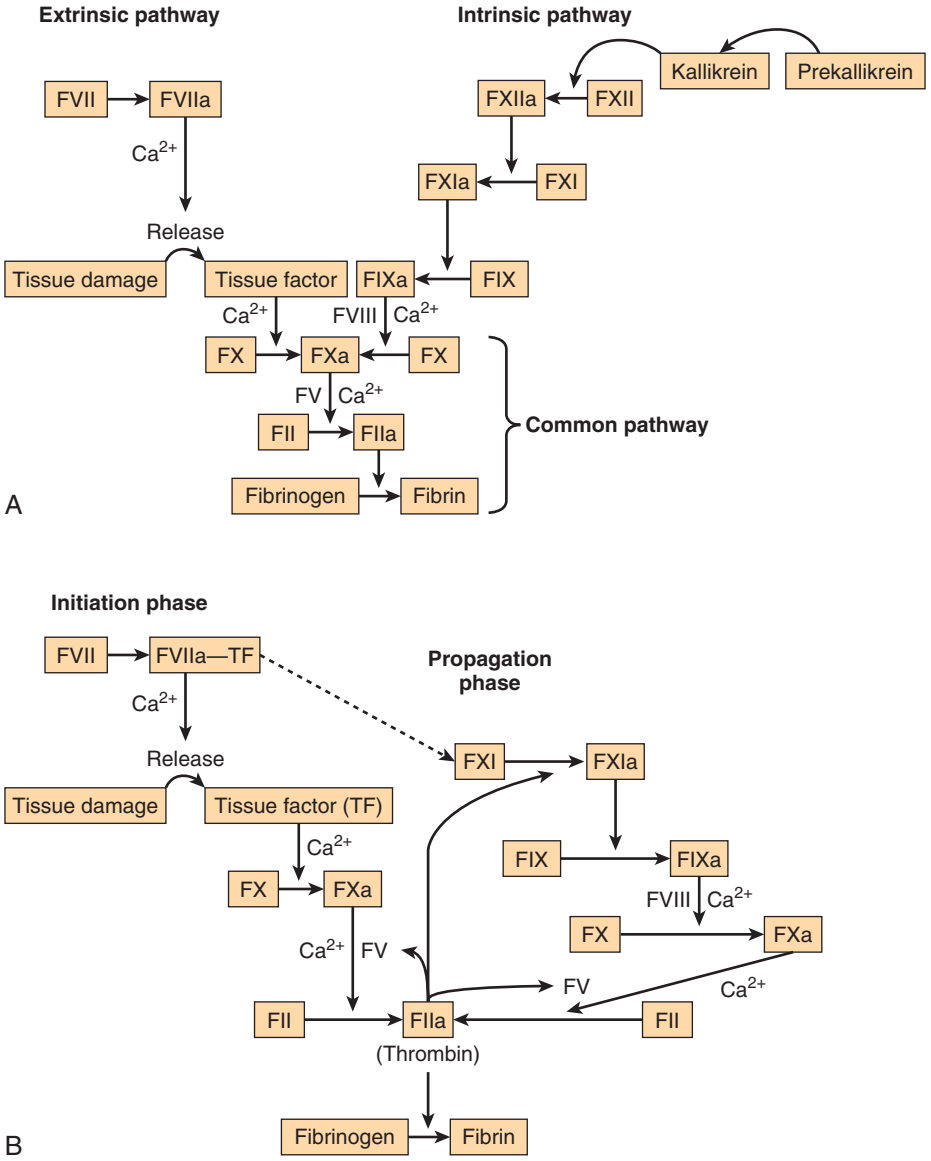

FIGURE 50-2 **A,** The classic view of the coagulation cascade. The laboratory-defined *extrinsic* and *intrinsic* pathways allow monitoring of anticoagulation by serial measurements of the prothrombin time (PT) and partial thromboplastin time (PTT), respectively. The PT primarily monitors factor VII activity, whereas the PTT is the best measure of XI and the hemophilic factors IX and VIII; both assays will detect deficiency of the common pathway factors (X, V, and II). **B,** In the more modern view of the coagulation cascade, initiation of clotting begins with exposure to tissue factor (TF), which combines with small amounts of circulating factor (F)VIIa to form the extrinsic tenase (Xase) complex and generate FXa. FXa forms the prothrombinase complex with FVa and FII, generating small amounts of thrombin (FIIa), which begins to cleave fibrinogen into weak fibrin monomers in the initiation phase of coagulation. Thrombin's ability to activate factors, especially on the activated platelet surface, is responsible for propagation of the coagulant response. Thrombin generates FXIa, which, in turn, activates FIX; the TF-VIIa complex (before it is shut down by TFPI) also generates FIXa. Thrombin-activated FVIIIa then combines with IXa to form the intrinsic Xase complex, generating large amounts of FXa and prothrombinase complex on the platelet surface to further amplify thrombin generation. The large amounts of thrombin now generate enough fibrin monomers to form stable polymers and fibrin clot. HMWK, High-molecular-weight kininogen; PK, prekallikrein; TFPI, tissue factor pathway inhibitor.

In the setting of high-velocity blood flow at an arterial bleeding site, platelets must activate and adhere to the injured vessel almost instantaneously (see Fig. 50-1A). Two molecules that are present in the subendothelium are critical for this process: vWF and collagen. Control of bleeding in vessels under the highest shear stresses absolutely depends on the presence and function of vWF. vWF is a large molecule synthesized as multimeric *strings* in ECs and megakaryocytes, and multimeric vWF is both constitutively secreted into blood and stored in Weibel-Palade bodies of ECs. The *ultralarge* vWF multimers are the most active at binding platelets, particularly when *unfolded,* either by shear stress or after tethering to the vessel surface. The multimeric forms of vWF, which are immobilized by adherence to exposed subendothelial collagen, bind to the GPIb-IX-V complex on the platelet surface when normally cryptic loci are exposed by high shear stress. This binding is extremely rapid but has low affinity; therefore, the platelets are slowed at this interface, but they are left only weakly adherent to subendothelial vWF. With platelets no longer streaming by, but instead tumbling or sliding over the subendothelium, the high shear stress in tandem with