(see Fig. 4–10). The resulting *fibrin split products* (*FSPs*, or so-called *fibrin degradation products*) can also act as weak anticoagulants. As a clinical correlate, elevated levels of these FSPs are helpful in diagnosing abnormal thrombotic states such as disseminated intravascular coagulation, deep venous thrombosis, or pulmonary thromboembolism (described in detail later). Any free plasmin rapidly complexes with circulating α_2-antiplasmin and is inactivated so that excess plasmin does not lyse clots elsewhere in the body (see Fig. 4–10).

- Endothelial cells further modulate the coagulation/anticoagulation balance by releasing *plasminogen activator inhibitors (PAIs);* these block fibrinolysis and confer an overall procoagulation effect (see Fig. 4–10). The PAIs are increased by certain cytokines and probably play a role in the intravascular thrombosis accompanying severe inflammations.

Thrombosis

Having discussed the process of normal hemostasis, we can now turn our attention to the dysregulation that underlies pathologic thrombus formation.

Pathogenesis. Three primary influences predispose to thrombus formation, the so-called *Virchow triad*: (1) endothelial injury, (2) stasis *or* turbulence of blood flow, and (3) blood hypercoagulability (Fig. 4–11).

- *Endothelial injury* is the dominant influence and by itself can lead to thrombosis. It is particularly important in thrombus formation in the heart and arterial circulation, for example, within the cardiac chambers when there has been endocardial injury (e.g., myocardial infarction or valvulitis), over ulcerated plaques in severely atherosclerotic arteries, or at sites of traumatic or inflammatory vascular injury. *It is important to note that endothelium does not need to be denuded or physically disrupted to contribute to the development of thrombosis; any perturbation in the dynamic balance of prothrombotic and antithrombotic effects can influence local clotting events* (see Fig. 4–6). Thus, significant endothelial dysfunction may occur from the hemodynamic stresses of hypertension, turbulent flow over scarred valves, or bacterial endotoxins. Even relatively subtle influences such as homocystinuria, hypercholesterolemia, radiation, or products absorbed from cigarette smoke may be sources of endothelial injury and dysregulation. Regardless of the cause, physical loss of endothelium leads to exposure of subendothelial collagen (and other platelet activators), adherence of platelets, release of tissue factor, and local depletion of PGI_2 and PA (see Fig. 4–6). Dysfunctional endothelium may elaborate greater amounts of procoagulant factors (e.g., adhesion molecules to bind platelets, tissue factor, PAI, etc.) and smaller amounts of anticoagulant effectors (e.g., thrombomodulin, PGI_2, t-PA).
- *Alterations in normal blood flow. Turbulence* contributes to arterial and cardiac thrombosis by causing endothelial injury or dysfunction, as well as by forming countercurrents and local pockets of stasis; *stasis* is a major factor in the development of venous thrombi. Normal blood flow is *laminar* such that the platelet elements flow centrally in the vessel lumen, separated from the endothelium by a slower-moving clear zone of plasma. Stasis and turbulence therefore (1) disrupt laminar flow and bring platelets into contact with the endothelium, (2) prevent dilution of activated clotting factors by fresh-flowing blood, (3) retard the inflow of clotting factor inhibitors and permit the build-up of thrombi, and (4) promote endothelial cell activation, predisposing to local thrombosis, leukocyte adhesion, and a variety of other endothelial cell effects.

  Turbulence and stasis contribute to thrombosis in a number of clinical settings. Ulcerated atherosclerotic plaques not only expose subendothelial ECM but also generate local turbulence. Abnormal aortic and arterial dilations called *aneurysms* cause local stasis and are favored sites of thrombosis (Chapter 10). Myocardial infarctions not only have associated endothelial injury but also have regions of noncontractile myocardium, adding an element of stasis in the formation of mural thrombi. Mitral valve stenosis (e.g., after rheumatic heart disease) results in left atrial dilation. In conjunction with atrial fibrillation, a dilated atrium is a site of profound stasis and a prime location for development of thrombi. *Hyperviscosity syndromes* (such as *polycythemia*; Chapter 12) increase resistance to flow and cause small vessel stasis; the deformed red cells in sickle cell anemia (Chapter 12) cause vascular occlusions, with the resultant stasis predisposing to thrombosis.
- *Hypercoagulability* generally contributes less frequently to thrombotic states but is nevertheless an important (and interesting) component in the equation. It is loosely defined as any alteration of the coagulation pathways that predisposes to thrombosis, and it can be divided into *primary* (genetic) and *secondary* (acquired) disorders (Table 4–2).

  Of the inherited causes of hypercoagulability, mutations in the factor V gene and prothrombin gene are the most common. The characteristic alteration is a mutant factor Va that cannot be inactivated by protein C; as a result, an important antithrombotic counter-regulatory pathway is lost (see Fig. 4–6). Approximately 2% to

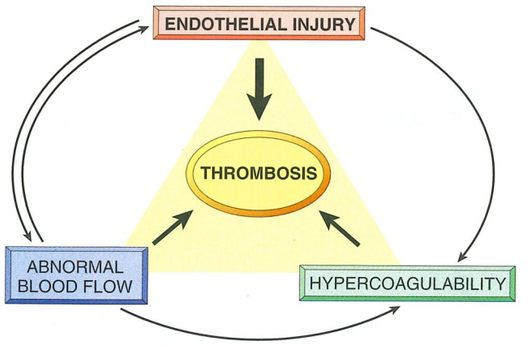

Figure 4–11 ■

Virchow triad in thrombosis. Endothelial integrity is the single most important factor. Injury to endothelial cells can also alter local blood flow and affect coagulability. Abnormal blood flow (stasis or turbulence), in turn, can cause endothelial injury. The factors may act independently or may combine to cause thrombus formation.

Table 4–2. CONDITIONS ASSOCIATED WITH AN INCREASED RISK OF THROMBOSIS

Primary (Genetic)
Factor V mutations
Prothrombin mutation
Antithrombin III deficiency
Protein C or S deficiency
Secondary (Acquired)
High risk for thrombosis
Prolonged bed rest or immobilization
Myocardial infarction
Tissue damage (surgery, fracture, burns)
Cancer
Prosthetic cardiac valves
Disseminated intravascular coagulation
Lupus anticoagulant
Low risk for thrombosis
Atrial fibrillation
Cardiomyopathy
Nephrotic syndrome
Hyperestrogenic states
Oral contraceptive use
Sickle cell anemia
Smoking

15% of the white population carries a specific factor V mutation (referred to as the Leiden mutation, after the Dutch city in which it was first discovered); among patients with recurrent deep vein thrombosis, the frequency is much higher, approaching 60% in some studies. A mutation in the 3' untranslated region of prothrombin gene (so-called G20210A mutation) is associated with an increased level of prothrombin and hence susceptibility to venous thrombosis. Less common primary hypercoagulable states include inherited deficiencies of anticoagulants such as antithrombin III, protein C, or protein S; affected patients typically present with venous thrombosis and recurrent thromboembolism in adolescence or early adult life. Congenitally elevated levels of homocysteine contribute to arterial and venous thromboses (and indeed to the development of atherosclerosis; Chapter 10), likely via inhibitory effects on antithrombin III and endothelial thrombomodulin.

Although these hereditary disorders are uncommon, the basis of the thrombotic tendencies is reasonably well understood. However, the pathogenesis of *acquired thrombotic diatheses* in a number of common clinical settings is more complicated and multifactorial. In some of the acquired conditions (e.g., cardiac failure or trauma), factors such as stasis or vascular injury may be most important. Even inactivity for the duration of an overseas plane flight may be sufficient to induce deep leg vein thromboses; in such cases, heterozygosity for factor V Leiden or the G20210A prothrombin gene may be synergistic with each other and with acquired causes of hypercoagulability listed in Table 4–2. Among acquired causes (oral contraceptive use and the hyperestrogenic state of pregnancy), hypercoagulability may be related to increased hepatic synthesis of coagulation factors and reduced synthesis of antithrombin III. In disseminated cancers, release of procoagulant tumor products predisposes to thrombosis. The hypercoagulability seen with advancing age may be due to increasing platelet aggregation and reduced PGI_2 release by endothelium. Smoking and obesity promote hypercoagulability by unknown mechanisms.

Among the acquired causes of thrombotic diathesis, the so-called *heparin-induced thrombocytopenia (HIT) syndrome* and *antiphospholipid antibody syndrome* (APS; previously called the *lupus anticoagulant syndrome*) deserve special mention.

- *HIT syndrome.* This syndrome is estimated to affect 3% to 5% of the population; it occurs when administration of unfractionated heparin (for purposes of therapeutic anticoagulation) induces circulating antibodies that can bind to molecular complexes of heparin and a platelet membrane protein (platelet factor 4) (Chapter 12). This antibody can then attach to similar complexes present on platelet and endothelial surfaces; the result is platelet activation and endothelial cell injury, and *a prothrombotic state*. To circumvent this problem, specially manufactured low-molecular-weight heparin preparations that retain anticoagulant activity but do not interact with platelets (and have the additional advantage of a prolonged serum half-life) are used.
- A*PS.* This syndrome refers to a number of heterogeneous clinical manifestations—including recurrent thrombosis—associated with high titers of antibodies directed against anionic phospholipids (e.g., cardiolipin) or, more accurately, plasma protein antigens that are unveiled by binding to such phospholipids. In vitro, these antibodies interfere with the assembly of phospholipid complexes and inhibit coagulation (hence the designation *lupus anticoagulant*). In contrast, the antibodies in vivo induce a hypercoagulable state. The exact incidence of the syndrome is unknown, although it is being increasingly recognized as a possible culprit in a number of thrombotic states; for example, approximately 20% of patients with a recent stroke were found to have anticardiolipin antibodies, versus none in age-matched controls without stroke.

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Thrombi may develop anywhere in the cardiovascular system: within the cardiac chambers, on valve cusps, or in arteries, veins, or capillaries. They are of variable size and shape, depending on the site of origin and the circumstances leading to their development. Arterial or cardiac thrombi usually begin at a site of endothelial injury (e.g., atherosclerotic plaque) or turbulence (vessel bifurcation); venous thrombi characteristically occur in sites of stasis. An area of attachment to the underlying vessel or heart wall, frequently firmest at the point of origin, is characteristic of all thrombi. Arterial thrombi tend to grow in a retrograde direction from the point of attachment; venous thrombi extend in the direction of blood flow, that is, toward the heart. The propagat-

ing tail may not be well attached and, particularly in veins, is prone to fragment, creating an **embolus.**

When formed in the heart or aorta, thrombi may have grossly (and microscopically) apparent laminations called **lines of Zahn;** these are produced by pale layers of platelets and fibrin that alternate with darker layers containing more red cells. Lines of Zahn are significant only in that they imply thrombosis at a site of blood flow; in veins or in smaller arteries, the laminations are typically not as apparent, and, in fact, thrombi formed in the sluggish venous flow usually resemble statically coagulated blood (much like blood clotted in a test tube). Nevertheless, careful evaluation generally reveals irregular, somewhat ill-defined laminations.

When arterial thrombi arise in heart chambers or in the aortic lumen, they are usually applied to the wall of the underlying structure and are termed **mural thrombi.** Abnormal myocardial contraction (arrhythmias, dilated cardiomyopathy, or myocardial infarction) or injury to the endomyocardial surface (myocarditis, catheter trauma) leads to the formation of cardiac mural thrombi (Fig. 4–12*A*), while ulcerated atherosclerotic plaques and aneurysmal dilation are the precursors of aortic thrombus formation (Fig. 4–12*B*).

Arterial thrombi are usually **occlusive;** the most common sites, in descending order, are coronary, cerebral, and femoral arteries. The thrombus is usually superimposed on an atherosclerotic plaque, although other forms of vascular injury (vasculitis, trauma) may be involved. The thrombi typically are firmly adherent to the injured arterial wall and are gray-white and friable, composed of a tangled mesh of platelets, fibrin, erythrocytes, and degenerating leukocytes.

Venous thrombosis, or **phlebothrombosis,** is almost invariably occlusive; the thrombus often creates a long cast of the vein lumen. Because these thrombi form in the slowly moving venous blood, they tend to contain more enmeshed erythrocytes and are therefore known as **red,** or **stasis, thrombi. Phlebothrombosis most commonly (90% of cases) affects the veins of the lower extremities.** Less commonly, venous thrombi may develop in the upper extremities, periprostatic plexus, or ovarian and periuterine veins; under special circumstances they may be found in the dural sinuses, portal vein, or hepatic vein (Chapter 16). At autopsy, postmortem clots may be mistaken for venous thrombi. Postmortem clots are gelatinous with a dark red dependent portion where red cells have settled by gravity, and a yellow "chicken fat" supernatant; they are usually not attached to the underlying wall. In contrast, red thrombi are firmer, almost always have a point of attachment, and on transection reveal vague strands of pale gray fibrin.

Under special circumstances, thrombi may form on heart valves. Bacterial or fungal blood-borne infections may lead to valve damage and the development of large thrombotic masses, or **vegetations (infective endocarditis,** Chapter 11). Sterile vegetations can also develop on noninfected valves in patients with hypercoagulable states, so-called **nonbacterial thrombotic endocarditis** (Chapter 11). Less commonly, noninfective, **verrucous (Libman-Sacks) endocarditis** may occur in patients who have systemic lupus erythematosus (Chapter 5).

Fate of the Thrombus. If a patient survives the immediate effects of a thrombotic vascular obstruction, thrombi undergo some combination of the following four events in the ensuing days or weeks (Fig. 4–13):

- *Propagation.* The thrombus may accumulate more platelets and fibrin (propagate), eventually obstructing some critical vessel.
- *Embolization.* Thrombi may dislodge and be transported to other sites in the vasculature.
- *Dissolution.* Thrombi may be removed by fibrinolytic activity.

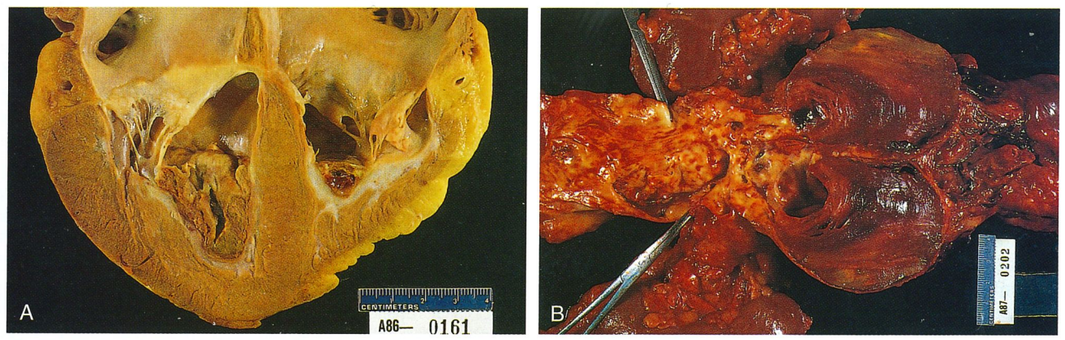

Figure 4–12

Mural thrombi. *A,* Thrombus in the left and right ventricular apices, overlying a white fibrous scar. *B,* Laminated thrombus in a dilated abdominal aortic aneurysm. Numerous friable mural thrombi are also superimposed on advanced atherosclerotic lesions of the more proximal aorta *(left side of picture).*

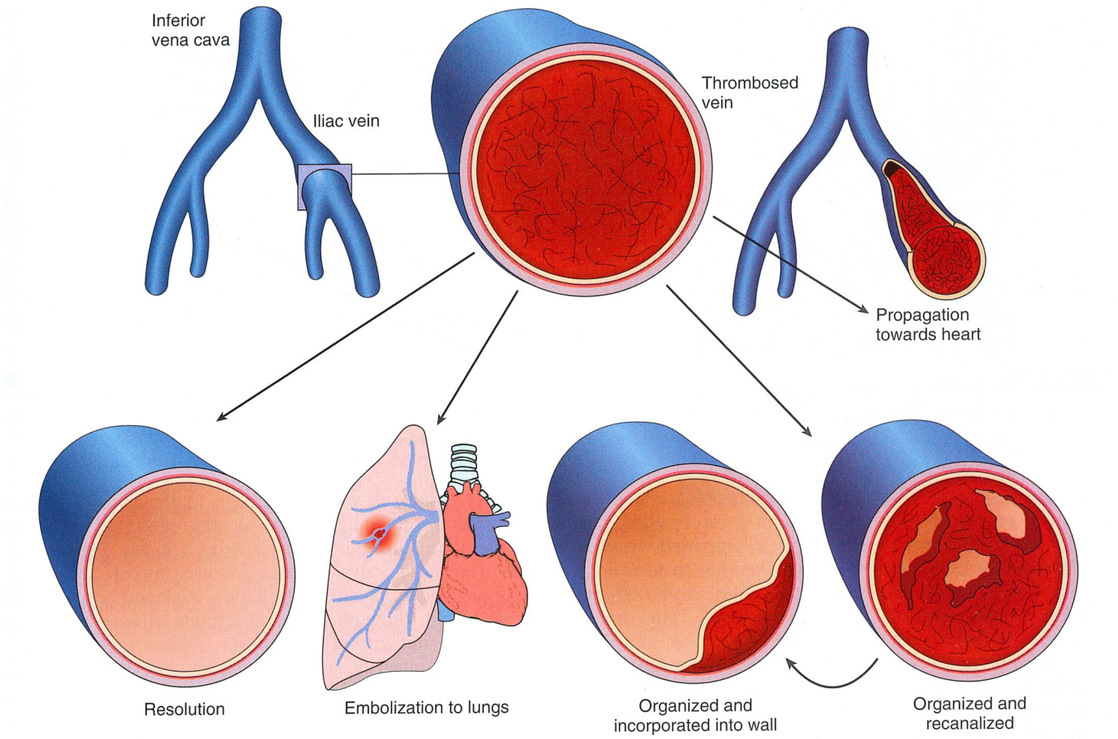

Figure 4–13

Potential outcomes of venous thrombosis (see text).

- *Organization and recanalization.* Thrombi may induce inflammation and fibrosis *(organization)* and may eventually become *recanalized* (re-establish vascular flow), or they may be incorporated into a thickened vascular wall.

Embolization is discussed in greater detail later. As for dissolution, activation of the fibrinolytic pathways can lead to rapid shrinkage and even total lysis of *recent* thrombi. With older thrombi, extensive fibrin polymerization renders the thrombus substantially more resistant to proteolysis, and lysis is ineffectual. This is important, because therapeutic infusions of fibrinolytic agents such as t-PA (e.g., for pulmonary thromboemboli or coronary thrombosis) are likely to be effective only for a short time after thrombi form.

Older thrombi tend to become *organized.* This refers to the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin-rich thrombus. In time, capillary channels are formed that may anastomose to create conduits from one end of the thrombus to the other, re-establishing to a limited extent the continuity of the original lumen (Fig. 4–14). Although the channels may not successfully restore significant flow to many obstructed vessels, such *recanalization* can potentially convert the thrombus into a vascularized mass of connective tissue that is eventually incorporated as a subendothelial swelling into the vessel wall. With time and contraction of the mesenchymal cells, only a fibrous lump may remain to mark the original thrombus site. Occasionally, instead of organizing, the center of a thrombus undergoes enzymatic digestion, presumably because of the release of lysosomal enzymes from trapped leukocytes and platelets. This is particularly likely in large thrombi within aneurysmal dilations or the cardiac chambers. If bacterial seeding occurs, such degraded thrombus is an ideal culture medium, resulting in a so-called *mycotic aneurysm* (Chapter 10).

Clinical Correlations: Venous versus Arterial Thrombosis. Thrombi are significant because (1) they cause obstruction of arteries and veins and (2) they are possible sources of emboli. The importance of each is dependent on where the thrombus occurs. Thus, while venous thrombi may cause congestion and edema in vascular beds distal to an obstruction, a far graver consequence is that they may embolize to the lungs, causing death (p 95). Conversely, although arterial thrombi can embolize, their role in vascular obstruction at critical sites, such as coronary or cerebral vessels, is much more important.

- *Venous thrombosis (phlebothrombosis).* Most venous thrombi occur in either the superficial or the deep veins of the leg. Superficial venous thrombi usually occur in the saphenous system, particularly when there are varicosities. Such thrombi may cause local conges-

ROBBINS

BASIC PATHOLOGY

7th edition

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