BOX 57–1 HEMOSTASIS AND THROMBOSIS (*Continued*)

complex is capable of binding a single fibrinogen molecule. However, a fibrinogen molecule may bind to receptors on adjacent activated platelets, thus acting as a bridge to connect the platelets. Activated GP IIb/IIIa complexes can also bind von Willebrand factor and promote platelet aggregation when fibrinogen is lacking.

Aggregated platelets produce and release thromboxane A_2, which acts with ADP from platelet storage granules to promote additional GP IIb/IIIa activation, platelet secretion, and aggregate formation. The exposure of functional GP IIb/IIIa complexes is also stimulated by thrombin, which can directly stimulate thromboxane A_2 synthesis and granule secretion without initial aggregation. Collagen stimulates additional aggregation by increasing the production of thromboxane A_2 and storage granule secretion.

Overall, aggregated platelets release substances that recruit new platelets and stimulate additional aggregation. This activity helps the platelet plug become large enough to block blood flow out of a damaged blood vessel. If the opening is small, the platelet plug can stop blood loss. If the opening is large, a platelet plug and a blood clot are both required to stop the bleeding.

Procoagulant Activity

In addition to forming a platelet thrombus, platelets also activate and interact with circulating blood coagulation factors to form a larger and more stable blood clot. Activation of the previously inactive blood coagulation factors leads to formation of fibrin threads that attach to the platelets and form a tight meshwork of a fully developed blood clot.

More specifically, the platelet plug provides a surface on which coagulation enzymes, substrates, and cofactors interact at high local concentrations. These interactions lead to activation of coagulation factor X and the conversion of prothrombin to thrombin.

Blood Coagulation

The blood coagulation process causes hemostasis within 1 to 2 minutes. It involves sequential activation of clotting factors that are normally present in blood and tissues as inactive precursors and formation of a meshwork of fibrin strands that cements blood components together to form a stable, dense clot. Major phases include release of thromboplastin by disintegrating platelets and damaged tissue; conversion of prothrombin to thrombin, which requires thromboplastin and calcium ions; and conversion of fibrinogen to fibrin by thrombin.

Blood coagulation results from activation of the intrinsic or extrinsic coagulation pathway. Both pathways, which are activated when blood passes out of a blood vessel, are needed for normal hemostasis. The intrinsic pathway occurs in the vascular system; the extrinsic pathway occurs in the tissues. Although the pathways are initially separate, the terminal steps (ie, activation of factor X and thrombin-induced formation of fibrin) are the same.

The intrinsic pathway is activated when blood comes in contact with collagen in the injured vessel wall and coagulation factor XII interacts with biologic surfaces. The normal endothelium prevents factor XII from interacting with such surfaces. The activated form of factor XII is a protease that starts the interactions among factors involved in the intrinsic pathway (eg, prekallikrein, factor IX, factor VIII).

The extrinsic pathway is activated when blood is exposed to tissue extracts and tissue factor interacts with circulating coagulation factor VII. Activated factors VII and IX both act on factor X to produce activated factor X, which then interacts with factor V, calcium, and platelet factor 3. Platelet factor 3, a component of the platelet cell membrane, becomes available on the platelet surface only during platelet activation. The interactions among these substances lead to formation of thrombin, which then activates fibrinogen to form fibrin, and the clot is complete.

ond, embolization obstructs the blood supply when the embolus becomes lodged. The pulmonary arteries are common sites of embolization.

DRUGS USED IN THROMBOTIC AND THROMBOEMBOLIC DISORDERS

Drugs given to prevent or treat thrombosis alter some aspect of the blood coagulation process. Anticoagulants are widely used in thrombotic disorders. They are more effective in preventing venous thrombosis than arterial thrombosis. Antiplatelet drugs are used to prevent arterial thrombosis. Thrombolytic agents are used to dissolve thrombi and limit tissue damage in selected thromboembolic disorders. These drugs are described in the following sections and in Drugs at a Glance: Anticoagulant, Antiplatelet, and Thrombolytic Agents.

Anticoagulants

Anticoagulant drugs are given to prevent formation of new clots and extension of clots already present. They do not dissolve formed clots, improve blood flow in tissues around the clot, or prevent ischemic damage to tissues beyond the clot. Heparins and warfarin are commonly used anticoagulants; danaparoid and lepirudin are newer agents. Clinical indications include prevention or management of thromboembolic disorders, such as thrombophlebitis, DVT, and pulmonary embolism. The main adverse effect is bleeding.

Heparin

Heparin is a pharmaceutical preparation of the natural anticoagulant produced primarily by mast cells in pericapillary connective tissue. Endogenous heparin is found in various body tissues, most abundantly in the liver and lungs. Exogenous heparin is obtained from bovine lung or porcine intestinal mucosa and standardized in units of biologic activity.

Heparin combines with antithrombin III (a natural anticoagulant in the blood) to inactivate clotting factors IX, X, XI, and XII, inhibit the conversion of prothrombin to thrombin, and prevent thrombus formation. After thrombosis has developed, heparin can inhibit additional coagulation by inactivating thrombin, preventing the conversion of fibrinogen to