermost glycocalyx and continuing with the inner plasma membrane of the endothelial cell, its cytoplasm, outer plasma membrane, and basement membrane. Shortcuts to these barriers exist. Cells meet at intercellular junctions whose clefts remain permeable to water and low molecular weight, water-soluble solutes. At some places, the endothelial cell has "windows" or fenestrae that are more permeable to water and low molecular weight solutes. In other places, the continuity of the endothelial cells is interrupted by open gaps that allow nearly all materials to exchange with the extravascular fluid. More specific transport systems recognize specific proteins and carry them across the cell within vesicles. Water channels called aquaporins allow water to cross the membrane. There are multiple isoforms of aquaporin; AQP1 is the one present in endothelial cells.

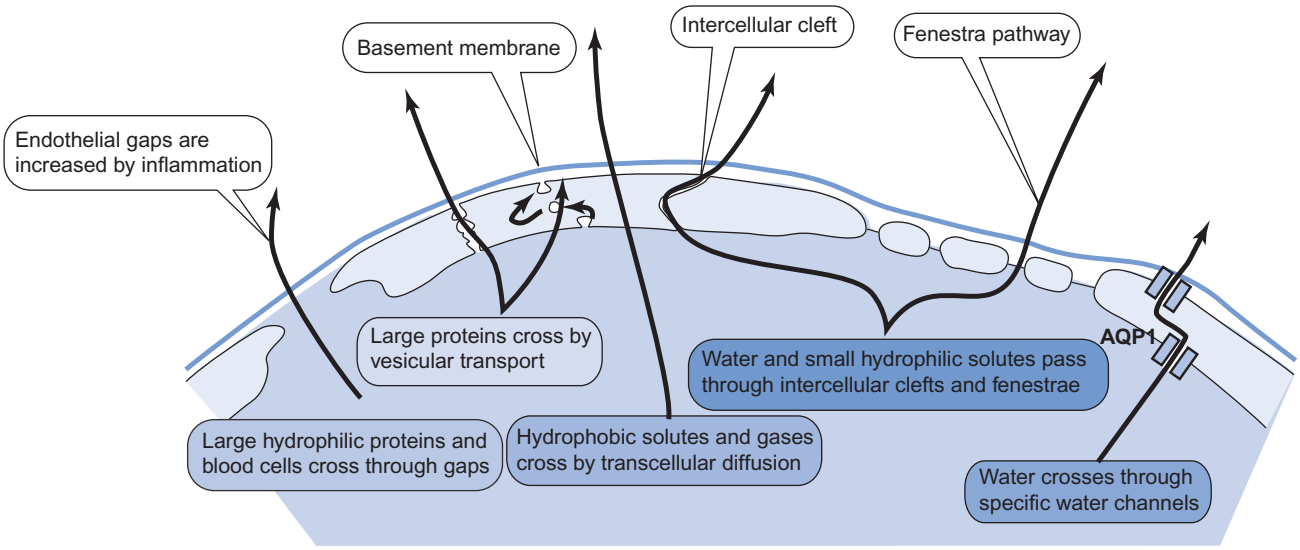

FIGURE 5.10.3 Routes of solute transfer across capillaries. (Source: Adapted from J.R. Levick, *Cardiovascular Physiology*, Arnold, New York, NY, 2003.)

PASSIVE DIFFUSION OBEYS FICK'S LAW OF DIFFUSION ACROSS MULTIPLE BARRIERS

In Chapter 2.5, we discussed diffusion through narrow pores and diffusion across a lipid membrane. In both cases the steady-state rate of diffusion was given by an equation of the form

[5.10.1] $$J_s = p\Delta C$$

where p is the **permeability** of the barrier, with units of cm s^{-1} when flux is in mol cm^{-2} s^{-1} and C is the concentration of solute in mol cm^{-3}. The value of the permeability depends on the microscopic character of the route of transfer. The permeability includes the diffusion coefficient of the solute, the partition coefficient of the solute if it permeates through the lipid membranes, the thickness of the membrane, and the number and size of channels or pores if the solute permeates through these. The flow is just the flux times the area:

[5.10.2] $$Q_s = Ap\Delta C$$

where Q_s is the flow of solute, in mol s^{-1}, and A is the area in cm^2. The driving force for diffusion is the concentration difference. This fundamental fact is modified when the diffusing material is a gas because the actual concentration of the gas depends on **the solubility** of the gas in different phases. With gases, the **partial pressure** of the gas drives diffusion. The partial pressure of the gas in solution is the partial pressure of gas that would be in equilibrium with its concentration. The solubility is a related concept: it is the coefficient that relates concentration to partial pressure. Thus, for gases we write

[5.10.3] $$[A] = \alpha_A P_A$$

where $[A]$ is the concentration of gas A, α_A is the solubility of gas A, and P_A is its partial pressure. The value of α depends on the units used for $[A]$ and P_A. This equation is discussed in more detail in Chapter 6.3. As a consequence of these facts, the diffusion of a gas across a single lipid barrier, for example, is given as

[5.10.4] $$Q_s = \frac{Ak_s\alpha_s D_s}{\delta}\Delta P_s$$

where Q_s is the diffusive flow of gas s, A is the area through which it flows, k_s is the partition coefficient in the lipid, α_s is the solubility in the aqueous phases, D_s is the diffusion coefficient through the lipid membrane, δ is the thickness of the membrane, and ΔP_s is the partial pressure difference between one side of the membrane and the other. This equation is also Eqn [6.3.14]. For a complex barrier consisting of several individual barriers, Eqn [5.10.4] must be modified, yet the result has a similar form. For oxygen, we write

[5.10.5] $$Q_{O_2} = \frac{Ak_{O_2}D_{O_2}}{\delta_{O_2}}\left[P_{O_2\,\text{capillary}} - P_{O_2\,\text{cell}}\right]$$

where k_{O_2} is a constant that incorporates both the partition coefficient and the solubility from Eqn [5.10.4]. In this equation, δ_{O_2} is the average diffusion distance for oxygen. Thus the flow of oxygen to the cells is enhanced by:

- increased area through which transfer occurs;
- decreased diffusion distance;
- increased oxygen gradient (ΔP_{O_2}).

The other variables in Eqn [5.10.5] that influence oxygen delivery, such as k_{O_2} and D_{O_2}, are characteristic of oxygen as a molecule and thus are not subject to physiological variation.

EITHER FLOW OR DIFFUSION CAN LIMIT DELIVERY OF MATERIALS TO CELLS

The relation between blood flow and delivery of materials to cells by diffusion from the blood can be illustrated for a simple system with the following assumptions:

- Flow is constant with the value Q_v. Blood velocity is also constant: $Q_v = AJ_V$.
- The concentration of material in the interstitial fluid that bathes the cells is constant.
- The system is at steady state: delivery of material to the cells exactly balances metabolism.
- Exchange occurs only across the capillary wall and the permeability is constant.
- The capillary is a right circular cylinder with radius r and length l.

The situation is shown in Figure 5.10.4.

Let the concentration of solute entering from the arteriolar side at the left be C_a, and the concentration leaving the capillary at the venule end be C_v. We investigate what happens to the material in a slab of the cylinder that is dx thick between x and $x + dx$. Its volume is $V = \pi r^2\, dx$ and its surface area $S = 2\pi r\, dx$; the cross-sectional area is $A = \pi r^2$. There is a flow of solute from the left which is the flow of the blood times the concentration of solute in the blood at x: $Q(x) = AJ_VC(x)$, where $C(x)$ is the concentration of solute at point x. The solute in the volume element leaves the element two ways: some diffuses out of the cylinder into the tissue and the remainder is carried forward to the next volume element in the cylinder. The amount that diffuses out of the cylinder per unit time, normal to the surface of the cylinder, is $Q_D = 2\pi r\, dx p[C(x) - C_i]$, where $C(x)$ is the concentration of material in the volume element and C_i is the constant concentration in the interstitial fluid. The amount carried forward to the next volume element is $Q(x + dx) = AJ_vC(x + dx)$. The conservation of material dictates that the input of material must be equal to the output:

$$[5.10.6] \qquad \begin{aligned} Q(x) &= Q_D + Q(x + dx) \\ AJ_VC(x) &= 2\pi rp\, dx[C(x) - C_i] + AJ_VC(x + dx) \end{aligned}$$

The second line of this equation can be rearranged to give

$$[5.10.7] \qquad \begin{aligned} \frac{[AJ_VC(x) - AJ_VC(x + dx)]}{dx} &= 2\pi rp[C(x) - C_i] \\ -\frac{dC(x)}{dx} &= \frac{2\pi rp}{AJ_V}[C(x) - C_i] \end{aligned}$$

where we have taken the limit as $dx \to 0$ and used the definition of the derivative. We may separate variables in Eqn [5.10.7] and integrate between $x = 0$ at the arteriolar end of the capillary to position x somewhere along the capillary:

$$[5.10.8] \qquad \begin{aligned} \int_0^x \frac{dC(x)}{(C(x) - C_i)} &= -\int_0^x \frac{2\pi rp}{AJ_V} dx \\ \ln\frac{(C(x) - C_i)}{(C_a - C_i)} &= -\frac{2\pi rp}{AJ_V} x \end{aligned}$$

Taking the exponent of both sides and rearranging gives C as a function of distance x along the capillary:

$$[5.10.9] \qquad C(x) = C_i + (C_a - C_i)e^{-(2\pi rp/AJ_V)x}$$

If we let $x = l$, then $C(l) = C_v$, the concentration of solute as it exits the capillary at the venule end:

$$[5.10.10] \qquad \begin{aligned} C_v &= C_i + (C_a - C_i)e^{-(2\pi rlp/AJ_V)} \\ C_v &= C_i + (C_a - C_i)e^{(-Sp/Q_V)} \end{aligned}$$

where S is the surface area of the capillary, p is its permeability, and Q_V is the flow through the capillary. This equation describes the rate of equilibration between the capillary contents and the interstitial fluid. The equation shows that the difference between C_a and C_i decays exponentially with distance along the capillary, and that the rate of this decay is directly related to the surface area of the capillary, directly related to its permeability and inversely related to its rate of flow. This all makes subjective sense: if the capillary is highly permeable to solute, it ought to equilibrate rapidly between blood and interstitial fluid. If the surface area is large, it also ought to equilibrate rapidly. If the flow is large, then the material washes out before it has time to equilibrate. The concentration profiles for $C(x)$ for various values of S, p, and Q_V are shown in Figure 5.10.5.

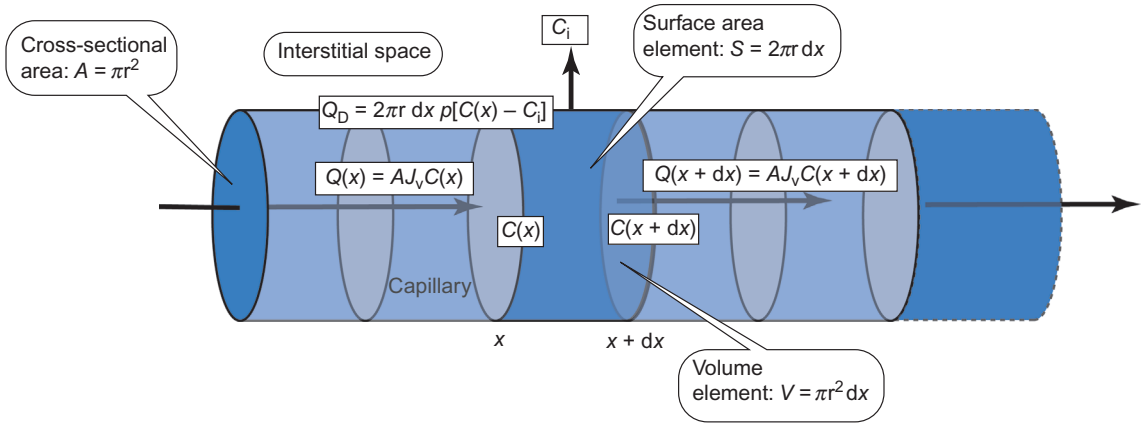

FIGURE 5.10.4 Movement of material across an idealized capillary. We use these definitions of flows to derive an expression for $C(x)$.

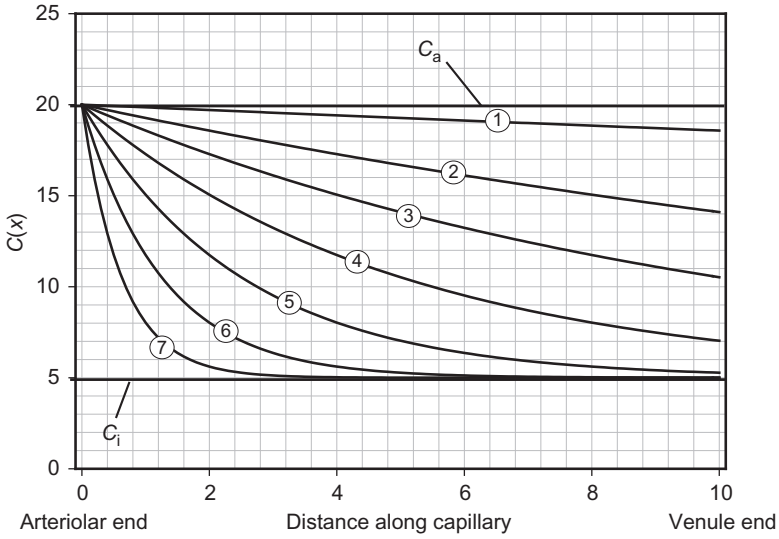

FIGURE 5.10.5 Concentration profile of the concentration of solute within the capillary when the interstitial fluid concentration is kept constant. For each simulation, the flow is steady. Values of Sp/Q_V were 0.1 (curve 1), 0.5 (curve 2), 1 (curve 3), 2 (curve 4), 4 (curve 5), 8 (curve 6), and 16 (curve 7).

One of the purposes of calculating the concentration profile as we have done is to allow calculation of the total diffusional transfer of solute over the length of the capillary. This can be done most easily by recognizing that the total diffusional transfer is just the input into the arteriolar end of the capillary minus the output at the venule end:

$$[5.10.11] \qquad Q_D = Q_V C_a - Q_V C_v$$

here Q_D is the total material flow from capillary to interstitial fluid, not the increment in flow as used in Eqn [5.10.6]. This is easily calculated because we know what C_v is by Eqn [5.10.10]. Insertion of Eqn [5.10.10] into Eqn [5.10.11] allows us to obtain

$$[5.10.12] \qquad Q_D = Q_V[C_a - C_i]\left[1 - e^{-(Sp/Q_V)}\right]$$

The graph of total diffusional transfer, Q_D, against blood flow, Q_V, is shown in Figure 5.10.6. This graph shows that at low flow the diffusional transfer of solute is **flow limited** because increases in flow directly increase the transfer of solute to the tissues. This makes sense with Figure 5.10.5 because, given the dimensions of the vessel and its permeability characteristics, diffusional flow can be increased only by increasing the gradient. The gradient in Figure 5.10.5 is greatest at high flows. In this case, transfer of materials becomes **diffusion limited**. These descriptions refer to general domains of the graph, and there is no sharp demarcation between them.

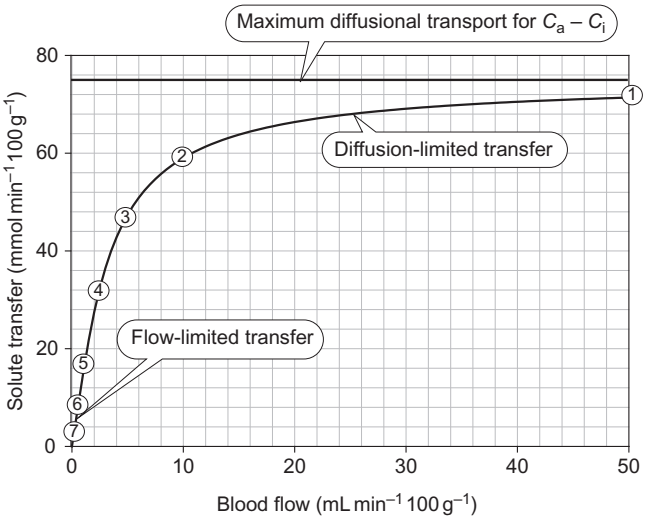

FIGURE 5.10.6 Diffusion and flow-limited diffusional transport across the capillary wall. For a given arterial and interstitial concentration of a solute, surface area, and permeability, flow can determine the transfer of material. Slow flow limits transfer to the amount of material the flowing fluid contains, fast flow maintains the highest diffusion gradient and the highest material transfer, so that increasing flow further only marginally increases transfer. Points 1–7 refer to the same values of S_p/Q_V as in Figure 5.10.5, obtained for constant values of S and p by varying Q_V.

THE INTERSTITIAL FLUID CONCENTRATION IS SET BY THE BALANCE BETWEEN CONSUMPTION AND DELIVERY

Equations [5.10.9] and [5.10.12] were derived with the assumption that the interstitial fluid concentration was constant, but actually it depends on the activity of the tissue in contact with it. In the case of oxygen, carbon dioxide, and nutrients, there are wide swings in the rate at which tissues consume or produce these materials. Let us consider a material like oxygen that is consumed during metabolism. In the steady state (another assumption!), the rate of metabolism equals the rate of transfer of material to the interstitial fluid. Let Q_m indicate the rate of metabolism. In the case of O_2 or glucose, Q_m is negative because these materials disappear from the interstitial fluid. Then Eqn [5.10.12] becomes

$$[5.10.13] \qquad -Q_m = Q_D = Q_V[C_a - C_i]\left[1 - e^{-(Sp/Q_V)}\right]$$

Here the expression

$$[5.10.14] \qquad \left[1 - e^{-(Sp/Q_V)}\right] = E$$

is called the **solute extraction**. It is equal to the fraction of arteriolar solute that would be transferred across the capillary wall if C_i were zero. It is a dimensionless number with range 0–1.0. We can solve Eqn [5.10.13] for C_i:

$$[5.10.15] \qquad C_i = \frac{Q_V C_a E + Q_m}{Q_V E}$$
$$C_i = \frac{C_a + Q_m}{Q_V E}$$

In the last equation, a negative Q_m causes C_i to be less than C_a. How much less depends on the flow, the extraction of the solute, and the rate of consumption. If a material is not consumed by the tissues, $Q_m = 0$ and Eqn [5.10.15] shows that at steady state its concentration will equal that in the arterial blood. Production of a solute such as CO_2 or lactic acid entails a positive Q_m so that the concentration of such a solute will be higher in the interstitial fluid than in the blood, and its concentration will also obey Eqn [5.10.15].

REGULATION OF PERFUSION REGULATES SOLUTE TRANSFER

The equation for diffusional transfer of solute that we derived from simplified assumptions is reproduced below:

$$[5.10.16] \qquad Q_D = Q_V[C_a - C_i]\left[1 - e^{-(Sp/Q_V)}\right]$$

To increase diffusional transfer, physiological systems can:

A. increase the blood flow (Q_V in Eqn [5.10.16]);
B. increase the gradient for diffusion ($(C_a - C_i)$ in Eqn [5.10.16]);
C. increase the effective area for diffusion (S in Eqn [5.10.16]), or increase the apparent permeability, p, by decreasing the effective diffusion distance or by changing the permeability barriers of the capillaries.

Diffusional transfer is increased by increasing S, p, and Q_V by increasing the number of open capillaries. Figure 5.10.7 shows a schematic of a muscle consisting of a population of muscle fibers. Each set of capillaries

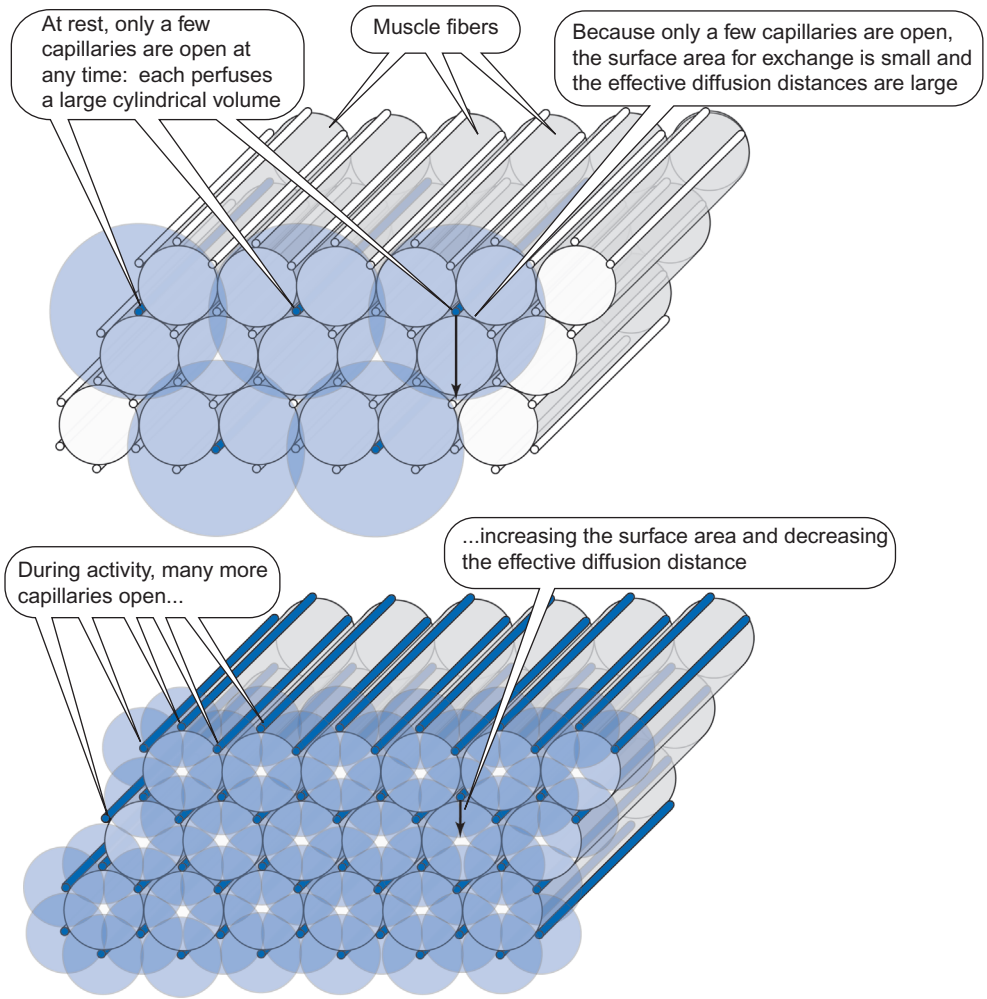

FIGURE 5.10.7 Regulation of solute delivery to the tissues. Top: at rest, tissues have low metabolic rates and low perfusion delivers sufficient nutrients and removes waste metabolites. Only a fraction of the capillaries are open, and these cycle between closed and open states. Bottom: during strenuous activity, metabolism increases, and the capillaries progressively open, increasing the effective surface area for exchange, and decreasing the effective diffusion distance, which both increase diffusional delivery of nutrients and removal of wastes.

arises from a separate terminal arteriole, which is invested with smooth muscle. At rest, many of these terminal arterioles close, so that each capillary perfuses a large volume. At rest, these arterioles cycle between open and closed states, a phenomenon called **vasomotion**. The capillaries that bear the perfusion burden change with time, and the various tissue parts are sometimes nearby and sometimes further away from open capillaries. At rest, tissue metabolism is slow and this lower perfusion is sufficient to supply nutrients and remove metabolites at the lower metabolic rate. Equation (5.10.15) shows that, for a constant extraction, the ratio of metabolism to perfusion dictates the concentration of solutes in the interstitial fluid. During strenuous activity, the metabolism of the muscle rises many fold and many more arterioles open up to perfuse the tissue, effectively increasing the area for diffusion, S, and the apparent permeability, p, by decreasing the effective diffusion distance.

SOME MACROMOLECULES CROSS THE CAPILLARY WALL BY *TRANSCYTOSIS*

Large molecules have low permeabilities through most of the diffusion barriers presented by the glycocalyx, endothelial cells, and basement membrane. These materials can still cross the capillary, albeit at low rates, by uptake into the endothelial cells and thence into **transcytotic vesicles**. The endothelial cell transports these vesicles across their narrow cytoplasm and they fuse with the opposite membrane on the tissue side of the capillary. Particular proteins, such as ferritin, may have specific recognition sites for uptake into these vesicles, whereas others may be taken up as part of **fluid phase endocytosis**. Transport in this way does not obey diffusion kinetics because the mechanism is not diffusion.

STARLING FIRST DESCRIBED THE FORCES THAT DRIVE BULK FLUID MOVEMENT ACROSS CAPILLARIES

The major pathway for water and fluid transport is not diffusion: it is pressure-driven flow. In Chapter 2.7, we derived an expression for the bulk flow of fluid across a membrane:

$$J_V = L_p[(P_L - P_R) - \sigma(\pi_L - \pi_R)] \quad [5.10.17]$$

where J_V is the volume flux, in cm s^{-1}, L_p is the **hydraulic conductivity**, P_L and P_R are the pressures on the left and right of the membrane, σ is the **reflection coefficient**, and π_L and π_R are the osmotic pressures on the left and right sides of the membrane. Here the hydraulic conductivity results from the combination of flows across all pathways provided by the set of AQP1 channels, gaps, fenestrae, and intercellular clefts. Similarly, the reflection coefficient is an aggregate character of the capillary wall. The net filtration or reabsorption of fluid from the capillaries to the interstitial fluid or from interstitial fluid to the capillary blood depends on the **net filtration pressure**, $\Delta P - \sigma\Delta\pi$. Ernest Starling first recognized the origin of the forces that contribute to the net filtration pressure in 1896. Strictly speaking, Eqn [5.10.17] is written as

$$J_V = L_p\left[(P_L - P_R) - \left(\sum_x \sigma_x \pi_{L,x} - \sum_x \sigma_x \pi_{R,x}\right)\right] \quad [5.10.18]$$

where the subscript x denotes each of the chemical species in solution on each side of the membrane. When applied to the capillary, the notation is

$$J_V = L_p\left[(P_C - P_i) - \left(\sum_x \sigma_x \pi_{C,x} - \sum_x \sigma_x \pi_{i,x}\right)\right] \quad [5.10.19]$$

where the subscript "C" denotes capillary and "i" denotes interstitial fluid. Thus, each dissolved constituent of either the capillary fluid or interstitial fluid contributes to the overall driving force. Many of the solutes in plasma are also present in the interstitial fluid, and their concentrations are nearly identical. In Eqn [5.10.19], their osmotic effects cancel each other because their osmotic pressure subtracts from both the capillary side and the interstitial fluid side. Because solutes having the same concentration on both sides of the capillary make no *net* osmotic force, we *define* a new osmotic pressure called the **colloid osmotic pressure**.

Large proteins, the **colloids**, cannot easily cross the capillary wall, whereas the **crystalloids**, the small highly soluble salts, easily cross. Because these proteins are negatively charged, their unequal distribution sets up a Donnan effect in which the concentration of positive ions is slightly greater on the side with greater concentration of impermeable negative ions. The combination of the osmotic effects of the protein and its attendant Donnan effect is called the **colloid osmotic pressure**. A synonym for it is the **oncotic pressure**. We rewrite Eqn [5.10.19] as

$$Q_V = Ak_f[(P_C - P_i) - \sigma(\pi_C - \pi_i)] \quad [5.10.20]$$

where Q_V is the volume flow, not flux, A is the available surface area through which bulk fluid flow occurs, k_f is the **filtration coefficient** that is characteristic of the capillary, and which is identical to L_p, and π_C and π_i now denote the **oncotic pressure** in the capillary and in the interstitial fluid, respectively.

IN MOST ORGANS, NET FILTRATION PRESSURE DRIVES FLUID OUT OF THE CAPILLARIES AT THE ARTERIOLAR END

The oncotic pressure of plasma, 25 mmHg, normally does not vary significantly with location in the body because the plasma is regulated and it mixes rapidly. The oncotic pressure of the interstitial fluid varies depending on the leakiness of the capillaries to plasma

proteins. Direct measurement of interstitial fluid oncotic pressure is difficult because samples cannot be obtained easily. Because **lymph** drains the interstitial fluid, the oncotic pressure of lymph approximates the interstitial fluid oncotic pressure, and this differs with location. Sinusoidal or discontinuous capillaries such as those in the liver result in lymph with 4–6 g protein per dL; lymph from the leg contains 1–3 g dL^{-1}; in the intestine it is 3–4 g dL^{-1} and in the lung it is 4–5 g dL^{-1}. The oncotic pressure is influenced by which proteins are present as well as their concentration by weight, because the oncotic pressure is produced by the number of dissolved particles. These proteins do not obey van't Hoff's law, in which osmotic pressure is linearly related to concentration, because these proteins are not ideal. The empirical relation between protein concentration and osmotic pressure is

$$\pi_{albumin} = 2.8C + 0.18C^2 + 0.012C^3$$
$$\pi_{globulin} = 1.6C + 0.15C^2 + 0.006C^3 \quad [5.10.21]$$

where π is in mmHg and C, the concentration of albumin or globulin, is in g dL^{-1}. The interstitial fluid oncotic pressure varies from nearly the same as plasma to values less than one-third that of plasma.

The capillary hydrostatic pressure, P_C, also varies with location in the body. The renal corpuscle is specialized for rapid filtration, and its capillary pressure at the arteriolar end of the capillary is as high as 60 mmHg, whereas those in the lung are low, nearly 10 mmHg. Average values at the arteriolar end are 32–36 mmHg. Because the fluid encounters resistance along the capillary, its pressure falls from the arteriolar end to an average of 12–25 mmHg at the venule end.

The interstitial fluid hydrostatic pressure is generally thought to be small, but it depends on the location. Subatmospheric interstitial fluid pressures have been recorded in the lung, skeletal muscle, and subcutaneous tissues, whereas small positive pressures have been recorded in the kidney, liver, and intestine. Values of P_i range from −2 mmHg in the lungs to +10 mmHg in the kidney.

Table 5.10.1 lists typical values for the Starling forces at the arteriolar and venule end of an idealized capillary, and Figure 5.10.8 shows approximately how these forces vary with distance along the capillary. The end result is that fluid is filtered out of the capillaries at the arteriolar end and reabsorbed back into the capillaries at the venule end. Note that this is not the case in all capillary beds.

THE LYMPHATICS DRAIN THE FLUID FILTERED THROUGH THE CAPILLARIES BACK INTO THE BLOOD

As shown in Figure 5.10.8 and Table 5.10.1, many capillaries filter fluid at their arteriolar end and reabsorb it at their venule end. Generally more fluid is filtered out than reabsorbed. The extra fluid is collected into specialized vessels that collectively make up the **lymphatic system**. The lymphatic system's functions include:

- preservation of the circulatory volume;
- absorption of nutrients;
- defense against bacterial and viral invasion.

Each day the aggregate capillaries of the body filter some 2–4 L more than is reabsorbed. The lymph vessels return the capillary filtrate to the general circulation by draining into the large veins near the neck. This completes the extravascular circulation of fluid and protein as shown in Figure 5.10.9. If lymph flow is blocked, the tissues develop **lymphedema**, a severe accumulation of massive amounts of protein-rich fluid in the tissues.

Lymph vessels in the intestine transport fat as **chylomicrons** (see Chapter 8.5). These are tiny globules of fat that are coated with proteins to help carry them in the blood. Because these tiny globules scatter light, they make their suspension appear white. For this reason, the lymph vessels that drain the intestine are called **lacteals**, because they appear milky white after the ingestion of a fatty meal. These lymph vessels coalesce and eventually form the **thoracic duct**, which empties into the left subclavian vein.

As lymph drains the tissues, it carries bacteria, viruses, and other foreign matter to the lymph nodes that contain cells that comprise part of the reticuloendothelial system. These macrophages engulf these foreign particles, thereby scrubbing the lymph clean. The foreign particles in the lymph can mobilize white blood cells from the lymph nodes, thereby helping prevent bacterial invasion of the bloodstream, **septicemia**.

MUSCLE ACTIVITY HELPS PUMP LYMPH THROUGH THE LYMPHATICS

Lymph must be pumped along the lymphatics because the pressure at the venous outlet is higher than in the initial lymphatics. Lymph is pumped along by

TABLE 5.10.1 Starling Forces at the Arteriolar and Venule Ends of Idealized Subcutaneous Capillaries in the Legs and Lungs

Location		P_C (mmHg)	P_i (mmHg)	π_C (mmHg)	π_i (mmHg)	Net Pressure (mmHg)
Legs, subcutaneous	Arteriolar	35	−1	25	3	14
	Venule	15	−1	25	3	−6
Lungs	Arteriolar	10	−2	25	18	5
	Venule	8	−2	25	18	3

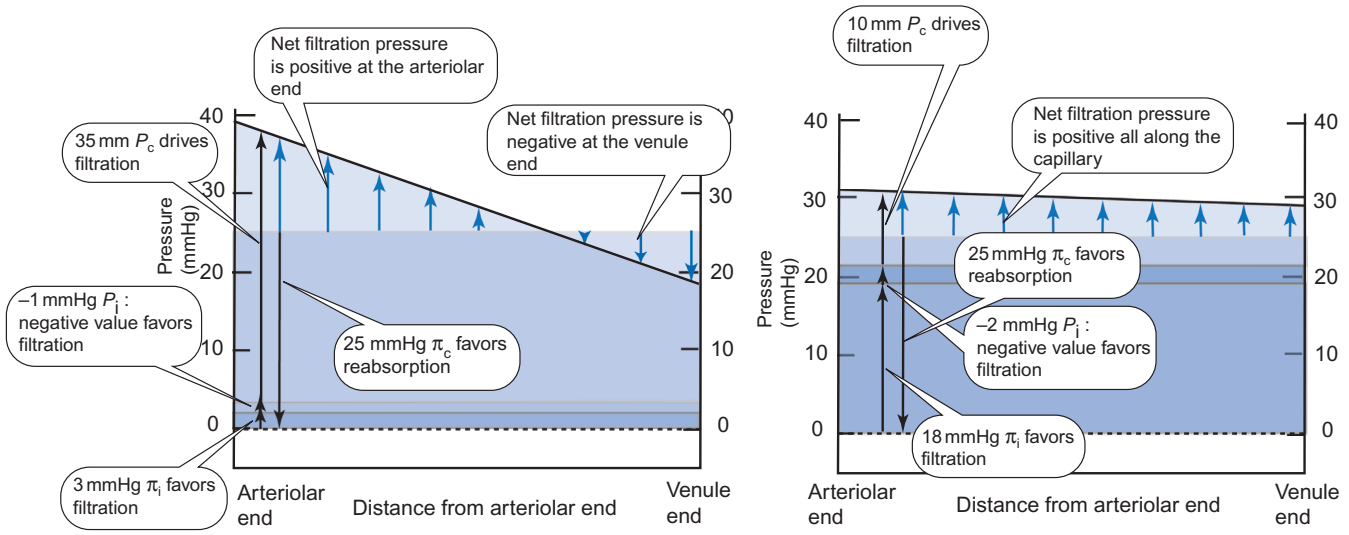

FIGURE 5.10.8 Balance of forces for net filtration across capillaries in the legs (left) and lungs (right) as a function of distance along the capillary. At the arteriolar end in the legs the capillary hydrostatic pressure is high, about 35 mmHg, and it gradually diminishes as the blood encounters resistance through the capillary, to reach 15 mmHg at the venule end. This filtration pressure is augmented by the low interstitial oncotic pressure and the negative interstitial fluid pressure. It is opposed by the interstitial fluid oncotic pressure. The sum of all forces favors filtration at the arteriolar end and reabsorption at the venule end. In other capillary beds, such as the lung, the high interstitial oncotic pressure drives a net filtration along the entire length of the capillary.

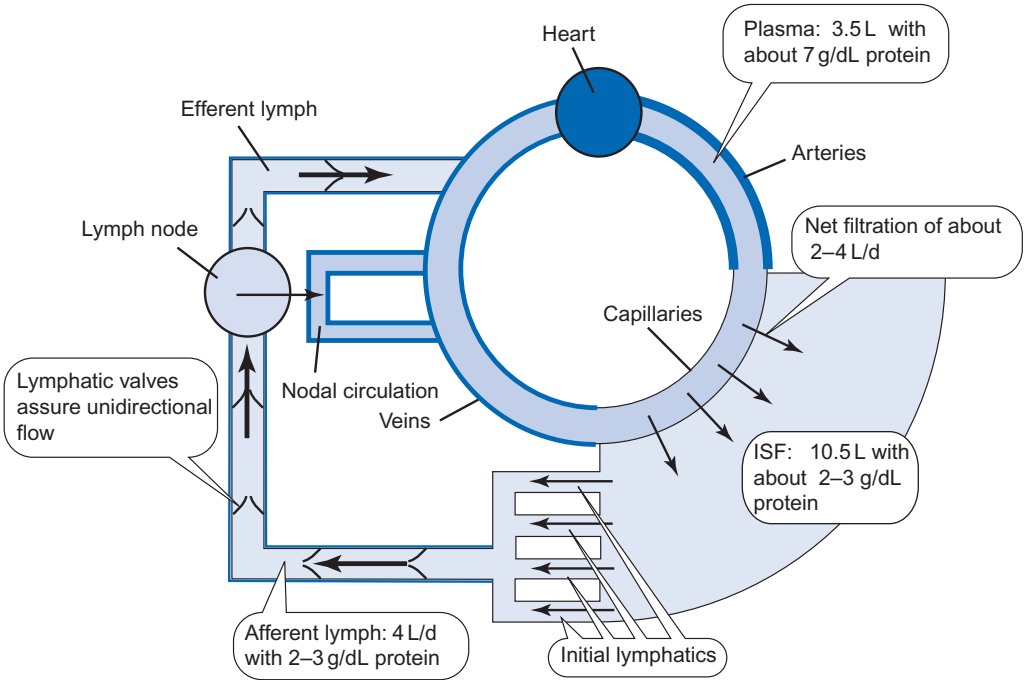

FIGURE 5.10.9 The lymphatic circulation. Net filtration at the capillaries produces some 2–4 L of fluid per day that is added to the interstitial fluid. This is continually returned to the circulation via the lymphatics. Some of this fluid returns by nodal circulation, the remainder through the thoracic duct. Valves in the lymph vessels assure unidirectional flow toward the circulation.

two main mechanisms: **extrinsic propulsion** caused by tissue movements—both passive and active—and **intrinsic propulsion** caused by rhythmic contractions of lymphatic smooth muscle. The lymph vessels possess valves that assure unidirectional flow from the tissues to the circulation. Muscle activity contributes to the extrinsic propulsion.

SUMMARY

The central purpose of the cardiovascular system is to exchange materials and heat between the blood and the tissues, and all of this exchange occurs in the small vessels—the terminal arterioles, capillaries, and small venules. The capillaries are located between the

Clinical Applications: Edema

Edema is defined as an excess of interstitial fluid. Edema can occur locally. Excess subcutaneous interstitial fluid is called **peripheral edema**. In the lungs it is **pulmonary edema** and in the abdominal cavity it is called **ascites**. Whenever capillary filtration rate exceeds lymphatic drainage, fluid accumulates and produces edema. So edema can be caused by either excessive capillary filtration or reduced lymphatic drainage.

Increased capillary filtration can be caused by elevated capillary hydrostatic pressure (P_C in Eqn [5.10.20]), decreased plasma oncotic pressure (π_C in Eqn [5.10.20]), or increased capillary permeability (k_f in Eqn [5.10.20]).

Capillary pressures rise when venous pressure rises, and this occurs when the heart fails to pump blood out of the veins back into the arteries. Thus, right ventricular failure leads to systemic edema and left ventricular failure leads to pulmonary edema.

Decreased oncotic pressure results from insufficient formation of plasma proteins or excessive loss. Decreased formation occurs in protein malnutrition. The big bellies of small children who suffer from malnutrition results from ascites when these children are displaced from their mother's breast by the next baby. Their diet of mother's milk is replaced by a high-carbohydrate, protein-poor diet that does not support synthesis of adequate plasma protein. Africans have named this condition **kwashiorkor**, the disease of the displaced child. Plasma albumin, the most abundant single class of plasma proteins, is made in the liver, along with fibrinogen and α and β globulins. **Liver failure** reduces the synthesis of these and lowers plasma oncotic pressure, leading to edema. In the **nephrotic syndrome**, the kidney loses protein in the urine, sometimes more than 20 g per day. This excessive loss cannot be balanced by increased synthesis, and plasma oncotic pressure falls. Excessive protein loss can also result from intestinal disease.

Inflammation releases signaling molecules that vasodilate local blood vessels and increase capillary permeability. These cause the redness and swelling associated with the inflammatory response. Increased capillary permeability results in increased formation of a protein-rich interstitial fluid.

Anything that interferes with lymphatic drainage will lead to edema because the lymph is the only route for the return of escaped proteins to the circulation. Although surgery and radiation treatment for cancer can cause this, the most common cause worldwide is **lymphatic filariasis**, a nematode infection transmitted by mosquitoes. In chronic cases **elephantiasis** occurs, so called because the grossly swollen extremities resemble the limbs of elephants. The disease is caused by parasitic worms, including *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*. These are all carried to their human host by the bite of infected female mosquitoes. Injected microfilariae reproduce and spread throughout the bloodstream. As they accumulate, they block lymphatic drainage and can produce gross edema in the arms, legs, genitalia, and breasts.

arterioles and venules and fall into three classes: continuous, fenestrated, and discontinuous. Continuous capillaries are the tightest, fenestrated capillaries are leakier, and discontinuous capillaries allow large molecular weight proteins and blood cells to pass between blood and tissue. Continuous capillaries are the most abundant.

Capillary exchange occurs through three mechanisms: diffusion, transcytosis, and bulk flow of fluid. Many soluble materials cross the capillary by simple diffusion. Hydrophilic materials pass through intercellular clefts and fenestrae, and lipid-soluble materials can pass through the endothelial cell membranes. Increasing the perfusion of a tissue increases the delivery of materials by several means: (1) increasing the perfusion typically occurs by opening more capillaries. This increases the surface area through which diffusion occurs; (2) because opening more capillaries reduces the distance between capillaries, it also reduces the diffusion distance to the tissue, thereby increasing diffusive flux. Increasing the concentration gradient also increases the diffusive flux into the tissue. This can be accomplished by decreasing the interstitial fluid concentration or keeping the capillary concentration high by increasing the flow in the capillary.

Total material transfer can be flow limited or diffusion limited. These descriptions define different domains of the plot of material transfer against blood flow. In the flow-limited domain, increasing blood flow increases solute transfer proportionately. In this domain, the blood flowing through the tissues nearly equilibrates with the interstitial fluid. In this case, the extraction of the solute (the fraction of solute which is taken up by the tissues) is near 1.0. Additional flow in this case provides additional solute. In the diffusion-limited domain, increasing flow only marginally increases solute transfer because the concentration gradient is already maximal. In this case, the extraction of the solute is nearly 0 and only increases in the permeability of the capillary or surface area can increase solute transfer.

Bulk movement of fluid occurs through the intercellular clefts, fenestrae, and gaps in the capillaries. The forces that govern fluid movement include the hydrostatic pressures inside and outside of the capillaries, and the oncotic pressures inside and outside of the capillaries. The oncotic pressure of a solution is the osmotic pressure due to the impermeant proteins and the colloids, and their attendant affect on the distribution of ions (the Donnan effect). The oncotic pressure is also called the colloid osmotic pressure. In most tissues, the major driving force for filtration of fluid across the capillary wall is the capillary hydrostatic pressure. This is augmented by the interstitial fluid oncotic pressure, whose value depends on the tissue. It is high in liver and lung and low in most subcutaneous tissues and skeletal muscle. The plasma oncotic pressure provides

the major opposing force for filtration. It is relatively constant at about 25 mmHg. Positive interstitial fluid pressure also opposes filtration. The interstitial fluid pressure varies with location. It is generally small and sometimes negative. The balance of these forces causes filtration at the arteriolar end of some capillaries and reabsorption at the venule end. In other capillary beds, there is filtration throughout the length of the capillary. Capillaries produce a net fluid filtration that is collected by the lymphatics and drained back into the blood.

REVIEW QUESTIONS

1. What are the three different types of capillaries? Where are they found in the body?
2. How do things get across capillary walls? What kinds of things are retained by the capillaries?
3. What does flow-limited mean? What does diffusion-limited mean?
4. How can material exchange be increased?
5. What is vasomotion?
6. What is solute extraction?
7. What forces favor fluid extrusion into the interstitial fluid? What forces favor fluid reabsorption? What is colloid osmotic pressure? What is its typical value?
8. What happens to fluid that is filtered by the capillaries but not reabsorbed?
9. What would happen if lymph flow were blocked?