Bleeding Disorders: Hemorrhagic Diatheses

Excessive bleeding can result from (1) increased fragility of vessels, (2) platelet deficiency or dysfunction, (3) derangement of coagulation, and (4) combinations of these.

Before discussing these specific bleeding disorders, it is helpful to review normal hemostasis (Chapter 4) and the common laboratory tests used in the evaluation of a bleeding diathesis. It should be recalled from the discussion in Chapter 4 that the normal hemostatic response involves the blood vessel wall, the platelets, and the clotting cascade. Tests used to evaluate different aspects of hemostasis are the following:

- **Bleeding time.** This measures the time taken for a standardized skin puncture to stop bleeding and provides an in vivo assessment of platelet response to limited vascular injury. The reference range depends on the actual method employed and varies from 2 to 9 minutes. Prolongation generally indicates a defect in platelet numbers or function. Bleeding time test is fraught with variability and poor reproducibility. Hence new instrument-based assay systems such as platelet function analyzer-100 (PFA-100) that provide a quantitative measure of platelet function under conditions of high shear stress are being evaluated as replacements for the bleeding time test.  

- **Platelet counts.** These are obtained on anticoagulated blood using an electronic particle counter. The reference range is 150 to 300 × 10^3/μL. Counts well outside this range need to be confirmed by a visual inspection of a peripheral blood smear, as clumping of platelets can cause spurious “thrombocytopenia” during automated counting, and high counts may be indicative of a myeloproliferative disorder.

- **Prothrombin time (PT).** This assay tests the extrinsic and common coagulation pathways. The clotting of plasma after addition of an exogenous source of tissue thromboplastin (e.g., brain extract) and Ca^{2+} ions is measured in seconds. A prolonged PT can result from deficiency or dysfunction of factor V, factor VII, factor X, prothrombin, or fibrinogen.

- **Partial thromboplastin time (PTT).** This assay tests the intrinsic and common clotting pathways. The clotting of plasma after addition of kaolin, cephalin, and calcium ions is measured in seconds. Kaolin serves to activate the contact-dependent factor XII, and cephalin substitutes for platelet phospholipids. Prolongation of the PTT can be due to deficiency or dysfunction of factor V, VIII, IX, X, XI, or XII, prothrombin, or fibrinogen.

More specialized tests are available to measure the levels of specific clotting factors, fibrinogen, fibrin split products, the presence of circulating anticoagulants, and platelet function. With this overview, we can turn to the various categories of bleeding disorders.

**BLEEDING DISORDERS CAUSED BY VESSEL WALL ABNORMALITIES**

Disorders within this category, sometimes called nonthrombocytopenic purpuras, are relatively common but do not usually cause serious bleeding problems. Most often, they induce small hemorrhages (petechiae and purpura) in the skin or mucous membranes, particularly the gingivae.
On occasion, however, more significant hemorrhages can occur into joints, muscles, and subperiosteal locations or take the form of menorrhagia, nosebleeds, gastrointestinal bleeding, or hematuria. The platelet count, bleeding time, and results of the coagulation tests (PT, PTT) are usually normal.

The varied clinical conditions in which hemorrhages can be related to abnormalities in the vessel wall include the following:

- Many infections induce petechial and purpuric hemorrhages, but especially implicated are meningococcemia, other forms of septicemia, infective endocarditis, and several of the rickettsioses. The involved mechanism is presumably microbial damage to the microvasculature (vasculitis) or disseminated intravascular coagulation (DIC). Failure to recognize meningococcemia as a cause of petechiae and purpura can be catastrophic for the patient.

- Drug reactions sometimes induce cutaneous petechiae and purpura without causing thrombocytopenia. In many instances, the vascular injury is mediated by drug-induced antibodies and deposition of immune complexes in the vessel walls, leading to hypersensitivity (leukocytoclastic) vasculitis (Chapter 11).

- Scurvy and the Ehlers-Danlos syndrome are associated with microvascular bleeding resulting from impaired formation of collagens needed for support of vessel walls. The same mechanism may account for spontaneous purpura commonly seen in the very elderly. The predisposition to skin hemorrhages in Cushing syndrome, in which the protein-wasting effects of excessive corticosteroid production cause loss of perivascular supporting tissue, has a similar etiology.

- Henoch-Schönlein purpura is a systemic hypersensitivity disease of unknown cause characterized by a purpuric rash, colicky abdominal pain (presumably due to focal hemorrhages into the gastrointestinal tract), polyarthralgia, and acute glomerulonephritis (Chapter 20). All these changes result from the deposition of circulating immune complexes within vessels throughout the body and within the glomerular mesangial regions.

- Hereditary hemorrhagic telangiectasia is an autosomal dominant disorder characterized by dilated, tortuous blood vessels with thin walls that bleed readily. Bleeding can occur anywhere in the body but is most common under the mucous membranes of the nose (epistaxis), tongue, mouth, and eyes and throughout the gastrointestinal tract.

- Amyloid infiltration of blood vessels. Systemic amyloidosis is associated with perivascular deposition of amyloid and consequent weakening of blood vessel wall. This is most commonly observed in plasma cell dyscrasias (Chapter 14) and is manifested as mucocutaneous petechiae.

Bleeding in these conditions is rarely life threatening with the exception of some cases of hereditary telangiectasia. Recognition of the presenting symptoms should prompt further studies to establish a specific diagnosis.

**BLEEDING RELATED TO REDUCED PLATELET NUMBER: THROMBOCYTOPENIA**
Reduction in platelet number constitutes an important cause of generalized bleeding. Normal platelet counts range from 150,000 to 300,000/µL. A count below 100,000/µL is generally considered to constitute thrombocytopenia. However, spontaneous bleeding does not become evident until the count falls below 20,000/µL. Platelet counts in the range of 20,000 to 50,000/µL can aggravate post-traumatic bleeding. Bleeding resulting from thrombocytopenia alone is associated with a prolonged bleeding time and normal PT and PTT.

The important role of platelets in hemostasis is discussed in Chapter 4. It hardly needs reiteration that these cells are critical for hemostasis, as they form temporary plugs that quickly stop bleeding and promote key reactions in the clotting cascade. Spontaneous bleeding associated with thrombocytopenia most often involves small vessels. The common sites of such hemorrhage are the skin and the mucous membranes of the gastrointestinal and genitourinary tracts. Intracranial bleeding is a threat to any patient with a markedly depressed platelet count.

The many causes of thrombocytopenia can be classified into the four major categories listed in Table 13-9.

- **Decreased production of platelets.** This can accompany generalized diseases of bone marrow such as aplastic anemia and leukemias or result from diseases that affect the megakaryocytes somewhat selectively. In vitamin B₁₂ or folic acid deficiency, there is poor development and accelerated destruction of megakaryocytes within the bone marrow (ineffective megakaryopoiesis) because DNA synthesis is impaired.

- **Decreased platelet survival.** This important cause of thrombocytopenia can have an immunologic or nonimmunologic etiology. In the immune conditions, platelet destruction is caused by circulating antiplatelet antibodies or, less often, immune complexes. The antiplatelet antibodies can be directed against a self-antigen on the platelets (autoantibodies) or against platelet antigens that differ among different individuals (alloantibodies). Common antigenic targets of both autoantibodies and alloantibodies are the platelet membrane glycoprotein complexes IIb-IIIa and Ib-IX. Autoimmune thrombocytopenias include idiopathic thrombocytopenic purpura, certain drug-induced thrombocytopenias, and HIV-associated thrombocytopenias. All of these are discussed later. Alloimmune thrombocytopenias arise when an individual is exposed to platelets of another person, as may occur after blood transfusion or during pregnancy. In the latter case, neonatal or even fetal thrombocytopenia occurs by a mechanism analogous to erythroblastosis fetalis. Nonimmunologic destruction of platelets may be caused by mechanical injury, in a manner analogous to red cell destruction in microangiopathic hemolytic anemia. The underlying conditions are also similar, including prosthetic heart valves and diffuse narrowing of the microvessels (e.g., malignant hypertension).

- **Sequestration.** Thrombocytopenia, usually moderate in severity, may develop in any patient with marked splenomegaly, a condition sometimes referred to as hypersplenism (Chapter 14). The spleen normally sequesters 30% to 40% of the body's platelets, which remain in equilibrium with the circulating pool. When necessary, hypersplenic thrombocytopenia can be ameliorated by splenectomy.
Dilutional. Massive transfusions can produce a dilutional thrombocytopenia. Blood stored for longer than 24 hours contains virtually no viable platelets; thus, plasma volume and red cell mass are reconstituted by transfusion, but the number of circulating platelets is relatively reduced.

Table 13-9 -- Causes of Thrombocytopenia

<table>
<thead>
<tr>
<th>Decreased production of platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized diseases of bone marrow</td>
</tr>
<tr>
<td>Aplastic anemia: congenital and acquired (see Table 13-7)</td>
</tr>
<tr>
<td>Marrow infiltration: leukemia, disseminated cancer</td>
</tr>
<tr>
<td>Selective impairment of platelet production</td>
</tr>
<tr>
<td>Drug-induced: alcohol, thiazides, cytotoxic drugs</td>
</tr>
<tr>
<td>Infections: measles, human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>Ineffective megakaryopoiesis</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased platelet survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic destruction</td>
</tr>
<tr>
<td>Autoimmune: idiopathic thrombocytopenic purpura, systemic lupus erythematosus</td>
</tr>
<tr>
<td>Isoimmune: post-transfusion and neonatal</td>
</tr>
<tr>
<td>Drug-associated: quinidine, heparin, sulfa compounds</td>
</tr>
<tr>
<td>Infections: infectious mononucleosis, HIV infection, cytomegalovirus</td>
</tr>
<tr>
<td>Nonimmunologic destruction</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Giant hemangiomas</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sequestration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersplenism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dilutional</th>
</tr>
</thead>
</table>

Immune Thrombocytopenic Purpura (ITP)
ITP can occur in the setting of a variety of conditions and exposures (secondary ITP) or in the absence of any known risk factors (primary or idiopathic ITP). There are two clinical subtypes of primary ITP, acute and chronic; both are autoimmune disorders in which platelet destruction results from the formation of antiplatelet autoantibodies. We first discuss the more common chronic form of primary ITP; acute ITP, a self-limited disease of children, is discussed later.

Immunologically mediated destruction of platelets (immune thrombocytopenia) occurs in many different settings, including systemic lupus erythematosus, acquired immunodeficiency syndrome (AIDS), after viral infections, and as a complication of drug therapy. These secondary forms of immune thrombocytopenia can sometimes mimic the idiopathic autoimmune variety, and hence the diagnosis of this disorder should be made only after exclusion of other known causes of thrombocytopenia. Particularly important in this regard is systemic lupus erythematosus, a multisystem autoimmune disease (Chapter 6) that can present with thrombocytopenia.

Pathogenesis.

Chronic ITP is caused by the formation of autoantibodies against platelet membrane glycoproteins, most often IIb-IIIa or Ib-IX. Antibodies reactive with these membrane glycoproteins can be demonstrated in the plasma as well as bound to the platelet surface (platelet-associated immunoglobulins) in approximately 80% of patients. In the overwhelming majority of cases, the antiplatelet antibodies are of the IgG class.

The mechanism of platelet destruction is similar to that seen in autoimmune hemolytic anemias. Opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system. About 75% to 80% of patients are remarkably improved after splenectomy, indicating that the spleen is the major site of removal of sensitized platelets. Since it is also an important site of autoantibody synthesis, the beneficial effects of splenectomy may in part derive from removal of the source of autoantibodies. Although destruction of sensitized platelets is the major mechanism responsible for thrombocytopenia, there is some evidence that megakaryocytes may be damaged by autoantibodies, leading to impairment of platelet production. In most cases, however, megakaryocyte injury is not significant enough to deplete their numbers.

Morphology.

The principal morphologic lesions of thrombocytopenic purpura are found in the spleen and bone marrow but they are not diagnostic. Secondary changes related to the bleeding diathesis may be found in any tissue or structure in the body.

The spleen is normal in size. On histologic examination, there is congestion of the sinusoids and hyperactivity and enlargement of the splenic follicles, manifested by the formation of prominent germinal centers. In many instances, scattered megakaryocytes are found within the sinuses and sinusoidal walls. This may represent a very mild form of extramedullary hematopoiesis driven by elevated levels of thrombopoietin. These splenic findings are not sufficiently distinctive to be considered diagnostic.
Bone marrow reveals a modestly increased number of megakaryocytes. Some are apparently immature, with large, nonlobulated, single nuclei. These findings are not specific for autoimmune thrombocytopenic purpura but merely reflect accelerated thrombopoiesis, being found in most forms of thrombocytopenia resulting from increased platelet destruction. The importance of bone marrow examination is to rule out thrombocytopenias resulting from bone marrow failure. A decrease in the number of megakaryocytes argues against the diagnosis of ITP. The secondary changes relate to the hemorrhages that are dispersed throughout the body.

Clinical Features.

Chronic ITP occurs most commonly in adult women younger than age 40 years. The female-to-male ratio is 3:1. This disorder is often insidious in onset and is characterized by bleeding into the skin and mucosal surfaces. Cutaneous bleeding is seen in the form of pinpoint hemorrhages (petechiae), especially prominent in the dependent areas where the capillary pressure is higher. Petechiae can become confluent, giving rise to ecchymoses. Often there is a history of easy bruising, nosebleeds, bleeding from the gums, and hemorrhages into soft tissues from relatively minor trauma. The disease may manifest first with melena, hematuria, or excessive menstrual flow. Subarachnoid hemorrhage and intracerebral hemorrhage are serious consequences of thrombocytopenic purpura but, fortunately, are rare in treated patients. Splenomegaly and lymphadenopathy are uncommon in primary ITP, and their presence should lead one to consider other possible diagnoses.

The clinical signs and symptoms associated with ITP are not specific for this condition but rather reflective of thrombocytopenia. Destruction of platelets as the cause of thrombocytopenia is supported by the findings of a low platelet count and normal or increased megakaryocytes in the bone marrow. Accelerated thrombopoiesis often leads to the formation of abnormally large platelets (megathrombocytes), detected easily in a blood smear. The bleeding time is prolonged, but PT and PTT are normal. Tests for platelet autoantibodies are not widely available. Therefore, a diagnosis of ITP should be made only after other causes of platelet deficiencies, such as those listed in Table 13-9, have been ruled out.

Almost all patients respond to immunosuppressive doses of glucocorticoids, but many eventually relapse and come to splenectomy. Most maintain safe platelet counts postsplenectomy and require no further therapy. A significant minority, however, have refractory forms of ITP that can be very difficult to treat. Various immunosuppressive approaches may be effective in such patients.

Acute Immune Thrombocytopenic Purpura

Like chronic ITP, this condition is caused by antiplatelet autoantibodies, but its clinical features and course are distinct. Acute ITP is a disease of childhood occurring with equal frequency in both sexes. The onset of thrombocytopenia is abrupt and is preceded in many cases by a viral illness. The usual interval between the infection and onset of purpura is 2 weeks. Unlike the adult chronic form of ITP, the childhood disease is self-limited, usually resolving spontaneously within 6 months. Steroid therapy is indicated only if thrombocytopenia is severe. Approximately 20% of the children, usually those without a viral prodrome, have persistent low platelet counts beyond 6 months and appear to have chronic ITP similar in most respects to the adult disease.
Drug-Induced Thrombocytopenia: Heparin-Induced Thrombocytopenia

Like hemolytic anemia, thrombocytopenia can result from immunologically mediated destruction of platelets after drug ingestion. The drugs most commonly involved are quinine, quinidine, sulfonamide antibiotics, and heparin. Heparin-induced thrombocytopenia (HIT) is of particular importance because this anticoagulant is used widely and failure to make a correct diagnosis can have severe consequences. Thrombocytopenia occurs in approximately 5% of patients receiving heparin. Most develop so-called type I thrombocytopenia, which occurs rapidly after onset of therapy, is modest in severity and clinically insignificant, and may resolve despite continuation of heparin therapy. It most likely results from a direct platelet-aggregating effect of heparin.

Type II thrombocytopenia is more severe. It occurs 5 to 14 days after commencement of therapy (or sometimes sooner if the patient has been previously sensitized to heparin) and can, paradoxically, lead to life-threatening venous and arterial thrombosis. HIT is caused by an immune reaction directed against a complex of heparin and platelet factor 4, a normal component of platelet granules that binds tightly to heparin. It appears that heparin binding modifies the conformation of platelet factor 4, making it susceptible to immune recognition. Binding of antibody to platelet factor 4 produces immune complexes that activate platelets, promoting thrombosis even in the setting of marked thrombocytopenia. The mechanism of platelet activation is not understood. Unless therapy is immediately discontinued, clots within large arteries may lead to vascular insufficiency and limb loss, and emboli from deep venous thrombosis can cause fatal pulmonary thromboembolism.

HIV-Associated Thrombocytopenia

Thrombocytopenia is perhaps the most common hematologic manifestation of HIV infection. Both impaired platelet production and increased destruction are responsible. CD4, the receptor for HIV on T cells, has also been demonstrated on megakaryocytes, making it possible for these cells to be infected by HIV. Infected megakaryocytes are prone to apoptosis and are impaired in terms of platelet production. HIV infection also causes hyperplasia and dysregulation of B cells, which predispose to the development of immune-mediated thrombocytopenia. Antibodies directed against platelet membrane glycoprotein IIb-III complexes are detected in some patients’ sera. These autoantibodies, which sometimes cross-react with HIV-associated gp120, are believed to act as opsonins, thus promoting the phagocytosis of platelets by splenic phagocytes. Some studies also implicate nonspecific deposition of immune complexes on platelets as a factor in their premature destruction by the mononuclear phagocyte system.

Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic-Uremic Syndrome (HUS)

The term thrombotic microangiopathy encompasses a spectrum of clinical syndromes that includes TTP and HUS. TTP, as originally defined, is associated with the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished from TTP by the absence of neurologic symptoms, the prominence of acute renal failure, and frequent affliction of children. Recent studies, however, have tended to blur these clinical
distinctions. Many adult patients with "TTP" lack one or more of the five criteria, and some patients with "HUS" have fever and neurologic dysfunction. The common fundamental feature in both of these conditions is widespread formation of hyaline thrombi, comprised primarily of platelet aggregates, in the microcirculation. Consumption of platelets leads to thrombocytopenia, and the intravascular thrombi provide a likely mechanism for the microangiopathic hemolytic anemia and widespread organ dysfunction. It is believed the varied clinical manifestations of TTP and HUS are related to differing proclivities for thrombus formation in specific microvascular beds.

For many years, the pathogenesis of TTP was enigmatic, although treatment with plasma exchange (initiated in the early 1970s) changed an almost uniformly fatal condition into one that is successfully treated in more than 80% of cases. Recently, the underlying cause of many, but not all, cases of TTP has been elucidated. In brief, symptomatic patients are often deficient in an enzyme called ADAMTS 13. This enzyme is designated "vWF metalloprotease" and it normally degrades very high molecular weight multimers of von Willebrand factor (vWF). (ADAMTS 13 is unrelated to the other tissue metalloproteases that cleave extracellular matrix.) In the absence of this enzyme, very high molecular weight multimers of vWF accumulate in plasma and, under some circumstances, promote platelet microaggregate formation throughout the microcirculation, leading to the symptoms of TTP. Superimposition of endothelial cell injury (caused by some other condition) may further predispose a patient to microaggregate formation, thus initiating or exacerbating clinically evident TTP.

The deficiency of ADAMTS 13 may be inherited or acquired. In many patients an antibody that inhibits vWF metalloprotease is detected. Much less commonly the patients have inherited an inactivating mutation in the gene encoding this enzyme. Despite these advances, it is clear that factors other than vWF metalloprotease deficiency must be involved in triggering full-blown TTP, because symptoms are episodic even in those with hereditary deficiency of vWF metalloprotease. It is important to consider the possibility of TTP in any patient presenting with thrombocytopenia and microangiopathic hemolytic anemia, as any delay in diagnosis and treatment can be fatal. Plasma exchange can be life saving by providing the missing enzyme.

In contrast to TTP, most patients with HUS have normal levels of vWF metalloprotease, indicating that HUS usually has a different pathogenesis. One important cause of HUS in children and the elderly is infectious gastroenteritis caused by E. coli strain 0157:H7. This strain elaborates a Shiga-like toxin that is absorbed from the inflamed gastrointestinal mucosa. It binds to and damages endothelial cells in the glomerulus and elsewhere, thus initiating platelet activation and aggregation. Affected children present with bloody diarrhea, and a few days later HUS makes its appearance. With appropriate supportive care, affected children often recover completely, but irreversible renal damage and death can occur in more severe cases. HUS can also be seen in adults following exposures that damage endothelial cells (e.g., certain drugs, radiation therapy). The prognosis of adults with HUS is guarded, as it is most often seen in the setting of other chronic, life-threatening conditions.

While DIC and thrombotic microangiopathies share features such as microvascular occlusion and microangiopathic hemolytic anemia, they are pathogenetically distinct. In TTP and HUS (unlike
DIC, activation of the coagulation cascade is not of primary importance, and hence results of laboratory tests of coagulation, such as PT and PTT, are usually normal.

BLEEDING DISORDERS RELATED TO DEFECTIVE PLATELET FUNCTIONS

Qualitative defects of platelet function can be congenital or acquired. Several congenital disorders characterized by prolonged bleeding time and normal platelet count have been described. A brief discussion of these rare diseases is warranted by the fact that they provide excellent models for investigating the molecular mechanisms of platelet function.

Congenital disorders of platelet function can be classified into three groups on the basis of the specific functional abnormality: (1) defects of adhesion, (2) defects of aggregation, and (3) disorders of platelet secretion (release reaction).

Bleeding resulting from defective adhesion of platelets to subendothelial matrix is best illustrated by the autosomal recessive disorder Bernard-Soulier syndrome, which is caused by an inherited deficiency of the platelet membrane glycoprotein complex Ib-IX. This glycoprotein is a receptor for vWF and is essential for normal platelet adhesion to subendothelial matrix (Chapter 4).

Bleeding due to defective platelet aggregation is exemplified by Glanzmann's thrombasthenia, which is also transmitted as an autosomal recessive trait. Thrombasthenic platelets fail to aggregate in response to adenosine diphosphate (ADP), collagen, epinephrine, or thrombin owing to deficiency or dysfunction of glycoprotein IIb-IIIa, a protein complex that participates in the formation of "bridges" between platelets by binding fibrinogen and vWF.

Disorders of platelet secretion are characterized by normal initial aggregation with collagen or ADP, but subsequent responses, such as secretion of thromboxanes and release of granule-bound ADP, are impaired. The underlying biochemical defects of these so-called storage pool disorders are varied, complex, and beyond the scope of our discussion.

Among the acquired defects of platelet function, two are clinically significant. The first is ingestion of aspirin and other nonsteroidal anti-inflammatory drugs, which significantly prolongs the bleeding time. Aspirin is a potent, irreversible inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A2 and prostaglandins (Chapter 2). These mediators play important roles in platelet aggregation and subsequent release reactions (Chapter 4). The antiplatelet effects of aspirin form the basis for its use in the prophylaxis of thrombosis (Chapter 12). Uremia (Chapter 20) is the second condition exemplifying an acquired defect in platelet function. Although the pathogenesis of bleeding in uremia is complex and not fully understood, several abnormalities of platelet function are found.

HEMORRHAGIC DIATHESSES RELATED TO ABNORMALITIES IN CLOTTING FACTORS

A deficiency of every clotting factor has been reported to be the cause of a bleeding disorder, with the exception of factor XII deficiency, which does not cause bleeding. The bleeding in factor deficiencies differs from platelet deficiencies in that spontaneous petechiae or purpura are uncommon. Rather, the bleeding is manifested by large post-traumatic ecchymoses or hematomas,
or prolonged bleeding after a laceration or any form of surgical procedure. Bleeding into the gastrointestinal and urinary tracts, and particularly into weight-bearing joints, is common. Typical stories include the patient who continues to ooze for days after a tooth extraction or who develops a hemarthrosis after relatively trivial stress on a knee joint. The course of history may have been changed by a hereditary coagulation defect present in the intermarried royal families of Great Britain and other parts of Europe. Clotting abnormalities can also be acquired in many different conditions.

**Acquired disorders** are usually characterized by multiple clotting abnormalities. Vitamin K deficiency (Chapter 9) results in impaired synthesis of factors II, VII, IX, and X and protein C. Since the liver makes virtually all the clotting factors, severe parenchymal liver disease can be associated with a hemorrhagic diathesis. Disseminated intravascular coagulation produces a deficiency of multiple coagulation factors.

**Hereditary deficiencies** have been identified for each of the clotting factors. Deficiencies of factor VIII (hemophilia A) and of factor IX (Christmas disease, or hemophilia B) are transmitted as sex-linked recessive disorders. Most others follow autosomal patterns of transmission. *These hereditary disorders typically involve a single clotting factor.*

**Deficiencies of Factor VIII-vWF Complex**

Hemophilia A and von Willebrand disease, two of the most common inherited disorders of bleeding, are caused by qualitative or quantitative defects involving the factor VIII-vWF complex. Before we can discuss these disorders, it is essential to review the structure and function of these proteins. 

Plasma factor VIII-vWF is a complex made up of two separate proteins (factor VIII and vWF) that can be characterized according to functional, biochemical, and immunologic criteria. Factor VIII procoagulant protein, or factor VIII (Fig. 13-28; also see Chapter 4), is an intrinsic pathway component required for activation of factor X. Deficiency of factor VIII gives rise to hemophilia A. Circulating factor VIII is noncovalently associated with very large vWF multimers containing up to 100 subunits; the molecular mass of individual multimers can exceed 20 x 10^6 daltons. vWF also interacts with several other proteins involved in hemostasis, including collagen, heparin, and platelet membrane glycoproteins (Ib-IX and IIb-IIIa). Glycoprotein Ib-IX serves as the major receptor for vWF. The most important function of vWF in vivo is to promote the adhesion of platelets to subendothelial matrix, which is accomplished in two ways. Some vWF secreted by endothelial cells is normally deposited in the subendothelial matrix, where it promotes platelet adhesion should the endothelial lining be disrupted (see Fig. 13-28). Endothelial cells and platelets also release vWF into the circulation, and upon vascular injury this second pool of vWF is adsorbed to exposed subendothelial matrix and further augments platelet adhesion. vWF multimers can also promote platelet aggregation by binding to activated GpIIb/IIIa receptors; this activity may be of particular importance under conditions of high shear stress (such as occurs in small vessels). That vWF is crucial to the normal process of hemostasis (Chapter 4) is supported by the occurrence of a bleeding diathesis known as von Willebrand disease when there is deficiency of this factor.
Figure 13-28  Structure and function of factor VIII-von Willebrand factor (vWF) complex. Factor VIII is synthesized in the liver and kidney, and vWF is made in endothelial cells and megakaryocytes. The two associate to form a complex in the circulation. vWF is also present in the subendothelial matrix of normal blood vessels and the alpha granules of platelets. Following endothelial injury, exposure of subendothelial vWF causes adhesion of platelets, primarily via glycoprotein Ib platelet receptor. Circulating vWF and vWF released from the alpha granules of activated platelets can bind exposed subendothelial matrix, further contributing to platelet adhesion and activation. Activated platelets form hemostatic aggregates; fibrinogen (and possibly vWF) participate in aggregation through bridging interactions with the platelet receptor GpIIb/III. Factor VIII takes part in the coagulation cascade as a cofactor in the activation of factor X on the surface of activated platelets.

vWF multimers also serve as a carrier for factor VIII and are important for its stability. The half-life of factor VIII in the circulation is 12 hours if vWF levels are normal but only 2.4 hours if it is deficient or abnormal (as in patients with von Willebrand disease).

vWF can be assayed by immunologic techniques or by the so-called ristocetin agglutination test. This assay, which can be performed with formalin-fixed platelets, measures the ability of ristocetin (developed as an antibiotic) to promote the interaction between vWF and platelet membrane glycoprotein Ib. Multivalent ristocetin-dependent binding of vWF creates interplatelet "bridges," leading to the formation of platelet clumps (agglutination), an event easily measured in a device called an aggregometer. Thus, the degree of ristocetin-dependent platelet agglutination caused by the addition of patient plasma provides a bioassay for vWF.

The two components of the factor VIII-vWF complex are encoded by separate genes and synthesized in different cells. vWF is produced by endothelial cells and megakaryocytes and can be demonstrated in platelet α-granules. Endothelial cells are the major source of subendothelial and plasma vWF. Factor VIII is made in several tissues; sinusoidal endothelial cells and Kupffer
cells in the liver and glomerular and tubular epithelial cells in the kidney appear to be particularly important sites of synthesis. To summarize, the two components of factor VIII-vWF complex, synthesized separately, come together and circulate in the plasma as a unit that serves to promote clotting as well as platelet-vessel wall interactions necessary to ensure hemostasis. With this background, we can discuss the diseases resulting from deficiencies of factor VIII-vWF complex.

**Von Willebrand Disease**

With an estimated frequency of 1%, von Willebrand disease is believed to be one of the most common inherited disorders of bleeding in humans. Clinically, it is characterized by spontaneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia, and a prolonged bleeding time in the presence of a normal platelet count. In most cases, it is transmitted as an autosomal dominant disorder, but several rare autosomal recessive variants have been identified. More than 20 variants of von Willebrand disease have been described, which can be grouped into two major categories:

- Type 1 and type 3 von Willebrand disease are associated with a reduced quantity of circulating vWF. Type 1, an autosomal dominant disorder, accounts for approximately 70% of all cases and is relatively mild. Reduced penetrance and variable expressivity characterize this type, and hence clinical manifestations are varied. Type 3 (an autosomal recessive disorder) is associated with extremely low levels of functional vWF, and the clinical manifestations are correspondingly severe. Because a severe deficiency of vWF has a marked affect on the stability of factor VIII, some of the bleeding characteristics resemble those seen in hemophilia. The nature of the mutations in the vast majority of patients with type 1 disease is poorly defined. In some cases missense mutations have been found. In others, it is suspected that both alleles are affected by distinct mutations (compound heterozygotes) producing an apparent dominant inheritance. Type 3 disease is associated with deletions or frameshift mutations.

- Type 2 von Willebrand disease is characterized by qualitative defects in vWF; there are several subtypes, of which type 2A is the most common. It is inherited as an autosomal dominant disorder. Because of missense mutations, the vWF formed is abnormal, leading to defective multimer assembly. Large and intermediate multimers, representing the most active forms of vWF, are missing from plasma. Type 2 von Willebrand disease accounts for 25% of all cases and is associated with mild to moderate bleeding.

Patients with von Willebrand disease have prolonged bleeding time despite a normal platelet count. The plasma level of active vWF, measured as the ristocetin cofactor activity, is reduced. Because vWF stabilizes factor VIII by binding to it, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. This may be reflected by a prolongation of the PTT in von Willebrand disease types 1 and 3.

To summarize, patients with von Willebrand disease have a compound defect involving platelet function and the coagulation pathway. Even within families in which a single defective allele is
segregating, there is often wide variability in the clinical expression of von Willebrand disease. This appears to be due to additional genetic factors that influence circulating levels of vWF, which vary greatly in normal populations. However, except in the most severely affected type 3 patients, adverse complications of factor VIII deficiency, such as bleeding into the joints, are uncommon.

Hemophilia A (Factor VIII Deficiency)

Hemophilia A is the most common hereditary disease associated with serious bleeding. It is caused by a reduction in the amount or activity of factor VIII. This protein serves as a cofactor for factor IX in the activation of factor X in the coagulation cascade (Chapter 4). Hemophilia A is inherited as an X-linked recessive trait, and thus occurs in males and in homozygous females. However, excessive bleeding has been described in heterozygous females, presumably due to extremely unfavorable lyonization (inactivation of the normal X chromosome in most of the cells). Approximately 30% of patients have no family history; their disease is presumably caused by new mutations.

Hemophilia A exhibits a wide range of clinical severity that correlates well with the level of factor VIII activity. Those with less than 1% of normal activity develop severe disease; levels between 2% and 5% of normal are associated with moderate disease; and patients with 6% to 50% of activity develop mild disease. The variable degrees of factor VIII deficiency are largely explained by heterogeneity in the causative mutations. As with β-thalassemias, several genetic lesions (deletions, nonsense mutations that create stop codons, splicing errors) have been documented. Most severe deficiencies result from an unusual inversion involving the X chromosome that completely abolishes the synthesis of factor VIII. Less commonly, severe hemophilia A is associated with point mutations in factor VIII that impair the function of the protein. In such cases, levels of factor VIII appear normal by immunoassay. Mutations permitting some active factor VIII to be synthesized are associated with mild to moderate disease. The disease in such patients may be modified by other genetic factors that influence factor VIII expression levels, which vary widely in normal individuals.

In all symptomatic cases, there is a tendency toward easy bruising and massive hemorrhage after trauma or operative procedures. In addition, “spontaneous” hemorrhages frequently occur in regions of the body normally subject to trauma, particularly the joints, where they are known as hemarthroses. Recurrent bleeding into the joints leads to progressive deformities that can be crippling. Petechiae are characteristically absent.

Patients with hemophilia A typically have a normal bleeding time, platelet count, and PT, and a prolonged PTT. These tests point to an abnormality of the intrinsic coagulation pathway. Factor VIII-specific assays are required for diagnosis.

Given that one arm of the coagulation cascade, the extrinsic pathway, is intact in hemophilia A, it seems reasonable to ask, why do these patients bleed? Obviously, test tube assays of coagulation (discussed briefly below under DIC) are imperfect surrogates for what occurs in vivo, and it must be that in the face of factor VIII deficiency, fibrin deposition is inadequate to achieve hemostasis reliably. It is beyond our scope to discuss this issue in detail, but recent studies suggest the following. First, it appears that the chief role of the extrinsic pathway in hemostasis is to produce
a limited initial burst of thrombin activation upon tissue injury. This is reinforced and amplified by a critical feedback loop whereby thrombin activates factors XI and IX of the intrinsic pathway. In addition, high levels of thrombin are required to activate TAFI (thrombin activatable fibrinolysis inhibitor), a factor that augments fibrin deposition by inhibiting fibrinolysis. Thus, both inadequate coagulation (fibrinogenesis) and inappropriate clot removal (fibrinolysis) contribute to the bleeding diathesis in hemophilia. The precise explanation for the tendency of hemophiliacs to bleed at particular sites (joints, muscles, and the central nervous system) remains uncertain.

Treatment of hemophilia A involves infusion of recombinant factor VIII. Approximately 15% of patients with low or absent factor VIII develop antibodies that bind to and inhibit factor VIII. Inhibitors are most likely to develop in patients with severe factor VIII deficiency (possibly because the protein is perceived as foreign, having never been "seen" before by the immune system) and represent very difficult therapeutic challenges. There are other hazards of replacement therapy as well, the most serious of which has been the risk of transmission of viral diseases. Until the mid-1980s, before routine screening of blood for HIV antibodies was instituted, thousands of hemophiliacs received plasma-derived factor VIII concentrates containing HIV, and many developed AIDS (Chapter 6). With the availability of recombinant factor VIII, the risk of HIV transmission has been eliminated, but tragically too late for an entire generation of hemophiliacs. Efforts to develop somatic gene therapy for hemophilia are also under way.

Hemophilia B (Christmas Disease, Factor IX Deficiency)

Severe factor IX deficiency produces a disorder clinically indistinguishable from factor VIII deficiency (hemophilia A). This should not be surprising, given that factor VIII and IX function together to activate factor X. A wide spectrum of mutations involving the factor IX gene are found in hemophilia B. Like hemophilia A, it is inherited as an X-linked recessive trait and shows variable clinical severity. In about 14% of these patients, factor IX is present but nonfunctional. As with hemophilia A, the PTT is prolonged and the PT is normal, as is the bleeding time. Identification of Christmas disease (named after the first patient with this condition and not the holiday) is possible only by assay of the factor levels. Recombinant factor IX is used for treatment.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is an acute, subacute, or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases. It is characterized by activation of the coagulation sequence that leads to the formation of microthrombi throughout the microcirculation of the body, often in a quixotically uneven distribution. Sometimes the coagulopathy is localized to a specific organ or tissue. As a consequence of the thrombotic diathesis, there is consumption of platelets, fibrin, and coagulation factors and, secondarily, activation of fibrinolytic mechanisms. Thus, DIC can present with signs and symptoms relating to tissue hypoxia and infarction caused by the myriad microthrombi or as a hemorrhagic disorder related to depletion of the elements required for hemostasis (hence, the term "consumption coagulopathy" is sometimes used to describe DIC). Activation of the fibrinolytic mechanism aggravates the hemorrhagic diathesis.

Etiology and Pathogenesis.
At the outset, it must be emphasized that DIC is not a primary disease. It is a coagulopathy that occurs in the course of a variety of clinical conditions. In discussing the general mechanisms underlying DIC, it is useful to briefly review the normal process of blood coagulation and clot removal. Clotting can be initiated by either of two pathways: (1) the extrinsic pathway, which is triggered by the release of tissue factor (“tissue thromboplastin”), and (2) the intrinsic pathway, which involves the activation of factor XII by surface contact with collagen or other negatively charged substances. Both pathways, through a series of intermediate steps, result in the generation of thrombin, which in turn converts fibrinogen to fibrin. Once activated at the site of injury, thrombin further augments local fibrin deposition through feedback activation of the intrinsic pathway and inhibition of fibrinolysis. Remarkably, as excess thrombin is swept away in the blood from sites of tissue injury it is converted to an anticoagulant. Upon binding a surface protein called thrombomodulin on intact endothelial cells, thrombin becomes capable of activating protein C, an inhibitor of the pro-coagulant factors V and VIII. Other important clot-inhibiting factors include the activation of fibrinolysis by plasmin and the clearance of activated clotting factors by the mononuclear phagocyte system and the liver. These and additional checks and balances normally ensure that just enough clotting occurs at the right place and time.

From this brief review, it should be clear that DIC could result from pathologic activation of the extrinsic and/or intrinsic pathways of coagulation or impairment of clot-inhibiting influences. Since the latter rarely constitute primary mechanisms of DIC, we focus our attention on the abnormal initiation of clotting.  

Two major mechanisms trigger DIC (1) release of tissue factor or thromboplastic substances into the circulation and (2) widespread injury to the endothelial cells. Tissue thromboplastic substances can be derived from a variety of sources, such as the placenta in obstetric complications (Table 13-10) and the granules of leukemic cells in acute promyelocytic leukemia. Mucus released from certain adenocarcinomas can also act as a thromboplastic substance by directly activating factor X, independent of factor VII. In gram-negative sepsis (an important cause of DIC), bacterial endotoxins cause activated monocytes to release interleukin-1 and TNF, both of which increase the expression of tissue factor on endothelial cell membranes and simultaneously decrease the expression of thrombomodulin. The net result is a shift in balance toward procoagulation.

**Table 13-10** -- Major Disorders Associated with Disseminated Intravascular Coagulation

<table>
<thead>
<tr>
<th>Obstetric Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abruptio placentae</td>
</tr>
<tr>
<td>Retained dead fetus</td>
</tr>
<tr>
<td>Septic abortion</td>
</tr>
<tr>
<td>Amniotic fluid embolism</td>
</tr>
<tr>
<td>Toxemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative sepsis</td>
</tr>
</tbody>
</table>
Meningococcemia
Rocky Mountain spotted fever
Histoplasmosis
Aspergillosis
Malaria
Neoplasms
Carcinomas of pancreas, prostate, lung, and stomach
Acute promyelocytic leukemia

Massive Tissue Injury
Traumatic
Burns
Extensive surgery

Miscellaneous
Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease

**Endothelial injury**, the other major trigger, can initiate DIC by causing release of tissue factor, promoting platelet aggregation, and activating the intrinsic coagulation pathway. TNF is an extremely important mediator of endothelial cell inflammation and injury in septic shock. In addition to the effects previously mentioned, TNF up-regulates the expression of adhesion molecules on endothelial cells and thus favors adhesion of leukocytes, which in turn damage endothelial cells by releasing oxygen-derived free radicals and preformed proteases. Even subtle endothelial injury can unleash procoagulant activity by enhancing membrane expression of tissue factor. Widespread endothelial injury may be produced by deposition of antigen-antibody complexes (e.g., systemic lupus erythematosus), temperature extremes (e.g., heat stroke, burns), or microorganisms (e.g., meningococci, rickettsiae).

Several disorders associated with DIC are listed in Table 13-10. Of these, DIC is most likely to follow obstetric complications, malignant neoplasia, sepsis, and major trauma. The initiating factors in these conditions are often multiple and interrelated. For example, particularly in infections caused by gram-negative bacteria, released endotoxins can activate both the intrinsic and extrinsic pathways by producing endothelial cell injury and release of thromboplastins from inflammatory cells; furthermore, endotoxins inhibit the anticoagulant activity of protein C by suppressing thrombomodulin expression on endothelium. Endothelial cell damage can also be produced directly by meningococci, rickettsiae, and viruses. Antigen-antibody complexes formed during the infection can activate the classical complement pathway, and complement fragments can secondarily activate both platelets and granulocytes. Endotoxins as well as other bacterial products are also capable of directly activating factor XII. In massive trauma, extensive surgery, and severe
burns, the major mechanism of DIC is believed to be the release of tissue thromboplastins. In obstetric conditions, thromboplastins derived from the placenta, dead retained fetus, or amniotic fluid may enter the circulation. However, hypoxia, acidosis, and shock, which often coexist with the surgical and obstetric conditions, also cause widespread endothelial injury. Supervening infection can complicate the problems further. Among cancers, acute promyelocytic leukemia and carcinomas of the lung, pancreas, colon, and stomach are most frequently associated with DIC. These tumors release a variety of thromboplastic substances, including tissue factors, proteolytic enzymes, mucin, and other undefined tumor products.

The consequences of DIC are twofold. First, there is widespread deposition of fibrin within the microcirculation. This can lead to ischemia of the more severely affected or more vulnerable organs and to a hemolytic anemia resulting from fragmentation of red cells as they squeeze through the narrowed microvasculature (microangiopathic hemolytic anemia). Second, a hemorrhagic diathesis can dominate the clinical picture. This results from consumption of platelets and clotting factors as well as activation of plasminogen. Plasmin can not only cleave fibrin, but also digest factors V and VIII, thereby reducing their concentration further. In addition, fibrinolysis leads to the formation of fibrin degradation products, which inhibit platelet aggregation and fibrin polymerization and have antithrombin activity. All these influences lead to the hemostatic failure seen in DIC (Fig. 13-29).

![Figure 13-29](image)

**Figure 13-29** Pathophysiology of disseminated intravascular coagulation.

The bleeding manifestations of DIC are not dissimilar to those encountered in the hereditary and acquired disorders affecting the hemostatic mechanisms discussed earlier.

Morphology.
In general, thrombi are found in the following sites in decreasing order of frequency: brain, heart, lungs, kidneys, adrenals, spleen, and liver. However, no tissue is spared, and thrombi are occasionally found in only one or several organs without affecting others. In giant hemangiomas, for example, thrombi are localized to the neoplasm, where they are believed to form due to local stasis and recurrent trauma to fragile blood vessels. The affected kidneys can reveal small thrombi in the glomeruli that may evoke only reactive swelling of endothelial cells or, in severe cases, microinfarcts or even bilateral renal cortical necrosis. Numerous fibrin thrombi may be found in alveolar capillaries, sometimes associated with pulmonary edema and fibrin exudation, creating "hyaline membranes" reminiscent of acute respiratory distress syndrome (Chapter 15). In the central nervous system, fibrin thrombi can cause microinfarcts, occasionally complicated by simultaneous hemorrhage. Such changes are the basis for the bizarre neurologic signs and symptoms sometimes observed in DIC. The manifestations of DIC in the endocrine glands are of considerable interest. In meningococcemia, fibrin thrombi within the microcirculation of the adrenal cortex are the likely basis for the massive adrenal hemorrhages seen in Waterhouse-Friderichsen syndrome (Chapter 24). Similarly, Sheehan postpartum pituitary necrosis (Chapter 24) is a form of DIC complicating labor and delivery. In toxemia of pregnancy (Chapter 22), the placenta exhibits widespread microthrombi, providing a plausible explanation for the premature atrophy of the cytotrophoblast and syncytiotrophoblast encountered in this condition.

Clinical Course.

The onset can be fulminant, as in endotoxic shock or amniotic fluid embolism, or insidious and chronic, as in cases of carcinomatosis or retention of a dead fetus. Overall, about 50% of individuals with DIC are obstetric patients having complications of pregnancy. In this setting, the disorder tends to be reversible with delivery of the fetus. About 33% of the patients have carcinomatosis. The remaining cases are associated with the various entities previously listed.

It is almost impossible to detail all the potential clinical presentations, but a few common patterns are worthy of description. These include microangiopathic hemolytic anemia; dyspnea, cyanosis, and respiratory failure; convulsions and coma; oliguria and acute renal failure; and sudden or progressive circulatory failure and shock. In general, acute DIC, associated with obstetric complications or major trauma, for example, is dominated by a bleeding diathesis, whereas chronic DIC such as occurs in cancer patients, tends to present initially with thrombotic complications. Accurate clinical observation and laboratory studies are necessary for the diagnosis. It is usually necessary to monitor fibrinogen, platelets, PT, PTT, and fibrin degradation products.

The prognosis is highly variable and depends, to a considerable extent, on the underlying disorder. The management of these cases requires meticulous maneuvering between the Scylla of thrombosis and the Charybdis of bleeding diathesis. Administration of anticoagulants or procoagulants has been advocated in specific settings, but not without controversy. The only definitive treatment is to remove or treat the inciting cause whenever possible.