in arteries. This insight provides part of the reasoning behind the use of aspirin and other platelet inhibitors in coronary artery disease and acute myocardial infarction.

Obviously, severe endothelial injury may trigger thrombosis by exposing vWF and tissue factor. However, inflammation and other noxious stimuli also promote thrombosis by shifting the pattern of gene expression in endothelium to one that is "prothrombotic." This change is sometimes referred to as *endothelial activation* or *dysfunction* and can be produced by diverse exposures, including physical injury, infectious agents, abnormal blood flow, inflammatory mediators, metabolic abnormalities, such as hypercholesterolemia or homocystinemia, and toxins absorbed from cigarette smoke. Endothelial activation is believed to have an important role in triggering arterial thrombotic events.

The role of endothelial cell activation and dysfunction in arterial thrombosis is discussed in detail in Chapters 11 and 12. Here it suffices to mention several of the major prothrombotic alterations:

- *Procoagulant changes.* Endothelial cells activated by cytokines downregulate the expression of *thrombomodulin*, already described as a key modulator of thrombin activity. This may result in sustained activation of thrombin, which can in turn stimulate platelets and augment inflammation through PARs expressed on platelets and inflammatory cells. In addition, inflamed endothelium also downregulates the expression of other anticoagulants, such as protein C and tissue factor protein inhibitor, changes that further promote a procoagulant state.
- *Antifibrinolytic effects.* Activated endothelial cells secrete *plasminogen activator inhibitors* (PAIs), which limit fibrinolysis, and downregulate the expression of t-PA, alterations that also favor the development of thrombi.

Alternations in Normal Blood Flow

Turbulence contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents that contribute to local pockets of stasis. *Stasis* is a major contributor in the development of venous thrombi. Normal blood flow is *laminar* such that the platelets (and other blood cellular elements) flow centrally in the vessel lumen, separated from endothelium by a slower moving layer of plasma. Stasis and turbulence therefore:

- Promote endothelial activation, enhancing procoagulant activity and leukocyte adhesion, in part through flow-induced changes in the expression of adhesion molecules and pro-inflammatory factors
- Disrupt laminar flow and bring platelets into contact with the endothelium
- Prevent washout and dilution of activated clotting factors by fresh flowing blood and the inflow of clotting factor inhibitors

Altered blood flow contributes to thrombosis in several clinical settings. Ulcerated atherosclerotic plaques not only expose subendothelial vWF and tissue factor but also cause turbulence. Aortic and arterial dilations called *aneurysms* result in local stasis and are therefore fertile sites for thrombosis (Chapter 11). Acute myocardial infarctions result in areas of noncontractile myocardium and sometimes in cardiac aneurysms; both are associated with stasis and flow abnormalities that promote the formation of cardiac mural thrombi (Chapter 12). Rheumatic mitral valve stenosis results in left atrial dilation; in conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for thrombosis (Chapter 12). *Hyperviscosity* (such as is seen with polycythemia vera; Chapter 13) increases resistance to flow and causes small vessel stasis, and the deformed red cells in *sickle cell anemia* (Chapter 14) impede blood flow through small vessels, with the resulting stasis also predisposing to thrombosis.

Hypercoagulability

Hypercoagulability (also called thrombophilia) can be loosely defined as any disorder of the blood that predisposes to thrombosis. Hypercoagulability has a particularly important role in venous thrombosis and can be divided into *primary* (genetic) and *secondary* (acquired) disorders (Table 4-2). Of the inherited causes of hypercoagulability, point mutations in the factor V gene and prothrombin gene are the most common.

- Approximately 2% to 15% of Caucasians carry a single-nucleotide mutation in factor V that is called the *factor V Leiden,* after the city in The Netherlands where it was discovered. Among individuals with recurrent DVT, the frequency of this mutation is considerably higher, approaching 60%. The mutation results in a glutamine

Table 4-2 Hypercoagulable States

Primary (Genetic)
Common
Factor V mutation (Arg to Glu substitution in amino acid residue 506 leading to resistance to activated protein C; factor V Leiden)
Prothrombin mutation (G20210A noncoding sequence variant leading to increased prothrombin levels)
Increased levels of factors VIII, IX, XI, or fibrinogen (genetics unknown)
Rare
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Very Rare
Fibrinolysis defects
Homozygous homocystinuria (deficiency of cystathione β-synthetase)
Secondary (Acquired)
High Risk for Thrombosis
Prolonged bed rest or immobilization
Myocardial infarction
Atrial fibrillation
Tissue injury (surgery, fracture, burn)
Cancer
Prosthetic cardiac valves
Disseminated intravascular coagulation
Heparin-induced thrombocytopenia
Antiphospholipid antibody syndrome
Lower Risk for Thrombosis
Cardiomyopathy
Nephrotic syndrome
Hyperestrogenic states (pregnancy and postpartum)
Oral contraceptive use
Sickle cell anemia
Smoking