Chapter 18 – Blood, Microcirculation, Exchange, and Fluid Volumes

Objectives

Given the synopsis in this chapter, competence in each objective will be demonstrated by writing short essays, drawing diagrams, and responding to multiple choices or matching questions, at the level of 85% or greater proficiency for each student.hj[

A. To describe the composition and general function of the blood.
B. To explain the differences and functions of the erythrocytes, leukocytes, and thrombocytes.
C. To explain blood types, including A, B, AB, O, RH+ and RH-, and Rh incompatibility during pregnancy.
D. To explain hemostasis, including vascular responses, platelet responses, clotting, and clot removal.
E. To describe the capillary epithelium and explain its role in capillary diffusion and exchange.
F. To explain capillary filtration and absorption, and the role of vascular pressures and vasoconstriction in moving fluid into the vascular space.

Blood

Blood is the vehicle responsible for most of the functions of the cardiovascular system. Some of the major functions of blood are to:

- Transport oxygen and nutrients, and carbon dioxide and metabolic wastes
- Deliver enzymes and hormones
- Regulate pH and electrolyte composition of interstitial fluids
- Restrict fluid losses by way of the clotting reaction
- Defend the body against toxins and pathogens
- Help regulate body temperature

Composition of blood

Blood is composed of plasma, erythrocytes (red cells), leukocytes (white cells), and thrombocytes (platelets) as shown in Figure 18.1. Plasma makes up about 52% to 63% of blood in females and about 48% to 58% of blood in males. Red blood cells, white blood cells and platelets together make up about 37% to 48% of blood in females and about 42% to 52% of blood in males

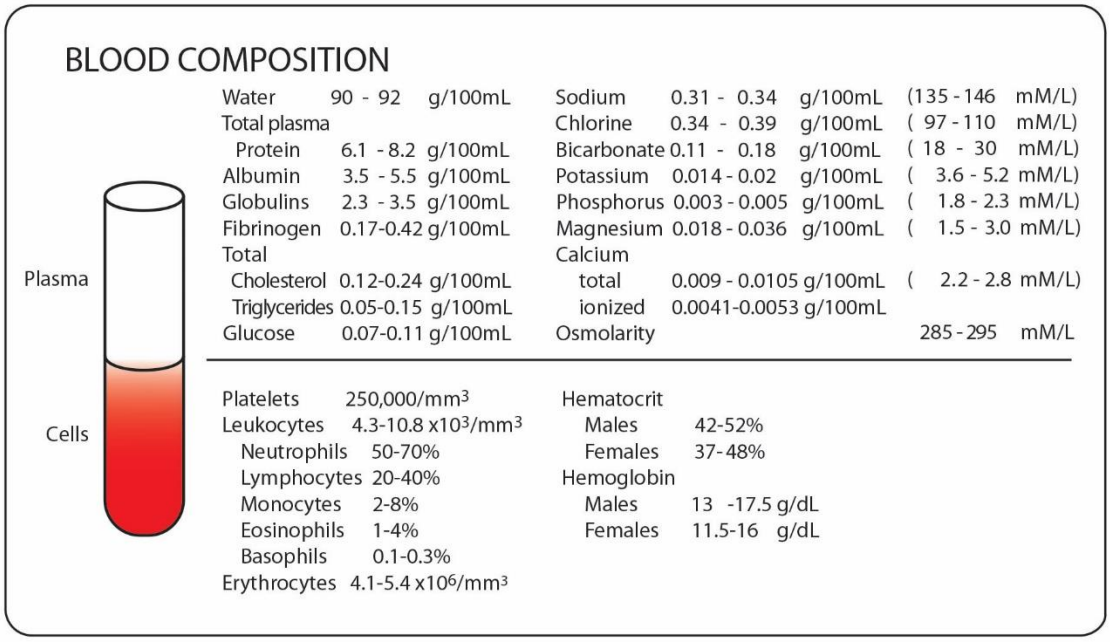
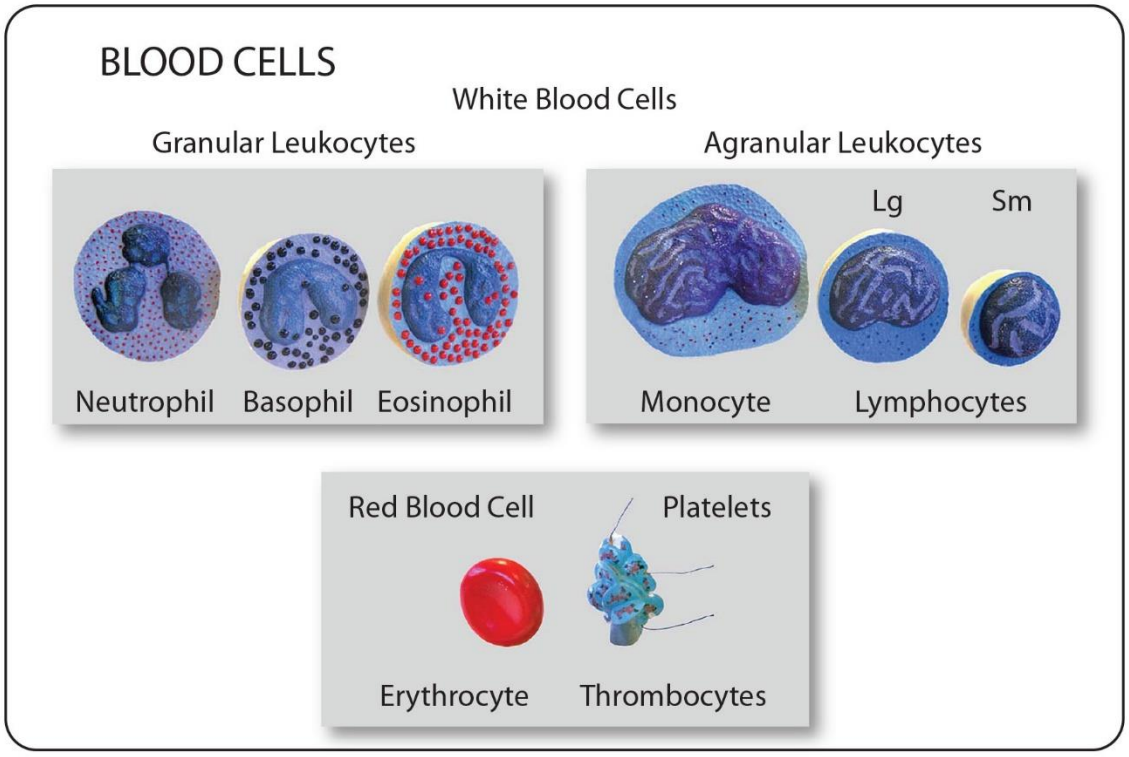


Figure 18.1 © 2016 David G. Ward, Ph.D.

- Plasma is about 90% to 93% water, with an osmolarity of 285 to 295 mOsm/L.
- About 6% to 8% of plasma is composed of three major groups of proteins.
    - Albumins boost osmolarity and transport lipids
    - Globulins transport ions, hormones, lipids and form immune complexes
    - Fibrinogen is the precursor for fibrin in the clotting reaction

- About 0.2% to 0.6% of plasma is composed of cholesterol, triglycerides, and glucose.
- About 0.8% to 1.0% of plasma is composed of electrolytes such as sodium, chlorine, bicarbonate, potassium, phosphorus, magnesium, and calcium. The electrolytes are the major source of the osmolarity of the extracellular fluids.
- The remainder of plasma contains a wide variety of proteins, peptides, and lipids with critical roles as chemical messengers and enzymes.

About 99.9% (by number) of the blood cells are red blood cells. The appearance and relative size of the blood cells is illustrated in Figure 18.2.



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Red blood cells (erythrocytes)

There are about a thousand times more red blood cells than white blood cells. Therefore, the hematocrit, which is the percentage of whole blood that is composed of red blood cells, is nearly identical to the percentage of total cells in the blood. Hematocrit is about 37 to 48 in females and about 42 to 52 in males.

- Erythrocytes are flattened cells with no nucleus, mitochondria or ribosomes
- The cytoplasm contains hemoglobin
- Erythrocytes transport oxygen and carbon dioxide
- The plasma membrane of erythrocytes contains proteins (antigens) that determine our blood type

White blood cells (leukocytes)

Although there are about a thousand times fewer white blood cells than red blood cells, the role of leukocytes in immunity is essential. Figure 18.2 illustrates the white blood cells according to their granulation. The granular leukocytes include the neutrophils, the basophils, and the eosinophils. The agranular leukocytes include the monocytes and lymphocytes. The white blood cells are listed below from most common to least common and briefly described.

- Neutrophils make up about 50% to 70% of white blood cells
    - engulf pathogens and debris
- Lymphocytes make up about 20% to 40% of white blood cells
    - B-lymphocytes form antibodies
    - T-lymphocytes attack viruses and invaded cells
    - NK-lymphocytes attack damaged or foreign cells
- Monocytes make up about 2% to 8% of white blood cells
    - engulf pathogens and debris
    - enter tissues to become macrophages
- Eosinophils make up about 1% to 4% of white blood cells
    - engulfs parasites and antibody bound pathogens
- Basophils make up about 0.1% to 0.3% of white blood cells
    - release histamine

Platelets (thrombocytes)

Platelets are cell fragments derived from megakaryocytes that play a critical role in hemostasis by clumping together and activating coagulation. Figure 18.2 illustrates a clump of about 20 platelets.

Blood types

Blood type is determined by the presence or absence of specific proteins (antigens) in the plasma membrane of the erythrocytes, as shown in Figure 18.3. "+" or "–" refers to presence or absence of the Rh antigen on the plasma membrane. "O" refers to the absence of the A and B antigens. "A" refers to the presence of the A antigen. "B" refers to the presence of the B antigen. "AB" refers to the presence of both the A and B antigens.

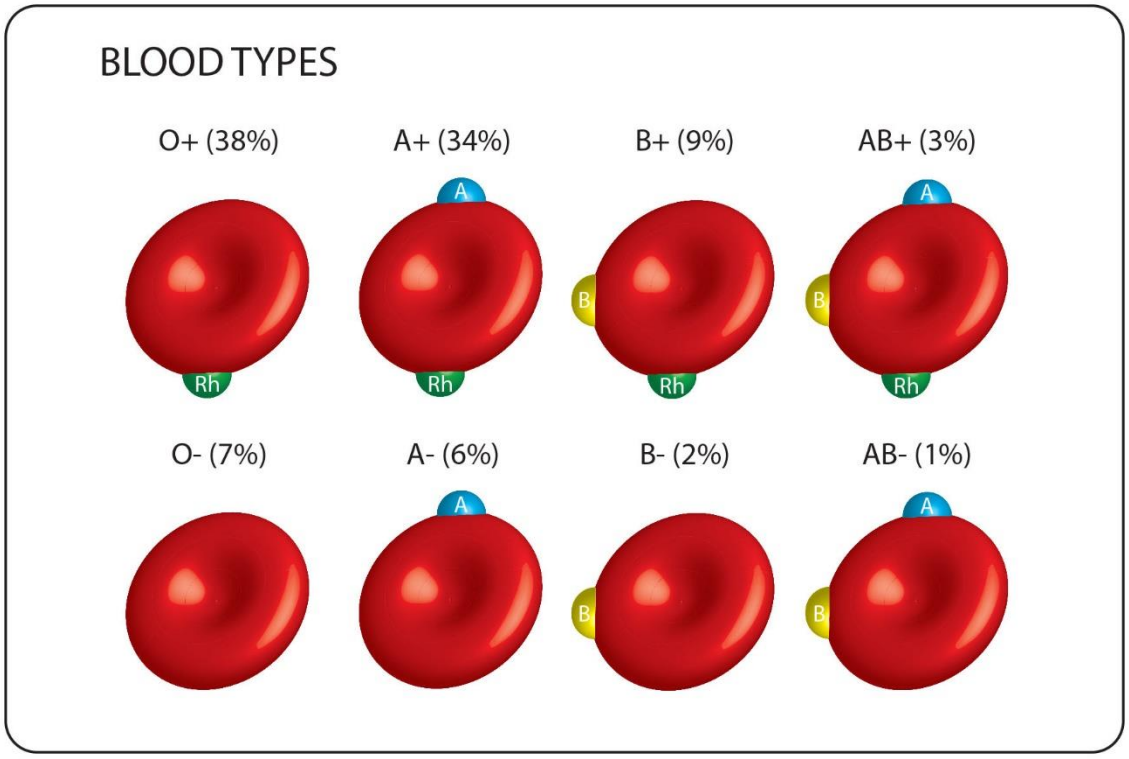


Figure 18.3 © 2007 David G. Ward, Ph.D.

Your blood plasma contains antibodies that attack foreign antigens as shown in Table 18.1. Antibodies are produced against the A and/or B antigens that are not naturally produced by the body. Older children and adults, 1) with A antigens have B antibodies, 2) with B antigens have A antibodies, 3) with both A and B antigens have no A and B antibodies, and 4) without the A and B antigens have both A and B antibodies. Infants and very young children do not exhibit the first three patterns. It is now recognized that early environmental exposure to foreign A and/or B type antigens stimulates the immune system to generate appropriate A and/or B antibodies.

Table 18.1. Blood types, surface antigens, and plasma antibodies

Blood Type	*Frequency*	*Surface Antigens*	*Antibodies in Plasma*
A	40%	A	anti-B
B	11%	B	anti-A
AB	4%	AB	None
O	45%	none	anti-A and anti-B
Rh+	84%	Rh	None
Rh-	16%	none	none (anti-Rh if exposed to Rh blood)

The immune system also responds to Rh antigens that are foreign. Accordingly, a person with Rh antigens naturally will not have Rh antibodies. Because environmental exposure to Rh type antigens typically does not occur, a person without Rh antigens will not produce Rh antibodies. However, if a person without Rh antigens is exposed to blood with Rh antigens, the immune system will see the Rh antigens as foreign and produce Rh antibodies. This will lead to a transfusion reaction, especially on second and later exposures to blood with Rh antigens.

Rh incompatibility occurs when a pregnant woman has blood without Rh antigens (Rh negative) and the fetus has blood with Rh antigens (Rh positive), inherited from a father who has blood with Rh antigens (RH positive). In about 13% of marriages in the United States, the man has blood with Rh antigen (Rh positive) and the woman has blood without Rh antigens (Rh negative). Problems can occur if the fetus's blood with Rh antigens enters the woman's bloodstream. The woman's immune system may recognize the red blood cells from the fetus as foreign and produce antibodies directed toward the Rh antigens.

During a first pregnancy, significant Rh antibody production is unlikely, because no significant amount of the fetus's blood is likely to enter the mother's bloodstream until delivery. So the fetus or newborn rarely has problems. However, once a woman is exposed to blood with Rh antigens, problems are more likely with each subsequent pregnancy in which the fetus's blood is Rh-positive. In each pregnancy, the woman produces antibodies against the Rh antigen, earlier and in larger amounts. If antibodies against the Rh antigens cross the placenta to the fetus, they may destroy some of the fetus's red blood cells. If red blood cells are destroyed faster than the fetus can produce new ones, the fetus can develop anemia. In severe cases, the fetus may die.

At the first visit to a doctor during a pregnancy, women are screened to determine whether they have blood with Rh antigens or blood without Rh antigens. If she has Rh negative blood, her blood is checked for Rh antibodies. If the father has blood with Rh antigens blood, Rh antibody production is a risk. In such cases, the blood of the pregnant mother is checked for Rh antibodies periodically during the pregnancy. The pregnancy can proceed as usual as long as no antibodies are detected. If antibodies are detected, steps may be taken to protect the fetus, depending on how high the antibody level is.

As a precaution, women who have blood without the Rh antigen (Rh negative) are given an injection of Rh immune globulins at 28 weeks of pregnancy and within 72 hours after delivery of a baby, a miscarriage, or an abortion of a baby who has blood with Rh antigens. The globulins given are called Rh_0(D) immune globulins (Rhogam). This treatment destroys any red blood cells from the baby that may have entered the bloodstream of the women. This process happens before the immune system of the mother (patient) generates an immune response. Thus, there are no red blood cells from the baby to trigger the production of antibodies by these women, and subsequent pregnancies are usually not endangered.

Hemostasis

Hemostasis refers to a series of processes that reduce loss of blood following tissue damage. These processes provide for a form of vascular "self-sealing" and include a vascular response, a platelet response, a clotting response, and finally a clot removal response.

Vascular response

As we saw in chapter 17, blood vessels exhibit myogenic responses to vessel stretch or vessel damage.

- Vessel stretch or damage leads to increased Ca^{2+} entry or release of endothelin-1 causing vasoconstriction and thus decreased blood flow.

Platelet response

Damage to the connective tissue of the blood vessels causes platelet activation and platelet clumping.

- vonWillebrand factor (vWF) produced by platelets and endothelial cells, binds to collagen and acts as a bridge to bind platelets to damaged blood vessels
- After binding, platelets secrete serotonin which causes vasoconstriction
- After binding, platelets secrete ADP and synthesize thromboxane A_2 (from arachidonic acid) which causes further platelet aggregation and the formation of platelet plugs.

Undamaged endothelium naturally synthesizes prostacyclin (from arachidonic acid) which inhibits platelet aggregation and causes vasodilation. Aspirin inhibits the formation of thromboxane A_2 from arachidonic acid, which explains it effectiveness in reducing the formation of platelet plugs and blood clots.

Clotting response

The end product of the clotting response is the formation of fibrin and fibrin strands from fibrinogen. This response is initiated by two mechanisms. One involves the exposure of collagen and the production of "platelet factors" (Intrinsic Pathway). The other involves exposure of the sub-endothelial cells and the production of "tissue factors" (Extrinsic Pathway). Regardless of whether the clotting response is initiated by the intrinsic pathway or the extrinsic pathway, thrombin is produced which leads to the formation of fibrin (Common Pathway). An overview of blood clotting is shown in Figure 18. 4.

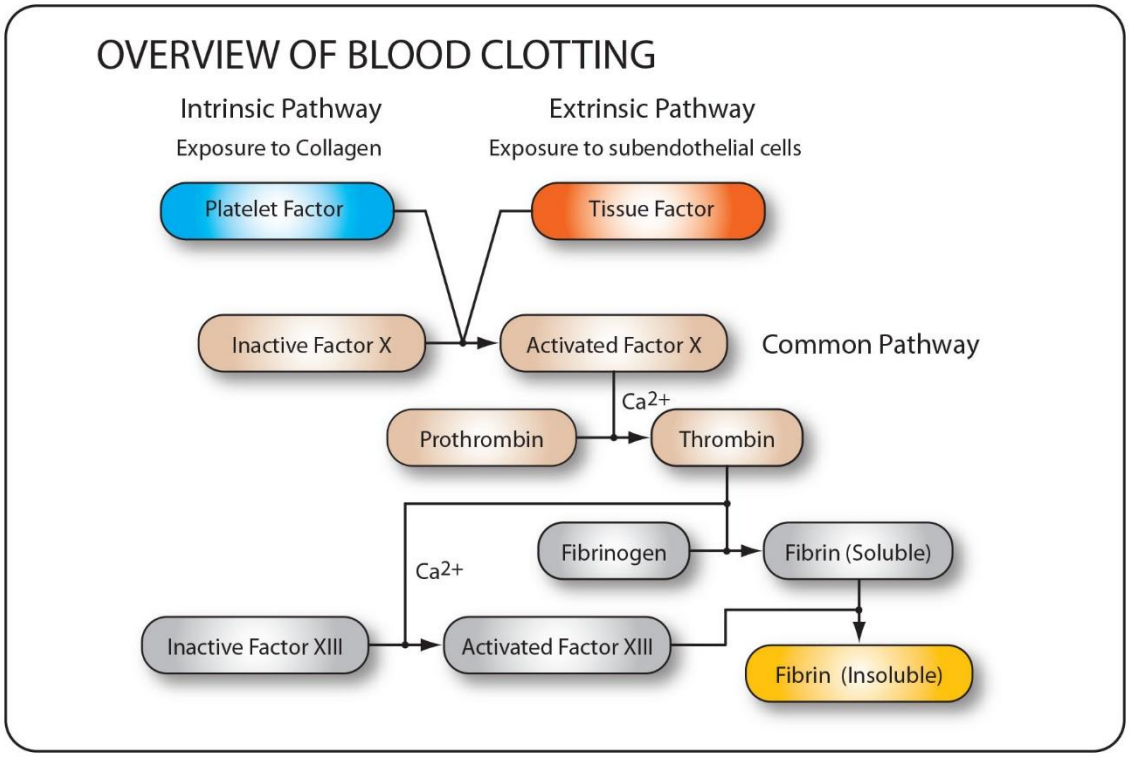


Figure 18.4 © 2007 David G. Ward, Ph.D.

Intrinsic (Platelet or Contact Activation) pathway

- Exposure to collagen fibers activates factor XII (factor XII to factor XIIa)
- Aggregating platelets produce platelet factor
- factor XIIa, together with platelet factor and Ca^{++} activate factor XI (factor XI to factor XIa)
- factor XIa, together with platelet factor and Ca^{++} activate factor IX (factor IX to factor IXa) and together form a factor IXa / platelet factor complex
- The factor IXa / platelet factor complex activates factor X (factor X to factor Xa)

Extrinsic (Tissue Factor) pathway

- Damage to blood vessels exposes a tissue factor (factor III) from sub-endothelial cells
- Tissue factor together with Ca^{++} activate factor VII (factor VII to factor VIIa) and together form a factor VIIa / tissue factor complex
- The factor VIIa / tissue factor complex activates factor X (factor X to factor Xa)

Common pathway

- Factor Xa together with Ca^{++} converts Prothrombin (factor II) into Thrombin (factor IIa)
- Thrombin converts Fibrinogen (factor I) into Fibrin factor Ia)
- Thrombin and Ca^{++} converts factor XIII into factor XIIIa
- Factor XIIIa causes Fibrin to form insoluble Fibrin strands

Clot removal

Blood clots are only temporary and need to be removed as tissue is repaired. As tissue heals:

- Plasminogen is activated by tissue plasminogen activator (TPA)
- Activated plasminogen produces plasmin which digests the fibrin

TPA (alteplase (Activase®)), and other clot dissolving (thrombolytic) drugs (streptokinase (Streptase®)) are a first-line of treatment for many heart attacks and strokes. Studies have shown that TPA and other clot-dissolving agents can reduce the amount of damage to the heart muscle and save lives. However, to be effective, they must be given within a few hours after symptoms begin. Cardiac catheterization is becoming more common when available in a timely manner.

Microcirculation

The microcirculation includes the blood capillaries and lymphatic capillaries and provides the gateway between the blood and the interstitial fluid, as shown in Figures 18.5 and 18.6. Fluid moves between blood (vascular space) and the interstitial space, and between the interstitial space and cells (intracellular space), as shown in Figure 18.6.

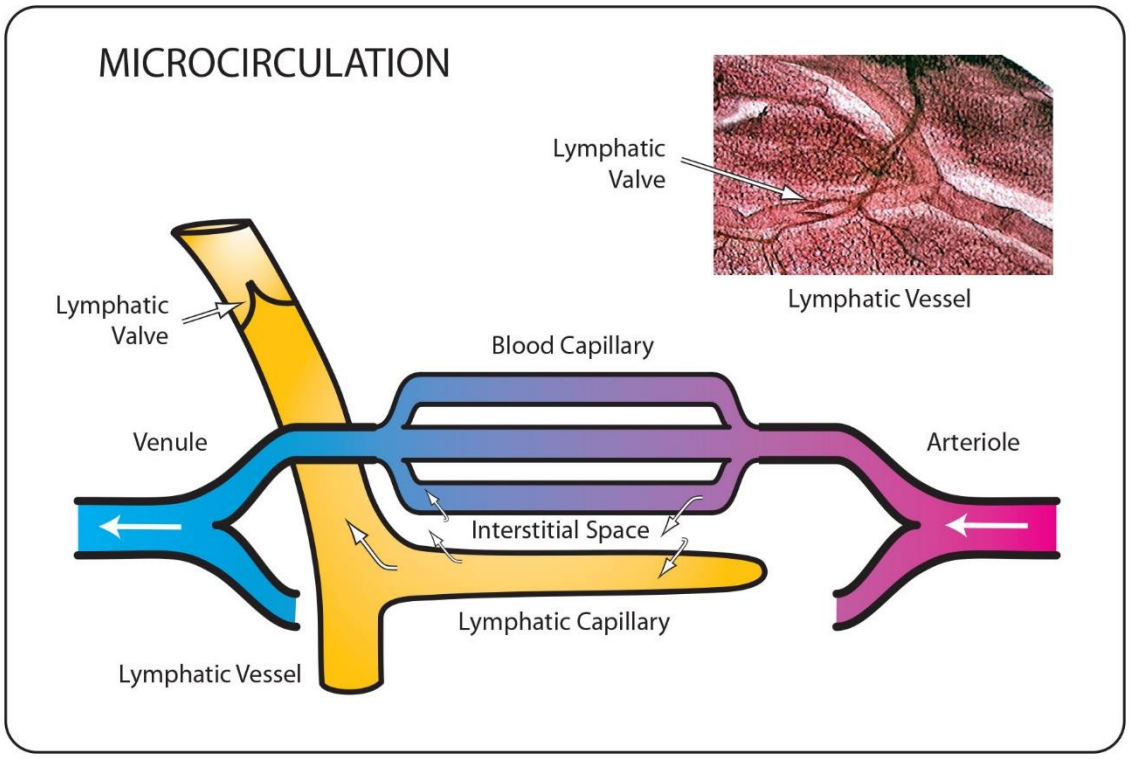


Figure 18.5 © 2007 David G. Ward, Ph.D.

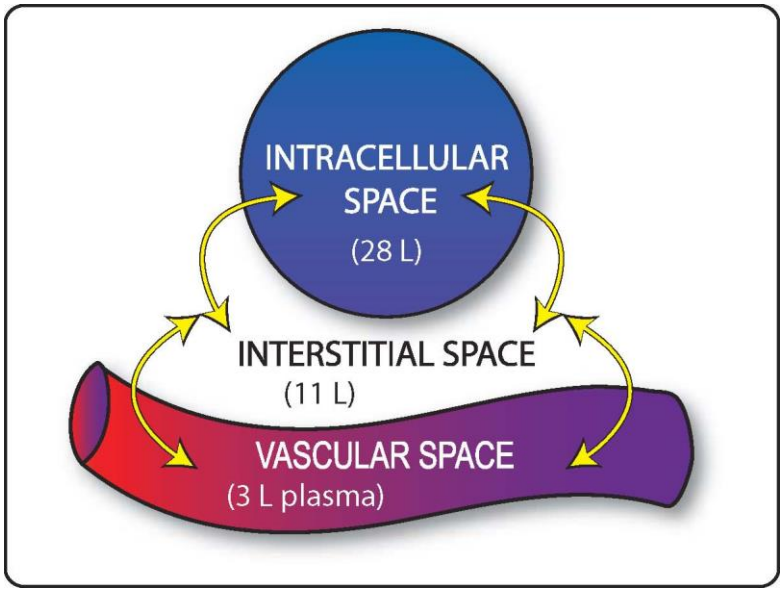


Figure 18.6 © 2007 David G. Ward, Ph.D.

- Blood capillaries are the site for exchange of oxygen and nutrients, and carbon dioxide and metabolic byproducts, between the blood and the cells of the body
- Lymphatic capillaries recover plasma lost from the blood capillaries for return to the systemic venous circulation
- Vascular space is the space in the blood vessels that contains the blood (vascular fluid, about 3 L plasma)
- Interstitial space is the space within the connective tissues between cells and the capillaries that contains the interstitial fluid (about 11 L)
- Intracellular space is the space inside of cells that contains the cytosol (intracellular fluid, about 28 L)

Capillary epithelium and permeability

As we saw in chapter 17 the blood capillaries consist of only endothelium (simple squamous epithelium.) The structure of the endothelium of blood capillaries is shown in more detail in Figure 18.7. The plasma membrane of the endothelial cells contains small water filled channels that are analogous if not identical to the channels we have considered in previous chapters. In addition, the plasma membrane may contain large fused vesicle channels. These are common in the liver. Finally, there are often intercellular clefts between the endothelial cells. Intercellular clefts are very prominent in glomerular capillaries of the kidney (chapter 20). Lymphatic capillaries have very large intercellular clefts.

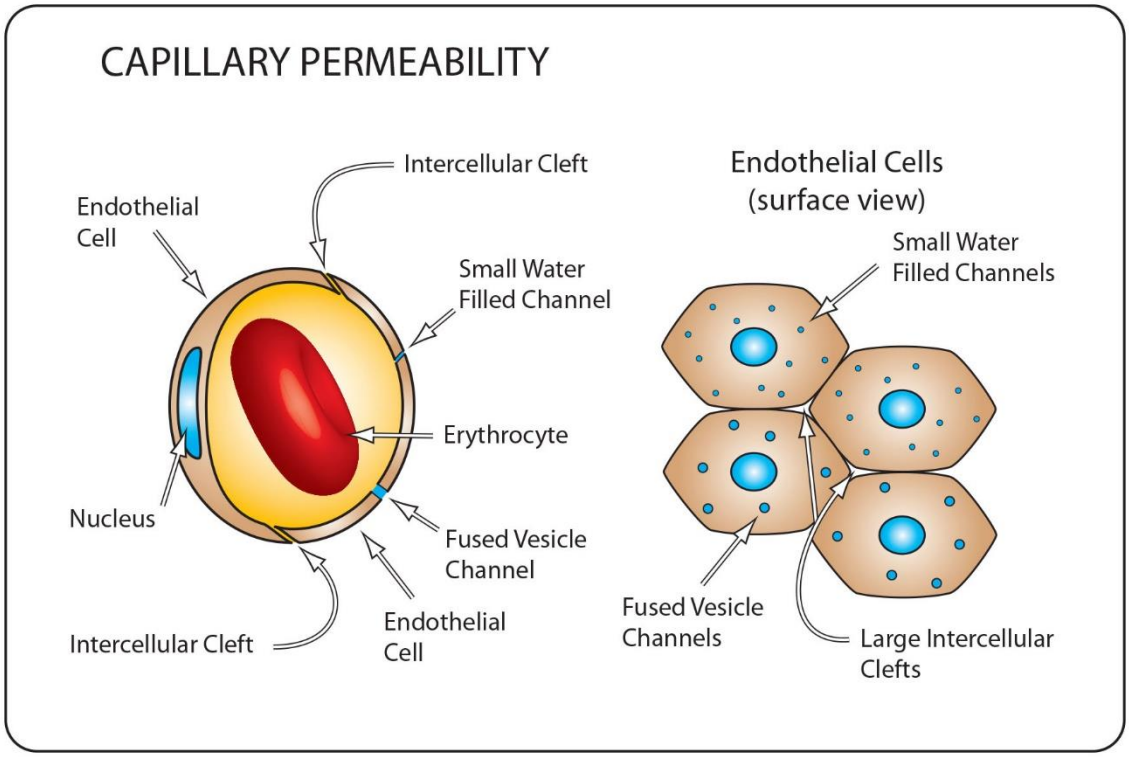


Figure 18.7 © 2007 David G. Ward, Ph.D.

Movement of substances through the capillary wall is by way of diffusion, vesicle transport (endocytosis, exocytosis), bulk flow, and in some cases mediated transport (usually by co-transporters or pumps).

Capillary diffusion

Except in the brain, diffusion is the only critical means by which net movement of oxygen and nutrients, and carbon dioxide and metabolic byproducts occurs across the capillary wall.

- Lipid soluble substances, including oxygen and carbon dioxide, easily diffuse through the plasma membranes of capillary epithelial cells.
- Ions and polar molecules, such as glucose, are poorly soluble in lipids and must pass through small water filled channels in the endothelium.
- Proteins generally (the liver is an exception) do not pass through water filled channels, but rather cross by endocytosis and exocytosis.
- In the brain, water soluble substances are transported through the endothelium usually by co-transporters or pumps.

In most tissues of the body, concentration gradient is the driving force moving substances from the blood into the interstitial space or from the interstitial space into the blood. The concentration gradients are established by diffusion in combination with

primary and secondary active transport that together moves substances from the interstitial space into the cells or from cells into the interstitial space. We will examine these processes further in chapter 20.

Capillary filtration and absorption

The movement of fluid into the interstitial space from the capillaries, or into the capillaries from the interstitial spaces is largely dependent on capillary and interstitial pressures. The processes involved in capillary filtration and absorption are shown in Figure 18.8.

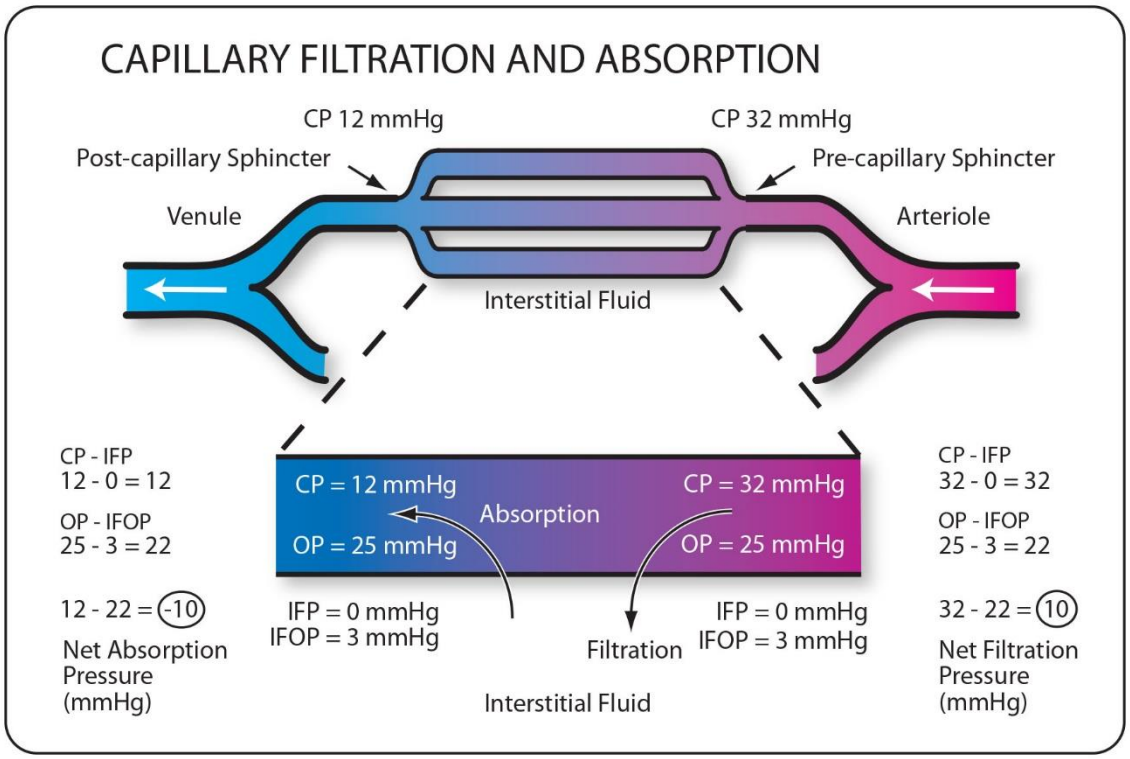


Figure 18.8 © 2014 David G. Ward, Ph.D.

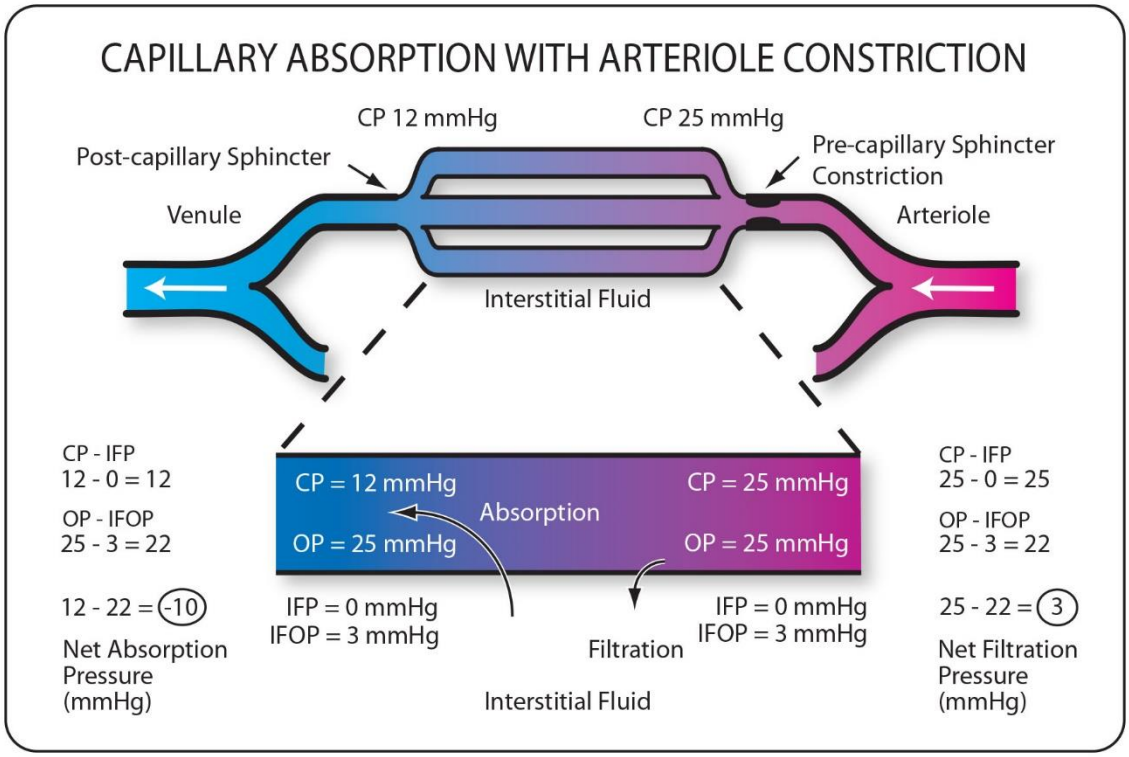
In normal fluid balance, the capillary blood pressure (CP) at the beginning of a typical systemic capillary is about 32 mmHg, and at the end of the capillary is about 12 mmHg. The interstitial fluid pressure (IFP) is close to 0 mmHg. The capillary osmotic pressure (OP) is about 25 mmHg at both the beginning and the end of the capillary. The interstitial fluid osmotic pressure (IFOP) is about 3 mmHg.

Due to the water filled channels in the endothelial membranes, fluid will move from an area of higher pressure to an area of lower pressure. At the beginning of the capillary there is a 32 mmHg difference in fluid pressure between the capillary (32 mmHg) and the interstitial space (0 mmHg). This pressure will push fluid out of the capillary and into the interstitial space. Opposing this movement is the presence of molecules in the blood that cannot pass through the water channels.

As we have seen, about 6% to 9% of plasma is composed of proteins. These proteins generate a large osmotic force (25 mmHg) that draws fluid back into the capillaries. Since only a relatively small number of larger molecules are found in the interstitial fluid, the osmotic force there is small (3 mmHg). Therefore, there is a 22 mmHg difference in osmotic pressure between the capillary (25 mmHg) and the interstitial space (3 mmHg). This osmotic pressure will draw fluid from the interstitial space into the capillary. At the beginning of the capillary, there is a 10 mmHg net filtration pressure (32mmHg - 22mmHg) to push fluid out of the capillary and into the interstitial space.

At the end of the capillary there is only a 12 mmHg difference in fluid pressure between the capillary (12 mmHg) and the interstitial space (0 mmHg). This pressure will push fluid out of the capillary and into the interstitial space. The capillary osmotic pressure and the interstitial fluid osmotic pressure are not changing. Therefore, there is a 22 mmHg difference in osmotic pressure between the capillary (25 mmHg) and the interstitial space (3 mmHg). This osmotic pressure will draw fluid from the interstitial space into the capillary. At the end of the capillary there is a -10 mmHg net absorption pressure (12 mmHg - 22mmHg) to pull fluid out of the interstitial space and back into the capillary.

In normal fluid balance, the movement of fluid out of the capillary at the beginning (+ 10 mmHg) is matched by the movement of fluid back into the capillary at the end (- 10 mmHg). As a result the volume of the blood does not change and the volume of the interstitial fluid does not change. In contrast, we will see a different picture if blood volume and/or arterial pressure is low, as shown in Figure 18.9.



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In the case of low blood volume, we can expect to see lowered arterial pressure and reflex arteriolar vasoconstriction. The change in pressure will depend of course on the decrease in blood volume. In this example the capillary blood pressure (CP) at the beginning of a typical systemic capillary has dropped to 25 mmHg, and at the end of the capillary is about 12 mmHg. The interstitial fluid pressure (IFP) is close to 0 mmHg. The capillary osmotic pressure (OP) is about 25 mmHg at both the beginning and the end of the capillary. The interstitial fluid osmotic pressure (IFOP) is about 3 mmHg.

Since only the blood pressure at the beginning of the capillary is different, there is no need to repeat the data for the interstitial fluid pressure or for the capillary and interstitial fluid osmotic pressures. At the beginning of the capillary there is a 25 mmHg difference in fluid pressure between the capillary (25 mmHg) and the interstitial space (0 mmHg). Together, at the beginning of the capillary there is a 3 mmHg net filtration pressure (25mmHg – 22mmHg) to push fluid out of the capillary and into the interstitial space. At the end of the capillary there is only a 12 mmHg difference in fluid pressure between the capillary (12 mmHg) and the interstitial s3pace (0 mmHg). Together, at the end of the capillary there is a -10 mmHg net absorption pressure (12mmHg – 22mmHg) to pull fluid out of the interstitial space and into the capillary.

In the case of low blood volume, the movement of fluid out of the capillary at the beginning (+3 mmHg) is exceeded by the movement of fluid back into the capillary at the end (-10 mmHg). As a result, the volume of the blood increases and the volume of the interstitial fluid decreases. This sort of mechanism goes into operation when you give a pint a blood, or simply do not drink enough fluid.

Quiz Yourself

1-5. Matching

A)	Blood plasma	contain(s) electrolytes, nutrients, organic wastes	1) _____
B)	Red blood cells	contain(s) hemoglobin	2) _____
C)	White blood cells	contain(s) fibrinogen	3) _____
		contain(s) albumins	4) _____
		contain(s) globulins	5) _____

6-10. Matching

A)	Basophils	engulf and digest parasites	6) _____
B)	Monocytes	large cells that restrain pathogens	7) _____
C)	Neutrophils	are the most common phagocytes	8) _____
D)	Eosinophils	are subdivided into B, T, and NK cells	9) _____
E)	Lymphocytes	release histamine that in turn dilates blood vessels	10) _____

11-15. Matching

A)	intracellular fluid	extracellular fluid	11) _____
B)	interstitial fluid	is about 3L of fluid	12) _____
C)	vascular fluid	is about 11L of fluid	13) _____
D)	B and C	is about 28L of fluid	14) _____
		found mainly in the spaces of connective tissues	15) _____

16-20. Place in order the events leading to blood clotting.

A)	blood vessels are damaged	16) _____
B)	fibrinogen converted to fibrin	17) _____
C)	prothrombin activator is formed	18) _____
D)	prothrombin converted to thrombin	19) _____
E)	platelets are activated and/or tissues factors are formed	20) _____

Fill in

21. As capillary blood pressure increases, fluid movement into the _____ _____ increases.

22. Increased capillary osmotic pressure enhances capillary _____ (fluid movement).

23. _____ converts fibrinogen to fibrin.

24. Fibrinolysis involves cleaving of plasminogen to _____ and the dissolving of clots.

25. Blood type O+ typically has antibodies to the _____ protein (s).

Study Questions

1. Explain the importance of blood plasma to the functions of blood.
2. Explain the inter-relationship between vascular fluid, interstitial fluid, and intracellular fluid. Include the role of capillary absorption and filtration.
3. Explain the process of hemostasis after tissue injury.
4. Explain the significance of Rh incompatibility, especially during pregnancy.