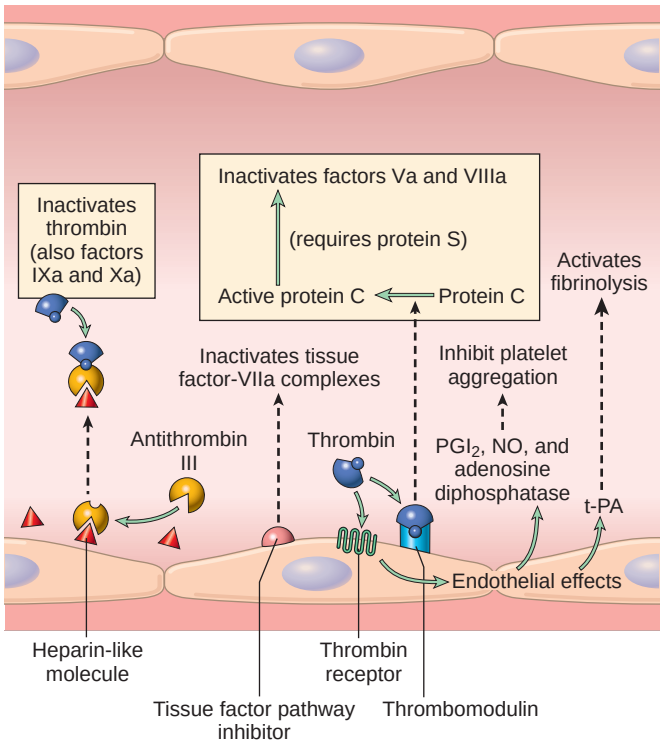

Figure 4-10 Anticoagulant activities of normal endothelium. NO, nitric oxide; PGI_2, prostacyclin; t-PA, tissue plasminogen activator; vWF, von Willebrand factor. The thrombin receptor is also called a protease-activated receptor (PAR).

Endothelium

The balance between the anticoagulant and procoagulant activities of endothelium often determines whether clot formation, propagation, or dissolution occurs. As alluded to earlier, normal endothelial cells express a multitude of factors that inhibit the procoagulant activities of platelets and coagulation factors and that augment fibrinolysis (Fig. 4-10). These factors act in concert to prevent thrombosis and to limit clotting to sites of vascular damage. However, if injured or exposed to proinflammatory factors, endothelial cells lose many of their antithrombotic properties. Here, we complete the discussion of hemostasis by focusing on the antithrombotic activities of normal endothelium; we return to the "dark side" of endothelial cells later when discussing thrombosis.

The antithrombotic properties of endothelium can be divided into activities directed at platelets, coagulation factors, and fibrinolysis.

- *Platelet inhibitory effects*. An obvious effect of intact endothelium is to serve as a barrier that shields platelets from subendothelial vWF and collagen. However, normal endothelium also releases a number of factors that inhibit platelet activation and aggregation. Among the most important are *prostacyclin (PGI_2)*, *nitric oxide (NO)*, and *adenosine diphosphatase*; the latter degrades ADP, already discussed as a potent activator of platelet aggregation. Finally, endothelial cells bind and alter the activity of thrombin, which is one of the most potent activators of platelets.
- *Anticoagulant effects.* Normal endothelium shields coagulation factors from tissue factor in vessel walls and expresses multiple factors that actively oppose coagulation, most notably thrombomodulin, endothelial protein C receptor, heparin-like molecules, and tissue factor pathway inhibitor. *Thrombomodulin* and *endothelial protein C receptor* bind thrombin and protein C, respectively, in a complex on the endothelial cell surface. When bound in this complex, thrombin loses its ability to activate coagulation factors and platelets, and instead cleaves and activates *protein C,* a vitamin K–dependent protease that requires a cofactor, protein S. Activated protein C/protein S complex is a potent inhibitor of coagulation factors Va and VIIIa. *Heparin-like molecules* on the surface of endothelium bind and activate antithrombin III, which then inhibits thrombin and factors IXa, Xa, XIa, and XIIa. The clinical utility of heparin and related drugs is based on their ability to stimulate antithrombin III activity. *Tissue factor pathway inhibitor* (TFPI), like protein C, requires protein S as a cofactor and, as the name implies, binds and inhibits tissue factor/factor VIIa complexes.
- *Fibrinolytic effects.* Normal endothelial cells synthesize t-PA, already discussed, as a key component of the fibrinolytic pathway.

Hemorrhagic Disorders

Disorders associated with abnormal bleeding inevitably stem from primary or secondary defects in vessel walls, platelets, or coagulation factors, all of which must function properly to ensure hemostasis. The presentation of abnormal bleeding varies widely. At one end of the spectrum are massive bleeds associated with ruptures of large vessels such as the aorta or of the heart; these catastrophic events simply overwhelm hemostatic mechanisms and are often fatal. Diseases associated with sudden, massive hemorrhage include aortic dissection in the setting of Marfan syndrome (Chapter 5), and aortic abdominal aneurysm (Chapter 11) and myocardial infarction (Chapter 12) complicated by rupture of the aorta or the heart. At the other end of the spectrum are subtle defects in clotting that only become evident under conditions of hemostatic stress, such as surgery, childbirth, dental procedures, menstruation, or trauma. Among the most common causes of mild bleeding tendencies are inherited defects in von Willebrand factor (Chapter 14), aspirin consumption, and uremia (renal failure); the latter alters platelet function through uncertain mechanisms. Between these extremes lie deficiencies of coagulation factors (the hemophilias, Chapter 14), which are usually inherited and lead to severe bleeding disorders if untreated.

Additional specific examples of disorders associated with abnormal bleeding are discussed throughout the book. The following are general principles related to abnormal bleeding and its consequences.

- *Defects of primary hemostasis (platelet defects or von Willebrand disease)* often present with small bleeds in skin or mucosal membranes. These bleeds typically take the form of petechiae, minute 1- to 2-mm hemorrhages (Fig. 4-11*A*), or *purpura*, which are slightly larger