factors. During platelet aggregation (platelet-platelet interaction), additional platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is anchored and stabilized by the developing fibrin mesh.

The platelet glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb}\beta_3$) complex is the most abundant receptor on the platelet surface. Platelet activation converts the normally inactive Gp IIb/IIIa receptor into an active receptor, enabling binding to fibrinogen and VWF. Because the surface of each platelet has about 50,000 Gp IIb/IIIa–binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. Because this receptor is the key mediator of platelet aggregation, it has become an effective target for antiplatelet therapy.

FIBRIN CLOT FORMATION

Plasma coagulation proteins (*clotting factors*) normally circulate in plasma in their inactive forms. The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a *waterfall* or a *cascade*. Two pathways of blood coagulation have been described in the past: the so-called extrinsic, or tissue factor, pathway and the so-called intrinsic, or contact activation, pathway. We now know that coagulation is normally initiated through tissue factor (TF) exposure and activation through the classic *extrinsic pathway* but with critically important amplification through elements of the classic *intrinsic pathway*, as illustrated in Fig. 78-1. These reactions take place on phospholipid surfaces, usually the activated platelet surface. Coagulation testing in the laboratory can reflect other influences due to the artificial nature of the in vitro systems used (see below).

The immediate trigger for coagulation is vascular damage that exposes blood to TF that is constitutively expressed on the surfaces of subendothelial cellular components of the vessel wall, such as smooth muscle cells and fibroblasts. TF is also present in circulating microparticles, presumably shed from cells including monocytes and platelets. TF binds the serine protease factor VIIa; the complex activates factor X to factor Xa. Alternatively, the complex can indirectly activate factor X by initially converting factor IX to factor IXa, which then activates factor X. The participation of factor XI in hemostasis is not dependent on its activation by factor XIIa but rather on its positive feedback activation by thrombin. Thus, factor XIa functions in the propagation and amplification, rather than in the initiation, of the coagulation cascade.

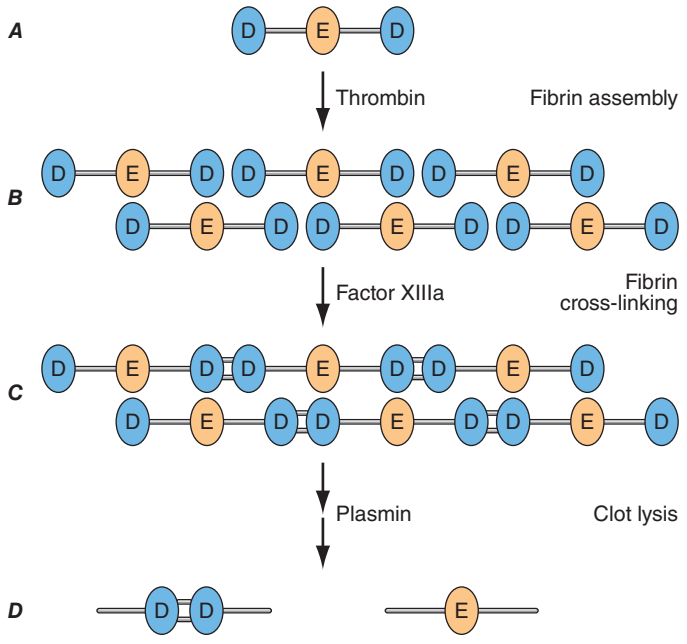

FIGURE 78-2 Fibrin formation and dissolution. (***A***) Fibrinogen is a trinodular structure consisting of two D domains and one E domain. Thrombin activation results in an ordered lateral assembly of protofibrils (***B***) with noncovalent associations. Factor XIIIa cross-links the D domains on adjacent molecules (***C***). Fibrin and fibrinogen (not shown) lysis by plasmin occurs at discrete sites and results in intermediary fibrin(ogen) degradation products (not shown). D-Dimers are the product of complete lysis of fibrin (***D***), maintaining the cross-linked D domains.

Factor Xa can be formed through the actions of either the TF/factor VIIa complex or factor IXa (with factor VIIIa as a cofactor) and converts prothrombin to thrombin, the pivotal protease of the coagulation system. The essential cofactor for this reaction is factor Va. Like the homologous factor VIIIa, factor Va is produced by thrombin-induced limited proteolysis of factor V. Thrombin is a multifunctional enzyme that converts soluble plasma fibrinogen to an insoluble fibrin matrix. Fibrin polymerization involves an orderly process of intermolecular associations (Fig. 78-2). Thrombin also activates factor XIII (fibrin-stabilizing factor) to factor XIIIa, which covalently cross-links and thereby stabilizes the fibrin clot.

The assembly of the clotting factors on activated cell membrane surfaces greatly accelerates their reaction rates and also serves to localize blood clotting to sites of vascular injury. The critical cell membrane components, acidic phospholipids, are not normally exposed on resting cell membrane surfaces. However, when platelets, monocytes, and endothelial cells are activated by vascular injury or inflammatory stimuli, the procoagulant head groups of the membrane anionic phospholipids become translocated to the surfaces of these cells or released as part of microparticles, making them available to support and promote the plasma coagulation reactions.

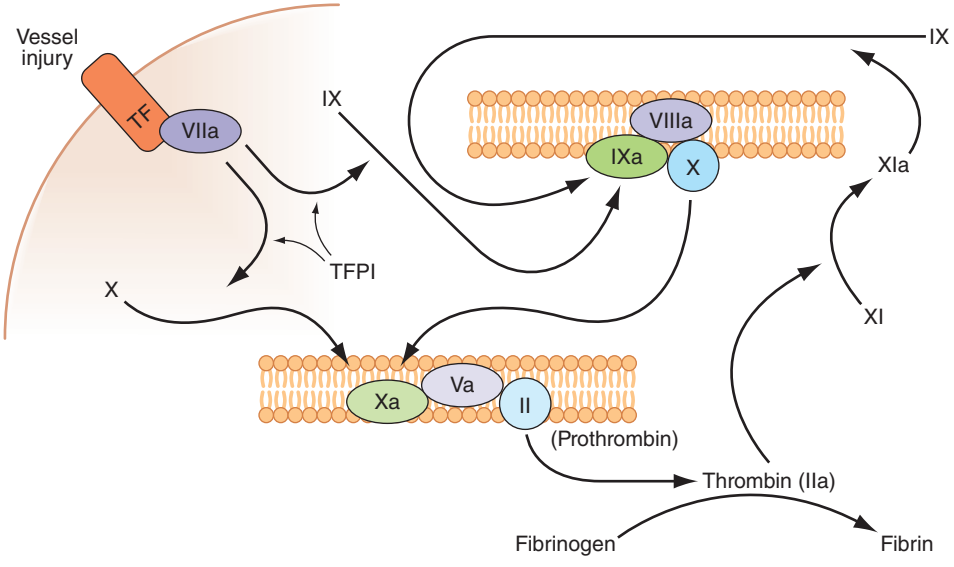

FIGURE 78-1 Coagulation is initiated by tissue factor (TF) exposure, which, with factor (F) VIIa, activates FIX and FX, which in turn, with FVIII and FV as cofactors, respectively, results in thrombin formation and subsequent conversion of fibrinogen to fibrin. Thrombin activates FXI, FVIII, and FV, amplifying the coagulation signal. Once the TF/FVIIa/FXa complex is formed, tissue factor pathway inhibitor (TFPI) inhibits the TF/FVIIa pathway, making coagulation dependent on the amplification loop through FIX/FVIII. Coagulation requires calcium (not shown) and takes place on phospholipid surfaces, usually the activated platelet membrane.