16

The Microcirculation and the Lymphatic System: Capillary Fluid Exchange, Interstitial Fluid, and Lymph Flow

The most purposeful function of the circulation occurs in the microcirculation: *transport of nutrients to the tissues and removal of cellular excreta.* The small arterioles control the blood flow to each tissue area, and local conditions in the tissues in turn control the diameters of the arterioles. Thus, each tissue, in most instances, controls its own blood flow in relation to its individual needs, a subject that is discussed in detail in Chapter 17.

The capillaries are extremely thin structures with tubular walls of single-layer, highly permeable *endothelial cells.* Here, interchange of nutrients and cellular excreta occurs between the tissues and the circulating blood. In the peripheral circulation of the whole body are about 10 billion capillaries with a total surface area estimated to be 500 to 700 square meters (about one-eighth the surface area of a football field). Indeed, it is rare that any single functional cell of the body is more than 20 to 30 micrometers away from a capillary.

The purpose of this chapter is to discuss the transfer of substances between the blood and interstitial fluid and especially to discuss the factors that affect transfer of fluid volume through the capillary walls between the circulating blood and the interstitial fluid.

STRUCTURE OF THE MICROCIRCULATION AND CAPILLARY SYSTEM

The microcirculation of each organ is organized specifically to serve that organ's needs. In general, each nutrient artery entering an organ branches six to eight times before the arteries become small enough to be called *arterioles,* which generally have internal diameters less than 20 micrometers. Then the arterioles themselves branch two to five times, reaching diameters of 5 to 9 micrometers at their ends where they supply blood to the capillaries.

Figure 16–1 shows the structure of a representative capillary bed as seen in the mesentery, showing that blood enters the capillaries through an *arteriole* and leaves by way of a *venule.* Blood from the arteriole passes into a series of *metarterioles,* which are called by some physiologists *terminal arterioles* and which have a structure midway between that of arterioles and capillaries. After leaving the metarteriole, the blood enters the *capillaries,* some of which are large and are called *preferential channels,* whereas others are small and are *true capillaries.* After passing through the capillaries, the blood enters the venule and returns to the general circulation.

The arterioles are highly muscular, and their diameters can change manyfold. The metarterioles (the terminal arterioles) do not have a continuous muscular coat, but smooth muscle fibers encircle the vessel at intermittent points, as shown in Figure 16–1 by the large black dots to the sides of the metarteriole.

At the point where each true capillary originates from a metarteriole, a smooth muscle fiber usually encircles the capillary. This is called the *precapillary sphincter.* This sphincter can open and close the entrance to the capillary.

The venules are larger than the arterioles and have a much weaker muscular coat. Yet it must be remembered that the pressure in the venules is much less than that in the arterioles, so that the venules still can contract considerably despite the weak muscle.

This typical arrangement of the capillary bed is not found in all parts of the body; however, some similar arrangement serves the same purposes. Most important, the metarterioles and the precapillary sphincters are in close contact with the tissues they serve. Therefore, the local conditions of the tissues—the concentrations of nutrients, end products of metabolism, hydrogen ions, and so forth—can cause direct effects on the vessels in controlling local blood flow in each minute tissue area.

Structure of the Capillary Wall. Figure 16–2 shows the ultramicroscopic structure of a typical capillary wall as found in most organs of the body, especially in muscles and connective tissue. Note that the wall is composed of a unicellular layer of endothelial cells and is surrounded by a basement membrane on the outside. The total thickness of the wall is only about 0.5 micrometer.

The internal diameter of the capillary is 4 to 9 micrometers, barely large enough for red blood cells and other blood cells to squeeze through.

"Pores" in the Capillary Membrane. Studying Figure 16–2, one sees two minute passageways connecting the interior of the capillary with the exterior. One of these is the *intercellular cleft,* which is the thin slit that lies between adjacent endothelial cells. Each cleft is interrupted periodically by short ridges of protein attachments that hold the endothelial cells together, but each ridge in turn is broken after a short distance, so that fluid can percolate freely through the cleft. The cleft normally has a uniform spacing with a width of about 6

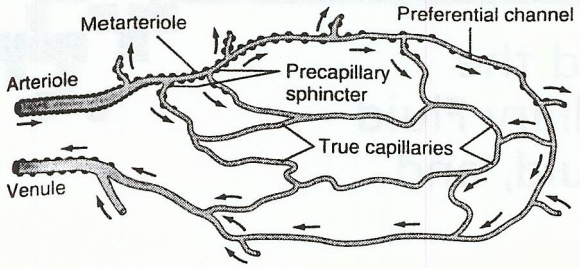

FIGURE 16–1

Structure of the mesenteric capillary bed. (Redrawn from Zweifach: Factors Regulating Blood Pressure. New York: Josiah Macy, Jr., Foundation, 1950.)

to 7 nanometers (60 to 70 angstroms), slightly smaller than the diameter of an albumin protein molecule.

Because the intercellular clefts are located only at the edges of the endothelial cells, they usually represent no more than 1/1000 of the total surface area of the capillary. Nevertheless, the rate of thermal motion of water molecules as well as most water-soluble ions and small solutes is so rapid that all of these diffuse with ease between the interior and exterior of the capillaries through these "slit-pores," the intercellular clefts.

Also present in the endothelial cells are many minute *plasmalemmal vesicles.* These form at one surface of the cell by imbibing small packets of plasma or extracellular fluid. They can then move slowly through the endothelial cell. It also has been postulated that some of these vesicles coalesce to form vesicular channels all the way through the endothelial cell, which also is demonstrated in Figure 16–2. However, careful measurements in laboratory animals probably have proved that these vesicular forms of transport are quantitatively of little importance.

Special Types of "Pores" Occur in the Capillaries of Certain Organs. The "pores" in the capillaries of some organs have special characteristics to meet the peculiar needs of the organs. Some of these characteristics are as follows:

1. In the *brain,* the junctions between the capillary endothelial cells are mainly "tight" junctions that allow only extremely small molecules such as water, oxygen, and carbon dioxide to pass into or out of the brain tissues.
2. In the *liver,* the opposite is true. The clefts between the capillary endothelial cells are wide open, so that almost all dissolved substances of the plasma, including the plasma proteins, can pass from the blood into the liver tissues.

The pores of the *intestinal membranes* are midway between those of the muscles and those of the liver.

3. In the *glomerular tufts of the kidney,* numerous small oval windows called *fenestrae* penetrate all the way through the middle of the endothelial cells, so that tremendous amounts of very small molecular and ionic substances can filter through the glomeruli without having to pass through the clefts between the endothelial cells.

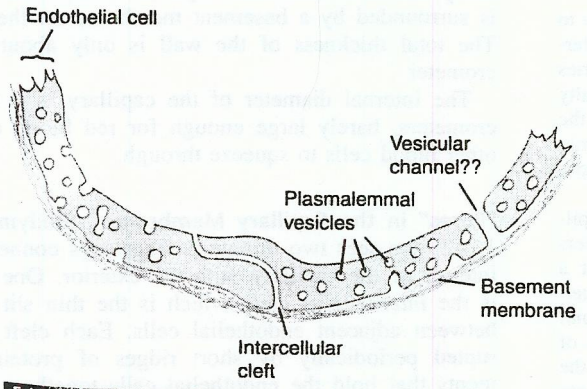

FIGURE 16–2

Structure of the capillary wall. Note especially the *intercellular cleft* at the junction between adjacent endothelial cells; it is believed that most water-soluble substances diffuse through the capillary membrane along this cleft.

FLOW OF BLOOD IN THE CAPILLARIES—VASOMOTION

Blood usually does not flow continuously through the capillaries. Instead, it flows intermittently, turning on and off every few seconds or minutes. The cause of this intermittency is the phenomenon called *vasomotion,* which means intermittent contraction of the metarterioles and precapillary sphincters (and sometimes even the very small arterioles as well).

Regulation of Vasomotion. The most important factor found thus far to affect the degree of opening and closing of the metarterioles and precapillary sphincters is the concentration of *oxygen* in the tissues. When the rate of oxygen usage is great so that tissue oxygen decreases, the intermittent periods of blood flow occur more often, and the duration of each period of flow lasts longer, thereby allowing the blood to carry increased quantities of oxygen (as well as other nutrients) to the tissues. This effect, along with multiple other factors that control local tissue blood flow, is discussed in Chapter 17.

Average Function of the Capillary System

Despite the fact that blood flow through each capillary is intermittent, so many capillaries are present in the tissues that their overall function becomes averaged. That is, there is an *average rate of blood flow* through each tissue capillary bed, an *average capillary pressure* within the capillaries, and an *average rate of transfer of substances* between the blood of the capillaries and the surrounding interstitial fluid. In the remainder of this chapter, we are concerned with these averages, although one must remember that the average functions are, in reality, the functions of literally billions of individual capillaries, each operating intermittently in response to the local conditions in the tissues.

EXCHANGE OF NUTRIENTS AND OTHER SUBSTANCES BETWEEN THE BLOOD AND INTERSTITIAL FLUID

Diffusion Through the Capillary Membrane

By far the most important means by which substances are transferred between the plasma and the interstitial fluid is by *diffusion*. Figure 16–3 demonstrates this process, showing that as the blood flows along the lumen of the capillary, tremendous numbers of water molecules and dissolved particles diffuse back and forth through the capillary wall, providing continual mixing between the interstitial fluid and the plasma. Diffusion results from thermal motion of the water molecules and dissolved substances in the fluid, the different molecules and ions moving first in one direction and then another, moving randomly in every direction.

Lipid-Soluble Substances Can Diffuse Directly Through the Cell Membranes of the Capillary Endothelium. If a substance is lipid soluble, it can diffuse directly through the cell membranes of the capillary without having to go through the pores. Such substances include oxygen and carbon dioxide. Because these substances can permeate all areas of the capillary membrane, their rates of transport through the capillary membrane are many times faster than the rates for lipid-insoluble substances, such as sodium ions and glucose.

Water-Soluble, Non–Lipid-Soluble Substances Diffuse Only Through Intercellular "Pores" in the Capillary Membrane. Many substances needed by the tissues are soluble in water but cannot pass through the lipid membranes of the endothelial cells; such substances include water molecules themselves, sodium ions, chloride ions, and glucose. Despite the fact that not more than $\frac{1}{1000}$ of the surface area of the capillaries is represented by the intercellular clefts between the endothelial cells, the velocity of thermal molecular motion in the clefts is so great that even this small area is sufficient to allow tremendous diffusion of water and water-soluble substances through these cleft-pores. To give one an idea of the rapidity with which these substances diffuse, *the rate at which water molecules diffuse through the capillary membrane is about 80 times as great as the rate at which plasma itself flows linearly along the capillary.* That is, the water of the plasma is exchanged with the water of the interstitial fluid 80 times before the plasma can go the entire distance through the capillary.

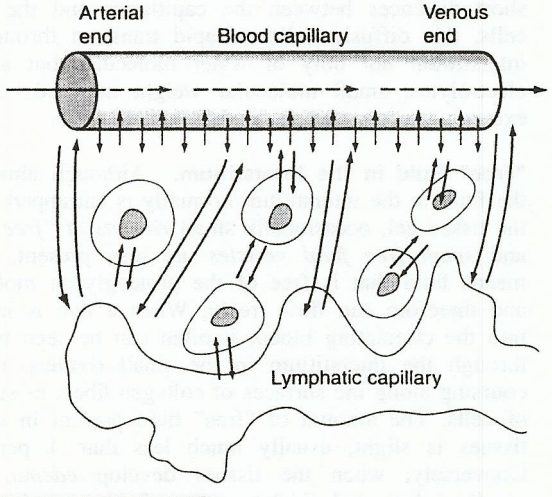

FIGURE 16–3

Diffusion of fluid molecules and dissolved substances between the capillary and interstitial fluid spaces.

Effect of Molecular Size on Passage Through the Pores. The width of the capillary intercellular cleft-pores, 6 to 7 nanometers, is about 20 times the diameter of the water molecule, which is the smallest molecule that normally passes through the capillary pores. Conversely, the diameters of plasma protein molecules are slightly greater than the width of the pores. Other substances, such as sodium ions, chloride ions, glucose, and urea, have intermediate diameters. Therefore, the permeability of the capillary pores for different substances varies according to their molecular diameters.

Table 16–1 gives the relative permeabilities of the capillary pores in muscle for substances commonly encountered, demonstrating, for instance, that the permeability for glucose molecules is 0.6 times that for water molecules, whereas the permeability for albumin molecules is very, very slight, only $\frac{1}{1000}$ that for water molecules.

A word of caution must be issued at this point. The capillaries in different tissues have extreme differences in their permeabilities. For instance, the membrane of the liver capillary sinusoids is so permeable that even plasma proteins pass freely through these walls, almost as easily as water and other substances. Also, the permeability of the renal glomerular membrane for water and electrolytes is about 500 times the permeability of the muscle capillaries, but the glomerular and muscle capillary permeabilities for protein are about the same. When we study these different organs later in this text,

TABLE 16–1

Relative Permeability of Muscle Capillary Pores to Different-Sized Molecules

Substance	Molecular Weight	Permeability
Water	18	1.00
NaCl	58.5	0.96
Urea	60	0.8
Glucose	180	0.6
Sucrose	342	0.4
Inulin	5,000	0.2
Myoglobin	17,600	0.03
Hemoglobin	68,000	0.01
Albumin	69,000	0.001

Modified from Pappenheimer JR: Passage of molecules through capillary walls. Physiol Rev 33:387, 1953.

it should become clear why some tissues—the liver, for instance—require greater degrees of capillary permeability than others to transfer tremendous amounts of nutrients between the blood and the liver parenchymal cells and the kidneys to allow filtration of large quantities of fluid for the formation of urine.

Effect of Concentration Difference on Net Rate of Diffusion Through the Capillary Membrane. The "net" rate of diffusion of a substance through any membrane is proportional to the *concentration difference* between the two sides of the membrane. That is, the greater the difference between the concentrations of any given substance on the two sides of the capillary membrane, the greater the net movement of the substance in one direction through the membrane. For instance, the concentration of oxygen in capillary blood is normally greater than in the interstitial fluid. Therefore, large quantities of oxygen normally move from the blood toward the tissues. Conversely, the concentration of carbon dioxide is greater in the tissues than in the blood, which causes the excess carbon dioxide to move into the blood and to be carried away from the tissues.

The rates of diffusion through the capillary membranes of most nutritionally important substances are so great that only slight concentration differences suffice to cause more than adequate transport between the plasma and interstitial fluid. For instance, the concentration of oxygen in the interstitial fluid immediately outside the capillary is no more than a few per cent less than its concentration in the plasma of the blood, yet this slight difference causes enough oxygen to move from the blood into the interstitial spaces to provide all the oxygen required for tissue metabolism, often as much as several liters of oxygen per minute.

THE INTERSTITIUM AND INTERSTITIAL FLUID

About one sixth of the body consists of spaces between cells, which collectively are called the *interstitium.* The fluid in these spaces is the *interstitial fluid.*

The structure of the interstitium is shown in Figure 16–4. It has two major types of solid structures: (1) *collagen fiber bundles* and (2) *proteoglycan filaments.* The collagen fiber bundles extend long distances in the interstitium. They are extremely strong and therefore provide most of the tensional strength of the tissues. The proteoglycan filaments, however, are extremely thin, coiled molecules composed of about 98 per cent hyaluronic acid and 2 per cent protein. These molecules are so thin that they can never be seen with a light microscope and are difficult to demonstrate even with the electron microscope. Nevertheless, they form a mat of very fine reticular filaments aptly described as a "brush pile."

"Gel" in the Interstitium. The fluid in the interstitium is derived by filtration and diffusion from the capillaries. It contains almost the same constituents as plasma except for much lower concentrations of proteins because proteins do not pass outward through the pores of the capillaries with ease. The interstitial fluid is entrapped mainly in the minute spaces among the proteoglycan filaments. This combination of the proteoglycan filaments and the fluid entrapped within them has the characteristics of a *gel* and therefore is called *tissue gel.*

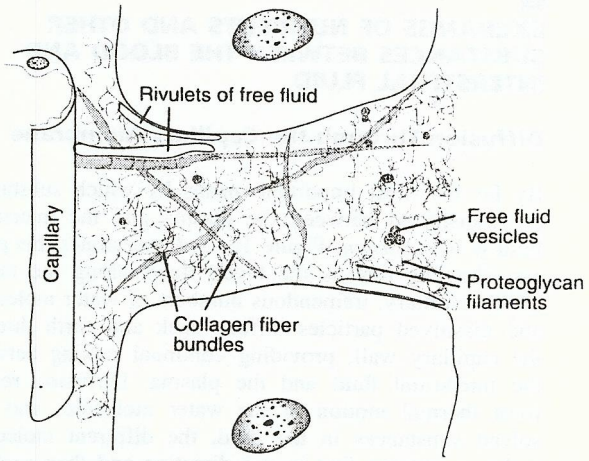

FIGURE 16–4

Structure of the interstitium. Proteoglycan filaments are everywhere in the spaces between the collagen fiber bundles. Free fluid vesicles and small amounts of free fluid in the form of rivulets occasionally also occur.

Because of the large number of proteoglycan filaments, it is difficult for fluid to *flow* easily through the tissue gel. Instead, it mainly *diffuses* through the gel; that is, it moves molecule by molecule from one place to another by kinetic motion rather than by large numbers of molecules moving together.

Diffusion through the gel occurs about 95 to 99 per cent as rapidly as it does through free fluid. For the short distances between the capillaries and the tissue cells, this diffusion allows rapid transport through the interstitium not only of water molecules but also of electrolytes, small molecular weight nutrients, cellular excreta, oxygen, carbon dioxide, and so forth.

"Free" Fluid in the Interstitium. Although almost all the fluid in the interstitium normally is entrapped within the tissue gel, occasionally small *rivulets of "free" fluid* and *small free fluid vesicles* are also present, which means fluid that is free of the proteoglycan molecules and therefore can flow freely. When a dye is injected into the circulating blood, it often can be seen to flow through the interstitium in the small rivulets, usually coursing along the surfaces of collagen fibers or surfaces of cells. The amount of "free" fluid present in *normal* tissues is slight, usually much less than 1 per cent. Conversely, when the tissues develop *edema, these small pockets and rivulets of free fluid expand tremendously* until one half or more of the edema fluid becomes freely flowing fluid independent of the proteoglycan filaments.

PROTEINS IN THE PLASMA AND INTERSTITIAL FLUID ARE ESPECIALLY IMPORTANT IN CONTROLLING PLASMA AND INTERSTITIAL FLUID VOLUMES

The pressure in the capillaries tends to force fluid and its dissolved substances through the capillary pores into the interstitial spaces. Conversely, osmotic pressure caused by the plasma proteins (called *colloid* osmotic pressure) tends to cause fluid movement by osmosis from the interstitial spaces into the blood: this osmotic pressure normally prevents significant loss of fluid volume from the blood into the interstitial spaces. Also important is the lymphatic system, which returns to the circulation the small amounts of protein and fluid that do leak from the blood into the interstitial spaces. In the remainder of this chapter, we discuss how these effects control the respective volumes of the plasma and the interstitial fluid.

Four Primary Forces That Determine Fluid Movement Through the Capillary Membrane. Figure 16–5 shows the four primary forces that determine whether fluid moves out of the blood into the interstitial fluid or in the opposite direction; called "Starling forces" in honor of the physiologist who first demonstrated their importance, they are

1. The *capillary pressure* (Pc), which tends to force fluid *outward* through the capillary membrane.
2. The *interstitial fluid pressure* (Pif), which tends to force fluid *inward* through the capillary membrane when Pif is positive but outward when Pif is negative.
3. The *plasma colloid osmotic pressure* (Πp), which tends to cause osmosis of fluid *inward* through the capillary membrane.
4. The *interstitial fluid colloid osmotic pressure* (Πif), which tends to cause osmosis of fluid *outward* through the capillary membrane.

Let us discuss each of these in detail.

Capillary Pressure

Two experimental methods have been used to estimate the capillary pressure: (1) *direct micropipette cannulation of the capillaries,* which has given an average mean capillary pressure of about 25 mm Hg, and (2) *indirect functional measurement of the capillary pressure,* which has given a capillary pressure averaging about 17 mm Hg.

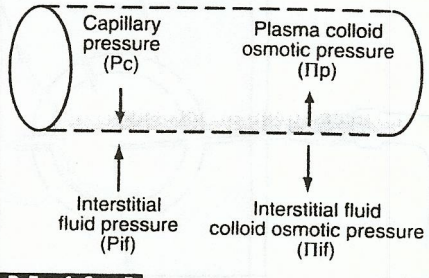

FIGURE 16–5

Fluid pressure and colloid osmotic pressure forces operate at the capillary membrane, tending to move fluid either outward or inward through the membrane pores.

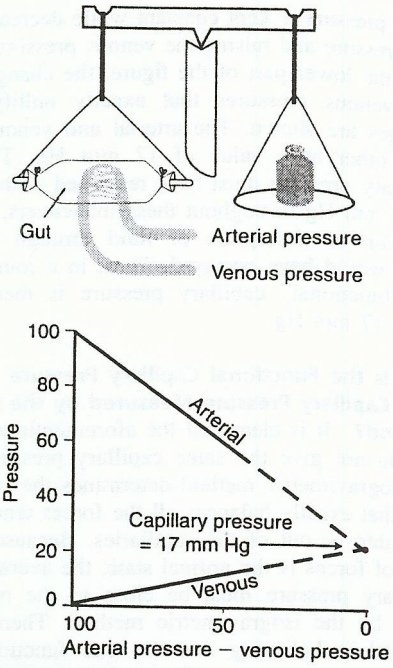

FIGURE 16–6

Isogravimetric method for measuring capillary pressure.

Micropipette Method for Measuring Capillary Pressure. To measure pressure in a capillary by cannulation, a microscopic glass pipette is thrust directly into the capillary, and the pressure is measured by an appropriate micromanometer system. Using this method, capillary pressures have been measured in capillaries of exposed tissues of animals and in large capillary loops of the eponychium at the base of the fingernail in humans. These measurements have given pressures of 30 to 40 mm Hg in the arterial ends of the capillaries, 10 to 15 mm Hg in the venous ends, and about 25 mm Hg in the middle.

Isogravimetric Method for Indirectly Measuring "Functional" Capillary Pressure. Figure 16–6 demonstrates an *isogravimetric* method for indirectly estimating capillary pressure. This figure shows a section of gut held by one arm of a gravimetric balance. Blood is perfused through the blood vessels of the gut wall. When the arterial pressure is decreased, the resulting decrease in capillary pressure allows the osmotic pressure of the plasma proteins to cause absorption of fluid out of the gut wall and makes the weight of the gut decrease. This immediately causes displacement of the balance arm. To prevent this weight decrease, the venous pressure is increased an amount sufficient to overcome the effect of decreasing the arterial pressure. In other words, the cap-

illary pressure is kept constant while decreasing the arterial pressure and raising the venous pressure.

In the lower part of the figure, the changes in arterial and venous pressures that exactly nullify all weight changes are shown. The arterial and venous lines meet each other at a value of 17 mm Hg. Therefore, the capillary pressure must have remained at this same level of 17 mm Hg throughout these maneuvers, or otherwise filtration or absorption of fluid through the capillary walls would have occurred. Thus, in a roundabout way, the "functional" capillary pressure is measured to be about 17 mm Hg.

Why Is the Functional Capillary Pressure Much Lower than Capillary Pressure Measured by the Micropipette Method? It is clear that the aforementioned two methods do not give the same capillary pressure. However, the isogravimetric method determines the capillary pressure that exactly balances all the forces tending to move fluid into or out of the capillaries. Because such a balance of forces is the normal state, the average functional capillary pressure must be close to the pressure measured by the isogravimetric method. Therefore, one is justified in believing that the true functional capillary pressure averages about 17 mm Hg.

It is easy to explain why the cannulation methods give higher pressure values. The most important reason is that these measurements usually are made in capillaries whose arterial ends are open and blood is actively flowing into the capillary. However, it should be recalled from the earlier discussion of capillary vasomotion that the metarterioles and precapillary sphincters normally are closed during a large part of the vasomotion cycle. When closed, the pressure in the capillaries beyond the closures should be almost equal to the pressure at the venous ends of the capillaries, about 10 mm Hg. Therefore, when averaged over a period of time, one would expect the *functional* mean capillary pressure to be much nearer to the pressure in the venous ends of the capillaries than to the pressure in the arterial ends.

There are two other reasons why the functional capillary pressure is less than the values measured by cannulation. First, there are far more venous capillaries than arterial capillaries. Second, the venous capillaries are several times as permeable as the arterial capillaries. Both of these effects further decrease the functional capillary pressure to a lower value.

Interstitial Fluid Pressure

As is true for the measurement of capillary pressure, there are several methods for measuring interstitial fluid pressure, and each of these gives slightly different values but usually values that are a few millimeters of mercury less than atmospheric pressure, that is, values called *negative interstitial fluid pressure.* The methods most widely used have been (1) direct cannulation of the tissues with a micropipette, (2) measurement of the pressure from implanted perforated capsules, and (3) measurement of the pressure from a cotton wick inserted into the tissue.

Measurement of Interstitial Fluid Pressure Using the Micropipette. The same type of micropipette used for measuring capillary pressure can also be used in some tissues for measuring interstitial fluid pressure. The tip of the micropipette is about 1 micrometer in diameter, but even this is 20 or more times larger than the sizes of the spaces between the proteoglycan filaments of the interstitium. Therefore, the pressure that is measured is probably the pressure in a free fluid pocket.

The first pressures measured using the micropipette method ranged from −1 to +2 mm Hg but were usually slightly positive. With experience in making such measurements, the more recent pressures have averaged about −2 mm Hg, giving average pressure values in *loose* tissues that are slightly less than atmospheric pressure.

Measurement of Interstitial Free Fluid Pressure in Implanted Perforated Hollow Capsules. Figure 16–7 shows an indirect method for measuring interstitial fluid pressure: A small hollow plastic capsule perforated by up to 100 small holes is implanted in the tissues, and the surgical wound is allowed to heal for about 1 month. At the end of that time, tissue will have grown inward through the holes to line the inner surface of the sphere. Furthermore, the cavity is filled with fluid that flows freely through the perforations back and forth between the fluid in the interstitial spaces and the fluid in the cavity. Therefore, the pressure in the cavity should equal the free fluid pressure in the surrounding/interstitial fluid spaces. A needle is inserted through the skin and through one of the perforations to the interior of the cavity, and the pressure is measured by use of an appropriate manometer.

Interstitial free fluid pressure measured by this method when using 2 centimeter diameter capsules in normal *loose* subcutaneous tissue averages about −6 mm Hg, but with smaller capsules, the values are not greatly different from the −2 mm Hg measured by the micropipette.

Measurement of Interstitial Free Fluid Pressure by Means of a Cotton Wick. Still another method is to insert into a tissue a small Teflon tube with about eight cotton fibers protruding from its end. The cotton fibers form a "wick" that makes excellent contact with the tissue fluids and transmits interstitial fluid pressure into the Teflon tube: the pressure can then be measured from the tube by usual manometric means. Pressures measured by this technique in *loose* subcutaneous tissue also have been negative, usually measuring −1 to −3 mm Hg.

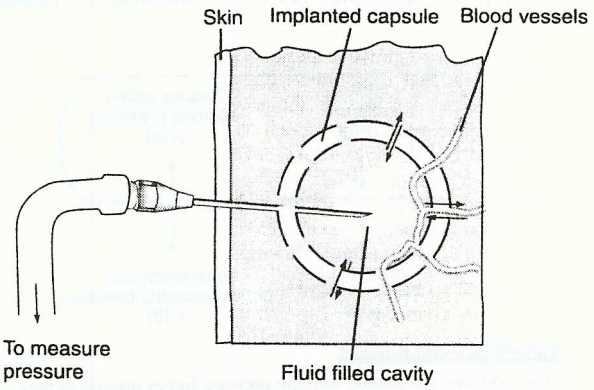

FIGURE 16–7

Perforated capsule method for measuring interstitial fluid pressure.

Interstitial Fluid Pressures in Tightly Encased Tissues

Some tissues of the body are surrounded by tight encasements, such as the cranial vault around the brain, the strong fibrous capsule around the kidney, the fibrous sheaths around the muscles, and the sclera around the eye. In most of these, regardless of the method used for measurement, the interstitial fluid pressures are usually positive. However, these interstitial fluid pressures almost invariably are still less than the pressures exerted on the outsides of the tissues by their encasements. For instance, the cerebrospinal fluid pressure surrounding the brain of an animal lying on its side averages about +10 mm Hg, whereas the brain interstitial fluid pressure averages about +4 to +6 mm Hg. In the kidneys, the capsular pressure surrounding the kidney averages about +13 mm Hg, whereas the reported interstitial fluid pressures have averaged about +6 mm Hg.

Thus, if one remembers that the pressure exerted on the skin is atmospheric pressure, which is considered to be zero pressure, one might formulate a general rule that the normal interstitial fluid pressure is usually several millimeters of mercury negative with respect to the pressure that surrounds each tissue.

Is the True Interstitial Fluid Pressure in Loose Subcutaneous Tissue Subatmospheric?

The concept that the interstitial fluid pressure is subatmospheric in many if not most tissues of the body began with clinical observations that could not be explained by the previously held concept that interstitial fluid pressure was always positive. Some of the pertinent observations are the following:

1. When a skin graft is placed on a concave surface of the body, such as in an eye socket after removal of the eye, before the skin becomes attached to the sublying socket, fluid tends to collect underneath the graft. Also, the skin attempts to shorten, which tries to pull it away from the concavity. Nevertheless, some negative force underneath the skin causes absorption of the fluid and usually literally pulls the skin back into the concavity.

2. Less than 1 mm Hg of positive pressure is required to inject tremendous volumes of fluid into loose subcutaneous tissues, such as beneath the lower eyelid, in the axillary space, and in the scrotum. Amounts of fluid calculated to be more than 100 times the amount of fluid normally in the interstitial space, when injected into these areas, cause no more than about 2 mm Hg of positive pressure. The importance of these observations is that they show that such tissues do not have strong fibers that can prevent the accumulation of fluid. Therefore, some other mechanism, such as a negative fluid pressure system, must be available to prevent such fluid accumulation.

3. In most natural cavities of the body where there is free fluid in dynamic equilibrium with the surrounding interstitial fluids, the pressures that have been measured have been negative. Some of these are the following:

   Intrapleural space: −8 mm Hg
   Joint synovial spaces: −4 to −6 mm Hg
   Epidural space: −4 to −6 mm Hg

4. The implanted capsule for measuring the interstitial fluid pressure can be used to record dynamic changes in this pressure. The changes are approximately those that one would calculate to occur (1) when the arterial pressure is increased or decreased. (2) when fluid is injected into the surrounding tissue space, or (3) when a highly concentrated colloid osmotic agent is injected into the blood to absorb fluid from the tissue spaces. It is not likely that these dynamic changes could be recorded this accurately unless the capsule pressure closely approximated the true interstitial pressure.

Summary—An Average Value for Negative Interstitial Fluid Pressure in Loose Subcutaneous Tissue. Although the aforementioned different methods give slightly different values for interstitial fluid pressure, there currently is a general belief among most physiologists that the true interstitial fluid pressure in *loose* subcutaneous tissue is slightly less than atmospheric pressure. A pressure value that many are beginning to accept is an average value of about −3 mm Hg.

Pumping by the Lymphatic System Is the Basic Cause of the Negative Pressure

The lymphatic system is discussed later in the chapter, but we need to understand here the basic role that this system plays in determining interstitial fluid pressure. The lymphatic system is a "scavenger" system that removes excess fluid, protein molecules, debris, and other matter from the tissue spaces. When fluid enters the terminal lymphatic capillaries, any motion in the tissue that intermittently compresses the lymphatic capillaries propels the lymph forward through the lymphatic system, eventually emptying the lymph back into the circulation. In this way, any time any free fluid accumulates in the tissues, it simply is pumped away as a consequence of tissue movement. When the amount of fluid leaking from the blood capillaries is slight, as is true for most tissues, research evidence suggests that any motion of the tissues and lymphatic capillaries actually can pump a slight intermittent negative pressure that gives an average negativity in the loose tissues. The details of this lymphatic pumping system are discussed later in the chapter.

Plasma Colloid Osmotic Pressure

Proteins in the Plasma Cause Colloid Osmotic Pressure. In the basic discussion of osmotic pressure in Chapter 4, it was pointed out that only those molecules or ions that fail to pass through the pores of a semipermeable membrane exert osmotic pressure. Because the proteins are the only significant dissolved constituents that do not readily penetrate the pores of the capillary membrane, it is the dissolved proteins of the plasma and interstitial fluids that are responsible for the osmotic pressures on the two sides of the capillary membrane. To distinguish this osmotic pressure from that which occurs at the cell membrane, it is called either *colloid osmotic pressure* or *oncotic pressure*. The term "colloid" osmotic pressure is derived from the fact that a protein solution resembles a colloidal solution despite the fact that it is actually a true molecular solution. (The osmotic pressure that occurs at the cell membrane is called *total osmotic pressure* to distinguish it from colloid osmotic pressure because essentially all dissolved substances of the body fluids exert osmotic pressure at

the cell membrane. This is not true at the capillary membrane because of the large sizes of the capillary pores.)

Normal Values for Plasma Colloid Osmotic Pressure. The colloid osmotic pressure of normal human plasma averages about 28 mm Hg; 19 mm of this is caused by molecular effects of the dissolved protein and 9 mm by the cations held in the plasma by the proteins, which is called the *Donnan effect.*

Effect of the Different Plasma Proteins on Colloid Osmotic Pressure. The plasma proteins are a mixture of proteins that contains albumin, with an average molecular weight of 69,000; globulins, 140,000; and fibrinogen, 400,000. Thus, 1 gram of globulin contains only half as many molecules as 1 gram of albumin, and 1 gram of fibrinogen contains only one sixth as many molecules as 1 gram of albumin. It should be recalled from the discussion of osmotic pressure in Chapter 4 that the osmotic pressure is determined by the *number of molecules* dissolved in a fluid rather than by the mass of these molecules. Therefore, when corrected for number of molecules rather than mass, the following chart gives both the relative mass concentrations of the different types of proteins in normal plasma and their respective contributions to the total plasma colloid osmotic pressure.

	g/dl	*Πp (mm Hg)*
Albumin	4.5	21.8
Globulins	2.5	6.0
Fibrinogen	0.3	0.2
Total	7.3	28.0

Thus, about 80 per cent of the total colloid osmotic pressure of the plasma results from the albumin fraction, 20 per cent from the globulins, and almost none from the fibrinogen. Therefore, from the point of view of capillary fluid dynamics, it is mainly albumin that is important.

Interstitial Fluid Colloid Osmotic Pressure

Although the size of the usual capillary pore is smaller than the molecular sizes of the plasma proteins, this is not true of all the pores. Therefore, small amounts of plasma proteins do leak through the pores into the interstitial spaces.

The total quantity of protein in the entire 12 liters of interstitial fluid of the body is slightly greater than the total quantity of protein in the plasma itself, but because this volume is four times the volume of plasma, the average protein *concentration* of the interstitial fluid is usually about 40 per cent of that in plasma, or about 3 g/dl. Quantitatively, one finds that the average colloid osmotic pressure for this concentration of proteins in the interstitial fluids is about 8 mm Hg.

Exchange of Fluid Volume Through the Capillary Membrane

Now that the different factors affecting fluid movement through the capillary membrane have been discussed, it is possible to put all these together to see how normal capillaries maintain normal fluid volume distribution between the plasma and the interstitial fluid.

The average capillary pressure at the arterial ends of the capillaries is 15 to 25 mm Hg greater than at the venous ends. Because of this difference, fluid "filters" out of the capillaries at their arterial ends, but at their venous ends fluid is reabsorbed back into the capillaries. Thus, a small amount of fluid actually "flows" through the tissues from the arterial ends of the capillaries to the venous ends. The dynamics of this flow are as follows.

Analysis of the Forces Causing Filtration at the Arterial End of the Capillary. The approximate average forces operative at the *arterial end* of the capillary that cause movement through the capillary membrane are shown as follows:

	mm Hg
Forces tending to move fluid outward:	
Capillary pressure (arterial end of capillary)	30
Negative interstitial free fluid pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	41
Forces tending to move fluid inward:	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Summation of forces:	
Outward	41
Inward	28
NET OUTWARD FORCE (AT ARTERIAL END)	13

Thus, the summation of forces at the arterial end of the capillary shows a net *filtration pressure* of 13 mm Hg, tending to move fluid in the outward direction through the capillary pores.

This 13-mm Hg filtration pressure causes, on the average, about 0.5 per cent of the plasma in the flowing blood to filter out of the arterial ends of the capillaries into the interstitial spaces each time the blood passes through each tissue.

Analysis of Reabsorption at the Venous End of the Capillary. The low blood pressure at the venous end of the capillary changes the balance of forces in favor of absorption as follows:

	mm Hg
Forces tending to move fluid inward:	
Plasma colloid osmotic pressure	28
TOTAL INWARD FORCE	28
Forces tending to move fluid outward:	
Capillary pressure (venous end of capillary)	10
Negative interstitial free fluid pressure	3
Interstitial fluid colloid osmotic pressure	8
TOTAL OUTWARD FORCE	21
Summation of forces:	
Inward	28
Outward	21
NET INWARD FORCE	7

Thus, the force that causes fluid to move into the capillary, 28 mm Hg, is greater than that opposing reabsorption, 21 mm Hg. The difference, 7 mm Hg, is the

net reabsorption pressure at the venous ends of the capillaries. This reabsorption pressure is considerably less than the filtration pressure at the capillary arterial ends, but remember that the venous capillaries are more numerous and more permeable than the arterial capillaries, so that less pressure is required to cause the inward movement of fluid.

The reabsorption pressure causes about nine tenths of the fluid that has filtered out of the arterial ends of the capillaries to be reabsorbed at the venous ends. The remainder flows into the lymph vessels.

Starling Equilibrium for Capillary Exchange

E. H. Starling pointed out a century ago that under normal conditions, a state of near-equilibrium exists at the capillary membrane. That is, the amount of fluid filtering outward from the arterial ends of capillaries equals almost exactly the fluid returned to the circulation by absorption. The slight disequilibrium that does occur accounts for the small amount of fluid that is eventually returned by way of the lymphatics.

The following chart shows the principles of the Starling equilibrium. For this chart, the pressures in the arterial and venous capillaries are averaged to calculate the mean *functional* capillary pressure for the entire length of the capillary. This calculates to be 17.3 mm Hg.

	mm Hg
Mean forces tending to move fluid outward:	
Mean capillary pressure	17.3
Negative interstitial free fluid pressure	3.0
Interstitial fluid colloid osmotic pressure	8.0
TOTAL OUTWARD FORCE	28.3
Mean force tending to move fluid inward:	
Plasma colloid osmotic pressure	28.0
TOTAL INWARD FORCE	28.0
Summation of mean forces:	
Outward	28.3
Inward	28.0
NET OUTWARD FORCE	0.3

Thus, for the total capillary circulation, we find a near-equilibrium between the total outward forces, 28.3 mm Hg, and the total inward force, 28.0 mm Hg. This slight imbalance of forces, 0.3 mm Hg, causes slightly more filtration of fluid into the interstitial spaces than reabsorption. This slight excess of filtration is called the *net filtration*, and it is the fluid that must be returned to the circulation through the lymphatics. The normal rate of net filtration *in the entire body* is only about 2 ml/min.

Filtration Coefficient. In the previous example, an average net imbalance of forces at the capillary membranes of 0.3 mm Hg causes a net rate of fluid filtration in the entire body of 2 ml/min. Expressing this for each millimeter of mercury imbalance, one finds a net filtration rate of 6.67 milliliters of fluid per minute per millimeter of mercury for the entire body. This expression is the *filtration coefficient*.

The filtration coefficient can also be expressed for different parts of the body in terms of the rate of filtration per minute per millimeter of mercury per 100 grams of tissue. On this basis, the filtration coefficient of the average tissue is about 0.01 ml/min/mm Hg/100 g of tissue. Because of extreme differences in permeabilities of the capillary systems in different tissues, this coefficient varies more than 100-fold among the different tissues. It is very small in both brain and muscle, moderately great in subcutaneous tissue, large in the intestine, and extreme in the liver and the glomerulus of the kidney where the pores are either numerous or wide open. By the same token, the permeation of proteins through the capillary membranes varies greatly as well. The concentration of protein in the interstitial fluid of muscles is about 1.5 g/dl; in subcutaneous tissue, 2 g/dl; in intestine, 4 g/dl; and in liver, 6 g/dl.

Effect of Abnormal Imbalance of Forces at the Capillary Membrane

If the mean capillary pressure rises above 17 mm Hg, the net force tending to cause filtration of fluid into the tissue spaces rises. Thus, a 20-mm Hg rise in mean capillary pressure causes an increase in the net filtration pressure from 0.3 mm Hg to 20.3 mm Hg, which results in 68 times as much net filtration of fluid into the interstitial spaces as normally occurs. To prevent accumulation of excess fluid in the spaces would require 68 times the normal flow of fluid into the lymphatic system, an amount that is usually 2 to 3 times too much for the lymphatics to carry away. As a result, fluid would begin to accumulate in the interstitial spaces and edema would result.

Conversely, if the capillary pressure falls very low, net reabsorption of fluid into the capillaries would occur instead of net filtration, and the blood volume would increase at the expense of the interstitial fluid volume.

The effects of imbalances at the capillary membrane in relation to the development of different kinds of edema are discussed in Chapter 25.

LYMPHATIC SYSTEM

The lymphatic system represents an accessory route by which fluid can flow from the interstitial spaces into the blood. Most important, the lymphatics can carry proteins and large particulate matter away from the tissue spaces, neither of which can be removed by absorption directly into the blood capillaries. This return of proteins to the blood from the interstitial spaces is an essential function, without which we would die within about 24 hours.

Lymph Channels of the Body

Almost all tissues of the body have lymph channels that drain excess fluid directly from the interstitial spaces. The exceptions include the superficial portions of the skin, the central nervous system, the endomysium of muscles, and the bones.

Even these tissues have minute interstitial channels called *prelymphatics* through which interstitial fluid can flow; this fluid eventually empties either into lymphatic vessels or, in the case of the brain, into the cerebrospinal fluid and then directly back into the blood.

Essentially all the lymph from the lower part of the body eventually flows up the *thoracic duct* and empties into the venous system at the juncture of the *left* internal jugular vein and subclavian vein, as shown in Figure 16–8.

Lymph from the left side of the head, the left arm, and parts of the chest region also enters the thoracic duct before it empties into the veins.

Lymph from the right side of the neck and head, the right arm, and parts of the right thorax enters the *right lymph duct*, which then empties into the venous system at the juncture of the *right* subclavian vein and internal jugular vein.

Terminal Lymphatic Capillaries and Their Permeability. Most of the fluid filtering from the *blood capillaries* flows among the cells and finally is reabsorbed back into the *venous ends* of the *blood capillaries;* but on the average, about 1/10 of the fluid instead enters the *lymphatic capillaries* and returns to the blood through the lymphatic system rather than through the venous capillaries. The total quantity of this lymph is normally only 2 to 3 liters each day.

The fluid that returns to the circulation by way of the lymphatics is extremely important because substances of high molecular weight, such as proteins, cannot be absorbed from the tissues in any other way, although they can enter the lymphatic capillaries almost unimpeded. The reason for this is a special structure of the lymphatic capillaries, demonstrated in Figure 16–9. This figure shows the endothelial cells of the lymphatic capillary attached by *anchoring filaments* to the surrounding connective tissue. At the junctions of adjacent endothelial cells, the edge of one endothelial cell overlaps the edge of the adjacent cell in such a way that the overlapping edge is free to flap inward, thus forming a minute valve that opens to the interior of the capillary. Interstitial fluid, along with its suspended particles, can push the valve open and flow directly into the lymphatic capillary. But this fluid has difficulty leaving the capillary once it has entered because any backflow closes the flap valve. Thus, the lymphatics have valves at the very tips of the terminal lymphatic capillaries as well as valves along their larger vessels up to the point where they empty into the blood circulation.

Formation of Lymph

Lymph is derived from interstitial fluid that flows into the lymphatics. Therefore, lymph as it first enters the

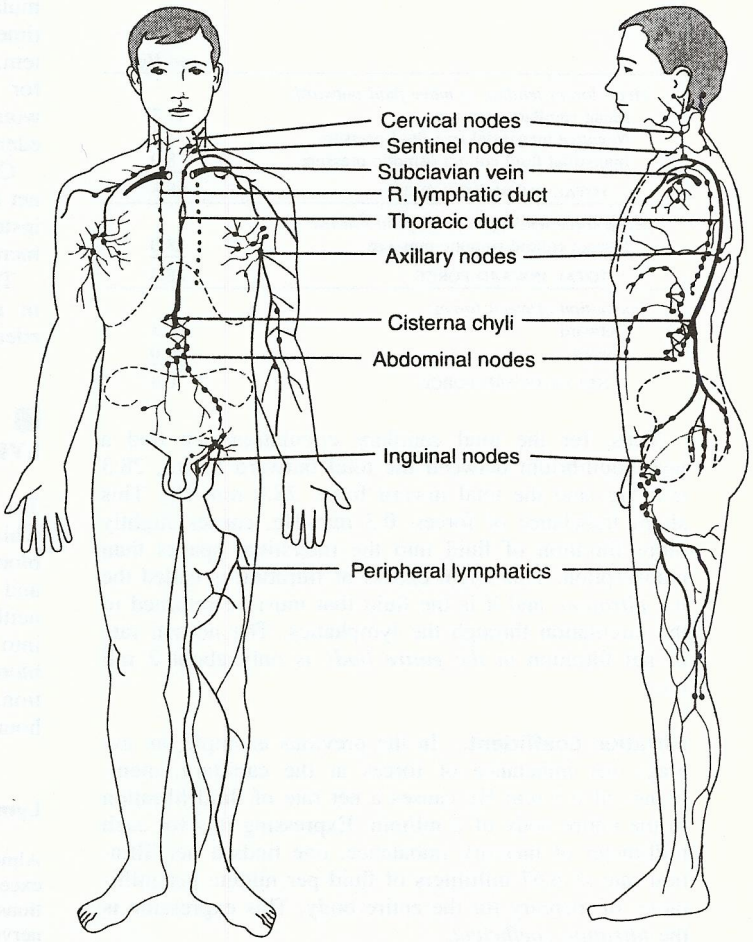

FIGURE 16–8
Lymphatic system.

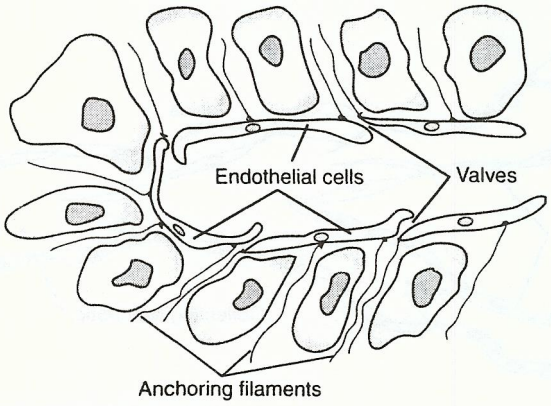

FIGURE 16–9

Special structure of the lymphatic capillaries that permits passage of substances of high molecular weight into the lymph.

terminal lymphatics has almost the same composition as the interstitial fluid.

The protein concentration in the interstitial fluid of most tissues averages about 2 g/dl, and the protein concentration of lymph flowing from these tissues is near this value. Conversely, lymph formed in the liver has a protein concentration as high as 6 g/dl, and lymph formed in the intestines has a protein concentration as high as 3 to 4 g/dl. Because about two thirds of all lymph normally is derived from the liver and intestines, the thoracic duct lymph, which is a mixture of lymph from all areas of the body, usually has a protein concentration of 3 to 5 g/dl.

The lymphatic system is also one of the major routes for absorption of nutrients from the gastrointestinal tract, being responsible principally for the absorption of fats, as discussed in Chapter 65. Indeed, after a fatty meal, thoracic duct lymph sometimes contains as much as 1 to 2 per cent fat.

Finally, even large particles, such as bacteria, can push their way between the endothelial cells of the lymphatic capillaries and in this way enter the lymph. As the lymph passes through the lymph nodes, these particles are removed and destroyed, as discussed in Chapter 33.

Rate of Lymph Flow

About 100 milliliters per hour of lymph flows through the *thoracic duct* of a resting human, and approximately another 20 milliliters flows into the circulation each hour through other channels, making a total estimated lymph flow of about 120 ml/hr, that is, between 2 and 3 liters per day.

Effect of Interstitial Fluid Pressure on Lymph Flow. Figure 16–10 shows the effect of different levels of interstitial fluid pressure on lymph flow as measured in dog legs. Note that the lymph flow is very little at interstitial fluid pressures more negative than −6 mm Hg. Then, as the pressure rises up to values greater than 0 mm Hg (atmospheric pressure), the flow increases more than 20-fold. Therefore, any factor that increases interstitial fluid pressure normally also increases lymph flow if the lymph vessels are functioning normally. Such factors include the following:

Elevated capillary pressure
Decreased plasma colloid osmotic pressure
Increased interstitial fluid colloid osmotic pressure
Increased permeability of the capillaries

All of these cause the balance of fluid exchange at the blood capillary membrane to favor fluid movement into the interstitium, thus increasing interstitial fluid volume, interstitial fluid pressure, and lymph flow all at the same time.

However, note in Figure 16–10 that when the interstitial fluid pressure becomes 1 or 2 millimeters greater than atmospheric pressure (0 mm Hg), lymph flow fails to rise further at still higher pressures. This results from the fact that the increasing tissue pressure not only increases entry of fluid into the lymphatic capillaries, but also compresses the outside surfaces of the larger lymphatics, thus impeding lymph flow. At the higher pressures, these two factors balance each other almost exactly so that lymph flow reaches what is called the "maximum lymph flow rate." This is illustrated by the upper level plateau in Figure 16–10.

Lymphatic Pump Increases Lymph Flow. Valves exist in all lymph channels; typical valves are shown in Figure 16–11 in collecting lymphatics into which the lymphatic capillaries empty.

Motion pictures of exposed lymph vessels, both in animals and in humans, show that when a collecting lymphatic or larger lymph vessel becomes stretched with fluid, the smooth muscle in the wall of the vessel automatically contracts. Furthermore, each segment of the

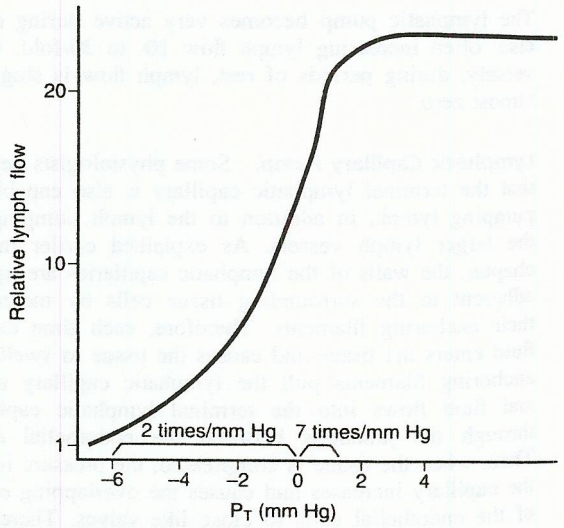

FIGURE 16–10

Relation between interstitial fluid pressure and lymph flow in the leg of a dog. Note that lymph flow reaches a maximum as the interstitial pressure, P_T, rises slightly above atmospheric pressure (0 mm Hg). (Courtesy Drs. Harry Gibson and Aubrey Taylor.)

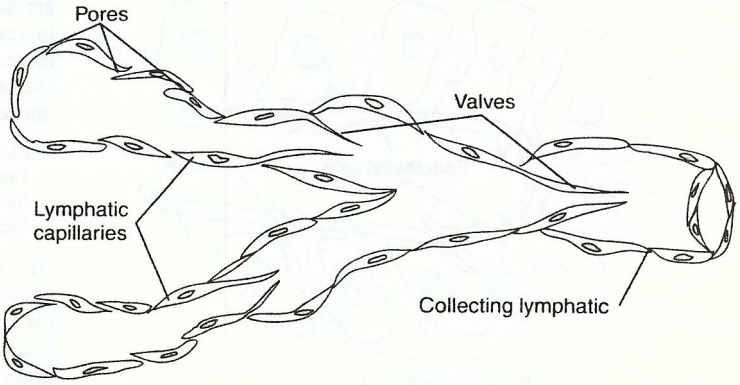

FIGURE 16–11

Structure of lymphatic capillaries and a collecting lymphatic, showing also the lymphatic valves.

lymph vessel between successive valves functions as a separate automatic pump. That is, filling of a segment causes it to contract, and the fluid is pumped through the next valve into the next lymphatic segment. This fills the subsequent segment, and a few seconds later it, too, contracts, the process continuing all along the lymph vessel until the fluid is finally emptied. In a very large lymph vessel such as the thoracic duct, this lymphatic pump can generate pressures as great as 50 to 100 mm Hg.

Pumping Caused by External Intermittent Compression of the Lymphatics. In addition to the pumping caused by intrinsic intermittent contraction of the lymph vessel walls, any external factor that intermittently compresses the lymph vessel also can cause pumping. In order of their importance, such factors are

Contraction of surrounding skeletal muscles
Movement of the parts of the body
Pulsations of arteries adjacent to the lymphatics
Compression of the tissues by objects outside the body

The lymphatic pump becomes very active during exercise, often increasing lymph flow 10- to 30-fold. Conversely, during periods of rest, lymph flow is sluggish, almost zero.

Lymphatic Capillary Pump. Some physiologists believe that the terminal lymphatic capillary is also capable of pumping lymph, in addition to the lymph pumping by the larger lymph vessels. As explained earlier in the chapter, the walls of the lymphatic capillaries are tightly adherent to the surrounding tissue cells by means of their anchoring filaments. Therefore, each time excess fluid enters the tissue and causes the tissue to swell, the anchoring filaments pull the lymphatic capillary open, and fluid flows into the terminal lymphatic capillary through the junctions between the endothelial cells. Then, when the tissue is compressed, the pressure inside the capillary increases and causes the overlapping edges of the endothelial cells to close like valves. Therefore, the pressure pushes the lymph forward into the collecting lymphatic instead of backward through the cell junctions.

The lymphatic capillary endothelial cells also contain contractile actomyosin filaments. In some animal tissues (e.g., the bat's wing) these filaments have been observed to cause rhythmical contraction of the lymphatic capillaries in the same way that many of the small blood and lymphatic vessels contract rhythmically. Therefore, it is probable that at least part of lymph pumping results from lymph capillary endothelial cell contraction in addition to contraction of the larger muscular lymphatics.

Summary of Factors That Determine Lymph Flow. From the above discussion, one can see that the two primary factors that determine lymph flow are (1) the interstitial fluid pressure and (2) the activity of the lymphatic pump. Therefore, one can state that, roughly, *the rate of lymph flow is determined by the product of interstitial fluid pressure times the activity of the lymphatic pump.*

Role of the Lymphatic System in Controlling Interstitial Fluid Protein Concentration, Interstitial Fluid Volume, and Interstitial Fluid Pressure

It is already clear that the lymphatic system functions as an "overflow mechanism" to return to the circulation excess proteins and excess fluid volume from the tissue spaces. Therefore, the lymphatic system also plays a central role in controlling (1) the concentration of proteins in the interstitial fluids, (2) the volume of interstitial fluid, and (3) the interstitial fluid pressure. Let us explain how these factors interact.

First, remember that small amounts of proteins leak continuously out of the blood capillaries into the interstitium. Only minute amounts, if any, of the leaked proteins return to the circulation by way of the venous ends of the blood capillaries. Therefore, these proteins tend to accumulate in the interstitial fluid, and this in turn increases the colloid osmotic pressure of the interstitial fluids.

Second, the increasing colloid osmotic pressure in the interstitial fluid shifts the balance of forces at the blood capillary membranes in favor of fluid filtration into the interstitium. Therefore, in effect, fluid is translocated osmotically outward through the capillary wall by the proteins and into the interstitium, thus increasing both interstitial fluid volume and interstitial fluid pressure.

Third, the increasing interstitial fluid pressure greatly increases the rate of lymph flow, as explained previously. This in turn carries away the excess interstitial fluid volume and excess protein that has accumulated in the spaces.

Thus, once the interstitial fluid protein concentration reaches a certain level and causes a comparable increase in interstitial fluid volume and interstitial fluid pressure, the return of protein and fluid by way of the lymphatic system becomes great enough to balance exactly the rate of leakage of these from the blood capillaries. Therefore, the quantitative values of all these factors reach a steady state; they will remain balanced at these levels until something changes the rate of leakage of proteins and fluid from the blood capillaries.

Significance of Negative Interstitial Fluid Pressure as a Means for Holding the Body Tissues Together

Traditionally, it has been assumed that the different tissues of the body are held together entirely by connective tissue fibers. However, at many places in the body, connective tissue fibers are very weak or even absent. This occurs particularly at points where tissues slide over one another, such as the skin sliding over the back of the hand or over the face. Yet even at these places, the tissues are held together by the negative interstitial fluid pressure, which is actually a partial vacuum. When the tissues lose their negative pressure, fluid accumulates in the spaces and the condition known as *edema* occurs, which is discussed in Chapter 25.

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