tate myocardial ischemia (angina or infarction) (see Chapter 53); in carotid or cerebral arteries, a thrombus may precipitate a stroke; in peripheral arteries, a thrombus may cause intermittent claudication (pain in the legs with exercise) or acute occlusion. Thus, serious impairment of blood flow may occur with a large atherosclerotic plaque or a relatively small plaque with superimposed vasospasm and thrombosis. Consequences and clinical manifestations of thrombi and emboli depend primarily on their location and size.

Normally, thrombi are constantly being formed and dissolved (thrombolysis), but the blood stays fluid and flow is not significantly obstructed. If the balance between thrombogenesis and thrombolysis is upset, thrombotic or bleeding disorders result. Thrombotic disorders occur much more often than bleeding disorders and are emphasized in this chapter; bleeding disorders may result from excessive amounts of drugs that inhibit clotting. To aid understanding of drug therapy for thrombotic disorders, normal hemostasis, endothelial functions in relation to blood clotting, platelet functions, blood coagulation, and characteristics of arterial and venous thrombosis are described.

## HEMOSTASIS

*Hemostasis* is prevention or stoppage of blood loss from an injured blood vessel and is the process that maintains the integrity of the vascular compartment. It involves activation of several mechanisms, including vasoconstriction, formation of a platelet plug (a cluster of aggregated platelets), sequential activation of clotting factors in the blood (Table 57–1), and growth of fibrous tissue (fibrin) into the blood clot to make it more stable and to repair the tear (opening) in the damaged blood vessel. Overall, normal hemostasis is a complex process involving numerous interacting activators and inhibitors, including endothelial factors, platelets, and blood coagulation factors (Box 57–1).

## CLOT LYSIS

When a blood clot is being formed, plasminogen (an inactive protein found in many body tissues and fluids) is bound to fibrin and becomes a component of the clot. After the outward blood flow is stopped and the tear in the blood vessel repaired, plasminogen is activated by plasminogen activator (produced by endothelial cells or the coagulation cascade) to produce plasmin. Plasmin is an enzyme that breaks down the fibrin meshwork that stabilizes the clot; this fibrinolytic or thrombolytic action dissolves the clot.

## THROMBOTIC AND THROMBOEMBOLIC DISORDERS

Thrombosis may occur in both arteries and veins. Arterial thrombosis is usually associated with atherosclerotic plaque, hypertension, and turbulent blood flow. These conditions damage arterial endothelium and activate platelets to initiate the coagulation process. Arterial thrombi cause disease by obstructing blood flow. If the obstruction is incomplete or temporary, local tissue ischemia (deficient blood supply) occurs. If the obstruction is complete or prolonged, local tissue death or infarction occurs.

Venous thrombosis is usually associated with venous stasis. When blood flows slowly, thrombin and other procoagulant substances present in the blood become concentrated in local areas and initiate the clotting process. With a normal rate of blood flow, these substances are rapidly removed from the blood, primarily by Kupffer cells in the liver. A venous thrombus is less cohesive than an arterial thrombus, and an embolus can easily become detached and travel to other parts of the body.

Venous thrombi cause disease by two mechanisms. First, thrombosis causes local congestion, edema, and perhaps inflammation by impairing normal outflow of venous blood (eg, thrombophlebitis, deep vein thrombosis [DVT]). Sec-

TABLE 57–1 **Blood Coagulation Factors**

| Number | Name | Functions |
|---|---|---|
| I | Fibrinogen | Forms fibrin, the insoluble protein strands that compose the supporting framework of a blood clot. Thrombin and calcium are required for the conversion. |
| II | Prothrombin | Forms thrombin, which catalyzes the conversion of fibrinogen to fibrin |
| III | Thromboplastin | Converts prothrombin to thrombin |
| IV | Calcium | Catalyzes the conversion of prothrombin to thrombin |
| V | Labile factor | Required for formation of active thromboplastin |
| VII | Proconvertin or stable factor | Accelerates action of tissue thromboplastin |
| VIII | Antihemophilic factor | Promotes breakdown of platelets and formation of active platelet thromboplastin |
| IX | Christmas factor | Similar to factor VIII |
| X | Stuart factor | Promotes action of thromboplastin |
| XI | Plasma thromboplastin antecedent | Promotes platelet aggregation and breakdown, with subsequent release of platelet thromboplastin |
| XII | Hageman factor | Similar to factor XI |
| XIII | Fibrin-stabilizing factor | Converts fibrin meshwork to the dense, tight mass of the completely formed clot |