one of these pathways is dysfunctional, activity of the other should be sufficient to maintain adequate clot formation. More recent models have made significant strides in clarifying the dynamics of coagulation (see Figs. 50-2B and 50-3).

Regulation of coagulation proteins is characterized by continuous low-grade factor activation and coordinated assembly of enzyme complexes, which are downregulated by circulating inhibitor proteins. These enzyme complexes consist of serine proteases, their cofactors, and zymogen substrates. In the absence of overt blood vessel disruption, enzyme complex formation and the resultant thrombin generation are both minimal and relatively slow; circulating anticoagulants are sufficient to inactivate these procoagulant complexes and prevent clot formation. However, once a procoagulant stimulus occurs that generates significant amounts of activated factors, formation of these enzyme complexes is rapidly amplified—partly by their assembly on a favorable membrane (phospholipid) surface—leading to intense thrombin formation and subsequent fibrin formation.

Clot Initiation

Coagulation in vivo occurs after exposure of the blood to a source of TF, typically on the surface of a fibroblast coming into contact with blood through a break in the vessel wall. The intrinsic or contact pathway of coagulation has no role in the earliest events in clotting. TF-initiated coagulation has two phases: an *initiation* phase and a *propagation* phase (see Fig. 50-2B). The initiation phase begins as the exposed TF binds to factor VIIa, picomolar amounts of which are present in the circulation at all times. This VIIa-TF complex catalyzes the conversion of very small amounts of factor X to Xa, which in turn, generates nanomolar amounts of thrombin. The seemingly trivial amount of thrombin formed during the initiation phase sparks the inception of the propagation phase, successful completion of which culminates in explosive thrombin generation and, ultimately, fibrin deposition.

Clot Propagation

Thrombin generated during the initiation phase is a potent platelet activator, supplying the developing clot with an activated platelet surface membrane and abundant platelet-released factor V. More than 96% of the total thrombin that is generated during clotting occurs during the propagation phase. Factor V is then promptly activated to Va by thrombin. Factor VIII, conveniently brought to the bleeding site by its carrier, vWF, is also activated by thrombin, a step that causes its release by vWF. VIIIa then complexes with the picomolar amounts of factor IXa generated by the TF-VIIa complex during the initiation phase to create the VIIIa-IXa complex. The formation of this complex on the platelet surface heralds the switch of the primary path of Xa generation from the TF-VIIa complex (the extrinsic Xase) to the intrinsic Xase (the VIIIa-IXa complex). This switch is of significant kinetic advantage, with the intrinsic Xase complex exhibiting 50-fold higher efficiency than the extrinsic Xase. The bleeding diathesis associated with hemophilia is testament to the physiologic importance of the exuberant thrombin generation engendered by the switch from extrinsic to intrinsic Xase. The aPTT, which measures the initiation phase of clotting begun by an artificial in vitro stimulant, is prolonged by severe deficiencies of either VIII or IX, but it is thrombin generation during the propagation phase, a function not evaluated by the aPTT, that is most impaired in hemophilia.

The activated platelet expresses receptors for VIIIa and IXa, and binding of these active proteases in complex with membrane phosphatidylserine enhances the binding of the enzyme's substrate, factor X, increasing the kinetic efficiency of the intrinsic Xase complex. Assembly of the prothrombinase complex is similarly dependent on the activated platelet surface for optimal activity. Like the Xase complex, the membrane-bound prothrombinase complex activates prothrombin with a rate enhancement 300,000-fold higher than that of free Xa acting on prothrombin in solution. Platelet-bound Xa is the rate-limiting enzyme in prothrombin cleavage for both the initiation and the propagation phases of clotting; its substrate, prothrombin, binds to GPIIb/IIIa on both activated and unactivated platelets. The net kinetic advantage conferred by platelet binding is such that assembly of the entire reaction on the platelet membrane increases the catalytic efficiency by 13 million–fold compared with proteases free in solution.

What roles do other intrinsic pathway factors play in coagulation? Evidence is growing that factor XI further amplifies the propagation phase of coagulation. Factor Xa is particularly rate-limiting once the switch to the intrinsic Xase has been made. Although small amounts of IXa are generated by the TF-VIIa complex, IXa generation in this manner is limited by TFPI. To generate Xa in amounts sufficient to fuel the propagation phase, a kinetically superior source of IXa is required. Factor XI is another zymogen activated by very small amounts of initiation phase–generated thrombin, but this activation is restricted to the activated platelet surface. Platelet-bound XIa activates IX on the platelet surface, thereby favoring assembly of the intrinsic Xase complex. Moreover, binding to the platelet surface protects XIa from its inhibitor, protease nexin 2. In summary, XIa generation on the activated platelet is instrumental for providing IXa in amounts sufficient to maintain peak Xa generation through the efficient intrinsic Xase complex.

Limiting Soluble Coagulation

Endogenous anticoagulants can either inactivate formed thrombin or prevent thrombin generation (see Fig. 50-3). The most important natural anticoagulant that inactivates thrombin is antithrombin (AT). AT is physiologically present at more than twice the concentration (3.2 μmol/L) of the highest local thrombin concentration (1.4 μmol/L) that can be reached during clotting, and AT activity against thrombin is potentiated 1000-fold by endogenous EC-associated heparan sulfate proteoglycans. Platelet surface membranes and platelet-released platelet factor 4 protect thrombin from inactivation at the clot. However, any thrombin that escapes into the circulation is immediately (<1 minute) inhibited by plasma AT, and in the microenvironment of healthy ECs that bind about 60,000 molecules of AT per cell, free thrombin is neutralized almost instantaneously. Therefore, early thrombin generation is critically dependent on protection by the activated platelet membrane to allow sufficient time to make the transition from the initiation to the propagation phase.

Among endogenous anticoagulants that target thrombin generation, the earliest in the coagulation process is TFPI, which inactivates factor Xa and the TF-VIIa complex. TFPI is