CHAPTER 32

Blood as a Circulatory Fluid & the Dynamics of Blood & Lymph Flow

OBJECTIVES

After studying this chapter, you should be able to:

■ Describe the components of blood and lymph, their origins, and the role of hemoglobin in transporting oxygen in red blood cells.

■ Understand the molecular basis of blood groups and the reasons for transfusion reactions.

■ Delineate the process of hemostasis that restricts blood loss when vessels are damaged, and the adverse consequences of intravascular thrombosis.

■ Identify the types of blood and lymphatic vessels that make up the circulatory system and the regulation and function of their primary constituent cell types.

■ Describe how physical principles dictate the flow of blood and lymph around the body.

■ Understand the basis of methods used to measure blood flow and blood pressure in various vascular segments.

■ Understand the basis of disease states where components of the blood and vasculature are abnormal, dysregulated, or both.

INTRODUCTION

The circulatory system supplies O₂ and substances absorbed from the gastrointestinal tract to the tissues, returns CO₂ to the lungs and other products of metabolism to the kidneys, functions in the regulation of body temperature, and distributes hormones and other agents that regulate cell function. The blood, the carrier of these substances, is pumped through a closed system of blood vessels by the heart. From the left ventricle, blood is pumped through the arteries and arterioles to the capillaries, where it equilibrates with the interstitial fluid. The capillaries drain through venules into the veins and back to the right atrium. Some tissue fluids enter another system of closed vessels, the lymphatics, which drain lymph via the thoracic duct and the right lymphatic duct into the venous system. The circulation is controlled by multiple regulatory systems that function in general to maintain adequate capillary blood flow when possible in all organs, but particularly in the heart and brain.

Blood flows through the circulation primarily because of the forward motion imparted to it by the pumping of the heart, although in the case of the systemic circulation, diastolic recoil of the walls of the arteries, compression of the veins by skeletal muscles during exercise, and the negative pressure in the thorax during inspiration also move the blood forward. The resistance to flow depends to a minor degree on the viscosity of the blood but mostly on the diameter of the vessels, principally the arterioles. The blood flow to each tissue is regulated by local chemical and general neural and humoral mechanisms that dilate or constrict the vessels of the tissue. All the blood flows through the lungs, but the systemic circulation is made up of numerous different circuits in parallel (Figure 32–1). The arrangement permits wide variations in regional blood flow without changing total systemic flow.
This chapter is concerned with blood and lymph and with the multiple functions of the cells they contain. It will also address general principles that apply to all parts of the circulation and with pressure and flow in the systemic circulation. The homeostatic mechanisms operating to adjust flow are the subject of Chapter 33. The special characteristics of pulmonary and renal circulation are discussed in Chapters 35 and 38. Likewise, the role of blood as the carrier of many immune effector cells will not be discussed here, but rather will be covered in Chapter 33.

**BLOOD AS A CIRCULATORY FLUID**

Blood consists of a protein-rich fluid known as plasma, in which are suspended cellular elements: white blood cells, red blood cells, and platelets. The normal total circulating blood volume is about 8% of the body weight (5600 mL in a 70-kg man). About 55% of this volume is plasma.

**BONE MARROW**

In the adult, red blood cells, many white blood cells, and platelets are formed in the bone marrow. In the fetus, blood cells are also formed in the liver and spleen, and in adults such extramedullary hematopoiesis may occur in diseases in which the bone marrow becomes destroyed or fibrosed. In children, blood cells are actively produced in the marrow cavities of all the bones. By age 20, the marrow in the cavities of the long bones, except for the upper humerus and femur, has become inactive (Figure 32–2). Active cellular marrow is called red marrow; inactive marrow that is infiltrated with fat is called yellow marrow.

The bone marrow is actually one of the largest organs in the body, approaching the size and weight of the liver. It is also one of the most active. Normally, 75% of the cells in the marrow belong to the white blood cell-producing myeloid series and only 25% are maturing red cells, even though there are over 500 times as many red cells in the circulation as there are white cells. This difference in the marrow reflects the fact that the average life span of white cells is short, whereas that of red cells is long.

Hematopoietic stem cells (HSCs) are bone marrow cells that are capable of producing all types of blood cells. They differentiate into one or another type of committed stem cells (progenitor cells). These in turn form the various differentiated types of blood cells. There are separate pools of progenitor cells for megakaryocytes, lymphocytes, erythrocytes, eosinophils, and basophils; neutrophils and monocytes arise from a common precursor. The bone marrow stem cells are also the source of osteoclasts (see Chapter 23), Kupffer cells (see Chapter 29), mast cells, dendritic cells, and Langerhans cells. The HSCs are few in number but are capable of completely replacing the bone marrow when injected into a host whose own bone marrow has been completely destroyed.

The HSCs are derived from uncommitted, totipotent stem cells that can be stimulated to form any cell in the body. Adults have a few of these, but they are more readily obtained from the blastocysts of embryos. There is not surprisingly immense interest in stem cell research due to its potential to regenerate diseased tissues, but ethical issues are involved, and debate on these issues will undoubtedly continue.

**WHITE BLOOD CELLS**

Normally, human blood contains 4000 to 11,000 white blood cells per microliter (Table 32–1). Of these, the granulocytes (polymorphonuclear leukocytes, PMNs) are the most numerous. Young granulocytes have horseshoe-shaped nuclei that become multilobed as the cells grow older (Figure 32–3).
Most of them contain neutrophilic granules (neutrophils), but a few contain granules that stain with acidic dyes (eosinophils). The other two cell types found normally in peripheral blood are lymphocytes, which have large round nuclei and scanty cytoplasm, and monocytes, which have abundant agranular cytoplasm and kidney-shaped nuclei (Figure 32–3). Acting together, these cells provide the body with powerful defenses against tumors and viral, bacterial, and parasitic infections that was discussed in Chapter 3.

**TABLE 32–1 Normal values for the cellular elements in human blood.**

<table>
<thead>
<tr>
<th>Cell</th>
<th>Cells/μL (average)</th>
<th>Approximate Normal Range</th>
<th>Percentage of Total White Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total white blood cells</td>
<td>9000</td>
<td>4000–11,000</td>
<td>...</td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>5400</td>
<td>3000–6000</td>
<td>50–70</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>275</td>
<td>150–300</td>
<td>1–4</td>
</tr>
<tr>
<td>Basophils</td>
<td>35</td>
<td>0–100</td>
<td>0.4</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2750</td>
<td>1500–4000</td>
<td>20–40</td>
</tr>
<tr>
<td>Monocytes</td>
<td>540</td>
<td>300–600</td>
<td>2–8</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>4.8 × 10⁶</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Males</td>
<td>5.4 × 10⁶</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Platelets</td>
<td>300,000</td>
<td>200,000–500,000</td>
<td>...</td>
</tr>
</tbody>
</table>

**ROLE OF THE SPLEEN**

The spleen is an important blood filter that removes aged or abnormal red cells. It also contains many platelets and plays a significant role in the immune system. Abnormal red cells are removed if they are not as flexible as normal red cells and consequently are unable to squeeze through the slits between the endothelial cells that line the splenic sinuses (see Clinical Box 32–1).

**HEMOGLOBIN**

The red, oxygen-carrying pigment in the red blood cells of vertebrates is hemoglobin, a protein with a molecular weight of 64,450. Hemoglobin is a globular molecule made up of four subunits (Figure 32–6). Each subunit contains a heme moiety conjugated to a polypeptide. Heme is an iron-containing porphyrin derivative (Figure 32–7). The polypeptides are referred to collectively as the globin portion of the hemoglobin molecule. There are two pairs of polypeptides in each hemoglobin molecule. In normal adult human hemoglobin (hemoglobin A), the two polypeptides are called α chains, each of which contains 141 amino acid residues, and β chains, each of which contains 146 amino acid residues. Thus, hemoglobin A is designated α₂β₂. Not all the hemoglobin in the blood of normal adults is hemoglobin A. About 2.5% of the hemoglobin is hemoglobin A₂, in which β chains are replaced by δ chains (α₂δ₂). The δ chains also contain 146 amino acid residues, but 10 individual residues differ from those in the β chains.

There are small amounts of hemoglobin A derivatives closely associated with hemoglobin A that represent glycated hemoglobins. One of these, hemoglobin A₁c (HbA₁c), has a glucose attached to the terminal valine in each β chain and is of special interest because it increases in the blood of patients with poorly controlled diabetes mellitus (see Chapter 21).

**REACIONS OF HEMOGLOBIN**

Hemoglobin binds O₂ to form oxyhemoglobin, O₂ attaching to the Fe²⁺ in the heme. The affinity of hemoglobin for O₂ is affected by pH, temperature, and the concentration in the red cells of 2,3-bisphosphoglycerate (2,3-BPG), 2,3-BPG and H⁺ decrease in the platelet count

Platelets are small, granulated bodies that aggregate at sites of vascular injury. They lack nuclei and are 2–4 μm in diameter (Figure 32–3). There are about 300,000/μL of circulating blood, and they normally have a half-life of about 4 d. The megakaryocytes, giant cells in the bone marrow, form platelets by pinching off bits of cytoplasm and extruding them into the circulation. Between 60% and 75% of the platelets that have been extruded from the bone marrow are in the circulating blood, and the remainder are mostly in the spleen. Splenectomy causes an increase in the platelet count (thrombocytosis).

**RED BLOOD CELLS**

The red blood cells (erythrocytes) carry hemoglobin in the circulation. They are biconcave disks (Figure 32–4) that are manufactured in the bone marrow. In mammals, they lose their nuclei before entering the circulation. In humans, they survive in the circulation for an average of 120 d. The average normal red blood cell count is 5.4 million/μL in men and 4.8 million/μL in women. Each human red blood cell is about 7.5 μm in diameter and 2 μm thick, and each contains approximately 29 pg of hemoglobin (Table 32–2). There are thus about 3 × 10¹² red blood cells and about 900 g of hemoglobin in the circulating blood of an adult man (Figure 32–5).

The feedback control of erythropoiesis by erythropoietin is discussed in Chapter 39, and the role of IL-1, IL-3, IL-6 (interleukin), and GM-CSF (granulocyte-macrophage colony-stimulating factor) in development of the relevant erythroid stem cells is shown in Figure 32–3.
compete with O\(_2\) for binding to deoxygenated hemoglobin, decreasing the affinity of hemoglobin for O\(_2\) by shifting the positions of the four peptide chains (quaternary structure). The details of the oxygenation and deoxygenation of hemoglobin and the physiologic role of these reactions in O\(_2\) transport are discussed in Chapter 36.

When blood is exposed to various drugs and other oxidizing agents in vitro or in vivo, the ferrous iron (Fe\(^{2+}\)) that is normally in the molecule is converted to ferric iron (Fe\(^{3+}\)), forming methemoglobin. Methemoglobin is dark-colored, and when it is present in large quantities in the circulation, it causes a dusky discoloration of the skin resembling cyanosis (see Chapter 36). Some oxidation of hemoglobin to methemoglobin occurs normally, but an enzyme system in the red cells, the dihydronicotinamide adenine dinucleotide (NADH)-methemoglobin reductase system, converts methemoglobin
TABLE 32–2 Characteristics of human red cells.\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (Hct) (%)</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>Red blood cells (RBC) ((10^6) μL)</td>
<td>5.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Hemoglobin (Hb) (g/dL)</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV) (fl)</td>
<td>= (\text{Hct} \times 10) (\text{RBC}(10^6) \mu\text{L})</td>
<td>87</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (MCH) (pg)</td>
<td>= (\text{Hb} \times 10) (\text{RBC}(10^6) \mu\text{L})</td>
<td>29</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (MCHC) (g/dL)</td>
<td>= (\frac{\text{Hb} \times 100}{\text{Hct}})</td>
<td>34</td>
</tr>
<tr>
<td>Mean cell diameter (MCD) (μm)</td>
<td>= \text{Mean diameter of 500 cells in smear}</td>
<td>7.5</td>
</tr>
</tbody>
</table>

\(^a\)Cells with MCVs > 95 fl are called macrocytes; cells with MCVs < 80 fl are called microcytes; cells with MCHs < 25 g/dL are called hypochromic.

**HEMOGLOBIN IN THE FETUS**

The blood of the human fetus normally contains fetal hemoglobin (hemoglobin F). Its structure is similar to that of hemoglobin A except that the β chains are replaced by γ chains; that is, hemoglobin F is \(α_2γ_2\). The γ chains also contain 146 amino acid residues but have 37 that differ from those in the β chain. Fetal hemoglobin is normally replaced by adult hemoglobin soon after birth (Figure 32–8). In certain individuals, it fails to disappear and persists throughout life. In the body, its \(O_2\) content at a given \(P_{\text{O}_2}\) is greater than that of adult hemoglobin because it binds 2,3-BPG less avidly. Hemoglobin F is critical to facilitate movement of \(O_2\) from the maternal to the fetal circulation, particularly at later stages of gestation where oxygen demand increases (see Chapter 34). In young embryos there are, in addition, ζ and ε chains, forming Gower I.
hemoglobin (ζ₂ε₂) and Gower 2 hemoglobin (α₂ε₂). There are two copies of the α globin gene on human chromosome 16. In addition, there are five globin genes in tandem on chromosome 11 that encode β, γ, and δ globin chains and the two chains normally found only during fetal life. Switching from one form of hemoglobin to another during development seems to be regulated largely by oxygen availability, with relative hypoxia favoring the production of hemoglobin F both via direct effects on globin gene expression, as well as up-regulated production of erythropoietin.

SYNTHESIS OF HEMOGLOBIN

The average normal hemoglobin content of blood is 16 g/dL in men and 14 g/dL in women, all of it in red cells. In the body of a 70-kg man, there are about 900 g of hemoglobin, and 0.3 g of hemoglobin is destroyed and 0.3 g synthesized every hour (Figure 32–5). The heme portion of the hemoglobin molecule is synthesized from glycine and succinyl-CoA (see Clinical Box 32–2).

CATABOLISM OF HEMOGLOBIN

When old red blood cells are destroyed by tissue macrophages, the globin portion of the hemoglobin molecule is split off, and the heme is converted to biliverdin. The enzyme involved is a subtype of heme oxygenase (see Figure 29–4), and CO is formed in the process. CO may be an intercellular messenger, like NO (see Chapters 2 and 3).

FIGURE 32–5 Red cell formation and destruction. RBC, red blood cells.

FIGURE 32–6 Diagrammatic representation of a molecule of hemoglobin A, showing the four subunits. There are two α and two β polypeptide chains, each containing a heme moiety. These moieties are represented by the disks. (Reproduced with permission from Harper HA et al: Physiologische Chemie. Springer, 1975.)
Abnormalities of Hemoglobin Production

There are two major types of inherited disorders of hemoglobin in humans: the hemoglobinopathies, in which abnormal globin polypeptide chains are produced, and the thalassemias and related disorders, in which the chains are normal in structure but produced in decreased amounts or absent because of defects in the regulatory portion of the globin genes. Mutant genes that cause the production of abnormal hemoglobins are widespread, and over 1000 abnormal hemoglobins have been described in humans. In one of the most common examples, hemoglobin S, the α chains are normal but the β chains have a single substitution of a valine residue for one glutamic acid, leading to sickle cell anemia (Table 32–3). When an abnormal gene inherited from one parent dictates formation of an abnormal hemoglobin (ie, when the individual is heterozygous), half the circulating hemoglobin is abnormal and half is normal. When identical abnormal genes are inherited from both parents, the individual is homozygous and all the hemoglobin is abnormal. It is theoretically possible to inherit two different abnormal hemoglobins, one from the father and one from the mother. Studies of the inheritance and geographic distribution of abnormal hemoglobins have made it possible in some cases to decide where the mutant gene originated and approximately how long ago the mutation occurred. In general, harmful mutations tend to die out, but mutant genes that confer traits with survival value persist and spread in the population. Many of the abnormal hemoglobins are harmless; however, some have abnormal O2 equilibriums, while others cause anemia. For example, hemoglobin S polymerizes at low O2 tensions, and this causes the red cells to become sickle-shaped, hemolyze, and form aggregates that block blood vessels. The sickle cell gene is an example of a gene that has persisted and spread in the population due to its beneficial effect when present in heterozygous form. It originated in Africa, and confers resistance to one type of malaria. In some parts of Africa, 40% of the population is heterozygous for hemoglobin S. There is a corresponding prevalence of 10% among African Americans in the United States. Hemoglobin F decreases the polymerization of deoxygenated hemoglobin S, and hydroxyurea stimulates production of hemoglobin F in children and adults. It has proved to be a very valuable agent for the treatment of sickle cell disease. In patients with severe sickle cell disease, bone marrow transplantation has also been shown to have some benefit.

In humans, most of the biliverdin is converted to bilirubin (Figure 32–9) and excreted in the bile (see Chapter 29). The iron from the heme is reused for hemoglobin synthesis. Exposure of the skin to white light converts bilirubin to biliverdin in humans, which has a shorter half-life than bilirubin. Photo-

FIGURE 32–8 Development of human hemoglobin chains.

therapy (exposure to light) is of value in treating infants with jaundice due to hemolysis. Iron is essential for hemoglobin synthesis; if blood is lost from the body and the iron deficiency is not corrected, iron deficiency anemia results. The metabolism of iron is discussed in Chapter 27.

BLOOD TYPES

The membranes of human red cells contain a variety of blood group antigens, which are also called agglutinogens. The most important and best known of these are the A and B antigens, but there are many more.

THE ABO SYSTEM

The A and B antigens are inherited as mendelian dominants, and individuals are divided into four major blood types on this basis. Type A individuals have the A antigen, type B have the B, type AB have both, and type O have neither. The A and B antigens are complex oligosaccharides that differ in their terminal sugar. An H gene codes for a fucose transferase that adds a terminal fucose, forming the H antigen that is usually present in individuals of all blood types (Figure 32–10). Individuals who are type A also express a second transferase that catalyzes placement of a terminal N-acetylgalactosamine on the H antigen, whereas individuals who are type B express a transferase that places a terminal galactose. Individuals who are type AB have both transferases. Individuals who are type O have neither, so the H antigen persists.

Antibodies against red cell agglutinogens are called agglutinins. Antigens very similar to A and B are common in intestinal bacteria and possibly in foods to which newborn individuals are exposed. Therefore, infants rapidly develop antibodies against the antigens not present in their own cells. Thus, type A individuals develop anti-B antibodies, type B individuals develop anti-A antibodies, type O individuals develop both, and type AB individuals develop neither (Table 32–4). When the plasma of a type A individual is mixed with type B red cells, the anti-B antibodies cause the type B red
cells to clump (agglutinate), as shown in Figure 32–11. The other agglutination reactions produced by mismatched plasma and red cells are summarized in Table 32–4. Blood typing is performed by mixing an individual’s red blood cells with antisera containing the various agglutinins on a slide and seeing whether agglutination occurs.

**TRANSFUSION REACTIONS**

Dangerous **hemolytic transfusion reactions** occur when blood is transfused into an individual with an incompatible blood type; that is, an individual who has agglutinins against the red cells in the transfusion. The plasma in the transfusion is usually so diluted in the recipient that it rarely causes agglutination even when the titer of agglutinins against the recipient’s cells is high. However, when the recipient’s plasma has agglutinins against the donor’s red cells, the cells agglutinate and hemolyze. Free hemoglobin is liberated into the plasma. The severity of the resulting transfusion reaction may vary from an asymptomatic minor rise in the plasma bilirubin level to severe jaundice and renal tubular damage leading to anuria and death.

Incompatibilities in the ABO blood group system are summarized in Table 32–4. Persons with type AB blood are “universal recipients” because they have no circulating agglutinins and can be given blood of any type without developing a transfusion reaction due to ABO incompatibility. Type O individuals are “universal donors” because they lack A and B antigens, and type O blood can be given to anyone without producing a transfusion reaction due to ABO incompatibility. This does not mean, however, that blood should ever be transfused without being cross-matched except in the most extreme emergencies, since the possibility of reactions or sensitization due to incompatibilities in systems other than ABO systems always
exists. In cross-matching, donor red cells are mixed with recipient plasma on a slide and checked for agglutination. It is advisable to check the action of the donor’s plasma on the recipient cells in addition, even though, as noted above, this is rarely a source of trouble.

A procedure that has recently become popular is to withdraw the patient’s own blood in advance of elective surgery and then infuse this blood back (autologous transfusion) if a transfusion is needed during the surgery. With iron treatment, 1000 to 1500 mL can be withdrawn over a 3-wk period. The popularity of banking one’s own blood is due primarily to fear of transmission of infectious diseases by heterologous transfusions, but of course another advantage is elimination of the risk of transfusion reactions.

**INHERITANCE OF A & B ANTIGENS**

The A and B antigens are inherited as mendelian allelomorphs, A and B being dominants. For example, an individual with type B blood may have inherited a B antigen from each parent or a B antigen from one parent and an O from the other; thus, an individual whose phenotype is B may have the genotype BB (homozygous) or BO (heterozygous).

When the blood types of the parents are known, the possible genotypes of their children can be stated. When both parents are type B, they could have children with genotype BB (B antigen from both parents), BO (B antigen from one parent, O from the other heterozygous parent), or OO (O antigen from both parents, both being heterozygous). When the blood types of a mother and her child are known, typing can prove that a man cannot be the father, although it cannot prove that he is the father. The predictive value is increased if the blood typing of the parties concerned includes identification of antigens other than the ABO agglutinogens. With the use of DNA fingerprinting (see Chapter 1), the exclusion rate for paternity rises to close to 100%.

**TABLE 32–4 Summary of ABO system.**

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Agglutinins in Plasma</th>
<th>Frequency in United States (%)</th>
<th>Plasma Agglutinates Red Cells of Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Anti-A, anti-B</td>
<td>45</td>
<td>A, B, AB</td>
</tr>
<tr>
<td>A</td>
<td>Anti-B</td>
<td>41</td>
<td>B, AB</td>
</tr>
<tr>
<td>B</td>
<td>Anti-A</td>
<td>10</td>
<td>A, AB</td>
</tr>
<tr>
<td>AB</td>
<td>None</td>
<td>4</td>
<td>None</td>
</tr>
</tbody>
</table>
OTHER AGGLUTINOGENS

In addition to the ABO system of antigens in human red cells, there are systems such as the Rh, MNSs, Lutheran, Kell, Kidd, and many others. There are over 500 billion possible known blood group phenotypes, and because undiscovered antigens undoubtedly exist, it has been calculated that the number of phenotypes is actually in the trillions.

The number of blood groups in animals is as large as it is in humans. An interesting question is why this degree of polymorphism developed and has persisted through evolution. Certain diseases are more common in individuals with one blood type or another, but the differences are not great. One, the Duffy antigen, is a chemokine receptor. Many of the others seem to be cell recognition molecules, but the significance of a recognition code of this complexity is unknown.

THE RH GROUP

Aside from the antigens of the ABO system, those of the Rh system are of the greatest clinical importance. The Rh factor, named for the rhesus monkey because it was first studied using the blood of this animal, is a system composed primarily of the C, D, and E antigens, although it actually contains many more. Unlike the ABO antigens, the system has not been detected in tissues other than red cells. D is by far the most antigenic component, and the term Rh-positive as it is generally used means that the individual has agglutinogen D. The D protein is not glycosylated, and its function is unknown. The Rh-negative individual has no D antigen and forms the anti-D agglutinin when injected with D-positive cells. The Rh typing serum used in routine blood typing is anti-D serum. Eighty-five percent of Caucasians are D-positive and 15% are D-negative; over 99% of Asians are D-positive. Unlike the antibodies of the ABO system, anti-D antibodies do not develop without exposure of a D-negative individual to D-positive red cells by transfusion or entrance of fetal blood into the maternal circulation. However, D-negative individuals who have received a transfusion of D-positive blood (even years previously) can have appreciable anti-D titers and thus may develop transfusion reactions when transfused again with D-positive blood.

HEMOLYTIC DISEASE OF THE NEWBORN

Another complication due to Rh incompatibility arises when an Rh-negative mother carries an Rh-positive fetus. Small amounts of fetal blood leak into the maternal circulation at the time of delivery, and some mothers develop significant titers of anti-Rh agglutinins during the postpartum period. During the next pregnancy, the mother’s agglutinins cross the placenta to the fetus. In addition, there are some cases of fetal–maternal hemorrhage during pregnancy, and sensitization can occur during pregnancy. In any case, when anti-Rh agglutinins cross the placenta to an Rh-positive fetus, they can cause hemolysis and various forms of hemolytic disease of the newborn (erythroblastosis fetalis). If hemolysis in the fetus is severe, the infant may die in utero or may develop anemia, severe jaundice, and edema (hydrops fetalis). Kernicterus, a neurologic syndrome in which unconjugated bilirubin is deposited in the basal ganglia, may also develop, especially if birth is complicated by a period of hypoxia. Bilirubin rarely penetrates the brain in adults, but it does in infants with erythroblastosis, possibly in part because the blood–brain barrier is more permeable in infancy. However, the main reasons that the concentration of unconjugated bilirubin is very high in this condition are that production is increased and the bilirubin-conjugating system is not yet mature.

About 50% of Rh-negative individuals are sensitized (develop an anti-Rh titer) by transfusion of Rh-positive blood. Because sensitization of Rh-negative mothers by carrying an Rh-positive fetus generally occurs at birth, the first child is usually normal. However, hemolytic disease occurs in about 17% of the Rh-positive fetuses born to Rh-negative mothers who have previously been pregnant one or more times with Rh-positive fetuses. Fortunately, it is usually possible to prevent sensitization from occurring the first time by administering a single dose of anti-Rh antibodies in the form of Rh immune globulin during the postpartum period. Such passive immunization does not harm the mother and has been demonstrated to prevent active antibody formation by the mother. In obstetric clinics, the institution of such treatment on a routine basis to unsensitized Rh-negative women who have delivered an Rh-positive baby has reduced the overall incidence of hemolytic disease by more than 90%. In addition, fetal Rh typing with material obtained by amniocentesis or chorionic villus sampling is now possible, and treatment with a small dose of Rh immune serum will prevent sensitization during pregnancy.

PLASMA

The fluid portion of the blood, the plasma, is a remarkable solution containing an immense number of ions, inorganic molecules, and organic molecules that are in transit to various parts of the body or aid in the transport of other substances. Normal plasma volume is about 5% of body weight, or roughly 3500 mL in a 70-kg man. Plasma clots on standing, remaining fluid only if an anticoagulant is added. If whole blood is allowed to clot and the clot is removed, the remaining fluid is called serum. Serum has essentially the same composition as plasma, except that its fibrinogen and clotting factors II, V, and VIII (Table 32–5) have been removed and it has a higher serotonin content because of the breakdown of platelets during clotting.

PLASMA PROTEINS

The plasma proteins consist of albumin, globulin, and fibrinogen fractions. Most capillary walls are relatively impermeable to the proteins in plasma, and the proteins therefore exert
TABLE 32–5 System for naming blood-clotting factors.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
</tr>
<tr>
<td>III</td>
<td>Thromboplastin</td>
</tr>
<tr>
<td>IV</td>
<td>Calcium</td>
</tr>
<tr>
<td>V</td>
<td>Proaccelerin, labile factor, accelerator globulin</td>
</tr>
<tr>
<td>VII</td>
<td>Proconvertin, SPCA, stable factor</td>
</tr>
<tr>
<td>VIII</td>
<td>Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG)</td>
</tr>
<tr>
<td>IX</td>
<td>Plasma thromboplastin component (PTC), Christmas factor, antihemophilic factor B</td>
</tr>
<tr>
<td>X</td>
<td>Stuart–Prower factor</td>
</tr>
<tr>
<td>XI</td>
<td>Plasma thromboplastin antecedent (PTA), antihemophilic factor C</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman factor, glass factor</td>
</tr>
<tr>
<td>XIII</td>
<td>Fibrin-stabilizing factor, Laki–Lorand factor</td>
</tr>
<tr>
<td>HMW-K</td>
<td>High-molecular-weight kininogen, Fitzgerald factor</td>
</tr>
<tr>
<td>Pre-Ka</td>
<td>Prekallikrein, Fletcher factor</td>
</tr>
<tr>
<td>Ka</td>
<td>Kallikrein</td>
</tr>
<tr>
<td>PL</td>
<td>Platelet phospholipid</td>
</tr>
</tbody>
</table>

*Factor VI is not a separate entity and has been dropped.

an osmotic force of about 25 mm Hg across the capillary wall (oncotic pressure; see Chapter 1) that pulls water into the blood. The plasma proteins are also responsible for 15% of the buffering capacity of the blood (see Chapter 39) because of the weak ionization of their substituent COOH and NH2 groups. At the normal plasma pH of 7.40, the proteins are mostly in the anionic form (see Chapter 1). Plasma proteins may have specific functions (eg, antibodies and the proteins concerned with blood clotting), whereas others function as carriers for various hormones, other solutes, and drugs.

**ORIGIN OF PLASMA PROTEINS**

Circulating antibodies are manufactured by lymphocytes. Most of the other plasma proteins are synthesized in the liver. These proteins and their principal functions are listed in Table 32–6.

Data on the turnover of albumin show that its synthesis plays an important role in the maintenance of normal levels. In normal adult humans, the plasma albumin level is 3.5 to 5.0 g/dL, and the total exchangeable albumin pool is 4.0 to 5.0 g/kg body weight; 38–45% of this albumin is intravascular, and much of the rest of it is in the skin. Between 6% and 10% of the exchangeable pool is degraded per day, and the degraded albumin is replaced by hepatic synthesis of 200 to 400 mg/kg/d. The albumin is probably transported to the extravascular areas by vesicular transport across the walls of the capillaries (see Chapter 2). Albumin synthesis is carefully regulated. It is decreased during fasting and increased in conditions such as nephrosis in which there is excessive albumin loss.

**HYPOPROTEINEMIA**

Plasma protein levels are maintained during starvation until body protein stores are markedly depleted. However, in prolonged starvation and in malabsorption syndromes due to intestinal diseases, plasma protein levels are low (hypoproteinemia). They are also low in liver disease, because hepatic protein synthesis is depressed, and in nephrosis, because large amounts of albumin are lost in the urine. Because of the decrease in the plasma oncotic pressure, edema tends to develop. Rarely, there is congenital absence of one or another plasma protein. An example of congenital protein deficiency is the congenital form of afibrinogenemia, characterized by defective blood clotting.

**RESPONSE TO INJURY**

When a small blood vessel is transected or damaged, the injury initiates a series of events (Figure 32–12) that lead to the formation of a clot. This seals off the damaged region and prevents further blood loss. The initial event is constriction of the vessel and formation of a temporary hemostatic plug of platelets that is triggered when platelets bind to collagen and aggregate. This is followed by conversion of the plug into the definitive clot. The constriction of an injured arteriole or small artery may be so marked that its lumen is obliterated, at least temporarily. The vasoconstriction is due to serotonin and other vasoconstrictors liberated from platelets that adhere to the walls of the damaged vessels.

**THE CLOTTING MECHANISM**

The loose aggregation of platelets in the temporary plug is bound together and converted into the definitive clot by fibrin. Fibrin formation involves a cascade of enzymatic reactions and a series of numbered clotting factors (Table 32–5). The fundamental reaction is conversion of the soluble plasma protein fibrinogen to insoluble fibrin (Figure 32–13). The process
involves the release of two pairs of polypeptides from each fibrinogen molecule. The remaining portion, fibrin monomer, then polymerizes with other monomer molecules to form fibrin. The fibrin is initially a loose mesh of interlacing strands. It is converted by the formation of covalent cross-linkages to a dense, tight aggregate (stabilization). This latter reaction is catalyzed by activated factor XIII and requires Ca\(^{2+}\).

The conversion of fibrinogen to fibrin is catalyzed by thrombin. Thrombin is a serine protease that is formed from its circulating precursor, prothrombin, by the action of activated factor X. It has additional actions, including activation of platelets, endothelial cells, and leukocytes via so-called protease activated receptors, which are G protein-coupled.

Factor X can be activated by either of two systems, known as intrinsic and extrinsic (Figure 32–13). The initial reaction in the intrinsic system is conversion of inactive factor XII to active factor XII (XIIa). This activation, which is catalyzed by high-molecular-weight kininogen and kallikrein (see Chapter 33), can be brought about in vitro by exposing the blood to glass, or in vivo by collagen fibers underlying the endothelium. Active factor XII then activates factor XI, and active factor XI activates factor IX. Activated factor IX forms a complex with

<table>
<thead>
<tr>
<th>Name</th>
<th>Principal Function</th>
<th>Binding Characteristics</th>
<th>Serum or Plasma Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Binding and carrier protein; osmotic regulator</td>
<td>Hormones, amino acids, steroids, vitamins, fatty acids</td>
<td>4500–5000 mg/dL</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>Uncertain; may have a role in inflammation</td>
<td>Trace; rises in inflammation</td>
<td></td>
</tr>
<tr>
<td>α1-Antiprotease</td>
<td>Trypsin and general protease inhibitor</td>
<td>Proteases in serum and tissue secretions</td>
<td>1.3–1.4 mg/dL</td>
</tr>
<tr>
<td>α-Fetoprotein</td>
<td>Osmotic regulation; binding and carrier protein(^a)</td>
<td>Hormones, amino acids</td>
<td>Found normally in fetal blood</td>
</tr>
<tr>
<td>α2-Macroglobulin</td>
<td>Inhibitor of serum endoproteases</td>
<td>Proteases</td>
<td>150–420 mg/dL</td>
</tr>
<tr>
<td>Antithrombin-III</td>
<td>Protease inhibitor of intrinsic coagulation system</td>
<td>1:1 binding to proteases</td>
<td>17–30 mg/dL</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>Transport of copper</td>
<td>Six atoms copper/mol</td>
<td>15–60 mg/dL</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Uncertain; has role in tissue inflammation</td>
<td>Complement C1q</td>
<td>&lt; 1 mg/dL; rises in inflammation</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Precursor to fibrin in hemostasis</td>
<td></td>
<td>200–450 mg/dL</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>Binding, transport of cell-free hemoglobin</td>
<td>Hemoglobin 1:1 binding</td>
<td>40–180 mg/dL</td>
</tr>
<tr>
<td>Hemopexin</td>
<td>Binds to porphyrins, particularly heme for heme recycling</td>
<td>1:1 with heme</td>
<td>50–100 mg/dL</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Transport of iron</td>
<td>Two atoms iron/mol</td>
<td>3.0–6.5 mg/dL</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>Assembly of lipoprotein particles</td>
<td>Lipid carrier</td>
<td></td>
</tr>
<tr>
<td>Angiotensinogen</td>
<td>Precursor to pressor peptide angiotensin I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins, coagulation factors II, VII, IX, X</td>
<td>Blood clotting</td>
<td></td>
<td>20 mg/dL</td>
</tr>
<tr>
<td>Antithrombin C, protein C</td>
<td>Inhibition of blood clotting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulinlike growth factor I</td>
<td>Mediator of anabolic effects of growth hormone</td>
<td>IGF-I receptor</td>
<td></td>
</tr>
<tr>
<td>Steroid hormone-binding globulin</td>
<td>Carrier protein for steroids in bloodstream</td>
<td>Steroid hormones</td>
<td>3.3 mg/dL</td>
</tr>
<tr>
<td>Thyroxine-binding globulin</td>
<td>Carrier protein for thyroid hormone in bloodstream</td>
<td>Thyroid hormones</td>
<td>1.5 mg/dL</td>
</tr>
<tr>
<td>Transthyretin (thyroid-binding prealbumin)</td>
<td>Carrier protein for thyroid hormone in bloodstream</td>
<td>Thyroid hormones</td>
<td>25 mg/dL</td>
</tr>
</tbody>
</table>

\(^a\)The function of α-fetoprotein is uncertain, but because of its structural homology to albumin it is often assigned these functions.
active factor VIII, which is activated when it is separated from von Willebrand factor. The complex of IXa and VIIIa activate factor X. Phospholipids from aggregated platelets (PL) and Ca\(^{2+}\) are necessary for full activation of factor X. The extrinsic system is triggered by the release of tissue thromboplastin, a protein–phospholipid mixture that activates factor VII. Tissue thromboplastin and factor VII activate factors IX and X. In the presence of PL, Ca\(^{2+}\), and factor V, activated factor X catalyzes the conversion of prothrombin to thrombin. The extrinsic pathway is inhibited by a tissue factor pathway inhibitor that forms a quaternary structure with tissue thromboplastin (TPL), factor VIIa, and factor Xa.

**ANTICLOTTING MECHANISMS**

The tendency of blood to clot is balanced in vivo by reactions that prevent clotting inside the blood vessels, break down any clots that do form, or both. These reactions include the interaction between the platelet-aggregating effect of thromboxane A\(_2\) and the antiaggregating effect of prostacyclin, which causes clots to form at the site when a blood vessel is injured but keeps the vessel lumen free of clot (see Chapter 33 and Clinical Box 32–3).

**Antithrombin III** is a circulating protease inhibitor that binds to serine proteases in the coagulation system, blocking their activity as clotting factors. This binding is facilitated by heparin, a naturally occurring anticoagulant that is a mixture of sulfated polysaccharides with molecular weights averaging 15,000–18,000. The clotting factors that are inhibited are the active forms of factors IX, X, and XII.

The endothelium of the blood vessels also plays an active role in preventing the extension of clots. All endothelial cells except those in the cerebral microcirculation produce thrombomodulin, a thrombin-binding protein, on their surfaces. In circulating blood, thrombin is a procoagulant that activates factors V and VIII, but when it binds to thrombomodulin, it becomes an anticoagulant in that the thrombomodulin–thrombin complex activates protein C (Figure 32–14). Activated protein C (APC), along with its cofactor protein S, inactivates factors V and VIII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin.

**Plasmin (fibrinolysin)** is the active component of the plasminogen (fibrinolytic) system (Figure 32–14). This enzyme lyases fibrin and fibrinogen, with the production of fibrinogen degradation products (FDP) that inhibit thrombin. Plasmin is formed from its inactive precursor, plasminogen, by the action of thrombin and tissue-type plasminogen activator (t-PA). It is also activated by urokinase-type plasminogen activator (u-PA). If the t-PA gene or the u-PA gene is knocked out in mice, some fibrin deposition occurs and clot lysis is slowed. However, when both are knocked out, spontaneous fibrin deposition is extensive.

Human plasminogen consists of a 560-amino-acid heavy chain and a 241-amino-acid light chain. The heavy chain, with glutamate at its amino terminal, is folded into five loop structures, each held together by three disulfide bonds (Figure 32–15). These loops are called kringle because of their...
Abnormalities of Hemostasis

In addition to clotting abnormalities due to platelet disorders, hemorrhagic diseases can be produced by selective deficiencies of most of the clotting factors (Table 32–7). Hemophilia A, which is caused by factor VIII deficiency, is relatively common. The disease has been treated with factor VIII-rich preparations made from plasma, or, more recently, factor VIII produced by recombinant DNA techniques. von Willebrand factor deficiency likewise causes a bleeding disorder (von Willebrand disease) by reducing platelet adhesion and by lowering plasma factor VIII. The condition can be congenital or acquired. The large von Willebrand molecule is subject to cleavage and resulting inactivation by the plasma metalloprotease ADAM 13 in vascular areas where fluid shear stress is elevated. Finally, when absorption of vitamin K is depressed along with absorption of other fat-soluble vitamins (see Chapter 27), the resulting clotting factor deficiencies may cause the development of a significant bleeding tendency.

Formation of clots inside blood vessels is called thrombosis to distinguish it from the normal extravascular clotting of blood. Thromboses are a major medical problem. They are particularly prone to occur where blood flow is sluggish because the slow flow permits activated clotting factors to accumulate instead of being washed away. They also occur in vessels where the intima is damaged by atherosclerotic plaques, and over areas of damage to the endocardium. They frequently occlude the arterial supply to the organs in which they form, and bits of thrombus (emboli) sometimes break off and travel in the bloodstream to distant sites, damaging other organs. An example is obstruction of the pulmonary artery or its branches by thrombi from the leg veins in the context of septicemia, extensive tissue injury, and other diseases in which fibrin is deposited in the vascular system and many small- and medium-sized vessels are thrombosed. The increased consumption of platelets and coagulation factors causes bleeding to occur at the same time. The cause of the condition appears to be increased generation of thrombin due to increased TPL activity with inadequate tissue factor inhibitory pathway activity.

Disseminated intravascular coagulation is another serious complication of sepsis, extensive tissue injury, and other diseases in which fibrin is deposited in the vascular system and many small- and medium-sized vessels are thrombosed. The increased consumption of platelets and coagulation factors causes bleeding to occur at the same time. The cause of the condition appears to be increased generation of thrombin due to increased TPL activity without adequate tissue factor inhibitory pathway activity.

In infancy. If this condition is diagnosed and treatment is instituted, the coagulation defect disappears. Resistance to activated protein C is another cause of thrombosis, and this condition is common. It is due to a point mutation in the gene for factor V, which prevents activated protein C from inactivating the factor. Mutations in protein S and antithrombin III may also commonly increase the incidence of thrombosis.

Recombinant factor VIII is now produced by recombinant DNA techniques for clinical use in myocardial infarction and stroke. Streptokinase, a bacterial enzyme, is also fibrinolytic and is also used in the treatment of early myocardial infarction (see Chapter 34).
**TABLE 32–7** Examples of diseases due to deficiency of clotting factors.

<table>
<thead>
<tr>
<th>Deficiency of Factor</th>
<th>Clinical Syndrome</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Afibrinogenemia</td>
<td>Depletion during pregnancy with premature separation of placenta; also congenital (rare)</td>
</tr>
<tr>
<td>II</td>
<td>Hypoprothrombinemia (hemorrhagic tendency in liver disease)</td>
<td>Decreased hepatic synthesis, usually secondary to vitamin K deficiency</td>
</tr>
<tr>
<td>V</td>
<td>Parahemophilia</td>
<td>Congenital</td>
</tr>
<tr>
<td>VII</td>
<td>Hypoconvertinemia</td>
<td>Congenital</td>
</tr>
<tr>
<td>VIII</td>
<td>Hemophilia A (classic hemophilia)</td>
<td>Congenital defect due to various abnormalities of the gene on X chromosome that codes for factor VIII; disease is therefore inherited as sex-linked characteristic</td>
</tr>
<tr>
<td>IX</td>
<td>Hemophilia B (Christmas disease)</td>
<td>Congenital</td>
</tr>
<tr>
<td>X</td>
<td>Stuart–Prower factor deficiency</td>
<td>Congenital</td>
</tr>
<tr>
<td>XI</td>
<td>PTA deficiency</td>
<td>Congenital</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman trait</td>
<td>Congenital</td>
</tr>
</tbody>
</table>

**ANTICOAGULANTS**

As noted above, heparin is a naturally occurring anticoagulant that facilitates the action of antithrombin III. Low-molecular-weight fragments with an average molecular weight of 5000 have been produced from unfractionated heparin, and these low-molecular-weight heparins are seeing increased clinical use because they have a longer half-life and produce a more predictable anticoagulant response than unfractionated heparin. The highly basic protein protamine forms an irreversible complex with heparin and is used clinically to neutralize heparin.

In vivo, a plasma Ca\(^{2+}\) level low enough to interfere with blood clotting is incompatible with life, but clotting can be prevented in vitro if Ca\(^{2+}\) is removed from the blood by the addition of substances such as oxalates, which form insoluble salts with Ca\(^{2+}\), or chelating agents, which bind Ca\(^{2+}\). Coumarin derivatives such as dicumarol and warfarin are also effective anticoagulants. They inhibit the action of vitamin K, which is a necessary cofactor for the enzyme that catalyzes the conversion of glutamic acid residues to \(\gamma\)-carboxyglutamic acid residues. Six of the proteins involved in clotting require conversion of a number of glutamic acid residues to \(\gamma\)-carboxyglutamic acid residues before being released into the circulation, and hence all six are vitamin K-dependent. These proteins are factors II (prothrombin), VII, IX, and X, protein C, and protein S (see above).

**LYMPH**

Lymph is tissue fluid that enters the lymphatic vessels. It drains into the venous blood via the thoracic and right lymphatic ducts. It contains clotting factors and clots on standing in vitro. In most locations, it also contains proteins that traverse capillary walls and return to the blood via the lymph. Its protein content is generally lower than that of plasma, which contains about 7 g/dL, but lymph protein content varies with the region from which the lymph drains (Table 32–8). Water-insoluble fats are absorbed from the intestine into the lymphatics, and the lymph in the thoracic duct after a meal is milky because of its high fat content (see Chapter 27). Lymphocytes enter the circulation principally through the lymphatics, and there are appreciable numbers of lymphocytes in thoracic duct lymph.

**STRUCTURAL FEATURES OF THE CIRCULATION**

Here, we will first describe the two major cell types that make up the blood vessels and then how they are arranged into the various vessel types that subserve the needs of the circulation.

**ENDOTHELIUM**

Located between the circulating blood and the media and adventitia of the blood vessels, the endothelial cells constitute a large and important organ. They respond to flow changes, stretch, a variety of circulating substances, and inflammatory mediators. They secrete growth regulators and vasoactive substances (see below and Chapter 33).

**TABLE 32–8** Probable approximate protein content of lymph in humans.

<table>
<thead>
<tr>
<th>Source of Lymph</th>
<th>Protein Content (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroid plexus</td>
<td>0</td>
</tr>
<tr>
<td>Ciliary body</td>
<td>0</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>4.1</td>
</tr>
<tr>
<td>Heart</td>
<td>4.4</td>
</tr>
<tr>
<td>Liver</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Data largely from JN Diana.
VASCULAR SMOOTH MUSCLE

The smooth muscle in blood vessel walls has been one of the most-studied forms of visceral smooth muscle because of its importance in the regulation of blood pressure and hypertension. The membranes of the muscle cells contain various types of K⁺, Ca²⁺, and Cl⁻ channels. Contraction is produced primarily by the myosin light chain mechanism described in Chapter 5. However, vascular smooth muscle also undergoes prolonged contractions that determine vascular tone. These may be due in part to the latch-bridge mechanism (see Chapter 5), but other factors also play a role. Some of the molecular mechanisms that appear to be involved in contraction and relaxation are shown in Figure 32–16.

Vascular smooth muscle cells provide an interesting example of the way high and low cytosolic Ca²⁺ can have different and even opposite effects (see Chapter 2). In these cells, influx of Ca²⁺ via voltage-gated Ca²⁺ channels produces a diffuse increase in cytosolic Ca²⁺ that initiates contraction. However, the Ca²⁺ influx also initiates Ca²⁺ release from the sarcoplasmic reticulum via ryanodine receptors (see Chapter 5), and the high local Ca²⁺ concentration produced by these Ca²⁺ sparks increases the activity of Ca²⁺-activated K⁺ channels in the cell membrane. These are also known as big K or BK channels because K⁺ flows through them at a high rate. The increased K⁺ efflux increases the membrane potential, shutting off voltage-gated Ca²⁺ channels and producing relaxation. The site of action of the Ca²⁺ sparks is the β₁ subunit of the BK channel, and mice in which this subunit is knocked out develop increased vascular tone and blood pressure. Obviously, therefore, the sensitivity of the β₁ subunit to Ca²⁺ sparks plays an important role in the control of vascular tone.

ARTERIES & ARTERIOLES

The characteristics of the various types of blood vessels are listed in Table 32–9. The walls of all arteries are made up of an outer layer of connective tissue, the adventitia; a middle layer of smooth muscle, the media; and an inner layer, the intima, made up of the endothelium and underlying connective tissue (Figure 32–17). The walls of the aorta and other arteries of large diameter contain a relatively large amount of elastic tissue, primarily located in the inner and external elastic laminas. They are stretched during systole and recoil on the blood during diastole. The walls of the arterioles contain less elastic tissue but much more smooth muscle. The muscle is innervated by noradrenergic nerve fibers, which function as constrictors, and in some instances by cholinergic fibers, which dilate the...
vessels. The arterioles are the major site of the resistance to blood flow, and small changes in their caliber cause large changes in the total peripheral resistance.

**CAPILLARIES**

The arterioles divide into smaller muscle-walled vessels, sometimes called metarterioles, and these in turn feed into capillaries (Figure 32–18). The openings of the capillaries are guarded by muscular precapillary sphincters. The diameters of the various vessels are determined by the state of the sphincters. When the sphincters are not dilated, the diameter of the capillaries is just sufficient to permit red blood cells to squeeze through in “single file.” As they pass through the capillaries, the red cells become thimble- or parachute-shaped, with the flow pushing the center ahead of the edges. This configuration appears to be due simply to the pressure in the center of the vessel whether or not the edges of the red blood cell are in contact with the capillary walls.

The total area of all the capillary walls in the body exceeds 6300 m² in the adult. The walls, which are about 1 μm thick, are made up of a single layer of endothelial cells. The structure of the walls varies from organ to organ. The junctions between the endothelial cells (Figure 32–19) permit the passage of molecules up to 10 nm in diameter. It also appears that plasma and its dissolved proteins are taken up by endocytosis, transported across the endothelial cells, and discharged by exocytosis (vesicular transport; see Chapter 2). However, this process can account for only a small portion of the transport across the endothelium. In the brain, the capillaries resemble the capillaries in muscle, but the junctions between endothelial cells are tighter, and transport across them is largely limited to small molecules. In most endocrine glands, the intestinal villi, and parts of the kidneys, the cytoplasm of the endothelial cells is attenuated to form gaps called fenestrations. These fenestrations are 20 to 100 nm in diameter and may permit the passage of larger molecules, although they appear to be closed by a thin membrane. An exception to this, however, is found in the liver, where the sinusoidal capillaries are extremely porous, the endothelium is discontinuous, and gaps occur between endothelial cells that are not closed by membranes (see Figure 29–2). Some of the gaps are 600 nm in diameter, and others may be as large as 5 μm.
as 3000 nm. They therefore permit the passage of large molecules, including plasma proteins, which is important for hepatic function (see Chapter 29). The permeabilities of capillaries in various parts of the body, expressed in terms of their hydraulic conductivity, are summarized in Table 32–10.

Capillaries and postcapillary venules have pericytes around their endothelial cells (Figure 32–19). These cells have long processes that wrap around the vessels. They are contractile and release a wide variety of vasoactive agents. They also synthesize and release constituents of the basement membrane and extracellular matrix. One of their physiologic functions appears to be regulation of flow through the junctions between endothelial cells, particularly in the presence of inflammation. They are closely related to the mesangial cells in the renal glomeruli (see Chapter 38).

LYMPHATICS

The lymphatics serve to collect plasma and its constituents that have exuded from the capillaries into the interstitial space. They drain from the body tissues via a system of vessels that coalesce and eventually enter the right and left subclavian veins at their junctions with the respective internal jugular veins. The lymph vessels contain valves and regularly traverse lymph nodes along their course. The ultrastructure of the small lymph vessels differs from that of the capillaries in several details: No fenestrations are visible in the lymphatic endothelium; very little if any basal lamina is present under the endothelium; and the junctions between endothelial cells are open, with no tight intercellular connections.

ARTERIOVENOUS ANASTOMOSSES

In the fingers, palms, and ear lobes, short channels connect arterioles to venules, bypassing the capillaries. These arteriovenous (A-V) anastomoses, or shunts, have thick, muscular walls and are abundantly innervated, presumably by vasoconstrictor nerve fibers.

VENULES & VEINS

The walls of the venules are only slightly thicker than those of the capillaries. The walls of the veins are also thin and easily distended. They contain relatively little smooth muscle, but considerable venoconstriction is produced by activity in the noradrenergic nerves to the veins and by circulating vasoconstrictors such as endothelins. Variations in venous tone are important in circulatory adjustments.

The intima of the limb veins is folded at intervals to form venous valves that prevent retrograde flow. The way these valves function was first demonstrated by William Harvey in the 17th century. No valves are present in the very small veins, the great veins, or the veins from the brain and viscera.
ANGIOGENESIS

When tissues grow, blood vessels must proliferate if the tissue is to maintain a normal blood supply. Therefore, angiogenesis, the formation of new blood vessels, is important during fetal life and growth to adulthood. It is also important in adulthood for processes such as wound healing, formation of the corpus luteum after ovulation, and formation of new endometrium after menstruation. Abnormally, it is important in tumor growth; if tumors do not develop a blood supply, they do not grow.

During embryonic development, a network of leaky capillaries is formed in tissues from angioblasts: this process is sometimes called vasculogenesis. Vessels then branch off from nearby vessels, hook up with the capillaries, and provide them with smooth muscle, which brings about their maturation. Angiogenesis in adults is presumably similar, but consists of new vessel formation by branching from pre-existing vessels rather than from angioblasts.

Many factors are involved in angiogenesis. A key compound is the protein growth factor vascular endothelial growth factor (VEGF). This factor exists in multiple isoforms, and there are three VEGF receptors that are tyrosine kinases, which also cooperate with non kinase co-receptors known as neuropilins in some cell types. VEGF appears to be primarily responsible for vasculogenesis, whereas the budding of vessels that connect to the immature capillary network is regulated by other as yet unidentified factors. Some of the VEGF isoforms and receptors may play a more prominent role in the formation of lymphatic vessels (lymphangiogenesis) than that of blood vessels.

The actions of VEGF and related factors have received considerable attention in recent years because of the requirement for angiogenesis in the development of tumors. VEGF antagonists and other angiogenesis inhibitors have now entered clinical practice as adjunctive therapies for many malignancies and are being tested as first line therapies as well.

FLOW, PRESSURE, & RESISTANCE

Physical principles and equations that describe the behavior of perfect fluids in rigid tubes have often been used indiscriminately to explain the behavior of blood in blood vessels. Blood vessels are not rigid tubes, and the blood is not a perfect fluid but a two-phase system of liquid and cells. Therefore, the behavior of the circulation deviates, sometimes markedly, from that predicted by these principles. However, the physical

Flow in any portion of the vascular system is equal to the effective perfusion pressure in that portion divided by the resistance. The effective perfusion pressure is the mean intraluminal pressure at the arterial end minus the mean pressure at the venous end. The units of resistance (pressure divided by flow) are dyne·s/cm². To avoid dealing with such complex units, resistance in the cardiovascular system is sometimes expressed in R units, which are obtained by dividing pressure in mm Hg by flow in mL/s (see also Table 34–1). Thus, for example, when the mean aortic pressure is 90 mm Hg and the left ventricular output is 90 mL/s, the total peripheral resistance is

\[
\frac{90 \text{ mm Hg}}{90 \text{ mL/s}} = 1 \text{ R unit}
\]

METHODS FOR MEASURING BLOOD FLOW

Blood flow can be measured by cannulating a blood vessel, but this has obvious limitations. Various noninvasive devices have therefore been developed to measure flow. Most commonly, blood velocity can be measured with Doppler flow meters. Ultrasonic waves are sent into a vessel diagonally, and the waves reflected from the red and white blood cells are picked up by a downstream sensor. The frequency of the reflected waves is higher by an amount that is proportionate to the rate of flow toward the sensor because of the Doppler effect.

Indirect methods for measuring the blood flow of various organs in humans include adaptations of the Fick and indicator dilution techniques described in Chapter 31. One example is the use of the Kety N₂O method for measuring cerebral blood flow (see Chapter 34). Another is determination of the renal blood flow by measuring the clearance of para-aminohippuric acid (see Chapter 38). A considerable amount of data on blood flow in the extremities has been obtained by plethysmography (Figure 32–20). The forearm, for example, is sealed in a water-tight chamber (plethysmograph). Changes in the volume of the forearm, reflecting changes in the amount of blood and interstitial fluid it contains, displace the water, and this displacement is measured with a volume recorder. When the venous drainage of the forearm is occluded, the rate of increase in the volume of the forearm is a function of the arterial blood flow (venous occlusion plethysmography).

APPLICABILITY OF PHYSICAL PRINCIPLES TO FLOW IN BLOOD VESSELS

Physical principles and equations that describe the behavior of perfect fluids in rigid tubes have often been used indiscriminately to explain the behavior of blood in blood vessels. Blood vessels are not rigid tubes, and the blood is not a perfect fluid but a two-phase system of liquid and cells. Therefore, the behavior of the circulation deviates, sometimes markedly, from that predicted by these principles. However, the physical
principles are of value when used as an aid to understanding what goes on in the body.

**LAMINAR FLOW**

The flow of blood in straight blood vessels, like the flow of liquids in narrow rigid tubes, is normally laminar. Within the blood vessels, an infinitely thin layer of blood in contact with the wall of the vessel does not move. The next layer within the vessel has a low velocity, the next a higher velocity, and so forth, velocity being greatest in the center of the stream (Figure 32–21). Laminar flow occurs at velocities up to a certain critical velocity. At or above this velocity, flow is turbulent. Laminar flow is silent, but turbulent flow creates sounds.

The probability of turbulence is also related to the diameter of the vessel and the viscosity of the blood. This probability can be expressed by the ratio of inertial to viscous forces as follows:

\[
Re = \frac{\rho D V}{\eta}
\]

where Re is the Reynolds number, named for the man who described the relationship; \(\rho\) is the density of the fluid; \(D\) is the diameter of the tube under consideration; \(V\) is the velocity of the flow; and \(\eta\) is the viscosity of the fluid. The higher the value of Re, the greater the probability of turbulence. When \(D\) is in cm, \(V\) is in cm/s\(^{-1}\), and \(\eta\) is in poise; flow is usually not turbulent if \(Re\) is less than 2000. When \(Re\) is more than 3000, turbulence is almost always present. Laminar flow can be disturbed at the branching points of arteries, and the resulting turbulence may increase the likelihood that atherosclerotic plaques will be deposited. Constriction of an artery likewise increases the velocity of blood flow through the constriction, producing turbulence and sound beyond the constriction (Figure 32–22). Examples are bruits heard over arteries constricted by atherosclerotic plaques and the sounds of Korotkoff heard when measuring blood pressure (see below).

In humans, the critical velocity is sometimes exceeded in the ascending aorta at the peak of systolic ejection, but it is usually exceeded only when an artery is constricted. Turbulence occurs more frequently in anemia because the viscosity of the blood is lower. This may be the explanation of the systolic murmurs that are common in anemia.

**SHEAR STRESS & GENE ACTIVATION**

Flowing blood creates a force on the endothelium that is parallel to the long axis of the vessel. This shear stress (\(\gamma\)) is proportionate to viscosity (\(\eta\)) times the shear rate (dy/dr), which...
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is the rate at which the axial velocity increases from the vessel wall toward the lumen.

\[ \gamma = \eta \left( \frac{dy}{dr} \right) \]

Change in shear stress and other physical variables, such as cyclic strain and stretch, produce marked changes in the expression of genes by endothelial cells. The genes that are activated include those that produce growth factors, integrins, and related molecules (Table 32–11).

### AVERAGE VELOCITY

When considering flow in a system of tubes, it is important to distinguish between velocity, which is displacement per unit time (eg, cm/s), and flow, which is volume per unit time (eg, cm³/s). Velocity (V) is proportional to flow (Q) divided by the area of the conduit (A):

\[ \dot{V} = \frac{Q}{A} \]

Therefore, Q = A × V, and if flow stays constant, velocity increases in direct proportion to any decrease in A (Figure 32–22).

The average velocity of fluid movement at any point in a system of tubes in parallel is inversely proportional to the total cross-sectional area at that point. Therefore, the average velocity of the blood is high in the aorta, declines steadily in the smaller vessels, and is lowest in the capillaries, which have 1000 times the total cross-sectional area of the aorta (Table 32–9). The average velocity of blood flow increases again as the blood enters the veins and is relatively high in the vena cava, although not so high as in the aorta. Clinically, the velocity of the circulation can be measured by injecting a bile salt preparation into an arm vein and timing the first appearance of the bitter taste it produces (Figure 32–23). The average normal arm-to-tongue circulation time is 15 s.

### POISEUILLE–HAGEN FORMULA

The relationship between the flow in a long narrow tube, the viscosity of the fluid, and the radius of the tube is expressed mathematically in the Poiseuille–Hagen formula:

\[ F = (P_A - P_B) \times \frac{\pi \left( \frac{1}{r} \right)}{\eta} \times \left( \frac{r^4}{L} \right) \]

where

- \( F \) = flow
- \( P_A - P_B \) = pressure difference between two ends of the tube
- \( \eta \) = viscosity
- \( r \) = radius of tube
- \( L \) = length of tube

Because flow is equal to pressure difference divided by resistance (R),

\[ R = \frac{8 \eta L}{\pi r^4} \]

Because flow varies directly and resistance inversely with the fourth power of the radius, blood flow and resistance in...
Vivo are markedly affected by small changes in the caliber of the vessels. Thus, for example, flow through a vessel is doubled by an increase of only 19% in its radius; and when the radius is doubled, resistance is reduced to 6% of its previous value. This is why organ blood flow is so effectively regulated by small changes in the caliber of the arterioles and why variations in arteriolar diameter have such a pronounced effect on systemic arterial pressure.

**VISCOSITY & RESISTANCE**

The resistance to blood flow is determined not only by the radius of the blood vessels (vascular hindrance) but also by the viscosity of the blood. Plasma is about 1.8 times as viscous as water, whereas whole blood is 3 to 4 times as viscous as water. Thus, viscosity depends for the most part on the hematocrit, that is, the percentage of the volume of blood occupied by red blood cells. The effect of viscosity in vivo deviates from that predicted by the Poiseuille–Hagen formula. In large vessels, increases in hematocrit cause appreciable increases in viscosity. However, in vessels smaller than 100 μm in diameter—that is, in arterioles, capillaries, and venules—the viscosity change per unit change in hematocrit is much less than it is in large-bore vessels. This is due to a difference in the nature of flow through the small vessels. Therefore, the net change in viscosity per unit change in hematocrit is considerably smaller in the body than it is in vitro (Figure 32–24). This is why hematocrit changes have relatively little effect on the peripheral resistance except when the changes are large. In severe polycythemia, the increase in resistance does increase the work of the heart. Conversely, in marked anemia, peripheral resistance is decreased, in part because of the decline in viscosity. Of course, the decrease in hemoglobin decreases the O₂-carrying ability of the blood, but the improved blood flow due to the decrease in viscosity partially compensates for this.

Viscosity is also affected by the composition of the plasma and the resistance of the cells to deformation. Clinically significant increases in viscosity are seen in diseases in which plasma proteins such as the immunoglobulins are markedly elevated as well as when red blood cells are abnormally rigid (hereditary spherocytosis).

**CRITICAL CLOSING PRESSURE**

In rigid tubes, the relationship between pressure and flow of homogeneous fluids is linear, but in thin-walled blood vessels in vivo it is not. When the pressure in a small blood vessel is reduced, a point is reached at which no blood flows, even though the pressure is not zero (Figure 32–25). This is because the vessels are surrounded by tissues that exert a small but definite pressure on them, and when the intraluminal pressure falls below the tissue pressure, they collapse. In inactive tissues, for example, the pressure in many capillaries is low because the precapillary sphincters and metarterioles are constricted, and many of these capillaries are collapsed. The pressure at which flow ceases is called the critical closing pressure.

**LAW OF LAPLACE**

The relationship between distending pressure and tension is shown diagrammatically in Figure 32–26. It is perhaps surprising that structures as thin-walled and delicate as the capillaries are not more prone to rupture. The principal reason for their relative invulnerability is their small diameter. The protective effect of small size in this case is an example of the operation of the law of Laplace, an important physical principle with several other applications in physiology. This law states that tension in the wall of a cylinder (T) is equal to the product of the transmural pressure (P) and the radius (r) divided by the wall thickness (w):

$$T = \frac{Pr}{w}$$
The transmural pressure is the pressure inside the cylinder minus the pressure outside the cylinder, but because tissue pressure in the body is low, it can generally be ignored and \( P \) equated to the pressure inside the viscus. In a thin-walled viscus, \( w \) is very small and it too can be ignored, but it becomes a significant factor in vessels such as arteries. Therefore, in a thin-walled viscus, \( P = T \) divided by the two principal radii of curvature of the viscus:

\[
P = \frac{T}{r_1 + \frac{1}{r_2}}
\]

In a sphere, \( r_1 = r_2 \), so

\[
P = \frac{2T}{r}
\]

In a cylinder such as a blood vessel, one radius is infinite, so

\[
P = \frac{T}{r}
\]

Consequently, the smaller the radius of a blood vessel, the lower the tension in the wall necessary to balance the distending pressure. In the human aorta, for example, the tension at normal pressures is about 170,000 dynes/cm, and in the vena cava it is about 21,000 dynes/cm; but in the capillaries, it is approximately 16 dynes/cm.

The law of Laplace also makes clear a disadvantage faced by dilated hearts. When the radius of a cardiac chamber is increased, a greater tension must be developed in the myocardium to produce any given pressure; consequently, a dilated heart must do more work than a nondilated heart. In the lungs, the radii of curvature of the alveoli become smaller during expiration, and these structures would tend to collapse because of the pull of surface tension if the tension were not reduced by the surface-tension-lowering agent, surfactant (see Chapter 35). Another example of the operation of this law is seen in the urinary bladder (see Chapter 38).

RESISTANCE & CAPACITANCE VESSELS

In vivo, the veins are an important blood reservoir. Normally, they are partially collapsed and oval in cross-section. A large amount of blood can be added to the venous system before the veins become distended to the point where further increments in volume produce a large rise in venous pressure. The veins are therefore called capacitance vessels. The small arteries and arterioles are referred to as resistance vessels because they are the principal site of the peripheral resistance (see below).

At rest, at least 50% of the circulating blood volume is in the systemic veins, 12% is in the heart cavities, and 18% is in the low-pressure pulmonary circulation. Only 2% is in the aorta, 8% in the arteries, 1% in the arterioles, and 5% in the capillaries (Table 32–9). When extra blood is administered by transfusion, less than 1% of it is distributed in the arterial system (the “high-pressure system”), and all the rest is found in the systemic veins, pulmonary circulation, and heart chambers other than the left ventricle (the “low-pressure system”).

ARTERIAL & ARTERIOLAR CIRCULATION

The pressure and velocities of the blood in the various parts of the systemic circulation are summarized in Figure 32–27. The general relationships in the pulmonary circulation are similar, but the pressure in the pulmonary artery is 25/10 mm Hg or less.

**FIGURE 32–26** Relationship between distending pressure \( (P) \) and wall tension \( (T) \) in a hollow viscus.

**FIGURE 32–27** Diagram of the changes in pressure and velocity as blood flows through the systemic circulation. TA, total cross-sectional area of the vessels, which increases from 4.5 cm² in the aorta to 4500 cm² in the capillaries (Table 32–9). RR, relative resistance, which is highest in the arterioles.
VELOCITY & FLOW OF BLOOD

Although the mean velocity of the blood in the proximal portion of the aorta is 40 cm/s, the flow is phasic, and velocity ranges from 120 cm/s during systole to a negative value at the time of the transient backflow before the aortic valve closes in diastole. In the distal portions of the aorta and in the large arteries, velocity is also much greater in systole than it is in diastole. However, the vessels are elastic, and forward flow is continuous because of the recoil during diastole of the vessel walls that have been stretched during systole (Figure 32–28). Pulsatile flow appears to maintain optimal function of the tissues, apparently via distinct effects on gene transcription. If an organ is perfused with a pump that delivers a nonpulsatile flow, inflammatory markers are produced, there is a gradual rise in vascular resistance, and ultimately tissue perfusion fails.

ARTERIAL PRESSURE

The pressure in the aorta and in the brachial and other large arteries in a young adult human rises to a peak value (systolic pressure) of about 120 mm Hg during each heart cycle and falls to a minimum (diastolic pressure) of about 70 mm Hg. The arterial pressure is conventionally written as systolic pressure over diastolic pressure, for example, 120/70 mm Hg. One millimeter of mercury equals 0.133 kPa, so in SI units (see Appendix) this value is 16.0/9.3 kPa. The pulse pressure, the difference between the systolic and diastolic pressures, is normally about 50 mm Hg. The mean pressure is the average pressure throughout the cardiac cycle. Because systole is shorter than diastole, the mean pressure is slightly less than the value halfway between systolic and diastolic pressure. It can actually be determined only by integrating the area of the pressure curve (Figure 32–29); however, as an approximation, mean pressure equals the diastolic pressure plus one-third of the pulse pressure.

The pressure falls very slightly in the large- and medium-sized arteries because their resistance to flow is small, but it falls rapidly in the small arteries and arterioles, which are the main sites of the peripheral resistance against which the heart pumps. The mean pressure at the end of the arterioles is 30 to 38 mm Hg. Pulse pressure also declines rapidly to about 5 mm Hg at the ends of the arterioles (Figure 32–26). The magnitude of the pressure drop along the arterioles varies considerably depending on whether they are constricted or dilated.

EFFECT OF GRAVITY

The pressures in Figure 32–28 are those in blood vessels at heart level. The pressure in any vessel below heart level is increased and that in any vessel above heart level is decreased by the effect of gravity. The magnitude of the gravitational effect is 0.77 mm Hg/cm of vertical distance above or below the heart at the density of normal blood. Thus, in an adult human in the upright position, when the mean arterial pressure at heart level is 100 mm Hg, the mean pressure in a large artery in the head (50 cm above the heart) is 62 mm Hg (100 – [0.77 × 50]) and the pressure in a large artery in the foot (105 cm below the heart) is 180 mm Hg (100 + [0.77 × 105]). The effect of gravity on venous pressure is similar (Figure 32–30).

METHODS OF MEASURING BLOOD PRESSURE

If a cannula is inserted into an artery, the arterial pressure can be measured directly with a mercury manometer or a suitably calibrated strain gauge. When an artery is tied off beyond the point at which the cannula is inserted, an end pressure is recorded, flow in the artery is interrupted, and all the kinetic energy of flow is converted into pressure energy. If, alternatively,
FIGURE 32–30  Effects of gravity on arterial and venous pressure. The scale on the right indicates the increment (or decrement) in mean pressure in a large artery at each level. The mean pressure in all large arteries is approximately 100 mm Hg when they are at the level of the left ventricle. The scale on the left indicates the increment in venous pressure at each level due to gravity. The manometers on the left of the figure indicate the height to which a column of blood in a tube would rise if connected to an ankle vein (A), the femoral vein (B), or the right atrium (C), with the subject in the standing position. The approximate pressures in these locations vary according to the recumbent position; that is, when the ankle, thigh, and right atrium are at the same level, the pressures are: A, 10 mm Hg; B, 7.5 mm Hg; and C, 4.6 mm Hg.

A T tube is inserted into a vessel and the pressure is measured in the side arm of the tube, the recorded side pressure, under conditions where pressure drop due to resistance is negligible, is lower than the end pressure by the kinetic energy of flow. This is because in a tube or a blood vessel the total energy—the sum of the kinetic energy of flow and the potential energy—is constant (Bernoulli’s principle).

It is worth noting that the pressure drop in any segment of the arterial system is due both to resistance and to conversion of potential into kinetic energy. The pressure drop due to energy lost in overcoming resistance is irreversible, since the energy is dissipated as heat; but the pressure drop due to conversion of potential to kinetic energy as a vessel narrows is reversed when the vessel widens out again (Figure 32–31).

Bernoulli’s principle also has a significant application in pathophysiology. According to the principle, the greater the velocity of flow in a vessel, the lower the lateral pressure distending its walls. When a vessel is narrowed, the velocity of flow in the narrowed portion increases and the distending pressure decreases. Therefore, when a vessel is narrowed by a pathologic process such as an atherosclerotic plaque, the lateral pressure at the constriction is decreased and the narrowing tends to maintain itself.

**AUSCULTATORY METHOD**

The arterial blood pressure in humans is routinely measured by the auscultatory method. An inflatable cuff (Riva–Rocci cuff) attached to a mercury manometer (sphygmomanometer) is wrapped around the arm and a stethoscope is placed over the brachial artery at the elbow. The cuff is rapidly inflated until the pressure is well above the expected systolic pressure in the brachial artery. The artery is occluded by the cuff, and no sound is heard with the stethoscope. The pressure in the cuff is then lowered slowly. At the point at which systolic pressure in the artery just exceeds the cuff pressure, a spur of blood passes through with each heartbeat and, synchronously with each beat, a tapping sound is heard below the cuff. The cuff pressure at which the sounds are first heard is the systolic pressure. As the cuff pressure is lowered further, the sounds become louder, then dull and muffled. These are the sounds of Korotkoff. Finally, in most individuals, they disappear. When direct and indirect blood pressure measurements are made simultaneously, the diastolic pressure in resting adults correlates best with the pressure at which the sound disappears. However, in adults after exercise and in children, the diastolic pressure correlates best with the pressure at which the sounds become muffled. This is also true in diseases such as hyperthyroidism and aortic insufficiency.

The sounds of Korotkoff are produced by turbulent flow in the brachial artery. When the artery is narrowed by the cuff, the velocity of flow through the constriction exceeds the critical velocity and turbulent flow results (Figure 32–22). At cuff pressures just below the systolic pressure, flow through the artery occurs only at the peak of systole, and the intermittent turbulence produces a tapping sound. As long as the pressure in the cuff is above the diastolic pressure in the artery, flow is...
interrupted at least during part of diastole, and the intermittent sounds have a staccato quality. When the cuff pressure is near the arterial diastolic pressure, the vessel is still constricted, but the turbulent flow is continuous. Continuous sounds have a muffled rather than a staccato quality.

**NORMAL ARTERIAL BLOOD PRESSURE**

The blood pressure in the brachial artery in young adults in the sitting position at rest is approximately 120/70 mm Hg. Because the arterial pressure is the product of the cardiac output and the peripheral resistance, it is affected by conditions that affect either or both of these factors. Emotion increases the cardiac output and peripheral resistance, and about 20% of hypertensive patients have blood pressures that are higher in the doctor’s office than at home, going about their regular daily activities ("white coat hypertension"). Blood pressure normally falls up to 20 mm Hg during sleep. This fall is reduced or absent in hypertension.

There is general agreement that blood pressure rises with advancing age, but the magnitude of this rise is uncertain because hypertension is a common disease and its incidence increases with advancing age (see Clinical Box 32–4). Individuals who have systolic blood pressures < 120 mm Hg at age 50 to 60 and never develop clinical hypertension still have systolic pressures that rise throughout life (Figure 32–32). This rise may be the closest approximation to the rise in normal individuals. Individuals with mild hypertension that is untreated show a significantly more rapid rise in systolic pressure. In both groups, diastolic pressure also rises, but then starts to fall in middle age as the stiffness of arteries increases. Consequently, pulse pressure rises with advancing age.

It is interesting that systolic and diastolic blood pressures are lower in young women than in young men until age 55 to 65, after which they become comparable. Because there is a positive correlation between blood pressure and the incidence of heart attacks and strokes (see below), the lower blood pressure before menopause in women may be one reason that, on average, they live longer than men.

**CAPILLARY CIRCULATION**

At any one time, only 5% of the circulating blood is in the capillaries, but this 5% is in a sense the most important part of the blood volume because it is the only pool from which O₂ and nutrients can enter the interstitial fluid and into which CO₂ and waste products can enter the bloodstream. Exchange across the capillary walls is essential to the survival of the tissues.

**METHODS OF STUDY**

It is difficult to obtain accurate measurements of capillary pressures and flows. Capillary pressure has been estimated by determining the amount of external pressure necessary to

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**FIGURE 32–32** Effects of age and sex on arterial pressure components in humans. Data are from a large group of individuals who were studied every 2 y throughout their adult lives. Group 1: Individuals who had systolic blood pressures < 120 mm Hg at age 50 to 60. Group 4: Individuals who had systolic blood pressure ≥ 160 mm Hg at age 50 to 60, that is, individuals with mild, untreated hypertension. The red line shows the values for women, and the blue line shows the values for men. (Modified and reproduced with permission from Franklin SS et al: Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. Circulation 1997;96:308.)
CLINICAL BOX 32–4

**Hypertension**

Hypertension is a sustained elevation of the systemic arterial pressure. It is most commonly due to increased peripheral resistance and is a very common abnormality in humans. It can be produced by many diseases (Table 32–12) and causes a number of serious disorders. When the resistance against which the left ventricle must pump (afterload) is elevated for a long period, the cardiac muscle hypertrophies. The initial response is activation of immediate-early genes in the ventricular muscle, followed by activation of a series of genes involved in growth during fetal life. Left ventricular hypertrophy is associated with a poor prognosis. The total O₂ consumption of the heart, already increased by the work of expelling blood against a raised pressure (see Chapter 31), is increased further because there is more muscle. Therefore, any decrease in coronary blood flow has more serious consequences in hypertensive patients than it does in normal individuals, and degrees of coronary vessel narrowing that do not produce symptoms when the size of the heart is normal may produce myocardial infarction when the heart is enlarged.

The incidence of atherosclerosis increases in hypertension, and myocardial infarcts are common even when the heart is not enlarged. Eventually, the ability to compensate for the high peripheral resistance is exceeded, and the heart fails. Hypertensive individuals are also predisposed to thromboses of cerebral vessels and cerebral hemorrhage. An additional complication is renal failure. However, the incidence of heart failure, strokes, and renal failure can be markedly reduced by active treatment of hypertension, even when the hypertension is relatively mild. In about 88% of patients with elevated blood pressure, the cause of the hypertension is unknown, and they are said to have essential hypertension. At present, essential hypertension is treatable but not curable. Effective lowering of the blood pressure can be produced by drugs that block α-adrenergic receptors, either in the periphery or in the central nervous system; drugs that block β-adrenergic receptors; drugs that inhibit the activity of angiotensin-converting enzyme; and calcium channel blockers that relax vascular smooth muscle. Essential hypertension is probably polygenic in origin, and environmental factors are also involved.

In other, less common forms of hypertension, the cause is known. A review of these is helpful because it emphasizes ways disordered physiology can lead to disease. Pathology that compromises the renal blood supply leads to renal hypertension, as does narrowing (coarctation) of the thoracic aorta, which both increases renin secretion and increases peripheral resistance. Pheochromocytomas, adrenal medullary tumors that secrete norepinephrine and epinephrine, can cause sporadic or sustained hypertension (see Chapter 22). Estrogens increase angiotensinogen secretion, and contraceptive pills containing large amounts of estrogen cause hypertension (pill hypertension) on this basis (see Chapter 25). Increased secretion of aldosterone or other mineralocorticoids causes renal Na⁺ retention, which leads to hypertension. A primary increase in plasma mineralocorticoids inhibits renin secretion. For unknown reasons, plasma renin is also low in 10–15% of patients with essential hypertension and normal circulating mineralocortical levels (low renin hypertension). Mutations in a number of single genes are also known to cause hypertension. These cases of monogenic hypertension are rare but informative. One of these is glucocorticoid-remediable aldosteronism (GRA), in which a hybrid gene encodes an adrenocorticotropic hormone (ACTH)-sensitive aldosterone synthase, with resulting hyperaldosteronism (see Chapter 22). 11β-hydroxylase deficiency also causes hypertension by increasing the secretion of deoxycorticosterone (see Chapter 22). Normal blood pressure is restored when ACTH secretion is inhibited by administering a glucocorticoid. Mutations that decrease 11β-hydroxysteroid dehydrogenase cause loss of specificity of the mineralocorticoid receptors (see Chapter 22) with stimulation of them by cortisol and, in pregnancy, by the elevated circulating levels of progesterone. Finally, mutations of the genes for ENaCs that reduce degradation of the β or γ subunits increase ENaC activity and lead to excess renal Na⁺ retention and hypertension (Liddle syndrome; see Chapter 38).

occlude the capillaries or the amount of pressure necessary to make saline start to flow through a micropipette inserted so that its tip faces the arteriolar end of the capillary.

**CAPILLARY PRESSURE & FLOW**

Capillary pressures vary considerably, but typical values in human nail bed capillaries are 32 mm Hg at the arteriolar end and 15 mm Hg at the venous end. The pulse pressure is approximately 5 mm Hg at the arteriolar end and zero at the venous end. The capillaries are short, but blood moves slowly (about 0.07 cm/s) because the total cross-sectional area of the capillary bed is large. Transit time from the arteriolar to the venular end of an average-sized capillary is 1 to 2 s.
As noted above, the capillary wall is a thin membrane made up of endothelial cells. Substances pass through the junctions between endothelial cells and through fenestrations when they are present. Some also pass through the cells by vesicular transport.

The factors other than vesicular transport that are responsible for transport across the capillary wall are diffusion and filtration (see Chapter 1). Diffusion is quantitatively much more important. O₂ and glucose are in higher concentration in the bloodstream than in the interstitial fluid and diffuse into the interstitial fluid, whereas CO₂ diffuses in the opposite direction.

The rate of filtration at any point along a capillary depends on a balance of forces sometimes called the Starling forces, after the physiologist who first described their operation in detail. One of these forces is the hydrostatic pressure gradient (the hydrostatic pressure in the capillary minus the hydrostatic pressure of the interstitial fluid) at that point. The interstitial fluid pressure varies from one organ to another, and there is considerable evidence that it is subatmospheric (about ~2 mm Hg) in subcutaneous tissue. It is, however, positive in the liver and kidneys and as high as 6 mm Hg in the brain. The other force is the osmotic pressure gradient across the capillary wall (colloid osmotic pressure of plasma minus colloid osmotic pressure of interstitial fluid). This component is directed inward.

Thus:

\[
\text{Fluid movement} = k[(P_c - P_i) - (\pi_c - \pi_i)]
\]

where

- \( k \) = capillary filtration coefficient
- \( P_c \) = capillary hydrostatic pressure
- \( P_i \) = interstitial hydrostatic pressure
- \( \pi_c \) = capillary colloid osmotic pressure
- \( \pi_i \) = interstitial colloid osmotic pressure

\( \pi_i \) is usually negligible, so the osmotic pressure gradient \((\pi_c - \pi_i)\) usually equals the oncotic pressure. The capillary filtration coefficient takes into account, and is proportional to, the permeability of the capillary wall and the area available for filtration. The magnitude of the Starling forces along a typical muscle capillary is shown in Figure 32–33. Fluid moves into the interstitial space at the arteriolar end of the capillary and into the capillary at the venular end. In other capillaries, the balance of Starling forces may be different. For example, fluid moves out of almost the entire length of the capillaries in the renal glomeruli. On the other hand, fluid moves into the capillaries through almost their entire length in the intestines. About 24 L of fluid is filtered through the capillaries per day. This is about 0.3% of the cardiac output. About 85% of the filtered fluid is reabsorbed into the capillaries, and the remainder returns to the circulation via the lymphatics.

It is worth noting that small molecules often equilibrate with the tissues near the arteriolar end of each capillary. In this situation, total diffusion can be increased by increasing blood flow; that is, exchange is flow-limited (Figure 32–34). Conversely, transfer of substances that do not reach equilibrium with the tissues during their passage through the capillaries is said to be diffusion-limited.

### TABLE 32–12 Estimated frequency of various forms of hypertension in the general hypertensive population.

<table>
<thead>
<tr>
<th>Percentage of Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
</tr>
<tr>
<td>Renal hypertension</td>
</tr>
<tr>
<td>Renovascular</td>
</tr>
<tr>
<td>Parenchymal</td>
</tr>
<tr>
<td>Endocrine hypertension</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Other adrenal forms</td>
</tr>
<tr>
<td>Miscellaneous (Liddle syndrome, coarctation of the aorta, etc)</td>
</tr>
</tbody>
</table>


### EQUILIBRATION WITH INTERSTITIAL FLUID

As noted above, the capillary wall is a thin membrane made up of endothelial cells. Substances pass through the junctions between endothelial cells and through fenestrations when they are present. Some also pass through the cells by vesicular transport.

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Thus:

\[
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where

- \( k \) = capillary filtration coefficient
- \( P_c \) = capillary hydrostatic pressure
- \( P_i \) = interstitial hydrostatic pressure
- \( \pi_c \) = capillary colloid osmotic pressure
- \( \pi_i \) = interstitial colloid osmotic pressure

\( \pi_i \) is usually negligible, so the osmotic pressure gradient \((\pi_c - \pi_i)\) usually equals the oncotic pressure. The capillary filtration coefficient takes into account, and is proportional to, the permeability of the capillary wall and the area available for filtration. The magnitude of the Starling forces along a typical muscle capillary is shown in Figure 32–33. Fluid moves into the interstitial space at the arteriolar end of the capillary and into the capillary at the venular end. In other capillaries, the balance of Starling forces may be different. For example, fluid moves out of almost the entire length of the capillaries in the renal glomeruli. On the other hand, fluid moves into the capillaries through almost their entire length in the intestines. About 24 L of fluid is filtered through the capillaries per day. This is about 0.3% of the cardiac output. About 85% of the filtered fluid is reabsorbed into the capillaries, and the remainder returns to the circulation via the lymphatics.
### Venous Circulation

Blood flows through the blood vessels, including the veins, primarily because of the pumping action of the heart. However, venous flow is aided by the heartbeat, the increase in the negative intrathoracic pressure during each inspiration, and contractions of the skeletal muscles that compress the veins.

### Venous Pressure & Flow

The pressure in the venules is 12 to 18 mm Hg. It falls steadily through all of the capillaries. Substance X equilibrates with the tissues (movement into the tissues equals movement out) well before the blood leaves the capillary, whereas substance Y does not equilibrate. If other factors stay constant, the amount of X entering the tissues can be increased only by increasing blood flow; that is, it is flow-limited. The movement of Y is diffusion-limited.

#### Active & Inactive Capillaries

In resting tissues, most of the capillaries are collapsed. In active tissues, the metarterioles and the precapillary sphincters dilate. The intracapillary pressure rises, overcoming the critical closing pressure of the vessels, and blood flows through all of the capillaries. Relaxation of the smooth muscle of the metarterioles and precapillary sphincters is due to the action of vasodilator metabolites formed in active tissue (see Chapter 33).

After noxious stimulation, substance P released by the axon reflex (see Chapter 34) increases capillary permeability. Bradykinin and histamine also increase capillary permeability. When capillaries are stimulated mechanically, they empty (white reaction; see Chapter 34), probably due to contraction of the precapillary sphincters.

#### Thoracic Pump

During inspiration, the intrapleural pressure falls from –2.5 to –6 mm Hg. This negative pressure is transmitted to the great veins and, to a lesser extent, the atria, so that central venous pressure fluctuates from about 6 mm Hg during expiration to approximately 2 mm Hg during quiet inspiration. The drop in venous pressure during inspiration aids venous return. When the diaphragm descends during inspiration, intra-abdominal pressure rises, and this also squeezes blood toward the heart because backflow into the leg veins is prevented by the venous valves.

#### Effects of Heartbeat

The variations in atrial pressure are transmitted to the great veins, producing the a, c, and v waves of the venous pressure-pulse curve (see Chapter 31). Atrial pressure drops sharply during the ejection phase of ventricular systole because the atrioventricular valves are pulled downward, increasing the capacity of the atria. This action sucks blood into the atria from the great veins. The sucking of the blood into the atria during systole contributes appreciably to the venous return, especially at rapid heart rates.

Close to the heart, venous flow becomes pulsatile. When the heart rate is slow, two periods of peak flow are detectable, one during ventricular systole, due to pulling down of the atrioventricular valves, and one in early diastole, during the period of rapid ventricular filling (Figure 32-28).

#### Muscle Pump

In the limbs, the veins are surrounded by skeletal muscles, and contraction of these muscles during activity compresses the veins. Pulses of nearby arteries may also compress veins. Because the venous valves prevent reverse flow, the blood moves toward the heart. During quiet standing, when the full effect of gravity is manifest, venous pressure at the ankle is 85–90 mm Hg (Figure 32–30). Pooling of blood in the leg veins reduces venous return, with the result that cardiac output is reduced, sometimes to the point where fainting occurs. Rhythmic contractions of the leg muscles while the person is standing...
serve to lower the venous pressure in the legs to less than 30 mm Hg by propelling blood toward the heart. This heartward movement of the blood is decreased in patients with varicose veins because their valves are incompetent. These patients may develop stasis and ankle edema. However, even when the valves are incompetent, muscle contractions continue to produce a basic heartward movement of the blood because the resistance of the larger veins in the direction of the heart is less than the resistance of the small vessels away from the heart.

VENOUS PRESSURE IN THE HEAD

In the upright position, the venous pressure in the parts of the body above the heart is decreased by the force of gravity. The neck veins collapse above the point where the venous pressure is close to zero. However, the dural sinuses have rigid walls and cannot collapse. The pressure in them in the standing or sitting position is therefore subatmospheric. The magnitude of the negative pressure is proportional to the vertical distance above the top of the collapsed neck veins, and in the superior sagittal sinus may be as much as –10 mm Hg. This fact must be kept in mind by neurosurgeons. Neurosurgical procedures are sometimes performed with the patient seated. If one of the sinuses is opened during such a procedure it sucks air, causing air embolism.

AIR EMBOLISM

Because air, unlike fluid, is compressible, its presence in the circulation has serious consequences. The forward movement of the blood depends on the fact that blood is incompressible. Large amounts of air fill the heart and effectively stop the circulation, causing sudden death because most of the air is compressed by the contracting ventricles rather than propelled into the arteries. Small amounts of air are swept through the heart with the blood, but the bubbles lodge in the small blood vessels. The surface capillarity of the bubbles markedly increases the resistance to blood flow, and flow is reduced or abolished. Blockage of small vessels in the brain leads to serious and even fatal neurologic abnormalities. Treatment with hyperbaric oxygen (see Chapter 37) is of value because the pressure reduces the size of the gas emboli. In experimental animals, the amount of air that produces fatal air embolism varies considerably, depending in part on the rate at which it enters the veins. Sometimes as much as 100 mL can be injected without ill effects, whereas at other times as little as 5 mL is lethal.

MEASURING VENOUS PRESSURE

Central venous pressure can be measured directly by inserting a catheter into the thoracic great veins. Peripheral venous pressure correlates well with central venous pressure in most conditions. To measure peripheral venous pressure, a needle attached to a manometer containing sterile saline is inserted into an arm vein. The peripheral vein should be at the level of the right atrium (a point half the chest diameter from the back in the supine position). The values obtained in millimeters of saline can be converted into millimeters of mercury (mm Hg) by dividing by 13.6 (the density of mercury). The amount by which peripheral venous pressure exceeds central venous pressure increases with the distance from the heart along the veins. The mean pressure in the antecubital vein is normally 7.1 mm Hg, compared with a mean pressure of 4.6 mm Hg in the central veins.

A fairly accurate estimate of central venous pressure can be made without any equipment by simply noting the height to which the external jugular veins are distended when the subject lies with the head slightly above the heart. The vertical distance between the right atrium and the place the vein collapses (the place where the pressure in it is zero) is the venous pressure in mm of blood.

Central venous pressure is decreased during negative pressure breathing and shock. It is increased by positive pressure breathing, straining, expansion of the blood volume, and heart failure. In advanced congestive heart failure or obstruction of the superior vena cava, the pressure in the antecubital vein may reach values of 20 mm Hg or more.

LYMPHATIC CIRCULATION & INTERSTITIAL FLUID VOLUME

LYMPHATIC CIRCULATION

Fluid efflux normally exceeds influx across the capillary walls, but the extra fluid enters the lymphatics and drains through them back into the blood. This keeps the interstitial fluid pressure from rising and promotes the turnover of tissue fluid. The normal 24-h lymph flow is 2 to 4 L.

Lymphatic vessels can be divided into two types: initial lymphatics and collecting lymphatics (Figure 32–35). The former lack valves and smooth muscle in their walls, and they are found in regions such as the intestine or skeletal muscle. Tissue fluid appears to enter them through loose junctions between the endothelial cells that form their walls. The fluid in them apparently is massaged by muscle contractions of the organs and contraction of arterioles and venules, with which they are often associated. They drain into the collecting lymphatics, which have valves and smooth muscle in their walls and contract in a peristaltic fashion, propelling the lymph along the vessels. Flow in the collecting lymphatics is further aided by movements of skeletal muscle, the negative intrathoracic pressure during inspiration, and the suction effect of high-velocity flow of blood in the veins in which the lymphatics terminate. However, the contractions are the principal factor propelling the lymph.
OTHER FUNCTIONS OF THE LYMPHATIC SYSTEM

Appreciable quantities of protein enter the interstitial fluid in the liver and intestine, and smaller quantities enter from the blood in other tissues. The macromolecules enter the lymphatics, presumably at the junctions between the endothelial cells, and the proteins are returned to the bloodstream via the lymphatics. The amount of protein returned in this fashion in 1 d is equal to 25–50% of the total circulating plasma protein. The transport of absorbed long-chain fatty acids and cholesterol from the intestine via the lymphatics has been discussed in Chapter 27.

INTERSTITIAL FLUID VOLUME

The amount of fluid in the interstitial spaces depends on the capillary pressure, the interstitial fluid pressure, the oncotic pressure, the capillary filtration coefficient, the number of active capillaries, the lymph flow, and the total extracellular fluid (ECF) volume. The ratio of precapillary to postcapillary venular resistance is also important. Precapillary constriction lowers filtration pressure, whereas postcapillary constriction raises it. Changes in any of these variables lead to changes in the volume of interstitial fluid. Factors promoting an increase in this volume are summarized in Table 32–13. Edema is the accumulation of interstitial fluid in abnormally large amounts.

In active tissues, capillary pressure rises, often to the point where it exceeds the oncotic pressure throughout the length of the capillary. In addition, osmotically active metabolites may temporarily accumulate in the interstitial fluid because they cannot be washed away as rapidly as they are formed. To the extent that they accumulate, they exert an osmotic effect that decreases the magnitude of the osmotic gradient due to the oncotic pressure. The amount of fluid leaving the capillaries is therefore markedly increased and the amount entering them reduced. Lymph flow is increased, decreasing the degree to which the fluid would otherwise accumulate, but exercising muscle, for example, still increases in volume by as much as 25%.

Interstitial fluid tends to accumulate in dependent parts because of the effect of gravity. In the upright position, the capillaries in the legs are protected from the high arterial pressure by the arterioles, but the high venous pressure is transmitted to them through the venules. Skeletal muscle contractions keep the venous pressure low by pumping blood toward the heart (see above) when the individual moves about; however, if one stands still for long periods, fluid accumulates and edema eventually develops. The ankles also swell during long trips when travelers sit for prolonged periods with their feet in a dependent position. Venous obstruction may contribute to the edema in these situations.

Whenever there is abnormal retention of salt in the body, water is also retained. The salt and water are distributed throughout the ECF, and since the interstitial fluid volume is therefore increased, there is a predisposition to edema. Salt and water retention is a factor in the edema seen in heart failure, nephrosis, and cirrhosis, but there are also variations in the mechanisms that govern fluid movement across the capillary walls in these diseases. In congestive heart failure, for example, venous pressure is usually elevated, with a consequent elevation in capillary pressure. In cirrhosis of the liver, oncotic

TABLE 32–13 Causes of increased interstitial fluid volume and edema.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased filtration pressure</td>
</tr>
<tr>
<td>Venular constriction</td>
</tr>
<tr>
<td>Increased venous pressure (heart failure, incompetent valves, venous obstruction, increased total ECF volume, effect of gravity, etc)</td>
</tr>
<tr>
<td>Decreased oncotic pressure gradient across capillary</td>
</tr>
<tr>
<td>Decreased plasma protein level</td>
</tr>
<tr>
<td>Accumulation of osmotically active substances in interstitial space</td>
</tr>
<tr>
<td>Increased capillary permeability</td>
</tr>
<tr>
<td>Substance P</td>
</tr>
<tr>
<td>Histamine and related substances</td>
</tr>
<tr>
<td>Kinins, etc</td>
</tr>
<tr>
<td>Inadequate lymph flow</td>
</tr>
</tbody>
</table>
pressure is low because hepatic synthesis of plasma proteins is depressed; and in nephrosis, oncotic pressure is low because large amounts of protein are lost in the urine.

Another cause of edema is inadequate lymphatic drainage. Edema caused by lymphatic obstruction is called lymphedema, and the edema fluid has a high protein content. If it persists, it causes a chronic inflammatory condition that leads to fibrosis of the interstitial tissue. One cause of lymphedema is radical mastectomy, during which removal of the axillary lymph nodes leads to reduced lymph drainage. In filariasis, parasitic worms migrate into the lymphatics and obstruct them. Fluid accumulation plus tissue reaction lead in time to massive swelling, usually of the legs or scrotum (elephantiasis).

CHAPTER SUMMARY

- Blood consists of a suspension of red blood cells (erythrocytes), white blood cells, and platelets in a protein-rich fluid known as plasma.
- Blood cells arise in the bone marrow and are subject to regular renewal; the majority of plasma proteins are synthesized by the liver.
- Hemoglobin, stored in red blood cells, transports oxygen to peripheral tissues. Fetal hemoglobin is specialized to facilitate diffusion of oxygen from mother to fetus during development. Mutated forms of hemoglobin lead to red cell abnormalities and anemia.
- Complex oligosaccharide structures, specific to groups of individuals, form the basis of the ABO blood group system. AB blood group oligosaccharides, as well as other blood group molecules, can trigger the production of antibodies in naïve individuals following inappropriate transfusions, with potentially serious consequences due to erythrocyte agglutination.
- Blood flows from the heart to arteries and arterioles, thence to capillaries, and eventually to venules and veins back to the heart. Each segment of the vasculature has specific contractile properties and regulatory mechanisms that subserve physiological function. Physical principles of pressure, wall tension, and vessel caliber govern the flow of blood through each segment of the circulation.
- Transfer of oxygen and nutrients from the blood to tissues, as well as collection of metabolic wastes, occurs exclusively in the capillary beds.
- Fluid also leaves the circulation across the walls of capillaries. Some is reabsorbed; the remainder enters the lymphatic system, which eventually drains into the subclavian veins to return fluid to the bloodstream.
- Hypertension is an increase in mean blood pressure that is usually chronic and is common in humans. Hypertension can result in serious health consequences if left untreated. The majority of hypertension is of unknown cause, but several gene mutations underlie rare forms of the disease and are informative about mechanisms that control the dynamics of the circulatory system and its integration with other organs.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. Which of the following has the highest total cross-sectional area in the body?
   A) arteries
   B) arterioles
   C) capillaries
   D) venules
   E) veins

2. Lymph flow from the foot is
   A) increased when an individual rises from the supine to the standing position.
   B) increased by massaging the foot.
   C) increased when capillary permeability is decreased.
   D) decreased when the valves of the leg veins are incompetent.
   E) decreased by exercise.

3. The pressure in a capillary in skeletal muscle is 35 mm Hg at the arteriolar end and 14 mm Hg at the venular end. The interstitial pressure is 0 mm Hg. The colloid osmotic pressure is 25 mm Hg in the capillary and 1 mm Hg in the interstitium. The net force producing fluid movement across the capillary wall at its arteriolar end is
   A) 3 mm Hg out of the capillary.
   B) 3 mm Hg into the capillary.
   C) 10 mm Hg out of the capillary.
   D) 11 mm Hg out of the capillary.
   E) 11 mm Hg into the capillary.

4. The velocity of blood flow
   A) is higher in the capillaries than the arterioles.
   B) is higher in the veins than in the venules.
   C) is higher in the veins than the arteries.
   D) falls to zero in the descending aorta during diastole.
   E) is reduced in a constricted area of a blood vessel.

5. When the radius of the resistance vessels is increased, which of the following is increased?
   A) systolic blood pressure
   B) diastolic blood pressure
   C) viscosity of the blood
   D) hematocrit
   E) capillary blood flow

6. When the viscosity of the blood is increased, which of the following is increased?
   A) mean blood pressure
   B) radius of the resistance vessels
   C) radius of the capacitance vessels
   D) central venous pressure
   E) capillary blood flow

7. A pharmacologist discovers a drug that stimulates the production of VEGF receptors. He is excited because his drug might be of value in the treatment of
   A) coronary artery disease.
   B) cancer.
   C) emphysema.
   D) diabetes insipidus.
   E) dysmenorrhea.
CHAPTER RESOURCES
