Figure 4-4 Normal hemostasis. **A,** After vascular injury, local neurohumoral factors induce a transient vasoconstriction. **B,** Platelets bind via glycoprotein Ib (GpIb) receptors to von Willebrand factor (vWF) on exposed extracellular matrix (ECM) and are activated, undergoing a shape change and granule release. Released adenosine diphosphate (ADP) and thromboxane A_2 (TxA_2) induce additional platelet aggregation through platelet GpIIb-IIIa receptor binding to fibrinogen, and form the *primary* hemostatic plug. **C,** Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, "cementing" the platelets into a definitive *secondary* hemostatic plug. **D,** Counterregulatory mechanisms, mediated by tissue plasminogen activator (t-PA, a fibrinolytic product) and thrombomodulin, confine the hemostatic process to the site of injury.

permanent plug that prevents further hemorrhage. At this stage, counterregulatory mechanisms (e.g., *tissue plasminogen activator, t-PA*) are set into motion that limit clotting to the site of injury (Fig. 4-4*D*) and eventually lead to clot resorption and tissue repair.

The following sections discuss the roles of the platelets, coagulation factors, and endothelium in hemostasis in greater detail.

Platelets

Platelets play a critical role in hemostasis by forming the primary plug that initially seals vascular defects and by providing a surface that binds and concentrates activated coagulation factors. Platelets are disc-shaped anucleate cell fragments that are shed from megakaryocytes in the bone marrow into the bloodstream. Their function depends on several glycoprotein receptors, a contractile cytoskeleton, and two types of cytoplasmic granules. *α-Granules* have the adhesion molecule P-selectin on their membranes (Chapter 3) and contain proteins involved in coagulation, such as fibrinogen, coagulation factor V, and vWF, as well as protein factors that may be involved in wound healing, such as fibronectin, platelet factor 4 (a heparin-binding chemokine), platelet-derived growth factor (PDGF), and transforming growth factor-β. *Dense* (or δ) *granules* contain adenosine diphosphate (ADP) and adenosine triphosphate, ionized calcium, serotonin, and epinephrine.

After a traumatic vascular injury, platelets encounter constituents of the subendothelial connective tissue, such as vWF and collagen. On contact with these proteins, platelets undergo a sequence of reactions that culminate in the formation of a platelet plug (Fig. 4-4*B*).

- *Platelet adhesion* is mediated largely via interactions with vWF, which acts as a bridge between the platelet surface receptor glycoprotein Ib (GpIb) and exposed collagen (Fig. 4-5). Notably, genetic deficiencies of vWF (von Willebrand disease, Chapter 14) or GpIb (Bernard-Soulier syndrome) result in bleeding disorders, attesting to the importance of these factors.
- *Platelets rapidly change shape* following adhesion, being converted from smooth discs to spiky "sea urchins" with greatly increased surface area. This change is accompanied by alterations in *glycoprotein IIb/IIIa* that increase its affinity for fibrinogen (see later), and by the translocation of *negatively charged phospholipids* (particularly phosphatidylserine) to the platelet surface. These phospholipids bind calcium and serve as nucleation sites for the assembly of coagulation factor complexes.
- *Secretion (release reaction) of granule contents* occurs along with changes in shape; these two events are