to arginine substitution at amino acid residue 506 that renders factor V resistant to cleavage and inactivation by protein C. As a result, an important antithrombotic counterregulatory pathway is lost (Fig. 4-10). Indeed, heterozygotes have a five-fold increased relative risk of venous thrombosis, and homozygotes have a 50-fold increase.

- A single nucleotide change (G20210A) in the 3′-untranslated region of the *prothrombin gene* is another common mutation (1% to 2% of the population) associated with hypercoagulability. It leads to elevated prothrombin levels and an almost three-fold increased risk of venous thrombosis.
- Elevated levels of *homocysteine* contribute to arterial and venous thrombosis, as well as the development of atherosclerosis (Chapter 11). The prothrombotic effects of homocysteine may be due to thioester linkages formed between homocysteine metabolites and a variety of proteins, including fibrinogen. Marked elevations of homocysteine may be caused by an inherited deficiency of cystathione β-synthetase.
- Rare inherited causes of primary hypercoagulability include deficiencies of anticoagulants such as antithrombin III, protein C, or protein S; affected individuals typically present with venous thrombosis and recurrent thromboembolism beginning in adolescence or early adulthood.

The most common thrombophilic genotypes found in various populations (heterozygosity for factor V Leiden and heterozygosity for the prothrombin G20210A variant) impart only a moderately increased risk of thrombosis; most individuals with these genotypes, when otherwise healthy, are free of thrombotic complications. However, factor V and prothrombin mutations are frequent enough that homozygosity and compound heterozygosity are not rare, and such genotypes are associated with greater risk. Moreover, individuals with such mutations have a significantly increased frequency of venous thrombosis in the setting of other acquired risk factors (e.g., pregnancy or prolonged bed rest). Thus, factor V Leiden heterozygosity may trigger DVT when combined with enforced inactivity, such as during prolonged airplane travel. Consequently, **inherited causes of hypercoagulability must be considered in patients younger than age 50 years who present with thrombosis—even when acquired risk factors are present.**

Unlike hereditary disorders, the pathogenesis of *acquired thrombophilia* is frequently multifactorial (Table 4-2). In some cases (e.g., cardiac failure or trauma), stasis or vascular injury may be most important. Hypercoagulability due to oral contraceptive use or the hyperestrogenic state of pregnancy is probably caused by increased hepatic synthesis of coagulation factors and reduced anticoagulant synthesis. In disseminated cancers, release of various procoagulants from tumors predisposes to thrombosis. The hypercoagulability seen with advancing age may be due to reduced endothelial PGI_2 production. Smoking and obesity promote hypercoagulability by unknown mechanisms.

Among the acquired thrombophilic states, the heparin-induced thrombocytopenia and the antiphospholipid antibody syndromes are particularly important clinical problems that deserve special mention.

Heparin-Induced Thrombocytopenia (HIT) Syndrome

HIT occurs following the administration of *unfractionated heparin*, which may induce the appearance of antibodies that recognize complexes of heparin and platelet factor 4 on the surface of platelets (Chapter 14), as well as complexes of heparin-like molecules and platelet factor 4-like proteins on endothelial cells. Binding of these antibodies to platelets results in their activation, aggregation, and consumption (hence the *thrombocytopenia* in the syndrome name). This effect on platelets and endothelial damage induced by antibody binding combine to produce a *prothrombotic state*, even in the face of heparin administration and low platelet counts. Low-molecular-weight heparin preparations induce HIT less frequently, and other classes of anticoagulants such as direct inhibitors of factor X and thrombin may also obviate the risk.

Antiphospholipid Antibody Syndrome

This syndrome (previously called the lupus anticoagulant syndrome) has protean clinical manifestations, including recurrent thromboses, repeated miscarriages, cardiac valve vegetations, and thrombocytopenia. Depending on the vascular bed involved, the clinical presentations can include pulmonary embolism (PE) (following lower extremity venous thrombosis), pulmonary hypertension (from recurrent subclinical pulmonary emboli), stroke, bowel infarction, or renovascular hypertension. Fetal loss does not appear to be explained by thrombosis, but rather seems to stem from antibody-mediated interference with the growth and differentiation of trophoblasts, leading to a failure of placentation. Antiphospholipid antibody syndrome is also a cause of renal microangiopathy, resulting in renal failure associated with multiple capillary and arterial thromboses (Chapter 20).

The name antiphospholipid antibody syndrome is misleading, as it is believed that the most important pathologic effects are mediated through binding of the antibodies to epitopes on proteins that are somehow induced or "unveiled" by phospholipids. Transfer of antiphospholipid antibodies to rodents can induce thrombosis, clearly indicating their pathogenicity, but the precise mechanisms remain uncertain. Suspected antibody targets include β2-glycoprotein I, a plasma protein that associates with the surfaces of endothelial cells and trophoblasts, and thrombin. In vivo, it is suspected that these antibodies bind to these and perhaps other proteins, thereby inducing a hypercoagulable state through uncertain mechanisms. However, in vitro, the antibodies interfere with phospholipids and thus inhibit coagulation. The antibodies also frequently give a false-positive serologic test for syphilis because the antigen in the standard assay is embedded in cardiolipin.

Antiphospholipid antibody syndrome has primary and secondary forms. Individuals with a well-defined autoimmune disease, such as systemic lupus erythematosus (Chapter 6), are designated as having *secondary antiphospholipid syndrome* (hence the earlier term *lupus anticoagulant syndrome*). In *primary antiphospholipid syndrome*, patients exhibit only the manifestations of a hypercoagulable state and lack evidence of other autoimmune disorders; occasionally, it appears following exposure to certain drugs or infections. Therapy involves anticoagulation and