secreted factors) express adhesive ligands on their surface, including the selectins (both E-selectin and P-selectin), β_1 and β_2 integrins, platelet endothelial cell adhesion molecule-1 (PECAM-1), and von Willebrand factor (vWF) multimers (see Table 50-1). On the EC surface, vWF multimers localize and promote platelet adhesion, whereas integrins mediate adhesion and subsequent transendothelial migration of leukocytes into the tissues. After EC damage, exposed subendothelial matrix also binds vWF multimers (Fig. 50-1A) to localize platelet adhesion. Subendothelial procoagulant proteins, including thrombospondin, fibronectin, and collagen, function both as ligands to capture platelets and as activators of adherent platelets. Collagen, in particular, is both a platelet ligand and a strong platelet agonist. The latter capability causes platelets to undergo dense granule release and to express conformationally active ligands such as glycoprotein IIb/IIIa (GPIIb/IIIa; see later discussion). Another critical procoagulant mediator exposed by EC damage is TF, which is constitutively expressed by subendothelial smooth muscle cells and fibroblasts. As outlined later, TF is the major initiator of the soluble coagulation system which, along with activated platelets, results in the formation of a definitive platelet-fibrin clot (Fig. 50-2).

PLATELET PHYSIOLOGY

The platelet functions as the cellular-based platform for hemostasis. Platelet surface receptors mediate primary hemostasis and allow platelets to bind directly to endothelium and subendothelium at sites of damage (see Fig. 50-1B). Platelet interactions with their ligands cause transmembrane signaling through surface receptors to induce platelet activation and promote procoagulant function through various pathways, including translocation of additional receptors to the membrane surface, receptor conformational change to active forms, release of granule contents that recruit platelet adhesion, and exposure of procoagulant membrane phospholipids. The procoagulant surface of the platelet then serves as a platform for enhanced assembly of the coagulation cascade to generate thrombin. Thrombin feeds back on platelets and the clotting cascade to amplify the procoagulant response and also produces fibrin to provide secondary, long-lasting hemostasis. Finally, the platelets assist thrombin in clot consolidation and in protection from fibrinolysis by contributing factor XIII and platelet factor 4, respectively, to the clot milieu (Table 50-2).

Platelet Hemostasis

Platelets are anucleate cells between 2 and 4 μm in diameter with a volume between 6 and 11 fL. Platelets are derived from the megakaryocyte cytoplasm after a maturation time of about 4 days, with each megakaryocyte contributing 1000 to 3000 circulating platelets in its lifetime. When platelets are released into the circulation, they survive for 7 to 10 days; platelets leave the circulation through a combination of senescence and the normal maintenance of vascular structural integrity. For the latter, very few platelets are needed; approximately 7100 platelets/μL are required for hemostasis per day if vascular structures are intact (e.g., no recent surgery or trauma) and if there is no increase in normal platelet consumption (e.g., sepsis).

The normal platelet count ranges between 150,000 and 450,000/μL, depending on the population used to establish the reference range. With platelet counts in the normal range and normal platelet function, the bleeding time, an in vivo measure of platelet function, is typically less than 8 minutes. However, if the number of normal functioning platelets is less than 100,000/μL, the bleeding time is prolonged. Therefore, in the presence of thrombocytopenia, the bleeding time cannot be used to determine whether bleeding is caused by abnormal platelet function or by connective tissue disease. The bleeding time is an operator-dependent, highly variable in vivo assay that can leave scars; many laboratories have therefore switched to a so-called in vitro bleeding time test such as the Platelet Function Analyzer-100 (PFA-100), which uses anticoagulated whole blood to examine "closure time" (details on the PFA-100 and other platelet function platforms are provided in Chapter 51). However, the PFA-100 and other like-minded tests are similar to the bleeding time test in that they are unable to distinguish between thrombocytopenia and abnormal platelet function when platelet counts are lower than 100,000/μL.

Shear-Induced Adhesion

The interaction between platelets and the vessel wall has been well characterized at the high flow velocities of the arterial circulation. The interaction between the vasculature and flowing blood, as shown on the left side of Figure 50-1A, creates parallel planes of blood moving at different velocities; the blood closest to the vessel wall moves more slowly than blood that is closer to the center of the vessel. These different velocities create shear stress that is greatest at the vessel wall and least at the center of the vessel. Shear rate therefore changes inversely with the vessel diameter, with levels estimated to vary between 500 s^{-1} in larger arteries and 5000 s^{-1} in the smallest arterioles. Shear rates at the surface of atherosclerotic plaques with modest (50%) stenosis reach 3000 to 10,000 s^{-1}, with even greater shear in more clinically significant stenoses. The high-velocity aspect of arterial blood flow actually opposes the tendencies to clot by (1) limiting the time available for procoagulant reactions to occur and (2) disrupting cells and proteins that are not tightly adherent to the vessel wall. However, once the vessel wall is damaged and bleeding occurs, platelets can rapidly and decisively respond to the loss of endothelial integrity while they simultaneously resist the tendency to be swept downstream.

One of the forces enhancing platelet readiness for wall adhesion in the arterial circulation is radial dispersion, the tendency of larger cells (erythrocytes and leukocytes) to stream in the center of the vessel, where shear is lowest. This process effectively pushes the smaller platelets toward the vessel wall and optimally positions them to respond to hemostatic challenges. This size-dependent flow may also explain the seemingly paradoxical ability of red blood cell transfusions to slow or stop bleeding in patients with thrombocytopenia or consumptive coagulopathy (see Chapter 51). This effect also underscores the importance of platelets in arterial hemostasis; reductions in platelet number or function may be associated with severe arterial hemorrhage after surgery or trauma. By contrast, the lesser shear forces experienced in the venous circulation permit more random cell movement and greater time for coagulation reactions to occur; for this reason, the minimum requirements for platelet number and function in venous hemostasis are less stringent.