Overview and Definitions

Coagulation is the clotting of blood or plasma. Hemostasis is the process by which bleeding is stopped, and is the first component of the host response to injury. Its product is a hemostatic plug or hemostatic clot. Thrombosis is inappropriate clot formation within an intact vascular structure. Its product is a thrombus. Blood coagulation can occur at a site of injury (hemostasis), within an intact vessel (thrombosis), or in a test tube, but hemostasis is a physiologic process that can occur only in a living, bleeding organism.

Hemostasis consists of primary hemostasis, in which platelets adhere and are activated at a site of injury, and secondary hemostasis, in which the initial platelet plug is consolidated in a meshwork of fibrin. The hemostatic process represents a delicate, tightly regulated balance between effective activation of local hemostatic mechanisms in response to injury and control by regulatory mechanisms that prevent inappropriate activation or extension of coagulation reactions. The interactions of the protein components of coagulation can be studied in cell-free plasma and have been described as a “cascade” of proteolytic reactions. By contrast, the process of hemostasis occurs on cell surfaces in a tissue environment and is subject to regulation by various biochemical and cellular mechanisms.

The adequacy of procoagulant levels can be assessed in the routine plasma clotting assays: the prothrombin time (PT) and activated partial thromboplastin time (aPTT). Platelet number and function can be assessed in the clinical laboratory. Levels of individual plasma coagulation inhibitors and other regulatory proteins can also be assayed. There is no laboratory test, however, that can provide a global assessment of the adequacy of hemostasis or the risk of thrombosis. Each laboratory test gives only a part of the picture, and the assessment of hemostatic function always requires that laboratory results be interpreted in the context of the clinical picture.

Hemostasis

Because hemostasis involves more than simply getting blood to clot—it must clot at the right time and place and only to the extent needed to stop bleeding—our understanding of hemostasis must include a consideration not only of the proteins, but also the cellular and tissue components that are needed to regulate the coagulation process adequately in vivo.

Necessary Components

Vascular Bed

It is very important that blood not clot within the vascular system. In the baseline state, vascular endothelial cells provide a nonthrombogenic interface with the circulating blood. Endothelial cells do not normally express molecules that support platelet adhesion or promote activation and activity of the coagulation proteins. In addition, the antithrombotic features of the endothelial surface go beyond simply being “inert” with respect to coagulation. The endothelium also expresses molecules that actively downregulate the coagulation reactions on its surface: principally thrombomodulin to localize activated protein C to the endothelial surface, and heparan sulfates to localize antithrombin (AT) to the endothelial surface. A further discussion of these mechanisms is presented in the section on thrombosis. These properties are crucial in preventing coagulation from being initiated at inappropriate sites within the vasculature and preventing appropriately initiated hemostatic reactions from spreading within the vascular tree.

Extravascular Tissues

When an injury disrupts a blood vessel, it allows blood to contact extravascular cells and matrix. Extracellular matrix proteins, such as collagen, fibronectin, thrombospondin, and laminin, interact with adhesive receptors on blood platelets and support formation of the initial platelet plug at the site of injury. Perivascular tissues also express significant levels of tissue factor (TF). Exposure of TF to blood initiates the process of thrombin generation on the surfaces of adherent platelets and ultimately leads to stabilization of the initial platelet plug in a fibrin clot (i.e., secondary hemostasis). Different tissues express different complements of matrix components and procoagulants. The tissue environment plays a role in determining the intensity of the procoagulant response to an injury.

Platelets

Membrane receptors for collagen and other subendothelial and extravascular matrix proteins are present on the platelet membrane and mediate binding of unactivated platelets at sites of
Injury. Platelet binding is also mediated by von Willebrand factor (vWF) bridging between collagen and the platelet receptor glycoprotein (GP) Ib. These receptor binding events also transmit an activation signal to the platelets. Full platelet activation also requires stimulation by thrombin, however, which is produced as the coagulation reactions are initiated. The platelet surface receptor for fibrinogen, GPIIb/IIa, rapidly changes conformation from an inactive to an active form on platelet activation. This change in conformation allows platelet aggregates to be stabilized by binding to fibrinogen even before conversion to fibrin begins. Platelet activation also initiates the synthesis of prostaglandins and thromboxanes—compounds that modulate platelet activation and promote vasoconstriction.

Platelet adhesion and activation at a site of injury, in concert with local vasoconstriction, provides initial hemostasis for small caliber vessels. When hemostasis is achieved by these mechanisms, the subsequent stabilization of the platelet plug in a fibrin meshwork can proceed more effectively than if bleeding continues. Initial hemostasis may be established even if a deficiency of plasma coagulation proteins is present. The platelet plug is insufficient, however, to provide long-term hemostasis, and delayed rebleeding occurs if it is not reinforced by a stable fibrin clot during secondary hemostasis.

Coagulation Proteins

Adequate levels and function of each of a series of procoagulant proteins are required for hemostasis. The coagulation proteins can be organized into several groups based on their structural features.

The vitamin K–dependent factors include factors II (prothrombin), VII, IX, and X. These factors each have a structural domain in which several glutamic acid residues are post-translationally modified to γ-carboxyglutamic acid (Gla) residues by a vitamin K–dependent carboxylase. The vitamin K cofactor is oxidized from a quinone to an epoxide in the process. A vitamin K epoxide reductase cycles the vitamin K back to the quinone form to allow carboxylation of additional glutamic acid residues. The negatively charged Gla residues bind calcium ions. These binding interactions hold the Gla-containing proteins in their active conformation. The calcium-bound form of the Gla-domain is responsible for mediating the binding of the coagulant proteins to phospholipid membranes. Lipids with negatively charged head groups, particularly phosphatidylserine, are required for binding and activity of the Gla-containing factors.

The carboxylation process is inhibited by the anticoagulant warfarin, which competes with vitamin K for binding to the reductase. Inhibition by warfarin results in the production of undercarboxylated forms of the vitamin K–dependent proteins, which are nonfunctional.

The vitamin K–dependent procoagulants are zymogens (inactive precursors) of serine proteases. Each is activated by cleavage of at least one peptide bond. The activated form is indicated by the letter “a.” Factors VIIa, IXa, and Xa each require calcium ions, a suitable cell (phospholipid) membrane surface, and a protein cofactor for their activity in hemostasis.

Factor Va (thrombin) is a little different from the activated forms of the other vitamin K–dependent factors. Its Gla domain is released from the protease domain during activation. It no longer binds directly to phospholipid membranes. It also does not require a cofactor to cleave fibrinogen and initiate fibrin assembly, or to activate platelet receptors. Factor Va is released from the protease domain during activation. It no longer binds directly to phospholipid membranes. It also does not require a cofactor to cleave fibrinogen and initiate fibrin assembly, or to activate platelet receptors. Factor Va that escapes the vicinity of a hemostatic plug can bind, however, to a cofactor on endothelial cell surfaces, thrombomodulin. After binding to thrombomodulin, factor IIa can no longer activate platelets or cleave fibrinogen. Instead, it triggers an antithrombotic pathway by activating protein C on the endothelial surface.

Proteins C and S are also vitamin K–dependent factors. They do not act as procoagulants, but rather as antithrombins on endothelial surfaces. Protein C is the zymogen of a protease, whereas protein S has no enzymatic activity, but serves as a cofactor for activated protein C. The activated protein C/protein S complex cleaves and inactivates factor Va and factor VIIIa, preventing propagation of thrombin generation on normal healthy endothelium.

Factors V and VIII are large structurally related glycoproteins that act as cofactors. They have no enzymatic activity of their own, but when activated by proteolytic cleavage, they dramatically enhance the proteolytic activity of factors Xa and IXa.

Factor VIII circulates in a noncovalent complex with vWF, which prolongs its half-life in the circulation. The vWF/factor VIII complex binds to the platelet surface via GPIIb as vWF mediates adhesion of platelets to collagen under high shear conditions. Cleavage and activation of factor VIII releases it from vWF so that it can assemble into a complex with factor IXa on the platelet surface, where it activates factor X.

Factor V circulates in the plasma, and it is packaged in the alpha granules of platelets. It is released on platelet activation in a partially activated form. Plasma and platelet-derived factor V can be fully activated by cleavage by factor Xa or IIa. Factor Va then assembles into a complex with factor Xa on the platelet surface, where it activates prothrombin to factor IIa.

TF is also a cofactor, but is structurally unrelated to any of the other coagulation factors. Instead, it is related to one class of cytokine receptors. This lineage emphasizes the close evolutionary and physiologic links between the coagulation system and the other components of the host response to injury. Rather than circulating in the plasma as do the other coagulation factors, TF is a transmembrane protein. TF serves as the cellular receptor and cofactor for factor VIIa. It is primarily expressed on cells outside the vascular space under normal conditions, although monocytes and endothelial cells can express TF in response to inflammatory cytokines. The factor VIIa/TF complex can activate factor IX and factor X, and is the major initiator of hemostatic coagulation.

Another group of related proteins are the contact factors—factors XI and XII, prekallikrein, and high-molecular-weight kininogen. These proteins share the feature of binding to charged surfaces. The only one of this group that is needed for normal hemostasis is factor XI. The other contact factors may play a role, however, in thrombosis in some settings. Factor XI is a zymogen that can be activated to a protease by factor XIIa, but is likely activated primarily by thrombin during the hemostatic process. Factor XIa activates factor IX.

Fibrinogen provides the key structural component of the hemostatic clot. Two small peptides, fibrinopeptides A and B, are cleaved from fibrinogen by thrombin, and the resulting fibrin monomer polymerizes into a network of fibers. The fibrin polymer is stabilized further when it is cross-linked by activated factor XIII. Factor XIIIa is a transglutaminase that is activated by thrombin coincident with fibrin formation.

Thrombin plays a key role in activating procoagulant and anticoagulant factors and triggering formation of fibrin. In addition,
thrombin has cytokine-like activities that bridge the transition between hemostasis, inflammatory/immune responses, and wound healing. Thrombin is truly a multifunctional molecule that affects the host response to injury at many levels.

Even before the structure and function of the various factors had been defined, their interactions had been studied during plasma clotting. In the 1960s, two groups proposed a “waterfall” or “cascade” model of the interactions of the coagulation factors leading to thrombin generation. These schemes were composed of a sequential series of steps in which activation of one clotting factor led to the activation of another, finally leading to a burst of thrombin generation. At that time, each clotting factor was thought to exist as a proenzyme that was activated by proteolysis. The existence of cofactors without enzymatic activity was not recognized until later. The original models were subsequently modified as information about the coagulation factors accumulated and eventually evolved into the Y-shaped scheme shown in Figure 9-1. The “cascade” model shows distinct intrinsic and extrinsic pathways that are initiated by factor XIIa and the factor VIIa/TF complex. The pathways converge on a “common” pathway at the level of the factor Xa/factor Va (prothrombinase) complex.

This scheme was not proposed as a literal model of the hemostatic process in vivo; rather, it was derived from studies of plasma clotting in a test tube and was intended to represent the biochemical interactions of the procoagulant factors. The coagulation “cascade” does reflect well the process of plasma clotting, as in the PT and aPTT tests. The lack of any other clear and predictive concept of hemostasis has meant, however, that until more recently most physicians have also viewed the “cascade” as a model of physiology, and the PT and aPTT as reflecting the risk of clinical bleeding.

The limitations of the coagulation cascade as a model of the hemostatic process in vivo are highlighted by certain clinical observations. Patients deficient in the initial components of the intrinsic pathway—factor XII, high-molecular-weight kininogen, or prekallikrein—have a greatly prolonged aPTT, but no bleeding tendency. Patients deficient in factor XI also have a prolonged aPTT, but usually have a mild to moderate bleeding tendency. Other components of the intrinsic pathway have a crucial role in hemostasis because patients deficient in factor VIII or factor IX have a serious bleeding tendency even though the extrinsic pathway is intact. Similarly, patients deficient in factor VII also have a serious bleeding tendency even though the intrinsic pathway is intact. Although the cascade model accurately reflects the protein interactions that lead to plasma clotting, and is an essential guide to interpretation of PT and aPTT results, it is not an adequate model of hemostasis in vivo.

The numbering of the coagulation factors does not follow their order in the cascade. The coagulation factors were numbered roughly in the order in which they were discovered. Because many workers had described the same molecules under different names, designating them with roman numerals seemed the fairest way to reconcile the nomenclature confusion.

**Process of Hemostasis**

Having all the right ingredients is not enough to ensure an effective hemostatic process. Cellular interactions are crucial to directing and controlling hemostasis. Normal hemostasis is impossible in the absence of platelets. In addition, TF is an integral membrane protein, and its activity is normally associated with cells, but platelets have little TF activity. Interactions between at least these two types of cells are necessary. Because different cells express different levels of procoagulants and anticoagulants and have different complements of receptors, it is logical that simply representing the cells involved in coagulation as phospholipid vesicles overlooks the active role of cells in directing hemostasis. Hemostasis in vivo can be conceptualized as occurring in a stepwise process, regulated by cellular components, as described subsequently.

**Step 1: Initiation of Coagulation on Tissue Factor–Bearing Cells**

The process of thrombin generation is initiated when TF-bearing cells are exposed to blood at a site of injury. TF is a transmembrane protein that acts as a receptor and cofactor for factor VII. When bound to TF, zymogen factor VII is rapidly converted to factor VIIa through mechanisms not yet completely understood, but that may involve factor Xa or noncoagulation proteases. The resulting factor VIIa/TF complex catalyzes activation of factor X and activation of factor IX. The factors Xa and IXa formed on TF-bearing cells have very distinct and separate functions in initiating blood coagulation. The factor Xa formed on TF-bearing cells interacts with its cofactor, factor Va, to form prothrombinase complexes and generate small amounts of thrombin on the TF cells (Fig. 9-2). The small amounts of factor Va required for prothrombinase assembly on TF-bearing cells are activated by

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![Figure 9-1](image-url)
factor Xa, activated by noncoagulation proteases produced by the cells, or released from platelets that adhere nearby. The activity of the factor Xa formed by the factor VIIa/TF complex is largely restricted to the TF-bearing cell because factor Xa that dissociates from the cell surface is rapidly inhibited by tissue factor pathway inhibitor (TFPI) or AT in the fluid phase.

In contrast to factor Xa, the factor IXa activated by factor VIIa/TF does not act on the TF-bearing cell and does not play a significant role in the initiation phase of coagulation. Factor IXa can diffuse to adjacent platelet surfaces because it is not inhibited by TFPI and is inhibited much more slowly by AT than factor Xa. Factor IXa can bind to a specific platelet surface receptor, interact with its cofactor, factor VIIIa; and begin to activate factor X directly on the platelet surface.

The small amount of thrombin produced on the TF-bearing cells is insufficient to clot fibrinogen, but it is sufficient to initiate events that amplify the initial procoagulant signal and “prime” the clotting system for a subsequent burst of platelet surface thrombin generation. This thrombin is responsible for (1) activating platelets, (2) activating factor V, (3) activating factor VIII and dissociating factor VIII from vWF, and (4) activating factor XI.

It is likely that most (extravascular) TF is bound to factor VIIa even in the absence of an injury, and that low levels of factor IXa, factor Xa, and thrombin are produced on TF-bearing cells at all times. This process is kept separated from key components of hemostasis, however, by an intact vessel wall. The very large components of the coagulation process are platelets and factor VIII bound to multimeric vWF. These components normally come into contact with the extravascular compartment only when an injury disrupts the vessel wall. Platelets and factor VIII/vWF leave the vascular space and adhere to collagen and other matrix components at the site of injury.

**Step 2: Amplification of the Procoagulant Signal by Thrombin Generated on the Tissue Factor–Bearing Cell**

Binding of platelets to collagen or via vWF during primary hemostasis leads to partial platelet activation. The coagulation process is most effectively initiated, however, when enough thrombin is generated on or near the TF-bearing cells to trigger full activation of platelets. Thrombin diffuses through the fluid phase and binds to its receptor GPIb and cleaves its proteolytically activated receptors. These two receptor types synergize in mediating platelet activation. The small amounts of thrombin generated during the initiation step are also responsible for activation of coagulation factors XI and VIII on the platelet surface in the amplification step, as illustrated in Figure 9-3.

Platelets not only plug the vascular defect at a site of injury, but also provide the specialized membrane surface on which activation of many of the coagulation proteins occurs. Unactivated platelets express a very low level of phosphatidylserine, the primary procoagulant phospholipid, on their surfaces. On activation, phosphatidylserine is rapidly translocated from the inner to the outer leaflet of the platelet plasma membrane. It is then available to support binding and activity of the coagulation complexes.

Platelet secretion of granule contents occurs more slowly after activation than membrane surface changes. Dense and alpha granules within the platelet cytoplasm contain numerous components that play a role in the coagulation process, such as partially activated factor V, factor VIII/vWF, factor XIII, fibrinogen, protease inhibitors, and platelet agonists (adenosine diphosphate [ADP], epinephrine, and serotonin). Secretion of these platelet agonists enhances platelet activation further. When platelets are activated, the cofactors Va and VIIIa are rapidly localized on the platelet surface. Factor IXa formed by the factor VIIa/TF complex can diffuse through the fluid phase, bind to the surface of activated platelets, and assemble into a complex with factor VIIIa. Factor XI activated by thrombin on the platelet surface can activate more factor IX from the plasma to factor IXa. At the end of the amplification phase, the platelets accumulated at the injury site are activated and have bound activated coagulation factors on their surfaces.

**Step 3: Propagation of Thrombin Generation on the Platelet Surface**

The multiple positive feedback mechanisms of the amplification phase rapidly lead to a burst of thrombin generation in the propagation phase, as illustrated in Figure 9-4. The “tenase” (factor IXa/factor VIIIa) complexes progressively activate factor X from the plasma to factor Xa on the platelet surface. Factor Xa then associates with factor Va to support a burst of thrombin generation of sufficient magnitude to produce a stable fibrin clot.

The large amount of thrombin generated on the platelet surface is responsible for stabilizing the hemostatic clot in more ways than just promoting fibrin polymerization. Most of the thrombin generated during the hemostatic process is produced after the initial fibrin clot is formed. The platelet-produced thrombin also stabilizes the clot by (1) activating factor XIII, (2) activating the thrombin-activated fibrinolysis inhibitor, (3) cleaving the platelet PAR-4 receptor, and (4) being incorporated into the structure of the clot. Activated factor XIII covalently cross-links the fibrin strands and increases resistance to plasmin degradation. Thrombin-activated fibrinolysis inhibitor also increases resistance to fibrinolysis by cleaving off lysines...
Regulation of Hemostasis and Thrombosis

from the fibrin strands that serve as sites for fibrinolytic enzyme binding. Activation of platelet PAR-4 receptors promotes clot contraction, which pulls together the edges of a wound and makes the hemostatic plug more dense and impermeable. “Excess” thrombin produced during the hemostatic process can remain bound within the fibrin polymer and retains its proteolytic activity. It can rapidly activate more platelets and clot more fibrinogen if the hemostatic plug is disrupted and bleeding resumes.

The role of factor XI in hemostasis has been controversial because even severe factor XI deficiency does not result in a hemorrhagic tendency as severe as that in severe factor VIII or factor IX deficiency. This situation can be explained if factor XI is viewed as a “booster” of thrombin generation. Factor XI is not essential for platelet-surface thrombin generation, as are factor IX and factor VIII. Rather, factor XIa activates additional factor IXa on the platelet surface to supplement factor IXa/factor VIIIa complex formation and enhance platelet surface factor Xa and thrombin generation. Its deficiency does not compromise hemostasis to as great an extent as factor IX or factor VIII deficiency.

Our knowledge of the platelet contribution to thrombin generation continues to evolve. There is evidence that there are multiple types of activated platelets. Platelets with the highest procoagulant activity are produced when they are stimulated with thrombin and collagen; these have been referred to as COAT (collagen and thrombin stimulated) platelets. These platelets have enhanced thrombin-generating ability because of enhanced binding of tenase and prothrombinase components. The in vivo relevance of the COAT platelet phenomenon is unclear, but it may be that the greatest procoagulant activity is generated on platelets that have bound to collagen matrix and been exposed to thrombin. When the exposed collagen is covered by a platelet/fibrin layer, additional platelets that
accumulate are not activated to the COAT state—tending to damp down the procoagulant signal when the area of the wound has been walled off by a hemostatic clot.

Even though each phase of the cell-based model of hemostasis has been depicted as a discrete step, the phases should be viewed as an overlapping continuum of events. Thrombin produced on the platelet surface early in the propagation phase may initially cleave substrates on the platelet surface and continue to amplify the procoagulant response, in addition to leaving the platelet and promoting fibrin assembly.

The cell-based model of hemostasis shows us that the extrinsic and intrinsic pathways are not redundant. We can consider the extrinsic pathway to consist of the factor VIIa/TF complex working with the factor Xa/Va complex, and the intrinsic pathway to consist of factor Xla working with the complexes of factors VIIIa/I Xa and factors Xa/Va. The extrinsic pathway operates on the TF-bearing cell to produce small amounts of thrombin that initiate the coagulation process and amplify the initial procoagulant signal. By contrast, the intrinsic pathway operates on activated platelet surfaces to produce the large burst of thrombin that leads to formation and stabilization of the fibrin clot.

**Regulatory Mechanisms to Control Coagulation**

Although the inability to provide effective hemostasis is a serious problem, the inability to limit coagulation to sites of hemostasis is at least as great a problem. Multiple biochemical and cellular regulatory mechanisms have evolved to limit and localize the coagulation reactions. The coagulation reactions do not “cascade” unimpeded into a torrent of thrombin production, but must instead overcome a series of regulatory barriers.

**Plasma Protease Inhibitors**

Several circulating protease inhibitors can inactivate one or more of the coagulation proteases. The coagulation proteases are relatively protected from inhibition while bound to a membrane surface. Proteases that escape into the fluid phase are subject to inhibition, however. The presence of inhibitors does not prevent activation and activity of coagulation, but tends to confine the coagulation proteases to act on the cell surfaces on which they were activated.

AT (formerly called antithrombin III) plays a particularly important role in regulating hemostasis. AT is a serine protease inhibitor (serpin) that can inhibit most of the procoagulant factors, including factors IIa, VIIa, IXa, Xa, and Xla. The effectiveness of AT is increased by binding to heparinoids on the endothelial surfaces and by exogenous heparins. Hereditary and acquired deficiencies of AT lead to a significant thrombotic tendency.

TFPI is also an important control mechanism. This molecule is a multifunctional Kunitz-type inhibitor. One of its Kunitz domains inhibits factor Xa. When it has bound factor Xa, another Kunitz domain can bind factor VIIa in the factor VIIa/TF complex. TFPI can assist in localizing factor Xa to the cell surface on which it was activated and limiting the activity of the TF pathway.

Not only are the plasma protease inhibitors key players in confining a clot to the proper location, but they also impose a threshold effect on activation of coagulation. In the presence of inhibitors, coagulation does not proceed unless procoagulant factors are generated in sufficient amounts to overcome the effects of inhibitors. If the triggering event is not sufficiently strong, the system returns to baseline rather than continuing through the coagulation process. Under pathologic conditions, the trigger for clotting may be so strong as to overwhelm the control mechanisms and lead to disseminated intravascular coagulation or thrombosis.

**Endothelial Antithrombotic Mechanisms**

When a fibrin/platelet clot is formed over an area of injury, the clotting process must be terminated to avoid thrombotic occlusion in adjacent normal areas of the vasculature. If the coagulation mechanism were not controlled, clotting could extend throughout the vascular tree after even a modest procoagulant stimulus.

Endothelial cells play a major role in confining the coagulation reactions to a site of injury. Conversely, endothelial damage or dysfunction can play a major role in promoting thrombosis. Endothelial cells have several types of anticoagulant/antithrombotic activities (Fig. 9-5). The protein C/protein S/thrombomodulin system is activated in response to thrombin generation. Some of the thrombin formed during hemostasis can diffuse away or be swept downstream from a site of injury. When thrombin reaches an intact endothelial cell, it binds to thrombomodulin on its surface. The thrombin/thrombomodulin complex activates protein C, which is localized to the endothelial surface by binding to the endothelial protein C receptor (EPCR). The activated protein C can move into a complex with its cofactor, protein S, and inactivate any factor Va or factor VIIIa that has found its way to the endothelial cell membrane; this prevents the generation of additional thrombin in the intact vasculature.

Endothelial cells also localize anticoagulant protease inhibitors to their surfaces. AT binds to the glycosaminoglycan heparan sulfate on the endothelial surface, which enhances inactivation of proteases near the endothelium.41 TFPI can also be bound to heparan sulfate or linked to the endothelial surface via a glycosyl phosphatidylinositol (GPI) anchor. Endothelial
cells also inhibit platelet activation by releasing the inhibitors prostacyclin and nitric oxide, and degrading ADP by their membrane ecto-ADPase, CD39.42

Fibrinolysis
Even as the fibrin clot is being formed in the body, the fibrinolytic system is being initiated to disrupt it. The final effector of the fibrinolytic system is plasmin, which cleaves fibrin into soluble degradation products. Plasmin is produced from the inactive precursor plasminogen by the action of two plasminogen activators: urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). The plasminogen activators are regulated by plasminogen activator inhibitors. Plasminogen is found at a much higher plasma concentration than the plasminogen activators. The availability of the two plasminogen activators in the plasma generally determines the extent of plasmin formation. tPA release from endothelial cells is provoked by thrombin and venous occlusion.43 tPA and plasminogen bind to the evolving fibrin polymer. When plasminogen is activated to plasmin, it cleaves fibrin at specific lysine and arginine residues, resulting in dissolution of the fibrin clot. The fibrinolytic system is crucial to removing an appropriate hemostatic clot as wound healing occurs. It is also essential to removing intravascular thrombi before significant tissue injury can occur. The pulmonary vasculature can release large amounts of fibrinolytic enzymes to remove small thromboemboli that become lodged there.

Intravascular deposition of fibrin is also associated with the development of atherosclerosis. An effective fibrinolytic system tends to protect against the chronic process of atherosclerotic vascular disease and the acute process of thrombosis. Conversely, defects of fibrinolysis increase the risk of atherothrombotic disease. Elevated levels of plasminogen activator inhibitor-1, an inhibitor of fibrinolysis, are associated with an increased risk of atherosclerosis and thrombosis,44 as are decreased levels of plasminogen.45 The effectiveness of hemostasis in vivo depends not only on the procoagulant reactions, but also on the fibrinolytic process.

Clinical Laboratory Testing
The commonly used clinical coagulation tests do not reflect the complexity of hemostasis in vivo; this does not mean that the PT and aPTT are useless. Clinicians need to understand what these tests can and cannot tell us. These “screening” coagulation tests are abnormal when there is a deficiency of one or more of the soluble coagulation factors. They do not predict what the risk of clinical bleeding will be. Two patients with identical aPTT values can have drastically different risks of hemorrhage. All of the common coagulation tests, including the PT, aPTT, thrombin clotting time, fibrinogen levels, and coagulation factor levels, tell us something about the plasma level of soluble factors required for hemostasis. Their clinical implications must be evaluated by the ordering physician. Just because the PT and aPTT are within the normal range, it does not follow that the patient is at no risk for bleeding. Conversely, a mild elevation in these clotting times does not mean that the patient is at risk for bleeding after an invasive procedure.

Many whole-blood coagulation tests are being presented as a means of evaluating overall hemostatic status in selected clinical settings. Although whole-blood tests have the advantage that they may reflect the contributions of platelets to the hemostatic process, they still do not reflect the contributions of the TF-bearing cells and local tissue conditions. Any laboratory test requires skilled interpretation and clinical correlation in evaluating the true risk of bleeding.

What Can Go Wrong with Hemostasis
Hemorrhage
Many patients who develop hemorrhage do not have a pre-existing bleeding tendency. Bleeding after surgical or accidental trauma or during a medical illness is often associated with the development of an acquired coagulopathy. The hallmark of coagulopathy is microvascular bleeding, which is oozing from cut surfaces and minor sites of trauma, such as needle-sticks. Microvascular bleeding can lead to massive blood loss. Causes of coagulopathic bleeding include consumption of coagulation factors and platelets, excessive fibrinolysis, hypothermia, and acidosis.

Consumption of Coagulation Components
Disseminated intravascular coagulation (DIC) normally comes to mind in relation to consumption. Clotting factors and platelets can also be consumed, however, during appropriate physiologic attempts at hemostasis. In this case, it is appropriate to replace the depleted factors with transfusion therapy. DIC can be much more complicated to manage.46 The mainstay of treatment is to treat the underlying disorder, such as sepsis. In early or mild/compensated DIC, administration of low-dose heparin may be considered to control the procoagulant response to inflammation, infection, or malignancy. In more severe or advanced DIC, replacement therapy may be necessary to attempt to manage the bleeding tendency associated with depletion of coagulation factors and platelets.

Excessive Fibrinolysis
The process of fibrinolysis is initiated as the fibrin clot assembles. Fibrin serves as the framework to which plasminogen binds and is activated to plasmin by tPA and uPA. Even when formation of a fibrin clot does not succeed at establishing hemostasis, a significant amount of fibrinolytic activity may still be generated and thwart subsequent efforts at hemostasis. Fibrinolytic inhibitors have proven to be useful in some circumstances.

Hypothermia
Many patients become hypothermic during medical illness or after surgical or accidental trauma.47 Hypothermia can directly interfere with the hemostatic process by slowing the activity of the coagulation enzymes. Less well recognized is the finding that platelet adhesion and aggregation is impaired even in mild hypothermia.48 In hypothermic coagulopathic patients, increasing the core temperature can have a beneficial effect on bleeding by improving platelet function and coagulation enzyme activity.

Acidosis
Acidosis can have an even more profound effect on the coagulation process than hypothermia, and the two metabolic abnormalities often coexist. A decrease in the pH from 7.4 to 7.2 reduces the activity of each of the coagulation proteases by more than half.49 Acidosis should be considered as a possible contributor to coagulopathic bleeding in medical and surgical patients.


**Thrombosis**

Disruption of the normal regulatory functions of any of the components of hemostasis can result in thrombosis. Generally, thrombosis is a multifactorial problem—congenital and acquired abnormalities in the antithrombotic activities of the vascular endothelium can synergize with enhanced platelet reactivity and alterations in procoagulant or anticoagulant levels ultimately to produce thrombosis. The risk of thrombosis in any given individual at and any given time is a product of the individual’s accumulated genetic, environmental, and lifestyle risk factors.

Inflammation can trigger numerous responses that predispose further to thrombosis. The coagulation and inflammatory responses interface at the levels of the tissue factor pathway, the protein C/protein S system, and the fibrinolytic system. Proinflammatory cytokines can affect all of these coagulation mechanisms, and coagulation proteases, anticoagulants, and fibrinolytic enzymes can modulate inflammation by specific cell receptors. Inflammatory cytokines can promote an increase in tissue factor and a decrease in thrombomodulin by the endothelium. Activation of coagulation is closely linked with the progression of atherosclerotic vascular lesions. Progressively impaired vascular function further predisposes to thrombosis. Ultimately, rupture of an unstable atherosclerotic plaque can expose procoagulant activity and provoke an acute thrombotic event. Management of cardiovascular disease often involves preventing and managing thrombosis and its consequences. Venous and arterial thrombosis tend to have different mechanisms and risk factors, and are best managed by different strategies.

**Venous Thrombosis**

The major mechanism of venous thrombosis is related to inappropriate activation of the coagulation reactions—often on inflamed endothelium. Stasis can play an exacerbating role when activated factors are not rapidly diluted in flowing blood. Abnormalities of coagulation factors and increased levels of coagulation factors that potentially increase thrombin generation are linked to venous thrombosis. The inherited hemostatic abnormalities most often associated with venous thromboembolism are factor V Leiden and factor II G20210A mutations, and deficiencies in AT, protein C, and protein S. Acquired abnormalities also play a major role. Major clinical risk factors for venous thromboembolism include malignancy, myeloproliferative disorders, trauma, surgery (especially orthopedic surgery), immobilization or paralysis, and prior venous thromboembolism. Minor risk factors include advanced age, obesity, bed rest, use of hormone replacement therapy or oral contraceptives, pregnancy and postpartum period, and inflammatory bowel disease.

Venous thrombosis is extremely common in hospitalized patients. Although it is often asymptomatic, it is a significant cause of morbidity and of mortality from pulmonary embolism. Incidence of venous thrombosis can be reduced dramatically by the appropriate use of thromboprophylaxis with anticoagulants such as heparin and low-molecular-weight heparins.

**Arterial Thrombosis**

Arterial thrombosis is primarily related to formation of platelet aggregates at sites of high shear and turbulent flow. As atherosclerotic plaques develop, they not only alter the nonthrombogenic nature of the endothelium, but also disrupt normal laminar blood flow and produce increased turbulence. Although increased platelet reactivity can contribute to arterial thrombosis, the vascular alterations play a key role in promoting platelet adhesion and activation. There is also considerable evidence that TF-mediated activation of the coagulation system and thrombin generation can be important contributors to arterial thrombosis. Thrombin generation at a site of plaque rupture can be the trigger for platelet activation and adhesion.

The risk factors most closely linked to arterial thrombosis are smoking, hypertension, dyslipidemia, and diabetes. Inherited thrombophilia plays much less of a role in arterial than venous thrombosis. Lifestyle changes can have a significant impact on the risk of arterial thrombosis. The most effective management is by therapies targeting platelet activation and adhesion. The results of more recent studies indicate that in addition to the efficacy of aspirin in reducing cardiac events in patients with acute coronary syndromes, more potent antiplatelet and anticoagulant therapies are valuable in high-risk patients.

**What Happens after the Bleeding Stops**

When hemostasis is completed, the process of wound healing can begin. Many of the activities involved in wound healing are influenced by thrombin. Thrombin plays a major role in platelet activation and degranulation. Several key cytokines modulating wound healing are released from activated platelets, including transforming growth factor-β and platelet-derived growth factor. The amount and rate of thrombin generated during hemostasis influences the initial structure of the fibrin clot—the framework on which cell migration occurs. In addition, thrombin has chemotactic and mitogenic activities for macrophages, fibroblasts, smooth muscle cells, and endothelial cells. Generation of the “right” amount of thrombin during the coagulation process not only may be essential for effective hemostasis, but also may set the stage for effective wound healing. Conversely, thrombin generation at sites of vascular injury plays a role in the development of local inflammatory changes and progression of atherosclerotic lesions.

**References**