residues of fibrin fragments to enhance these reactions further. This creates a highly efficient mechanism to generate plasmin focally on the fibrin clot, which then becomes plasmin's substrate for digestion to fibrin degradation products.

Plasmin cleaves fibrin at distinct sites of the fibrin molecule, leading to the generation of characteristic fibrin fragments during the process of fibrinolysis (Fig. 78-2). The sites of plasmin cleavage of fibrin are the same as those in fibrinogen. However, when plasmin acts on covalently cross-linked fibrin, D-dimers are released; hence, D-dimers can be measured in plasma as a relatively specific test of fibrin (rather than fibrinogen) degradation. D-Dimer assays can be used as sensitive markers of blood clot formation and have been validated for clinical use to exclude the diagnosis of deep venous thrombosis (DVT) and pulmonary embolism in selected populations. In addition, D-dimer measurement can be used to stratify patients, particularly women, for risk of recurrent venous thromboembolism (VTE) when measured 1 month after discontinuation of anticoagulation given for treatment of an initial idiopathic event. D-Dimer levels may be elevated in the absence of VTE in elderly people.

Physiologic regulation of fibrinolysis occurs primarily at three levels: (1) plasminogen activator inhibitors (PAIs), specifically PAI-1 and PAI-2, inhibit the physiologic plasminogen activators; (2) the thrombin-activatable fibrinolysis inhibitor (TAFI) limits fibrinolysis; and (3) α_2-antiplasmin inhibits plasmin. PAI-1 is the primary inhibitor of tPA and uPA in plasma. TAFI cleaves the N-terminal lysine residues of fibrin, which aid in localization of plasmin activity. α_2-Antiplasmin is the main inhibitor of plasmin in human plasma, inactivating any nonfibrin clot-associated plasmin.

APPROACH TO THE PATIENT: Bleeding and Thrombosis

CLINICAL PRESENTATION

Disorders of hemostasis may be either inherited or acquired. A detailed personal and family history is key in determining the chronicity of symptoms and the likelihood of the disorder being inherited, as well as providing clues to underlying conditions that have contributed to the bleeding or thrombotic state. In addition, the history can give clues as to the etiology by determining (1) the bleeding (mucosal and/or joint) or thrombosis (arterial and/or venous) site and (2) whether an underlying bleeding or clotting tendency was enhanced by another medical condition or the introduction of medications or dietary supplements.

History of Bleeding A history of bleeding is the most important predictor of bleeding risk. In evaluating a patient for a bleeding disorder, a history of at-risk situations, including the response to past surgeries, should be assessed. Does the patient have a history of spontaneous or trauma/surgery-induced bleeding? Spontaneous hemarthroses are a hallmark of moderate and severe factor VIII and IX deficiency and, in rare circumstances, of other clotting factor deficiencies. Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease (VWD), termed *disorders of primary hemostasis or platelet plug formation.* Disorders affecting primary hemostasis are shown in Table 78-1.

A bleeding score has been validated as a tool to predict patients more likely to have type 1 VWD (International Society on Thrombosis and Haemostasis Bleeding Assessment Tool [*www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf*]). This is most useful tool in excluding the diagnosis of a bleeding disorder, and thus avoiding unnecessary testing. One study found that a low bleeding score (≤3) and a normal activated partial thromboplastin time (aPTT) had 99.6% negative predictive value for the diagnosis of VWD. Bleeding symptoms that appear to be more common in patients with bleeding disorders include prolonged bleeding with surgery, dental procedures and extractions, and/or trauma, menorrhagia or postpartum hemorrhage, and large bruises (often described with lumps).

TABLE 78-1 PRIMARY HEMOSTATIC (PLATELET PLUG) DISORDERS

Defects of Platelet Adhesion
Von Willebrand disease
Bernard-Soulier syndrome (absence or dysfunction of platelet Gp Ib-IX-V)
Defects of Platelet Aggregation
Glanzmann's thrombasthenia (absence or dysfunction of platelet glycoprotein [Gp] IIb/IIIa)
Afibrinogenemia
Defects of Platelet Secretion
Decreased cyclooxygenase activity
Drug-induced (aspirin, nonsteroidal anti-inflammatory agents, thienopyridines)
Inherited
Granule storage pool defects
Inherited
Acquired
Nonspecific inherited secretory defects
Nonspecific drug effects
Uremia
Platelet coating (e.g., paraprotein, penicillin)
Defect of Platelet Coagulant Activity
Scott's syndrome

Easy bruising and menorrhagia are common complaints in patients with and without bleeding disorders. Easy bruising can also be a sign of medical conditions in which there is no identifiable coagulopathy; instead, the conditions are caused by an abnormality of blood vessels or their supporting tissues. In Ehlers-Danlos syndrome, there may be posttraumatic bleeding and a history of joint hyperextensibility. Cushing's syndrome, chronic steroid use, and aging result in changes in skin and subcutaneous tissue, and subcutaneous bleeding occurs in response to minor trauma. The latter has been termed *senile purpura*.

Epistaxis is a common symptom, particularly in children and in dry climates, and may not reflect an underlying bleeding disorder. However, it is the most common symptom in hereditary hemorrhagic telangiectasia and in boys with VWD. Clues that epistaxis is a symptom of an underlying bleeding disorder include lack of seasonal variation and bleeding that requires medical evaluation or treatment, including cauterization. Bleeding with eruption of primary teeth is seen in children with more severe bleeding disorders, such as moderate and severe hemophilia. It is uncommon in children with mild bleeding disorders. Patients with disorders of primary hemostasis (platelet adhesion) may have increased bleeding after dental cleanings and other procedures that involve gum manipulation.

Menorrhagia is defined quantitatively as a loss of >80 mL of blood per cycle, based on the quantity of blood loss required to produce iron-deficiency anemia. A complaint of heavy menses is subjective and has a poor correlation with excessive blood loss. Predictors of menorrhagia include bleeding resulting in iron-deficiency anemia or a need for blood transfusion, passage of clots >1 inch in diameter, and changing a pad or tampon more than hourly. Menorrhagia is a common symptom in women with underlying bleeding disorders and is reported in the majority of women with VWD, women with factor XI deficiency, and symptomatic carriers of hemophilia. Women with underlying bleeding disorders are more likely to have other bleeding symptoms, including bleeding after dental extractions, postoperative bleeding, and postpartum bleeding, and are much more likely to have menorrhagia beginning at menarche than women with menorrhagia due to other causes.

Postpartum hemorrhage (PPH) is a common symptom in women with underlying bleeding disorders. In women with type 1 VWD and symptomatic carriers of hemophilia A in whom levels of VWF and factor VIII usually normalize during pregnancy, PPH