**Bleeding Disorders: (Hemorrhagic Diatheses)**

Excessive bleeding can result from:
1. Increased fragility of vessels.
2. Platelet deficiency or dysfunction.
3. Derangement of coagulation.
4. Combinations of these.

**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.
- **Platelet counts:** These are obtained on anticoagulated blood using an electronic particle counter. The reference range is 150 to $400 \times 10^3/\mu L$.
- **Prothrombin time (PT):** This assay tests the extrinsic and common coagulation pathways. A prolonged PT can result from deficiency or dysfunction of: factor VII, factors X, V, prothrombin, or fibrinogen.
- **Partial thromboplastin time (PTT):** This assay tests the intrinsic and common clotting pathways. Prolongation of the PTT can be due to deficiency or dysfunction of: factors VIII, IX, XI, or XII, factors X, V, prothrombin, or fibrinogen.

**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. 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).**
- **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.**
- **Scurvy, Cushing syndrome and Ehlers-Danlos syndrome are associated with microvascular bleeding resulting from impaired formation of collagens needed for support of vessel walls.**
• 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), polyarthritis, and acute glomerulonephritis. All these changes result from the deposition of circulating immune complexes within vessels throughout the body and within the glomerular mesangial regions. It is an Ig A-mediated vasculitis.

• Hereditary hemorrhagic telangiectasia is an autosomal dominant disorder characterized by dilated, tortuous blood vessels with thin walls that bleed readily.

**Bleeding Related to Reduced Platelet Number:**

**Thrombocytopenia:** Reduction in platelet number constitutes an important cause of generalized bleeding. A count below 100,000 platelets/μL is generally considered to constitute thrombocytopenia. However, spontaneous bleeding does not become evident until platelet counts fall below 20,000 platelets/μL. Platelet counts in the range of 20,000 to 50,000 platelets/μL can aggravate post-traumatic bleeding. Bleeding resulting from thrombocytopenia is associated with a normal PT and PTT. Spontaneous bleeding associated with thrombocytopenia most often involves small vessels. Common sites for such hemorrhages are the skin and the mucous membranes of the gastrointestinal and genitourinary tracts. The many causes of thrombocytopenia can be classified into the four major categories:

- **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). 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.
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.

**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.

**Chronic ITP:**
Pathogenesis: Chronic ITP is caused by the formation of autoantibodies against platelet membrane glycoproteins. 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 as follows: Opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system especially of the spleen. 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.

Acute ITP: 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.

Drug-induced immune thrombocytopenia: An immunological mechanism has been demonstrated as the cause of many drug-induced thrombocytopenias. Quinine, quinidine and heparin are particularly common causes. An antibody-drug-protein complex is deposited on the platelet surface. If complement is attached and the sequence goes to completion, the platelet may be lysed directly. Otherwise, it is removed by reticuloendothelial cells because of opsonization with immunoglobulin and / or the C3 component of complement. The platelet count is often less than 10 x 10^9/L, and the bone
marrow shows normal or increased numbers of megakaryocytes. Drug dependent antibodies against platelets may be demonstrated in the sera of some patients.

**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. 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.
3. Disorders of platelet secretion (release reaction).

Acquired defects of platelet function:
- 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.
- Uremia: Several abnormalities of platelet function are found.

**Hemorrhagic Diatheses 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. 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. Plasma factor VIII-vWF is a complex made up of two separate proteins (factor VIII and vWF). Factor VIII; 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. The most important function of vWF in vivo is to promote the adhesion of platelets to subendothelial matrix. 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. vWF gene is located on chromosome 12. 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. Factor VIII gene is located on X chromosome.

**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. In this disorder there is either a reduced level or abnormal function of VWF resulting from a point mutation or major deletion. Patients with von Willebrand disease have defects in platelet function despite a normal platelet count.

**Lab findings:**
Patients with von Willebrand disease typically have:
- A prolonged bleeding time.
- A normal platelet count.
- The plasma level of active vWF 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. In most cases, it is transmitted as an autosomal dominant disorder, but several rare autosomal recessive variants have been identified. 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.

**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. 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.
- 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. Several genetic lesions (deletions, nonsense mutations that create stop codons, splicing errors) have been documented.
Lab findings:
Patients with hemophilia A typically have:
• A normal bleeding time.
• A normal platelet count, and a normal PT.
• A prolonged PTT.
(These tests point to an abnormality of the intrinsic coagulation pathway).
► Factor VIII-specific assays are required for diagnosis.

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. Wide spectrums 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.

Lab findings:
Patients with hemophilia B typically have:
• A normal bleeding time.
• A normal platelet count, and a normal PT.
• A prolonged PTT.
► Factor IX-specific assays are required for diagnosis.

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
 • 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. Two major mechanisms trigger DIC:
1. Release of tissue factor or thromboplastic substances into the circulation: Tissue thromboplastic substances can be derived from a variety of sources, such as the placenta in obstetric complications 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.

2. Widespread injury to the endothelial cells: 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. 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).

The initiating factors in these conditions are often multiple and interrelated. The consequences of DIC are twofold:

- There is widespread deposition of fibrin within the microcirculation. This can lead to:
  - Ischemia of the more severely affected or more vulnerable organs
  - A hemolytic anemia resulting from fragmentation of red cells as they squeeze through the narrowed microvasculature (microangiopathic hemolytic anemia).

- 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.

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.

**Acquired disorders** are usually characterized by multiple clotting abnormalities. Vitamin K deficiency: 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.