The term hemostasis refers to the stoppage of blood flow. The normal process of hemostasis is regulated by a complex array of activators and inhibitors that maintain blood fluidity and prevent blood from leaving the vascular compartment. Hemostasis is normal when it seals a blood vessel to prevent blood loss and hemorrhage. It is abnormal when it causes inappropriate blood clotting or when clotting is insufficient to stop the flow of blood from the vascular compartment. Disorders of hemostasis fall into two main categories: the inappropriate formation of clots within the vascular system (i.e., thrombosis) and the failure of blood to clot in response to an appropriate stimulus (i.e., bleeding).

MECHANISMS OF HEMOSTASIS

Hemostasis is divided into five stages: vessel spasm, formation of the platelet plug, blood coagulation or development of an insoluble fibrin clot, clot retraction, and clot dissolution (Fig. 12-1).

Vessel Spasm

Vessel spasm is initiated by endothelial injury and caused by local and humoral mechanisms. A spasm constricts the vessel and reduces blood flow. It is a transient event that usually lasts less than 1 minute. Thromboxane A₂ (TXA₂), a prostaglandin released from the platelets, contributes to the vasoconstriction. A second prostaglandin, prostacyclin, released from the vessel endothelium, produces vasodilation and inhibits platelet aggregation.

Formation of the Platelet Plug

The platelet plug, the second line of defense, is initiated as platelets come in contact with the vessel wall. Small breaks in the vessel wall are often sealed with a platelet plug and do not require the development of a blood clot.

Platelets, also called thrombocytes, are large fragments from the cytoplasm of bone marrow cells called megakaryocytes. They are enclosed in a membrane but have no nucleus and cannot reproduce. Their cytoplasmic granules release mediators for hemostasis. Although they lack a nucleus, they have many of the characteristics of a whole cell. They have mitochondria and enzyme systems for producing adenosine triphosphate (ATP) and adenosine diphosphate (ADP), and they have the enzymes needed for synthesis of prostaglandins, which are required for their function in hemostasis. Platelets also produce a growth factor that causes vascular endothelial cells, smooth muscle cells, and fibroblasts to proliferate and grow.

The life span of a platelet is only 8 to 9 days. A protein called thrombopoietin causes proliferation and maturation of megakaryocytes. The sources of thrombopoietin include the liver, kidney, smooth muscle, and bone marrow, which controls platelet production. Its production and release are regulated by the number of platelets in the circulation. The newly formed
of acute coronary myocardial infarction (see Chapter 17). In addition, the platelet membrane contains large amounts of phospholipids that play a role in activating several points in the blood-clotting process.

Platelet plug formation involves adhesion and aggregation of platelets. Platelet adhesion also requires a protein molecule called von Willebrand factor (vWF). vWF, which is produced by the endothelial cells of blood vessels, performs two important functions: it aids in platelet adhesion, and it circulates in the blood as a carrier protein for coagulation factor VIII.

Platelets are attracted to a damaged vessel wall, become activated, and change from smooth disks to spiny spheres, exposing receptors on their surfaces. Adhesion to the vessel subendothelial layer occurs when the platelet receptor binds to vWF at the injury site, linking the platelet to exposed collagen fibers (Fig. 12-2A). The process of adhesion is controlled by local hormones and substances released by platelet granules. As the platelets adhere to the collagen fibers on the damaged vessel wall, they begin to release large amounts of ADP and TXA$_2$. Platelet aggregation and formation of a loosely organized platelet plug occur as the ADP and TXA$_2$ cause nearby platelets to become sticky and adhere to the original platelets. Stabilization of the platelet plug occurs as the coagulation

platelets that are released from the bone marrow spend as long as 8 hours in the spleen before they are released into the blood.

The cell membrane of the platelet is important to its function. The outside of the platelet membrane is coated with glycoproteins that repulse adherence to the normal vessel endothelium, while causing adherence to injured areas of the vessel wall, particularly the subendothelial layer.$^2$ The platelet membrane also has glycoprotein receptors that bind fibrinogen and link platelets together. Glycoprotein receptor antagonists have been developed and are selectively used in the treatment

| FIGURE 12-1 | Steps in hemostasis.

| FIGURE 12-2 | (A) The platelet plug occurs seconds after vessel injury. Von Willebrand’s factor, released from the endothelial cells, binds to platelet receptors, causing adhesion of platelets to the exposed collagen. Platelet aggregation is induced by release of thromboxane A$_2$ and adenosine diphosphate. (B) Coagulation factors, activated on the platelet surface, lead to the formation of thrombin and fibrin, which stabilize the platelet plug. (C) Control of the coagulation process and clot dissolution are governed by thrombin and plasminogen activators. Thrombin activates protein C, which stimulates the release of plasminogen activators. The plasminogen activators in turn promote the formation of plasmin, which digests the fibrin strands.

**KEY CONCEPTS**

**HEMOSTASIS**

- Hemostasis is the orderly, stepwise process for stopping bleeding that involves vasospasm, formation of a platelet plug, and the development of a fibrin clot.

- The blood clotting process requires the presence of platelets produced in the bone marrow, von Willebrand factor generated by the vessel endothelium, and clotting factors synthesized in the liver, using vitamin K.

- The final step of the process involves fibrinolysis or clot dissolution, which prevents excess clot formation.
Defective platelet plug formation causes bleeding in persons who are deficient in platelet receptor sites or vWF. In addition to sealing vascular breaks, platelets play an almost continuous role in maintaining normal vascular integrity. They may supply growth factors for the endothelial cells and arterial smooth muscle cells. Persons with platelet deficiency have increased capillary permeability and sustain small skin hemorrhages from the slightest trauma or change in blood pressure.

Blood Coagulation

Blood coagulation is controlled by many substances that promote clotting (i.e., procoagulation factors) or inhibit it (i.e., anticoagulation factors). Each of the procoagulation factors, identified by Roman numerals, performs a specific step in the coagulation process. The action of one coagulation factor or proenzyme is designed to activate the next factor in the sequence (i.e., cascade effect). Because most of the inactive procoagulation factors are present in the blood at all times, the multistep process ensures that a massive episode of intravascular clotting does not occur by chance. It also means that abnormalities of the clotting process occur when one or more of the factors are deficient or when conditions lead to inappropriate activation of any of the steps.

The chemical events in the blood coagulation process involve a number of essential steps that result in the conversion of fibrinogen, a circulating plasma protein, to the fibrin strands that enmesh platelets, blood cells, and plasma to form the clot (Fig. 12-3). The initiation of the clotting process occurs by way of the intrinsic or the extrinsic coagulation pathways (Fig. 12-4). The intrinsic pathway, which is a relatively slow process, begins in the blood itself. The extrinsic pathway, which is a much faster process, begins with tissue or vessel trauma and the subsequent release of a complex of several factors, called tissue factor, or tissue thromboplastin. The terminal steps in both pathways are the same: the activation of factor X, the conversion of prothrombin to thrombin, and the conversion of fibrinogen to fibrin. Prothrombin is an unstable plasma protein, which is easily split into smaller parts, one of which is thrombin. Thrombin, in turn, acts as an enzyme to convert fibrinogen to fibrin.

Both the intrinsic and extrinsic pathways are needed for normal hemostasis, and many interrelations exist between them. Each system is activated when blood passes out of the vascular system. The intrinsic system is activated as blood comes in contact with collagen in the injured vessel wall and the extrinsic system when blood is exposed to tissue extracts. Bleeding, when it occurs because of defects in the extrinsic system, usually is not as severe as that which results from defects in the intrinsic pathway.

With few exceptions, almost all the blood-clotting factors are synthesized in the liver. Vitamin K is required for the synthesis of prothrombin, factors VII, IX, X, and protein C. Calcium (factor IV) is required in all but the first two steps of the clotting process. The body usually has sufficient amounts of calcium for these reactions. Inactivation of the calcium ion prevents blood from clotting when it is removed from the body. The addition of citrate to blood stored for transfusion purposes prevents clotting by chelating ionic calcium. Another chelator, EDTA, is often added to blood samples used for analysis in the clinical laboratory.

Coagulation is regulated by several natural anticoagulants. Antithrombin III inactivates coagulation factors and neutralizes thrombin, the last enzyme in the pathway for the conversion of fibrinogen to fibrin. When antithrombin III is complexed with naturally occurring heparin, its action is accelerated and provides protection against uncontrolled thrombus formation on the endothelial surface. Protein C, a plasma protein, acts as an anticoagulant by inactivating factors V and VIII. Protein S, another plasma protein, accelerates the action of protein C. Plasmin breaks down fibrin into fibrin degradation products that act as anticoagulants. It has been suggested that some of these natural anticoagulants may play a role in the bleeding that occurs with disseminated intravascular coagulation (DIC; discussed later).

The anticoagulant drugs heparin and warfarin are used to prevent venous thrombi and thromboembolic disorders, such as deep vein thrombosis and pulmonary embolism. Heparin is naturally formed by basophilic mast cells located at the precapillary junctions in tissues throughout the body. These cells continuously secrete small amounts of heparin, which is released into the circulation. Pharmacologic preparations of heparin, extracted from animal tissues, are available for treatment of coagulation disorders. Heparin binds to antithrombin III, causing a conformational change that increases the ability of antithrombin III to inactivate factor Xa, thrombin, and other clotting factors. By promoting the inactivation of clotting factors, heparin ultimately suppresses the formation of fibrin. Heparin is unable to cross the membranes of the gastrointestinal tract and must be given by injection. Warfarin acts by

![FIGURE 12-3](Scanning electron micrograph of a blood clot (×3600). The fibrous bridges that form a meshwork between red blood cells are fibrin fibers. (© Oliver Meckes, Science Source/Photo Researchers))
decreasing prothrombin and other procoagulation factors. It alters vitamin K such that it reduces its availability to participate in synthesis of the vitamin K-dependent coagulation factors in the liver. Warfarin is readily absorbed after oral administration. Its maximum effect takes 36 to 72 hours because of the varying half-lives of preformed clotting factors that remain in the circulation.

**Clot Retraction**

After the clot has formed, clot retraction, which requires large numbers of platelets, contributes to hemostasis by squeezing serum from the clot and joining the edges of the broken vessel.

**Clot Dissolution**

The dissolution of a blood clot begins shortly after its formation; this allows blood flow to be re-established and permanent tissue repair to take place (see Fig. 12-2C). The process by which a blood clot dissolves is called fibrinolysis. As with clot formation, clot dissolution requires a sequence of steps controlled by activators and inhibitors (Fig. 12-5). Plasminogen, the proenzyme for the fibrinolytic process, normally is present in the blood in its inactive form. It is converted to its active form, plasmin, by plasminogen activators formed in the vascular endothelium, liver, and kidneys. The plasmin formed from plasminogen digests the fibrin strands of the clot and certain clotting factors, such as fibrinogen, factor V, factor VIII, prothrombin, and factor XII. Circulating plasmin is rapidly inactivated by α2-plasmin inhibitor, which limits fibrinolysis to the local clot and prevents it from occurring in the entire circulation.

Two naturally occurring plasminogen activators are tissue-type plasminogen activator and urokinase-type plasminogen activator. The liver, plasma, and vascular endothelium are the major sources of physiologic activators. These activators are released in response to a number of stimuli, including vasoactive drugs, venous occlusion, elevated body temperature, and exercise. The activators are unstable and rapidly inactivated by inhibitors synthesized by the endothelium and the liver. For this reason, chronic liver disease may cause altered
fibrinolytic activity. A major inhibitor, plasminogen activator inhibitor-1, in high concentrations has been associated with deep vein thrombosis, coronary artery disease, and myocardial infarction.3

In summary, hemostasis is designed to maintain the integrity of the vascular compartment. The process is divided into five phases: vessel spasm, which constricts the size of the vessel and reduces blood flow; platelet adherence and formation of the platelet plug; formation of the fibrin clot, which cements together the platelet plug; clot retraction, which pulls the edges of the injured vessel together; and clot dissolution, which involves the action of plasmin that dissolves the clot and allows blood flow to be re-established and tissue healing to take place. Blood coagulation requires the stepwise activation of coagulation factors, carefully controlled by activators and inhibitors.

### HYPERCOAGULABILITY STATES

Hypercoagulability represents hemostasis in an exaggerated form and predisposes to thrombosis. Arterial thrombi caused by turbulence are composed of platelet aggregates, and venous thrombi caused by stasis of flow are largely composed of platelet aggregates and fibrin complexes that result from excess coagulation. There are two general forms of hypercoagulability states: conditions that create increased platelet function and conditions that cause accelerated activity of the coagulation system. Chart 12-1 summarizes conditions commonly associated with hypercoagulability states.

#### Increased Platelet Function

Increased platelet function predisposes to platelet adhesion, formation of a platelet or blood clot, and disturbance of blood flow. The causes of increased platelet function are disturbances in flow, endothelial damage, and increased sensitivity of platelets to factors that cause adheriveness and aggregation. Atherosclerotic plaques disturb flow, cause endothelial damage, and promote platelet adherence. Platelets that adhere to the vessel wall release growth factors that can cause proliferation of smooth muscle and thereby contribute to the development of atherosclerosis. Smoking, elevated levels of blood lipids and cholesterol, hemodynamic stress, diabetes mellitus, and immune mechanisms may cause vessel damage, platelet adherence, and, eventually, thrombosis. Some cancers and other diseases are associated with high platelet counts and the potential for thrombosis. The term thrombocytosis is used to describe platelet counts greater than 1,000,000/mm3. This occurs in some malignancies and inflammatory states and after splenectomy. Myeloproliferative disorders that result in excess platelet production may predispose to thrombosis or, paradoxically, bleeding when the rapidly produced platelets are defective.

### Increased Clotting Activity

Increased clotting activity results from factors that increase the activation of the coagulation system, including stasis of blood flow and alterations in the coagulation components of the blood (i.e., an increase in procoagulation factors or a decrease in anticoagulation factors). Stasis of blood flow causes the accumulation of activated clotting factors and platelets and prevents their interactions with inhibitors. Slow and disturbed flow is a common cause of venous thrombosis in the immobilized or postoperative patient. Heart failure also contributes to venous congestion and thrombosis. Elevated levels of estrogen tend to increase hepatic synthesis of many of the coagulation factors and decrease the synthesis of antithrombin III.4 The incidence of stroke, thromboemboli, and myocardial infarction is greater in women who use oral contraceptives, particularly after age 35 years, and in heavy smokers. Clotting factors are also increased during normal pregnancy. These changes, along with limited activity during the puerperium (immediate postpartum period), predispose to venous thrombosis. A hypercoagulability state is also common in cancer and sepsis. Many tumor cells are thought to release tissue factor molecules that, along with the increased immobility and sepsis seen in patients with malignant disease, contribute to increased risk of both venous and arterial thrombosis.

A reduction in anticoagulants such as antithrombin III, protein C, and protein S predisposes to venous thrombosis.5

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<thead>
<tr>
<th>CHART 12-1 Conditions Associated With Hypercoagulability States</th>
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<tbody>
<tr>
<td><strong>Increased Platelet Function</strong></td>
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<tr>
<td>Atherosclerosis</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Smoking</td>
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<td>Elevated blood lipid and cholesterol levels</td>
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<td>Increased platelet levels</td>
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<td><strong>Accelerated Activity of the Clotting System</strong></td>
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<td>Pregnancy and the puerperium</td>
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<td>Use of oral contraceptives</td>
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<td>Postoperative state</td>
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<td>Immobility</td>
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<td>Congestive heart failure</td>
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<td>Malignant diseases</td>
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### KEY CONCEPTS

#### HYPERCOAGULABILITY STATES

- Hypercoagulability states increase the risk of clot or thrombus formation in either the arterial or venous circulations.
- Arterial thrombi are associated with conditions that produce turbulent blood flow and platelet adherence.
- Venous thrombi are associated with conditions that cause stasis of blood flow with increased concentrations of coagulation factors.
Deficiencies of these inhibitor proteins are uncommon inherited defects. It has been suggested that high circulating levels of homocysteine also predispose to venous and arterial thrombosis by activating platelets and altering antithrombotic mechanisms.\(^6\)

Another cause of increased venous and arterial clotting is a condition known as the antiphospholipid syndrome.\(^7\) The syndrome is associated with a number of clinical manifestations, including multiple thromboses. The condition can manifest as a primary disorder in persons who exhibit only the manifestations of the hypercoagulable state or as a secondary disorder in persons with well-defined autoimmune disorders, such as systemic lupus erythematosus. Thrombosis may be precipitated by trauma, surgical conditions, use of drugs such as oral contraceptives, or abrupt withdrawal of anticoagulant drugs. Persons with the disorder have a history of having one or more of the following: deep venous thrombosis; arterial thrombosis, including stroke, myocardial infarction, or gangrene; or thrombocytopenia.\(^7\) Antiphospholipid antibody syndrome is also a cause of renal microangiopathy, resulting in renal failure caused by multiple capillary and arterial thromboses.

Women with the disorder often have a history of recurrent pregnancy losses within the fetal period (10 weeks or more gestation) because of ischemia and thrombosis of placental vessels.\(^7\) Pregnanies in women with antiphospholipid syndrome can also be complicated by premature delivery caused by pregnancy-associated hypertension and uteroplacental insufficiency.

In most persons with antiphospholipid syndrome, thrombotic events occur singly. However, recurrences may occur months or years after the initial event. Occasionally, someone will present with multiple almost simultaneous vascular occlusions involving different organ systems. The condition, sometimes termed catastrophic antiphospholipid syndrome, is a serious and sometimes fatal condition.

Exactly how antiphospholipid antibodies, which interact with cardiolipin, a mitochondrial phospholipid, produce thrombosis is unclear. Possible mechanisms include activation or injury of vascular endothelial cells, direct platelet activation, or inactivation of anticoagulation factors (e.g., antithrombin III or protein C).

Treatment focuses on prophylaxis, treatment of acute thrombotic events, and prevention of future thrombotic events.\(^7\) Prophylaxis focuses on removal or reduction in factors that predispose to thrombosis, such as smoking and the use of estrogen-containing oral contraceptives by women. Treatment during a thrombotic event includes the use of anticoagulant medications (heparin and warfarin) and immune suppression in refractory cases. Aspirin and anticoagulant drugs may be used to prevent further thrombosis.

In summary, hypercoagulability causes excessive clotting and contributes to thrombus formation. It results from conditions that create increased platelet function or that cause accelerated activity of the coagulation system. Increased platelet function usually results from disorders such as atherosclerosis that damage the vessel endothelium and disturb blood flow or from conditions such as smoking that cause increased sensitivity of platelets to factors that promote adhesiveness and aggregation. Factors that cause accelerated activity of the coagulation system include blood flow stasis, resulting in an accumulation of coagulation factors, and alterations in the components of the coagulation system (i.e., an increase in procoagulation factors or a decrease in anticoagulation factors). Another cause of increased venous and arterial clotting is the antiphospholipid syndrome, which can manifest as a primary disorder or as a secondary disorder in persons with autoimmune disorders, such as systemic lupus erythematosus.

**Bleeding Disorders**

Bleeding disorders or impairment of blood coagulation can result from defects in any of the factors that contribute to homeostasis. Defects are associated with platelets, coagulation factors, and vascular integrity.

**Platelet Defects**

Platelets provide one of the first defenses against bleeding. Bleeding can occur as a result of a decrease in the number of circulating platelets or impaired platelet function. The depletion of platelets must be relatively severe (10,000 to 20,000/mm\(^3\), compared with the normal values of 150,000 to 400,000/mm\(^3\)) before hemorrhagic tendencies or spontaneous bleeding become evident. Bleeding that results from platelet deficiency commonly occurs in small vessels and is characterized by petechiae (i.e., pinpoint purplish-red spots) and purpura (i.e., purple areas of bruising) on the arms and thighs. Bleeding from mucous membranes of the nose, mouth, gastrointestinal tract, and vagina is characteristic. Bleeding of the intracranial vessels is a rare danger with severe platelet depletion.

**Key Concepts**

**Bleeding Disorders**

- Bleeding disorders are caused by defects associated with platelets, coagulation factors, and vessel integrity.
- Disorders of platelet plug formation include a decrease in platelet numbers due to inadequate platelet production (bone marrow dysfunction), excess platelet destruction (thrombocytopenia), abnormal platelet function (thrombocythopathia), or defects in von Willebrand factor.
- Impairment of the coagulation stage of hemostasis is caused by a deficiency in one or more of the clotting factors.
- Disorders of blood vessel integrity result from structurally weak vessels or vessel damage due to inflammation and immune mechanisms.
Thrombocytopenia
Thrombocytopenia represents a decrease in the number of circulating platelets (usually less than 100,000/mm³). It can result from decreased platelet production by the bone marrow, increased pooling of platelets in the spleen, or decreased platelet survival caused by immune or nonimmune mechanisms. Dilutional thrombocytopenia can result from massive transfusions because blood stored for more than 24 hours has virtually no platelets.

Decreased platelet production can result from suppression or failure of bone marrow function, such as occurs in aplastic anemia (see Chapter 13), or from replacement of bone marrow by malignant cells, such as occurs in leukemia (see Chapter 11). Infection with human immunodeficiency virus (HIV) suppresses the production of megakaryocytes. Radiation therapy and drugs such as those used in the treatment of cancer may suppress bone marrow function and reduce platelet production.

There may be normal production of platelets but excessive pooling of platelets in the spleen. The spleen normally sequesters approximately 30% to 40% of the platelets. However, as much as 80% of the platelets can be sequestered when the spleen is enlarged (splenomegaly). Splenomegaly occurs in cirrhosis with portal hypertension and in lymphomas.

Decreased platelet survival is an important cause of thrombocytopenia. In many cases, premature destruction of platelets is caused by antiplatelet antibodies or immune complexes. The antibodies can be directed against self-antigens (autoimmunity) or against nonself platelet antigens (from blood transfusions). Autoimmune thrombocytopenias include idiopathic thrombocytopenic purpura and HIV-associated thrombocytopenias. Decreased platelet survival may also occur as the result of mechanical injury associated with prosthetic heart valves.

Drug-Induced Thrombocytopenia. Some drugs, such as quinine, quinidine, and certain sulfa-containing antibiotics, may induce thrombocytopenia. These drugs act as a hapten (see Chapter 8) and induce antigen–antibody response and formation of immune complexes that cause platelet destruction by complement-mediated lysis. In persons with drug-associated thrombocytopenia, there is a rapid fall in platelet count within 2 to 3 days of resuming use of a drug or 7 or more days (i.e., the time needed to mount an immune response) after starting use of a drug for the first time. The platelet count rises rapidly after the drug use is discontinued.

The anticoagulant drug heparin has been increasingly implicated in thrombocytopenia and, paradoxically, in thrombosis. The complications typically occur 5 days after the start of therapy and result from production of heparin-dependent antiplatelet antibodies that cause aggregation of platelets and their removal from the circulation. The antibodies often bind to vessel walls, causing injury and thrombosis. The newer, low–molecular-weight heparin has been shown to be effective in reducing the incidence of heparin-induced complications compared with the older, high–molecular-weight form of the drug.8

Idiopathic Thrombocytopenic Purpura. Idiopathic thrombocytopenic purpura, an autoimmune disorder, results in platelet antibody formation and excess destruction of platelets. The IgG antibody binds to two identified membrane glycoproteins while in the circulation. The platelets, which are made more susceptible to phagocytosis because of the antibody, are destroyed in the spleen.

Acute idiopathic thrombocytopenic purpura is more common in children and usually follows a viral infection. It is characterized by sudden onset of petechiae and purpura and is a self-limited disorder with no treatment. In contrast, the chronic form is usually seen in adults and seldom follows an infection. It is a disease of young people, with a peak incidence between the ages of 20 and 50 years, and is seen twice as often in women as in men. It may be associated with other immune disorders such as acquired immunodeficiency syndrome (AIDS) or systemic lupus erythematosus. The condition occasionally presents precipitously with signs of bleeding, often into the skin (i.e., purpura and petechiae) or oral mucosa. There is commonly a history of bruising, bleeding from gums, epistaxis (i.e., nosebleeds), and abnormal menstrual bleeding. Because the spleen is the site of platelet destruction, splenic enlargement may occur.

Diagnosis usually is based on severe thrombocytopenia (platelet counts <20,000/mL), and exclusion of other causes. Treatment includes the initial use of corticosteroid drugs, often followed by splenectomy and the use of immunosuppressive agents.

Thrombotic Thrombocytopenic Purpura. Thrombotic thrombocytopenic purpura (TTP) is a combination of thrombocytopenia, hemolytic anemia, signs of vascular occlusion, fever, and neurologic abnormalities. The onset is abrupt, and the outcome may be fatal. Widespread vascular occlusions consist of thrombi in arterioles and capillaries of many organs, including the heart, brain, and kidneys. Erythrocytes become fragmented as they circulate through the partly occluded vessels and cause the hemolytic anemia. The clinical manifestations include purpura and petechiae and neurologic symptoms ranging from headache to seizures and altered consciousness.

Although TTP may have diverse causes, the initiating event seems to be widespread endothelial damage and activation of intravascular thrombosis. Toxins produced by certain strains of Escherichia coli (e.g., E. coli O157:H7) are a trigger for endothelial damage and an associated condition called the hemolytic-uremic syndrome (see Chapter 27).

Treatment for TTP includes plasmapheresis, a procedure that involves removal of plasma from withdrawn blood and replacement with fresh-frozen plasma. The treatment is continued until remission occurs. With plasmapheresis treatment, there is a complete recovery in 80% to 90% of cases.

Impaired Platelet Function
Impaired platelet function (also called thrombocytopenia) may result from inherited disorders of adhesion (e.g., von Willebrand disease) or acquired defects caused by drugs, disease, or extracorporeal circulation. Defective platelet function is also common in uremia, presumably because of unexcreted waste products. Cardiopulmonary bypass also causes platelet defects and destruction.

Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is the most common cause of impaired platelet function. Aspirin (acetylsalicylic acid) produces irreversible acetylation of platelet cyclooxygenase (COX), the enzyme required for TXA₂ synthesis. The antiplatelet effects of aspirin last
for the life of the platelet, usually approximately 8 to 9 days. Because aspirin prolongs bleeding time, it is usually recommended that aspirin use be avoided for a week before surgery. The antiplatelet effects of other NSAIDs, which do not contain the acetyl group, are reversible and last only for the duration of drug action. Because of aspirin’s antiplatelet function, low doses of the drug (usually 81 mg daily) are commonly used in the prevention of heart attack and stroke.

Coagulation Defects

Impairment of blood coagulation can result from deficiencies of one or more of the known clotting factors. Deficiencies can arise because of defective synthesis, inherited defects, or increased consumption of the clotting factors. Bleeding that results from clotting factor deficiency typically occurs after injury or trauma. Large bruises, hematomas, or prolonged bleeding into the gastrointestinal or urinary tracts or joints are common.

Impaired Synthesis of Coagulation Factors

Coagulation factors V, VII, IX, X, XI, and XII; prothrombin; and fibrinogen are synthesized in the liver. In liver disease, synthesis of these clotting factors is reduced, and bleeding may result. Of the coagulation factors synthesized in the liver, factors VII, IX, and X and prothrombin require the presence of vitamin K for normal activity. In vitamin K deficiency, the liver produces the clotting factor, but in an inactive form. Vitamin K is a fat-soluble vitamin that is continuously being synthesized by intestinal bacteria. This means that a deficiency in vitamin K is not likely to occur unless intestinal synthesis is interrupted or absorption of the vitamin is impaired. Vitamin K deficiency can occur in the newborn infant before the establishment of the intestinal flora; it can also occur as a result of treatment with broad-spectrum antibiotics that destroy intestinal flora. Because vitamin K is a fat-soluble vitamin, its absorption requires bile salts. Vitamin K deficiency may result from impaired fat absorption caused by liver or gallbladder disease.

Hereditary defects have been reported for each of the clotting factors, but most are rare diseases. The bleeding disorders are hemophilia A, which affects 1 in 10,000 males, and von Willebrand disease, which occurs in 1% of the population. Factor IX deficiency (i.e., hemophilia B) occurs in approximately 1 in 50,000 persons and is genetically and clinically similar to hemophilia A.

Circulating factor VIII is part of a complex molecule, bound to vWF. Factor VIII coagulant protein is the functional portion produced by the liver and endothelial cells. vWF, synthesized by the endothelium and megakaryocytes, binds and stabilizes factor VIII in the circulation by preventing proteolysis. It is also required for platelet adhesion to the subendothelial layer.

Hemophilia A

Hemophilia A, which is caused by a deficiency in factor VIII, is an X-linked recessive disorder that primarily affects males. Although it is a hereditary disorder, there is no family history of the disorder in approximately one third of newly diagnosed cases, suggesting that it has arisen as a new mutation in the factor VIII gene. Approximately 90% of persons with hemophilia produce insufficient quantities of the factor, and 10% produce a defective form. The percentage of normal factor VIII activity in the circulation depends on the genetic defect and determines the severity of hemophilia (i.e., 6% to 50% in mild hemophilia, 2% to 5% in moderate hemophilia, and 1% or less in severe forms of hemophilia). In mild or moderate forms of the disease, bleeding usually does not occur unless there is a local lesion or trauma such as surgery or dental procedures. The mild disorder may not be detected in childhood. In severe hemophilia, bleeding usually occurs in childhood (e.g., it may be noticed at the time of circumcision) and is spontaneous and severe. Characteristically, bleeding occurs in soft tissues, the gastrointestinal tract, and the hip, knee, elbow, and ankle joints. Joint bleeding usually begins when a child begins to walk. Often, a target joint is prone to repeated bleeding. The bleeding causes inflammation of the synovium, with acute pain and swelling. Without proper treatment, chronic bleeding and inflammation cause joint fibrosis and contractures, resulting in major disability. There is also the potential for life-threatening intracranial hemorrhage.

Factor VIII replacement therapy is initiated when bleeding occurs or as prophylaxis with repeated bleeding episodes. The purpose is to limit the extent of tissue damage. Highly purified factor VIII concentrates prepared from human plasma are the usual replacement products for persons with severe hemophilia. Before blood was tested for infectious diseases, these products were prepared from multiple donor samples and carried a high risk of exposure to viruses for hepatitis and HIV. Donor screening and the development of effective virus-inactivation procedures have effectively reduced the transmission of hepatitis viruses and HIV through clotting concentrates. Recombinant factor VIII, although expensive, is now available and should reduce the risk of transmitting HIV or other viruses. Desmopressin acetate (DDAVP, 1-desamino-8-D-arginine vasoconstrictor) may be used to prevent bleeding in persons with mild hemophilia. It stimulates the release of vWF (the carrier for factor VIII) from the endothelium, thus increasing factor VIII levels twofold to threefold for several hours.

The cloning of the factor VIII gene and progress in gene delivery systems have led to the hope that hemophilia A may be cured by gene therapy. Carrier detection and prenatal diagnosis can now be done by analysis of direct gene mutation or DNA linkage studies.

Von Willebrand Disease

Von Willebrand disease, which typically is diagnosed in adulthood, is the most common hereditary bleeding disorder. Transmitted as an autosomal trait, it is caused by a deficiency of or defect in vWF. This deficiency results in reduced platelet adhesion. There are many variants of the disease, and manifestations range from mild to severe. Because vWF carries factor VIII, its deficiency may also be accompanied by reduced levels of factor VIII and results in defective clot formation. Symptoms include bruising, excessive menstrual flow, and bleeding from the nose, mouth, and gastrointestinal tract. Many persons with the disorder receive a diagnosis when surgery or dental extraction results in prolonged bleeding. Most cases are mild and untreated.

In severe cases, factor VIII products that contain vWF are infused to replace the deficient clotting factors. The disorder also responds to desmopressin acetate (DDAVP), a synthetic ana-
log of the hormone vasopressin, which stimulates the endothelial cells to release vWF and plasminogen activator. DDAVP can also be used to treat platelet dysfunction caused by uremia, heart bypass, and the effects of aspirin.11

**Disseminated Intravascular Coagulation**

Disseminated intravascular coagulation is a paradox in the hemostatic sequence and is characterized by widespread intravascular coagulation and bleeding. It is not a primary disease but occurs as a complication of a wide variety of conditions. DIC begins with massive activation of the coagulation sequence as a result of unregulated generation of thrombin, resulting in systemic formation of fibrin. In addition, levels of all the major anticoagulants are reduced (Fig. 12-6). The generation of microthrombi results in vessel occlusion and tissue ischemia. Multiple organ failure may ensue. Clot formation consumes all available coagulation proteins and platelets, and severe hemorrhage results.

The disorder can be initiated by activation of the intrinsic or extrinsic pathways, both of which involve the formation of thrombin (see Fig. 12-4). Initiation of DIC through the extrinsic pathway, as occurs with trauma and cancer, begins with the liberation of tissue factor. The intrinsic pathway may be activated through extensive endothelial damage caused by viruses, infections, or immune mechanisms, or stasis of blood. Obstetric disorders that involve necrotic placental or fetal tissue commonly are associated with DIC. Other inciting clinical conditions include massive trauma, burns, sepsis, shock, meningococemia, and malignant disease. The initiating factors in these conditions are multiple and often related. For example, in infections, particularly those caused by gram-negative bacteria, endotoxins released from the bacteria activate both the intrinsic and extrinsic pathways. In addition, endotoxins inhibit the anticoagulant activity of protein C. In obstetric conditions, tissue factor released from the necrotic placental or fetal tissue may enter the circulation. At the same time, the shock, hypoxia, and acidosis that often coexist with the obstetrical condition can also cause widespread endothelial injury.5 Chart 12-2 summarizes the conditions associated with DIC.

There is also evidence that the fibrinolytic system may be involved in the pathogenesis of DIC. It may be suppressed and thereby contribute to the formation of microthrombi, or it may be the source of fibrin degradation products that contribute to the bleeding that occurs. Finally, regardless of the inciting event, DIC may be a systemic inflammatory disorder with release of proinflammatory cytokines that mediate the derangement of coagulation and fibrin breakdown.12

Although coagulation and formation of microemboli initiate the events that characterize DIC, its acute manifestations usually are more directly related to the bleeding problems that occur. The bleeding may be present as petechiae, purpura, ooze from puncture sites, or severe hemorrhage. Cardiovascular shock is a common complication. Uncontrolled postpartum bleeding may indicate DIC. Microemboli may obstruct blood

![FIGURE 12-6](null) Pathophysiology of disseminated intravascular coagulation.
Unit Three: Alterations in the Hematologic System

vessels and cause tissue hypoxia and necrotic damage to organ structures, such as the kidneys, heart, lungs, and brain. As a result, common clinical signs may be caused by renal, circulatory, or respiratory failure. A form of hemolytic anemia may develop as red cells are damaged as they pass through vessels partially blocked by thrombus.

The treatment of DIC is directed toward managing the primary disease, replacing clotting components, and preventing further activation of clotting mechanisms. Transfusions of fresh-frozen plasma, platelets, or fibrinogen-containing cryoprecipitate may correct the clotting factor deficiency. Heparin may be given to decrease blood coagulation, thereby interrupting the clotting process.

Vascular Disorders

Bleeding from small blood vessels may result from vascular disorders. These disorders may occur because of structurally weak vessel walls or because of damage to vessels by inflammation or immune responses. Among the vascular disorders that cause bleeding are hemorrhagic telangiectasia, an uncommon autosomal dominant disorder characterized by thin-walled, dilated capillaries and arterioles; vitamin C deficiency (i.e., scurvy), resulting in poor collagen synthesis and failure of the endothelial cells to be cemented together properly, which causes a fragile wall; Cushing’s disease, causing protein wasting and loss of vessel tissue support because of excess cortisol; and senile purpura (i.e., bruising in elderly persons) caused by the aging process. Vascular defects also occur in the course of DIC as a result of the presence of microthrombi and corticosteroid therapy.

Vascular disorders are characterized by easy bruising and the spontaneous appearance of petechiae and purpura of the skin and mucous membranes. In persons with bleeding disorders caused by vascular defects, the platelet count and results of other tests for coagulation factors are normal.

CHART 12-2 Conditions That Have Been Associated With DIC

Obstetric Conditions
- Abruptio placentae
- Dead fetus syndrome
- Preeclampsia and eclampsia
- Amniotic fluid embolism

Cancers
- Metastatic cancer
- Leukemia

Infections
- Acute bacterial infections (e.g., meningococcal meningitis)
- Acute viral infections
- Rickettsial infections (e.g., Rocky Mountain spotted fever)
- Parasitic infection (e.g., malaria)

Shock
- Septic shock
- Severe hypovolemic shock

Trauma or Surgery
- Burns
- Massive trauma
- Surgery involving extracorporeal circulation
- Snake bite
- Heatstroke

Hematologic Conditions
- Blood transfusion reactions

In summary, bleeding disorders or impairment of blood coagulation can result from defects in any of the factors that contribute to hemostasis: platelets, coagulation factors, or vascular integrity. The number of circulating platelets can be decreased (i.e., thrombocytopenia), or platelet function can be impaired (i.e., thrombocytopenia). Impairment of blood coagulation can result from deficiencies of one or more of the known clotting factors. Deficiencies can arise because of defective synthesis (i.e., liver disease or vitamin K deficiency), inherited diseases (i.e., hemophilia A or von Willebrand disease), or increased consumption of the clotting factors (DIC). Bleeding may also occur from structurally weak vessels that result from impaired synthesis of vessel wall components (i.e., vitamin C deficiency, excessive cortisol levels such as in Cushing’s disease, or the aging process) or from damage by genetic mechanisms (i.e., hemorrhagic telangiectasia) or the presence of microthrombi.

REVIEW QUESTIONS

- Relate the function of the platelet to platelet clot formation in myocardial infarction and thrombocytopenia.
- Explain the physiologic basis for the antiplatelet effects of low-dose aspirin.
- Explain the mechanisms whereby immobility, dehydration, oral contraceptive medications, and the antiphospholipid syndrome predispose to blood clotting.
- State the mechanisms of drug-induced thrombocytopenia and idiopathic thrombocytopenia and the differing features in terms of onset and resolution of the disorders.
- Newborn infants often receive an injection of vitamin K shortly after birth. Explain the rationale for this treatment.
- Differentiate between the mechanisms of bleeding in hemophilia A and von Willebrand disease.
- Explain why desmopressin acetate (DDAVP, 1-desamino-8-D-arginine vasopressin) is sometimes used in the treatment of mild hemophilia.
- Use information related to blood coagulation to explain the differing actions of the anticoagulant drugs heparin and warfarin.
- Describe the physiologic events that occur with acute disseminated intravascular coagulation.
REFERENCES