Figure 2. Cell-based model of hemostasis. Tissue factor pathway inhibitor (TFPI), activated protein C (APC), and antithrombin (AT) limit clot propagation by inhibiting the TF-Factor VIIa complex, Factors Va and VIIIa, and Factors IIa, IXa and XIa, respectively. [Modified from Hoffman et al. *Blood Coagul Fibrinol* 1998;9(Suppl 1):S61.]

The small amount of thrombin generated by the initial activation of prothrombin becomes essential to amplification and propagation of the clot by activating platelets and Factors V and VIII. As the reaction progresses, action of the intrinsic factor tenase on the activated platelet membrane results in >90% of Factor Xa generated. (In hemophilia A and B, this amplification does not occur.) The membrane-bound complex formed by Factors Va and Xa (prothrombinase) catalyzes the formation of most of the thrombin generated in this process.

Thrombin not only functions in clot initiation and propagation (as well as platelet activation) but also induces the polymerization of the soluble plasma protein fibrinogen, producing insoluble fibrin. (See Fig 3.) Fibrin is covalently crosslinked by Factor XIII, resulting in a stable fibrin clot. Thrombin also catalyzes the conversion of Factor XI to Factor XIa, which in turn
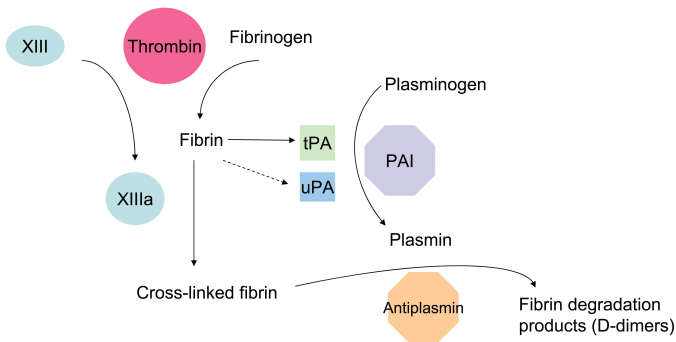
Figure 3. Fibrin formation and regulation. Fibrinolysis inhibitors include plasminogen activator inhibitor (PAI), which inhibits tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), and antiplasmin, which inhibits plasmin.

activates Factor IX. This positive feedback loop in turn results in generation of more thrombin.

The Anticoagulant and Fibrinolytic Systems

In vivo, hemostasis is limited by two general mechanisms. Anticoagulation regulates the generation of thrombin. Fibrinolysis is the process by which fibrin is cleared.

In anticoagulation, thrombin contributes to its own downregulation by binding to thrombomodulin on the vascular cell surface and by converting protein C to activated protein C, which in turn cleaves Factors Va and VIIIa, decreasing thrombin generation. (See Fig 2.) Protein S functions as a cofactor in this reaction, increasing the activity of activated protein C 10-fold.[5]

TF pathway inhibitor forms a complex with Factor Xa that inactivates the TF-Factor VIIa complex, decreasing thrombin generation. Antithrombin is a serpin proteinase that inhibits the proteases thrombin and Factors IXa, Xa, and XIa; heparin increases antithrombin activity 1000-fold.

Fibrinolysis is tightly regulated by a complex series of activators, inhibitors, cofactors, and receptors. (See Fig 3.) Fibrin serves as a cofactor in its own degradation. In the presence of fibrin, tissue plasminogen activator (tPA) is released from endothelial cells and interacts with plasminogen. This tPA-plasminogen-fibrin complex increases plasmin generation 500-fold. Urokinase also activates plasminogen but is only minimally enhanced by fibrin. Plasmin binds to and degrades cross-linked fibrin, generating soluble fibrin degradation products in the process.[6] In turn, there are fibrinolysis inhibitors. Plasmin generation is regulated by α_2-antiplasmin (α_2-AP), which inhibits plasmin, and plasminogen activator inhibitor 1 (PAI-1), which inhibits tPA. On the surface of a fibrin clot, plasmin and tPA are protected from their inhibitors, but, upon release into the circulation (when the fibrin clot is gone), they are neutralized and cleared. In the presence of thrombomodulin, thrombin can activate thrombin-activatable fibrinolysis inhibitor (TAFI), which decreases tPA-mediated fibrinolysis.

Hemostasis in Neonates and Children

Platelets

In both preterm and term neonates, normal platelet counts are similar to those in children and adults. Studies of fetal blood from cordocentesis samples show that the platelet count ranges from 116,000/μL to 184,000/μL by the end of the first trimes-

ter.[7] Traditionally, thrombocytopenia in all age groups is defined as a platelet count below 150,000/μL. For infants, with <28 weeks of gestation at birth, thrombocytopenia may be defined as below 135,000/μL.[8] Thrombocytopenia occurs in up to 25% of admissions to neonatal intensive care units.[9] Five to 10% will have severe thrombocytopenia (50,000/μL). Thrombopoietin is found in fetal liver as early as 6 weeks of gestation. Although the response to thrombocytopenia is blunted in comparison to that in older subjects, neonatal megakaryocyte progenitors appear to be more sensitive to thrombopoietin.[10]

There are observed differences in measured platelet function among preterm neonates, full-term neonates, infants, and adults; older children are thought to have platelet function similar to that of adults. In preterm neonates, platelet responsiveness to agonists, adhesion under shear conditions, activation, and granule secretion are decreased.[11] In full-term neonates, in contrast, platelet adhesion is enhanced compared to that in adults, which is thought to be due to increased vWF levels and platelet binding.[12] In addition, children under 12 months of age demonstrated faster clot initiation/development by thromboelastography than did older children and adults.[13] Furthermore, clinical measures of platelet function are difficult to perform and interpret on a routine basis in neonates because of the relatively large amounts of blood required and the lack of reference range values. Premature neonates have longer template bleeding times than do term newborns,[14] who in turn have shorter bleeding times than older children and adults.[15] Also, in neonates, the Platelet Function Analyzer-100 (PFA-100, Dade Behring, Deerfield, IL) closure time is generally shorter than in adults, which correlates with the higher hematocrit and vWF levels in infants.[16] (See Evaluation of Bleeding, below.)

It is important to note that these observed differences in platelet function between neonates and older children and adults are not associated with clinical bleeding in healthy newborns. How these differences contribute to bleeding in ill or preterm infants is unknown.