Thalassemia

Pathophysiology
This anemia results from a genetic defect in which one or more genes for hemoglobin are missing or variant. When two genes are involved, thalassemia is moderate to severe. This abnormality interferes with the production of the globin chains, and therefore, the amount of hemo- globin synthesized and the number of RBCs is reduced. Hemoglobin is normally composed of four globin chains, two alpha and two beta (see structure in Fig. 10-1A). Thalassemia alpha refers to a reduction in or lack of alpha chains. Thalassemia beta refers to a decrease or lack of beta chains. In either case, less normal hemoglobin can be made. In addition to missing chains, there is an accumulation of the other available chains, damaging the RBCs. For example, when a beta chain is missing, the extra alpha chains collect in RBCs and damage the cell membrane, leading to hemolysis and anemia. Homozygotes have thalassemia major (Cooley’s anemia) a severe form of the anemia; heterozygotes have thalassemia minor and exhibit mild signs of anemia. In severe cases, increased hemolysis of RBCs aggravates the anemia and causes splenomegaly, hepatomegaly, and hyperbilirubinemia. The bone marrow is hyperactive, trying to compensate.

Etiology
Thalassemia is the most common genetic disorder in the world and it occurs in two common forms. Thalassemia beta (autosomal dominant inheritance) occurs frequently in people from Mediterranean countries such as Greece or Italy, and thalassemia beta is the more common form. The alpha form is found in those of Indian, Chinese, or Southeast Asian descent. Because more than one gene is involved, there are many possible gene mutations with varied effects on hemoglobin synthesis and the severity of the resultant anemia.

Signs and Symptoms
The usual signs of anemia and increased hemolysis are present as described earlier. The child’s growth and development are impaired directly by the hypoxia and indirectly by the fatigue and inactivity. Hyperactivity in the bone marrow leads to invasion of bone and impaired normal skeletal development. Heart failure develops as a result of the compensation mechanism increasing cardiac work load.

Diagnostic Tests
Red blood cells are microcytic, often varying in size, and hypochromic (low hemoglobin). There is an increase in erythropoietin levels. Often an iron overload exists. Pernicious anemia can be due to chronic villus assay at 12 weeks or by amniocentesis at 16 weeks.

Treatment
Blood transfusions are the only treatment available at this time. Iron chelation therapy may be necessary.

### TABLE 10-2 Comparison of Selected Anemias

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Characteristic RBC</th>
<th>Etiology</th>
<th>Additional Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>Microcytic, hypochromic</td>
<td>Decreased dietary intake, malabsorption, blood loss</td>
<td>Only effects of anemia</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Decreased hemoglobin production</td>
<td>Deficit of intrinsic factor owing to immune reaction</td>
<td>Neuropathic damage</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Megabloblasts (immature nucleated cells)</td>
<td>Bone marrow damage or failure</td>
<td>Excessive bleeding and multiple infections</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>Often normal cells</td>
<td>Recessive inheritance</td>
<td>Painful crises with multiple infections</td>
</tr>
</tbody>
</table>

*FIGURE 10-19 A, Facial eczematoses. B, Petechiae. (From Young NS: Bone Marrow Failure Syndromes, Philadelphia, 2000, Saunders.)*

### Cardiovascular System Disorders

**WARNING SIGNS OF EXCESSIVE BLEEDING AND POSSIBLE BLOOD-CLOTTING DISORDERS**

- Persistent bleeding from the gums (around the teeth) or repeated nosebleeds
- Petechiae—pinpoint flat red spots on skin or mucous membranes (like a rash); result from bleeding from a capillary or small arteriole (see Fig. 10-19B)
- Frequent purpura and ecchymoses—large, purplish red or greenish areas on the skin (bruises) (see Fig. 10-19A)
- More persistent bleeding than warranted by a trauma
- Bleeding into a joint—hemarthroses—swollen, red, and painful
- Coughing up blood—hemoptysis—bright red flecks in sputum
- Vomiting blood—hematemesis—often coarse brown particles (coffee grounds); may be red
- Blood in feces—often black (tarry) or occult (hidden)
- Anemia
- Feeling faint and anxious, low blood pressure, rapid pulse

**Blood-Clothing Disorders**

Spontaneous bleeding or excessive bleeding following minor tissue trauma often indicates a blood-clotting disorder. Note: The following warning signs may also be caused by other factors, such as infections and damaged or fragile blood vessels (e.g., vitamin C deficit).
Excessive bleeding has many causes:

- Thrombocytopenia may be caused by acute viral infections in children (usually resolves in 6 months) or autoimmune reactions in adults (chronic idiopathic thrombocytopenic purpura). The chronic form occurs primarily in adults, especially in young women when thrombocytes are destroyed by antibodies. Human immunodeficiency virus infection, hepatitis B, hepatitis C, and spleenomegaly, and certain drugs also lead to thrombocytopenia.

- Chemotherapy, radiation treatments, and cancers such as leukemia also reduce platelet counts, causing bleeding.

- Defective platelet function is associated with uremia (end-stage kidney failure) and ingestion of aspirin (ASA). Anyone with a bleeding disorder should avoid ASA or ASA-containing drugs, as well as non-steroidal anti-inflammatory drugs because all these interfere with platelet adherence.

- Vitamin K deficiency may cause a decrease in prothrombin and fibrinogen levels. Vitamin K is a fat-soluble vitamin produced by the intestinal bacteria and is present in some foods as well. A deficiency of vitamin K may occur in patients with liver disease, accompanied by a decrease in bile production, and in those with malabsorption problems. However, vitamin K is a useful antidote when an excess of warfarin (Coumadin), an oral anticoagulant, causes bleeding.

- Liver disease reduces the available proteins and vitamin K, and thus interferes with the production of clotting factors in the liver and reduces the available proteins and vitamin K.

- Inherited defects cause bleeding disorders resulting from the deficiency of one of the clotting factors. Serum factor analysis and more specific tests are useful here. These include PT to measure the extrinsic pathway, activated partial thromboplastin time (aPTT) to measure the intrinsic pathway, and thrombin time for the final stage, fibrinogen to fibrin.

- Hemorrhagic fever viruses such as Ebola virus cause excessive bleeding and acute illness, affecting many organs.

- Anticoagulant drugs such as warfarin (Coumadin) are often prescribed on a long-term basis and the patient's hematologic ability requires close monitoring (see Fig. 10-6 for site of action of anticoagulant drugs). The difference remains a helpful therapeutic drug level and a blood level that causes bleeding is very small. Also, many foods, drugs, and herbal compounds can alter the effect of anticoagulant drugs, creating a dangerous situation.

- When a patient with any bleeding disorder is at risk for hemorrhage because of an invasive procedure, it is best to be prepared by using laboratory tests to check the current blood-clotting status and to administer prophylactic medications if needed. Personnel should be ready and supplies should be available for any emergency, including the application of pressure, cold dressings, and absorbable hemostatic packing agents such as Gelfoam or Oxycel and styptics.

### Hemophilia A

#### Pathophysiology

Hemophilia A, or classic hemophilia, is a deficit or abnormality of clotting factor VIII (see Fig. 10-9) and is the most common inherited clotting disorder. Ninety percent of hemophiliac patients have type A. The defect causing hemophilia A is transmitted as an X-linked recessive trait (see Chapter 21). With improved treatment and a longer lifespan for men, this pattern could change. An affected man and a carrier woman could produce a female child who inherits the gene from both parents.

Hemophilia B (Christmas disease) is similar and involves a deficit of factor IX; hemophilia C (Rosenthal's hemophilia) is a milder form resulting from a decrease in factor XI. Some cases of hemophilia result from a spontaneous gene mutation in a person with no previous family history of the disease.

There are approximately 18,000 to 20,000 cases of hemophilia in the United States and an estimated 400 infants are born each year with hemophilia. There are varying degrees of dependence on hemophilia, depending on the amount of the factor present in the blood. In mild forms (more than 5% factor VIII activity), excessive bleeding occurs only after trauma, whereas frequent spontaneous bleeding is common in people with severe deficiencies (less than 1% factor VIII activity). About 70% of affected individuals have the severe form.

#### Signs and Symptoms

Pathogenetic or severe hemorrhage occurs following minor tissue trauma. Persistent oozing of blood after minor injuries and hematomas is common. Spontaneous hemorrhage into joints (hemarthrosis) may occur, eventually causing partial or complete loss of function depending on the severity of hemorrhage and joint elasticity resulting from recurrent inflammation. Blood may appear in the urine (hematuria) or feces because of bleeding in the kidneys or digestive tract.

#### Diagnostic Tests

Bleeding time and PT are normal, but the PTT, APPT, and coagulation tests are prolonged. Serum levels of factor VIII are low. Thromboplastin generation time differentiates between deficits of factor VIII and factor IX.

#### Treatment

All precautions mentioned earlier should be followed. Treatment with desmopressin (DDAVP) may raise clotting factor levels in some clients. This drug stimulates the endothelial cells, which increases the release of factor VIII. Replacement therapy for factor VIII is available for intravenous administration at regular intervals and especially before any surgical or dental procedure. Unfortunately, hepatitis and HIV have been transmitted through blood products. Although blood is now treated to destroy known viruses, a risk remains that some unknown infection may be acquired by such treatment.

Some individuals have developed immune reactions to repeated replacement therapy. A newer recombinant DNA product (Advate), produced through genetic engineering, does not contain any material such as protein from human or animal blood, therefore reducing the risk of immune responses. A new drug Nplate has recently been approved by the FDA that stimulates platelet production in bone marrow. Research continues into gene therapy.

### von Willebrand Disease

#### Pathophysiology

This is the most common hereditary bleeding disorder. This disease is caused by a deficiency of the von Willebrand factor, a clotting factor that helps platelets clump and stick to the walls of blood vessels where damage has occurred. There are three major types of this disease which have signs/symptoms similar to, but much milder than hemophilia.

#### Signs and Symptoms

Depending on the type of the disease, signs and symptoms typically include: skin rashes, frequent nosebleeds, easy bruising, bleeding of the gums, and abnormal men- strual bleeding.

#### Diagnostic Tests

Although sometimes hard to diagnose due to nonspe- cific signs and symptoms, the tests that may be done to diagnose this disease include: bleeding time, blood type, vWF assay, and aggregation test, ristocetin cofactor test, and von Willebrand factor specific tests.

#### Treatment

Treatment is based on the type of von Willebrand disease and its severity. Because most cases of this disease are relatively mild, treatment may only be required in cases such as surgery, tooth extraction, or accident trauma. The mammade hormone desmopressin can be used to treat milder cases. The injection or nasal spray of this hormone increases the release of von Willebrand factor and factor VIII into the bloodstream. These factors can also be directly injected into a vein as a replacement therapy and are used in the more severe types of disease. The treatment of choice for these drugs that help prevent the breakdown of blood clots are often used after minor surgery or injury. In addition to these drugs, women with an abnormal menstrual flow caused by this disease can be treated with birth control pills as these also cause an increase in the release of the clotting factors.

### Disseminated Intravascular Coagulation

#### Pathophysiology

Disseminated intravascular coagulation (DIC) is a condi- tion, often life threatening, that involves both excessive bleeding and excessive clotting. It occurs as a complica- tion of numerous primary problems, which activate the clotting process in the microcirculation throughout the body (Fig. 10-21). Clotting may be induced by the release of tissue thromboplastin or by injury to the endothelial cells, causing platelet adhesion. The process causes multiple thromboses and infarctions but also consumes the available clotting factors and platelets and stimulates the fibrinolytic process. The severity of resulting consumptive clotting factors and fibrinolysis then leads to hemorrhage and eventually to hypotension or shock.

DIC is a multiorgan dysfunction and may be difficult to diagnose: Blood counts may be normal or abnormal. It is usually caused by chronic infection, and thromboembolism is the dominant feature.

#### Etiology

A variety of disorders can initiate DIC. It may result from an obliterative complication such as toxemia, anemi- a, phlegmasia, mastocytosis, or abruptio placentae in which the placenta is detached within the uterus. Various drugs or agents can also cause DIC by interfering with the clotting process.
monocytes. Many carcinomas release substances that activate plasmin. Many thrombi form throughout the microcirculation and platelets collect. Platelets release serotonin, which stimulates thrombocytopenia. If the thrombus is large, it may lodge in the heart or vessels in the brain or other organs.

Signs and Symptoms
The signs and symptoms of an abnormal clotting event are not specific and can affect any organ or system in which the clot may lodge and obstruct the blood supply. In cases in which the clot lodges in the heart or vessels of the lung, the result can be a myocardial infarction or an acute stroke.

Neoplastic Blood Disorders

Polycythemia

Pathophysiology
Primary polycythemia, or polycythemia vera, is a condition in which there is an increased production of erythrocytes and other cells in the bone marrow. It is considered a neoplastic disorder. Serum erythropoietin levels are low. Secondary polycythemia, or erythrocytosis, is an increase in RBCs that occurs in response to prolonged hypoxia and increased erythropoietin secretion. Usually the increase in RBCs is not as marked in secondary polycythemia, and more reticulocytes appear in the peripheral blood.

In polycythemia vera, there is a marked increase in erythrocytes and often in granulocytes and thrombocytes as well, resulting in increased blood volume and viscosity. Blood vessels are distended and blood flow is sluggish, leading to frequent thromboses and infarctions throughout the body, especially when platelet counts are high. Blood pressure is elevated and the heart hypertrophies. Hemorrhage is frequent in places where the blood vessels are distended. The spleen and liver are congested and enlarged, and the bone marrow is hypercellular.

In some patients, the bone marrow eventually becomes fibrotic, hematopoiesis develops in the spleen, and anemia follows. In a few patients, acute myeloblastic leukemia develops in the later stages, especially if treatment has involved chemotherapy.

Etiology
Primary polycythemia is a neoplastic disorder of unknown origin that commonly develops between the ages of 40 and 60 years, although younger individuals can be affected. Secondary polycythemia may be a complication of many other diseases, including chronic heart failure, chronic obstructive pulmonary disease, and arterial hypertension. In some patients, polycythemia may be a consequence of increased oxygen transport in the presence of chronic lung disease or heart disease or from living at high altitudes. Some cases result from erythropoietin-secreting tumors such as renal carcinoma.

Signs and Symptoms
The signs and symptoms of primary polycythemia include polycythemia, with the deep bluish-red tone of the skin and mucosa resulting from the engorged blood vessels and sluggish blood flow. Hepatomegaly, an enlarged liver, and splenomegaly are also present. Pruritus is common. Blood pressure increases, the pulse is full and bounding, and dyspnea, headaches, or visual disturbances are common. Thromboses and infarctions may affect the extremities, liver, or kidneys as well as the brain or heart. Congestive heart failure frequently develops because of the increased work load resulting from the increased volume and viscosity of blood. High levels of uric acid resulting from cell destruction result in severe joint pain.

Diagnostic Tests
Cell counts are increased, as are hemoglobin values, and hematocrit is elevated. In polycythemia vera, the malignant or abnormal cell is the erythrocyte. Bone marrow is hypercellular, with the red marrow replacing some fatty marrow. Hyperpigmentation is present because of the high cell destruction rate.
**Treatment**

Drugs or radiation may be used to suppress the activity of the bone marrow. There is significant risk that fibrosis or leukemia may develop with these methods. Periodic phlebotomy, or removal of blood, may be used to minimize the possibility of thromboses or hemorrhages.

**Think About 10-8**

Compare the general effects of anemia and polycythemia in terms of hemoglobin level, hematocrit, general appearance, and possible complications.

**The Leukemias**

The leukemias are a group of neoplastic disorders involving the white blood cells. The estimated number of new cases of leukemia each year is 31,000, including 2500 children. Of these cases, 11,000 are lymphoid, 15,000 are myelogenous, and 5000 fall into other categories. Although some types of leukemia respond well to chemotherapy, overall survival is about 45% with much higher survival rates seen in lymphoid types in children.

**Pathophysiology**

One or more of the leukocyte types are present as undifferentiated, immature, nonfunctional cells that multiply uncontrollably in the bone marrow and large quantities are released as such into the general circulation (Fig. 10-22). As the numbers of leukemic cells increase, they infiltrate the lymph nodes, spleen, liver, brain, and other organs. Acute leukemias are characterized by a high proportion of very immature, nonfunctional cells (blast cells) in the bone marrow and peripheral circulation; the onset is abrupt, with marked signs and complications. Chronic leukemias have a higher proportion of mature cells (although they may have reduced function), with an insidious onset, mild signs, and thus a better prognosis.

Depending on the particular stem cell affected, both acute and chronic leukemias can be further differentiated according to the cell type involved; for example, lymphocytic leukemia. The four major types are all acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML). Most cases of ALL involve the precursor to B-lymphocytes. Myelogenous leukemia affects one or more of the granulocytes. The neoplastic stem cell may, in some cases of myelogenous leukemia, involve all blood cells. The major groups are then further differentiated; for example, acute monoblastic leukemia, which is a type of myelogenous leukemia. In some severe forms of acute leukemia, only undifferentiated stem cells can be identified. When the cells are primitive, the term slat may be used in the name. Several detailed classifications for the leukemias are available. A brief summary can be found in Table 10-3.

The proliferation of leukemic cells in the bone marrow suppresses the production of other normal cells, leading to anemia, thrombocytopenia, and a lack of normal functional leukocytes (Fig. 10-25). The rapid turnover of cells leads to hyperuricemia and a risk of kidney stones and kidney failure, especially in patients who are receiving chemotherapy. The crowding of the bone marrow causes severe bone pain resulting from pressure on the nerves in the rigid bone and the stretching of the periosteum. As the malignancy progresses, the increased numbers of leukemic cells cause congestion and enlargement of lymphoid tissue, lymphadenopathy, splenomegaly, and hepateomegaly. Death usually results from a complication such as overwhelming infection or hemorrhage.

**Table 10-3** Types of Leukemias

<table>
<thead>
<tr>
<th>Type</th>
<th>Malignant Cell</th>
<th>Primary Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphocytic leukemia (ALL)</td>
<td>B-lymphocytes</td>
<td>Young children</td>
</tr>
<tr>
<td>Acute myelogenous for myelocytic leukemia (AML)</td>
<td>Granulocytic stem cells</td>
<td>Adults</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>B-lymphocytes</td>
<td>Adults greater than 50 years</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia (CML)</td>
<td>Granulocytic stem cells</td>
<td>Adults 30-50</td>
</tr>
<tr>
<td>Acute monocytic leukemia</td>
<td>Monocytes</td>
<td>Adults</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>B-lymphocytes</td>
<td>Males greater than 50 years</td>
</tr>
</tbody>
</table>

**Etiology**

Chronic leukemias are more common in older people, whereas acute leukemias occur primarily in children and younger adults. Acute lymphocytic leukemia (ALL), the most common childhood cancer, usually begins between the ages of 2 and 5 years and constitutes 80% of childhood leukemia cases. The cause in children has not been established. Acute myelogenous leukemia (AML) is common in adults. A number of factors have been shown to be associated with leukemia in adults, including exposure to radiation, chemicals such as benzene, and certain viruses. It may develop years after a course of chemotherapy, particularly those protocols incorporating alkylating agents.

There also appears to be a association of leukemia, particularly ALL, with chromosomal abnormalities, particularly translocations; this factor is evident in the increased incidence of leukemia in children with Down syndrome. Of interest is the fact that many adults with chronic myeloblastic leukemia have the Philadelphia chromosome (q22). A specific abnormal chromosomal translocation that serves as a marker in the diagnosis of chronic myeloblastic leukemia.

**Signs and Symptoms**

The onset of acute leukemia is usually marked by infection that is unresponsive to treatment or by excessive bleeding, and these problems persist throughout the course of the disease and may be life threatening.

- Multiple infections often develop because of the nonfunctional WBCs.
- Severe hemorrhage (in the brain or digestive tract) occurs because of thrombocytopenia.

**Diagnostic Tests**

Peripheral blood smears show the immature leukocytes and the altered numbers of WBCs, which are usually greatly increased. A high percentage of the WBCs are immature and appear abnormal. Numbers of RBCs and platelets are decreased. Bone marrow biopsy confirms the diagnosis.

**Treatment**

Chemotherapy is administered (see Chapter 20). Some types of leukemia, such as ALL, in young children, respond well to drugs, and the prognosis is excellent, with many children enjoying a cure. The best prognosis...
is found in children between 1 and 9 years of age, infants and adolescents respond less positively to chemotherapy. The more rapid the response to drugs, the more positive is the outlook. Chemotherapy is less successful in adults with AML, although remissions may be achieved. Biologic therapy, such as interferon, to stimulate the immune system, has been used in cases of CML. Even with treatment, the course of CML may accelerate in some cases to an acute stage. Individuals with chronic leukemia may live up to 30 years with treatment. The prognosis is often related to the WBC count and the proportion of blast cells present at the time of diagnosis.

It is important to try to maintain the proper level of nutrition and hydration, particularly if high uric acid levels develop. Alkalizing the urine by ingesting antacids may help prevent the formation of uric acid kidney stones. Chemotherapy may have to be temporarily discontinued if the blood cell counts drop too low, for example, in marked thrombocytopenia or neutropenia (a reduction in circulating neutrophils). Transfusions of platelets and/or blood cells may be required.

Bone marrow transplantation may be tried when chemotherapy is ineffective. Any tumor cells must be eradicated in the recipient's bone marrow, and a suitable donor must be located before transplantation is attempted (see earlier section on Aplastic Anemia).

CHAPTER SUMMARY

Blood serves many purposes in the body. Abnormalities involving blood cells, plasma proteins, or blood clotting factors frequently have widespread and possibly life-threatening effects on the body. When lymphatic disorders interfere with the immune response, serious consequences may result.

• Anemias may be caused by many factors, including dietary deficits, malabsorption syndromes, genetic defects, damage to the bone marrow, or blood loss.
• Chronic blood loss causes iron-deficiency anemia with production of hypochromic, microcytic RBCs.
• Pernicious anemia is a megaloblastic anemia resulting from a defect of intrinsic factor required for the absorption of vitamin B12. Peripheral nerve degeneration and hypochlothyric anemia accompany the anemia.
• Pancytopenia characterizes aplastic anemia, with impaired production of all blood cells.
• Sickle cell anemia and thalassemia are caused by inherited defects in hemoglobin synthesis. These result in excessive hemolysis and a low erythrocyte count.
• Polycythemia may occur as a primary or secondary problem. Increased RBCs cause vascular congestion.
• Hemophilia A is a genetic blood clotting disorder related to a deficit of factor VIII. Replacement therapy is now available. Infections such as hepatitis B and HIV have been transmitted through transfusions to many of these patients.
• When DIC develops as a complication of trauma, infection, or other primary problems, generalized blood clotting occurs, using up available blood clotting factors, and subsequently causing hemorrhage. The balance between coagulation and hemorrhage varies with the individual patient, the underlying problem, and the difficulty in treating the combination of problems.
• Myelodysplastic syndrome is comprised of a number of conditions in which the bone marrow does not produce adequate cellular elements for the blood. It may be related to prior history of chemotherapy or radiation.
• Leukemias may be acute or chronic. They are named by the specific neoplastic cell that is proliferating excessively in the bone marrow. The malignant cells are immature and nonfunctional, increasing the risk of infection. Thrombocytopenia and anemia are also present.

STUDY QUESTIONS

1. Name six substances that are transported in the blood and the function of each.
2. Explain the importance/function for each of the following:
   a. High elastic fiber content in the aorta
   b. Smooth muscle in the arterioles
   c. Extensive capillaries in the liver and lungs
   d. Valves in the leg veins
3. Explain the cause of incompatible blood transfusion.
4. List three types of clotting problems.
5. Explain how pernicious anemia may develop from chronic gastritis.
6. For which conditions could secondary polycythemia develop as compensation? VSD, CHF, chronic lung disease, aplastic anemia, multiple myeloma
7. Explain how DIC develops and state two signs of its development.
8. Explain why severe bone pain occurs with leukemia.