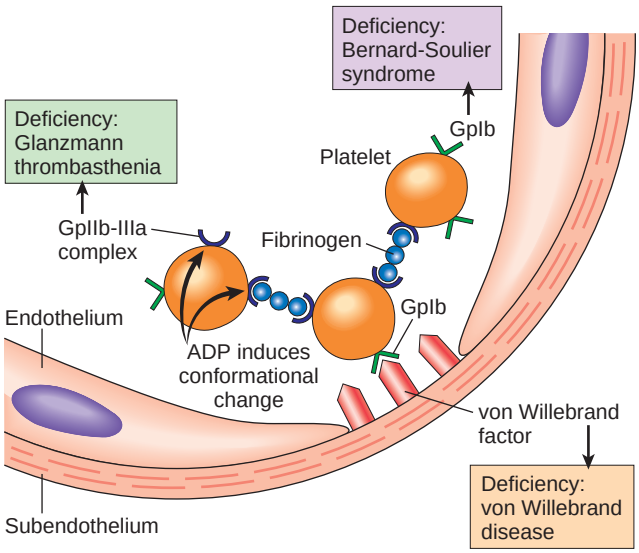

Figure 4-5 Platelet adhesion and aggregation. Von Willebrand factor functions as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor. Aggregation is accomplished by fibrinogen bridging GpIIb-IIIa receptors on different platelets. Congenital deficiencies in the various receptors or bridging molecules lead to the diseases indicated in the colored boxes. ADP, adenosine diphosphate.

often referred to together as *platelet activation*. Platelet activation is triggered by a number of factors, including he coagulation factor thrombin and ADP. Thrombin activates platelets through a special type of G-protein–coupled receptor referred to as a *protease-activated receptor* (PAR), which is switched on by a proteolytic cleavage carried out by thrombin. ADP is a component of dense-body granules; thus, platelet activation and ADP release begets additional rounds of platelet activation, a phenomenon referred to as *recruitment*. Activated platelets also produce the prostaglandin *thromboxane* A_2 (TxA_2), a potent inducer of platelet aggregation. *Aspirin* inhibits platelet aggregation and produces a mild bleeding defect by inhibiting cyclooxygenase, a platelet enzyme that is required for TxA_2 synthesis. Although the phenomenon is less well characterized, it is also suspected that growth factors released from platelets contribute to the repair of the vessel wall following injury.

- *Platelet aggregation* follows their activation. The conformational change in glycoprotein IIb/IIIa that occurs with platelet activation allows binding of fibrinogen, a large bivalent plasma polypeptide that forms bridges between adjacent platelets, leading to their aggregation. Predictably, inherited deficiency of GpIIb-IIIa results in a bleeding disorder called *Glanzmann thrombasthenia)*. The initial wave of aggregation is reversible, but concurrent activation of thrombin stabilizes the platelet plug by causing further platelet activation and aggregation, and by promoting irreversible *platelet contraction*. Platelet contraction is dependent on the cytoskeleton and consolidates the aggregated platelets. In parallel, thrombin also converts fibrinogen into insoluble *fibrin*, cementing the platelets in place and creating the definitive *secondary hemostatic plug*. Entrapped red cells and leukocytes are also found in hemostatic plugs, in part due to adherence of leukocytes to P-selectin expressed on activated platelets.

Coagulation Cascade

The coagulation cascade is series of amplifying enzymatic reactions that leads to the deposition of an insoluble fibrin clot. As discussed later, the dependency of clot formation on various factors differs in the laboratory in the laboratory test tube and in blood vessels in vivo (Fig. 4-6).

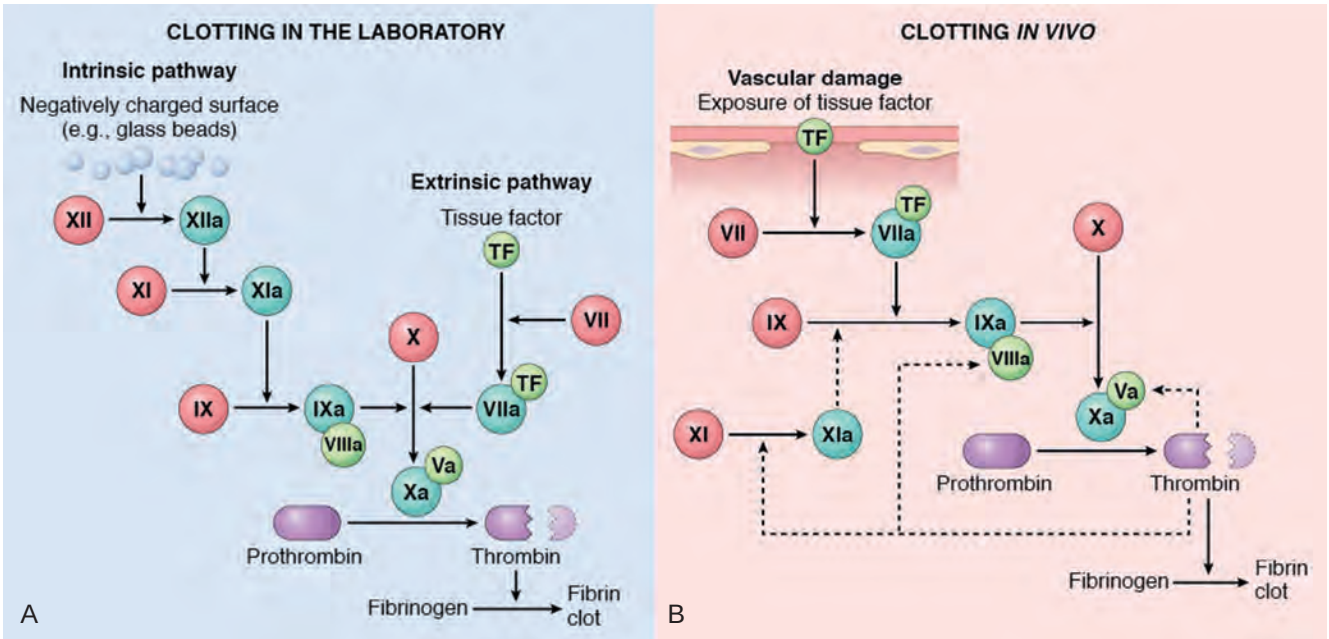

Figure 4-6 The coagulation cascade in the laboratory and in vivo. **A,** Clotting is initiated in the laboratory by adding phospholipids, calcium, and either a negative charged substance such as glass beads (intrinsic pathway) or a source of tissue factor (extrinsic pathway). **B,** In vivo, tissue factor is the major initiator of coagulation, which is amplified by feedback loops involving thrombin *(dotted lines)*. The red polypeptides are inactive factors, the dark green polypeptides are active factors, while the light green polypeptides correspond to cofactors..