

- Congestive heart failure may develop owing to constant efforts to improve the supply of oxygen and the increased peripheral resistance caused by the obstructions.
- Frequent infections occur because of the decreased defenses when the damaged spleen can no longer adequately filter the blood, the presence of necrotic tissues, and poor healing capabilities. Pneumonia is a common cause of death in children. Infections tend to cause more sickling, and a vicious cycle develops.

■ Diagnostic Tests

Carriers of the defective gene can be detected by a simple blood test (hemoglobin electrophoresis). This identification is useful in alerting those with sickle cell trait to avoid severe hypoxia and sickling episodes (e.g., with severe anemia, surgery, or at high altitudes), as well as in assisting prospective parents in decision making about the risk of having an affected child (see Chapter 21).

Prenatal diagnosis can be checked by DNA analysis of the fetal blood. In children more than 1 year of age, the diagnosis can be confirmed by the presence of sickled cells in peripheral blood and the presence of HbS. The bone marrow is hyperplastic, and more reticulocytes (immature RBCs) are released into the circulation.

■ Treatment

The search continues for more effective drugs to reduce sickling. The use of hydroxyurea (Hydrea) has reduced the frequency of crises and prolonged the lifespan for many, but is not effective for all patients. Dietary supplementation with folic acid (folate) is recommended even during asymptomatic periods. Avoidance of strenuous activity or high altitudes is helpful. Other supportive measures are utilized to prevent dehydration, acidosis, infection, or exposure to cold, all of which increase the sickling tendency and painful crises. Children should be immunized against pneumonia, influenza, and meningitis. Continued prophylactic penicillin may be necessary for two groups, young children and adults with severe cases. Gene therapy is under investigation. Bone marrow transplant is effective, but because of the limited number of African-American potential donors on bone marrow registries, it may be very difficult to find a match. In the past, patients rarely lived past their twenties, but recent improvements in care have extended the lifespan into middle age for many patients.

THINK ABOUT 10-6

- Explain why vascular occlusions are common in patients with sickle cell disease.
- Compare sickle cell trait and sickle cell anemia in terms of the genetic factor involved, the amount of HbS present, and the presence of clinical signs.

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 hemoglobin 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. 10-16A). 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 impairs 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. Prenatal diagnosis can be done by chorionic 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 to

TABLE 10-2 Comparison of Selected Anemias

| Anemia | Characteristic RBC | Etiology | Additional Effects |
|------------------------|---|--|--|
| Iron deficiency anemia | Microcytic, hypochromic Decreased hemoglobin production | Decreased dietary intake, malabsorption, blood loss | Only effects of anemia |
| pernicious anemia | Megaloblasts (immature nucleated cells) Short lifespan | Deficit of intrinsic factor owing to immune reaction | Neurologic damage Achlorhydria |
| Aplastic anemia | Often normal cells Pancytopenia | Bone marrow damage or failure | Excessive bleeding and multiple infections |
| Sickle cell anemia | RBC elongates and hardens in "sickle" shape when O ₂ levels are low—short lifespan | Recessive inheritance | Painful crises with multiple infarctions Hyperbilirubinemia |



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

remove the excess iron from numerous transfusions. Administration of folate is also recommended. Bone marrow transplants have been curative in some children and are in clinical research trials. Patients with mild forms of the disease have a normal lifespan, and those with moderate to severe disease live into their thirties with transfusions and chelation therapy. Those with very severe anemia may die in childhood.

Characteristics of the selected anemias are compared in Table 10-2.

Blood-Clotting 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).

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

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, hepatomegaly and splenomegaly, 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 adhesion.
- 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 a 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.

| | | NORMAL FATHER | | Probability |
|-----------------------|---|----------------------------|------------------------------|---|
| | | X | Y | |
| CARRIER X | X | XX normal | XY normal | For female child 50% carrier 50% normal |
| | | XX _h carrier | X _h Y affected | |
| MOTHER X _h | | | | |

A

- Anticoagulant drugs such as warfarin (Coumadin) are often prescribed on a long-term basis and the patient's hemostatic ability requires close monitoring (see Fig. 10-6 for site of action of anticoagulant drugs). The difference between 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 effects 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 (Fig. 10-20); therefore, it is manifest in men but is carried by women, who are asymptomatic (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 severity of hemophilia, depending on the amount of the factor present in the blood. In mild

| | | AFFECTED FATHER | | Probability |
|-----------------------|---|---|------------------------------|---|
| | | X _h | Y | |
| CARRIER X | X | XX _h carrier | XY normal | For female child 50% carrier 50% affected |
| | | X _h X _h affected | X _h Y affected | |
| MOTHER X _h | | | | |

B

FIGURE 10-20 Inheritance of hemophilia A.

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

Prolonged 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 painful and crippling deformities 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, APTT, and coagulation time 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 endothelium lining blood vessels to release stored 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 USFDA that stimulates platelet production in bone marrow. Research continues into gene therapy.

von Willebrand Disease

■ Pathophysiology

This is the most common hereditary blood clotting/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 menstrual bleeding.

■ Diagnostic Tests

Although sometimes hard to diagnose due to nonspecific signs and symptoms, the tests that may be done to diagnose this disease include: bleeding time, blood typing, factor VIII levels, platelet count 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 manmade hormone desmopressin can be used to treat milder cases. The injection or nasal spray of this hormone causes increased 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 the disease. Antifibrinolytic 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 release of the clotting factors.

Disseminated Intravascular Coagulation

■ Pathophysiology

Disseminated intravascular coagulation (DIC) is a condition, often life threatening, that involves both excessive bleeding and excessive clotting. It occurs as a complication 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 resulting consumption of clotting factors and fibrinolysis then leads to hemorrhage and eventually to hypotension or shock.

Chronic DIC is a milder form 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 obstetric complication such as toxemia, amniotic fluid embolus, or abruptio placentae, in which tissue thromboplastin is released from the placenta (see Chapter 22). Infection, particularly gram-negative infection, leads to endotoxins that cause endothelial damage or stimulate the release of thromboplastin from

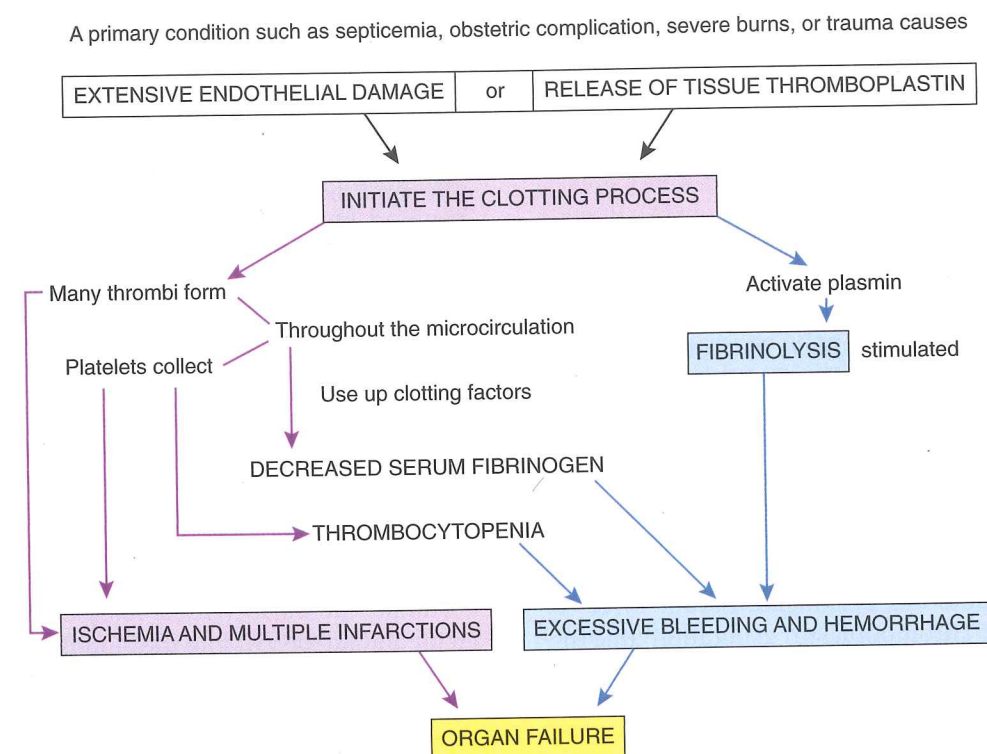


FIGURE 10-21 Disseminated intravascular coagulation.

monocytes. Many carcinomas release substances that trigger coagulation. Major trauma, such as burns or crush injuries, and widespread deposits of antigen-antibody complexes result in endothelial damage, releasing thromboplastin and initiating the process.

■ Signs and Symptoms

Whether hemorrhage or thrombosis dominates, the clinical effects depend somewhat on the underlying cause. Obstetric patients usually manifest increased bleeding, whereas cancer patients tend to have more thromboses. More often, hemorrhage is the critical problem. This is indicated by low plasma fibrinogen level, thrombocytopenia, and prolonged bleeding time, PT, APTT, and thrombin time. Accompanying hemorrhage are the effects of low blood pressure or shock. Multiple bleeding sites are common, petechiae or ecchymoses may be present on the skin or mucosa, mucosal bleeding is common, and hematuria may develop (see Fig. 10-19). Vascular occlusions are frequently present in small blood vessels but occasionally affect the large vessels as well, causing infarcts in the brain or other organs.

Respiratory impairment is evident as difficulty in breathing and cyanosis. Neurologic effects include seizures and decreased responsiveness. Acute renal failure with oliguria often accompanies shock.

■ Treatment

A fine balance is required to treat the coagulation imbalance, particularly in life-threatening cases. Treatment is

difficult, dependent on whether hemorrhages or thromboses are dominant. The underlying cause, such as infection, must be treated successfully, as well as the major current problem, whether it is excessive clotting or hemorrhage. The prognosis depends on the severity of the primary problem.

Thrombophilia

■ Pathophysiology

Thrombophilia is a group of inherited or acquired disorders that increase the risk of the development of abnormal clots in the veins or arteries. Abnormal clotting events can result in conditions such as a deep venous thrombosis, pulmonary embolism, or peripheral vascular disease.

Inherited thrombophilias are a result of mutations among the genes responsible for producing the coagulation proteins in the blood. Acquired thrombophilias commonly occur during events such as surgery, injury, or other medical conditions that allow for an increase of the amount of clotting factors in the blood or an accumulation of antibodies.

■ 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 cut off 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.

■ Diagnosis

Tests to diagnose thrombophilia involve blood testing for clotting factor levels and abnormal antibody levels.

■ Treatment

In cases in which the disorder has been provoked by another underlying medical condition, the causative condition should be treated to decrease the potential of acquired thrombophilia. In those cases in which the disorder is not provoked by another condition, anticoagulants such as warfarin (Coumadin) may be prescribed to reduce the risk of abnormal clot formation. The use of these types of medication must be weighed with the risks for excessive bleeding due to the interruption of the normal coagulation capability of the blood.

THINK ABOUT 10-7

- State the probability that a child with a carrier mother will have hemophilia A.
- Describe briefly three causes of excessive bleeding other than hemophilia.
- Explain how a deep vein thrombosis in a large vein in the leg can result in a life-threatening condition such as a stroke or myocardial infarction.

Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is the term used for diseases that involve inadequate production of cells by the bone marrow. It excludes disorders such as aplastic anemias and deficiency dyscrasias. Myelodysplastic diseases may be idiopathic or can often occur following chemotherapy or radiation treatment for other cancers. Several different types are described, including anemias and pancytopenias in which all cell types are reduced. Diagnosis is based on the patient's history, standard blood tests, and bone marrow biopsy. Treatment measures depend on the type of deficiency and include transfusion replacements, chelation therapy to reduce iron levels, and supportive therapies to prevent complications. Low level chemotherapy may be used with growth factors to stimulate more normal bone marrow function. Bone marrow transplants are curative, but often the patient's health will not allow this treatment. The prognosis for patients with MDS is dependent on age of onset, past treatment with chemotherapy or radiation, and response to treatment. Myelodysplastic syndrome may progress to chronic or acute leukemia in some cases if treatment is not effective in normalizing the blood picture.

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 hypertrophied. 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 compensation mechanism intended to provide 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 patient appears **plethoric** and **cyanotic**, 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 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 the 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. Hyperuricemia 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 usually is abrupt, with marked signs and complications. Chronic leukemias have a higher proportion of

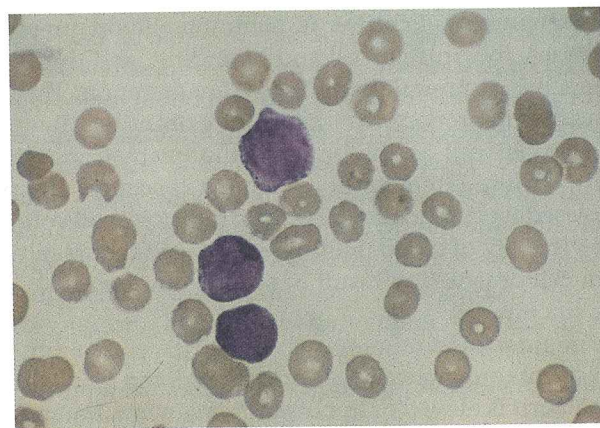


FIGURE 10-22 Acute lymphocytic leukemia, common in young children. Blood smear shows small lymphocytes and normocytic anemia. (From Stevens ML: Fundamentals of Clinical Hematology, Philadelphia, 1997, Saunders.)

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 acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML). Most cases of ALL involve the precursors 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 leukemias, only undifferentiated stem cells can be identified. When the cells are primitive, the term *blast* 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. 10-23). 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 hepatomegaly. Death usually results from a complication such as overwhelming infection or hemorrhage.

TABLE 10-3 Types of Leukemias

| Type | Malignant Cell | Primary Age Group |
|--|-------------------------|------------------------------|
| Acute lymphocytic leukemia (ALL) | B-lymphocytes | Young children |
| Acute myelogenous (or myelocytic) leukemia (AML) | Granulocytic stem cells | Adults |
| Chronic lymphocytic leukemia | B-lymphocytes | Adults greater than 50 years |
| Chronic myelogenous leukemia (CML) | Granulocytic stem cells | Adults 30-50 |
| Acute monocytic leukemia | Monocytes | Adults |
| Hairy cell leukemia | B-lymphocytes | Males greater than 50 years |

ACUTE LYMPHOCYTIC LEUKEMIA

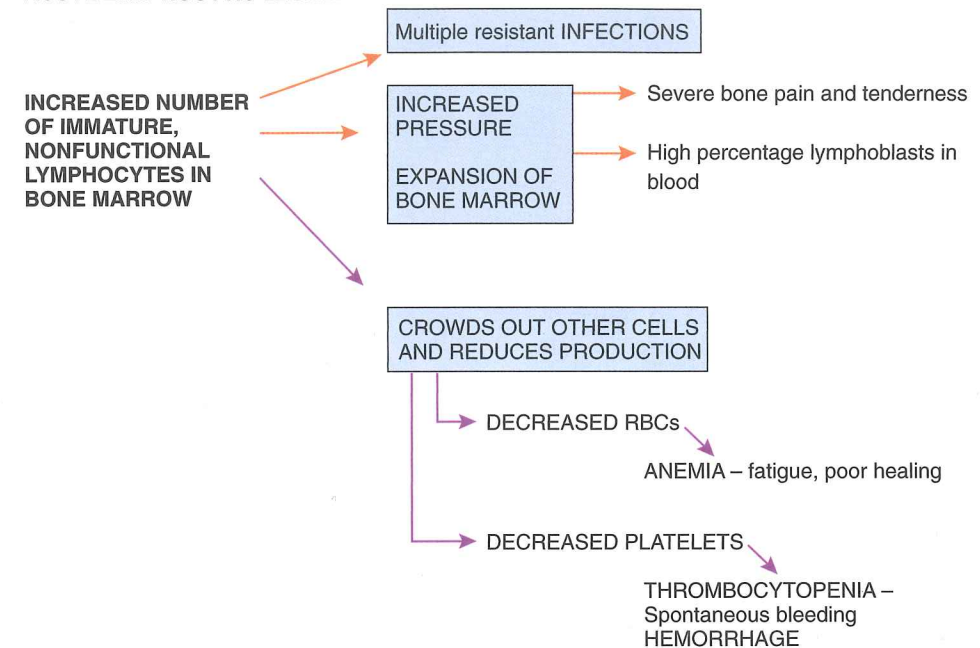


FIGURE 10-23 Effects of acute lymphocytic leukemia.

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 an 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 (#22), 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 through the active stages 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.

- The signs of anemia develop as the erythrocyte count drops.
- Bone pain is severe and steady, continuing during rest.
- Weight loss and fatigue result from the hypermetabolism associated with neoplastic growth, from anorexia caused by infection, from pain, and from the effects of chemotherapy.
- Fever may result from hypermetabolism or infection.
- The lymph nodes, spleen, and liver are often enlarged and may cause discomfort.
- If leukemic cells infiltrate the central nervous system, headache, visual disturbances, drowsiness, or vomiting follows.

Chronic leukemia tends to have a more insidious onset, with milder signs, and may be diagnosed during a routine blood check. Early signs include fatigue, weakness, and frequent infections.

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 10 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. Alkalinizing 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).

THINK ABOUT 10-9

- Compare and contrast the characteristics of acute and chronic leukemias, including the age groups involved, onset, and typical blood cell characteristics.
- Why are multiple opportunistic infections common in patients with leukemia?
- Explain why it is best to defer (if possible) any invasive procedures in leukemic patients, including dental treatment, until the blood counts become normal.
- The mouth and mucosa of the digestive tract are usually inflamed and ulcerated because of anemia, the effects of chemotherapy, and the presence of infections, such as candidiasis. Explain how this situation would affect food and fluid intake and list some possible subsequent effects on the patient with leukemia.

CASE STUDY A

Acute Lymphocytic Leukemia

P.M., aged 4 years, has returned to the family physician because of a recurrent sore throat and cough. Her mother mentions unusual listlessness and anorexia. The physician notices several bruises on her legs and arms and one on her back. The physician orders blood tests and a course of antibacterial drugs. Test results indicate a low hemoglobin level, thrombocytopenia, and a high lymphocyte count, with abnormally high numbers

of blast cells. Following a bone marrow aspiration, a diagnosis of ALL is confirmed.

- Describe the pathophysiology of ALL.
- State the rationale for each of P.M.'s signs.
- Explain the significance of blast cells in the peripheral blood.
- Describe the effects of hypermetabolism in leukemia.
- Explain how chemotherapy aggravates the effects of leukemia (refer to Chapter 20).
- Describe the possible effects if leukemic cells infiltrate the brain.
- Describe the pain associated with leukemia and explain the reason for it.

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 deficit of intrinsic factor required for the absorption of vitamin B₁₂. Peripheral nerve degeneration and hypochlorhydria 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

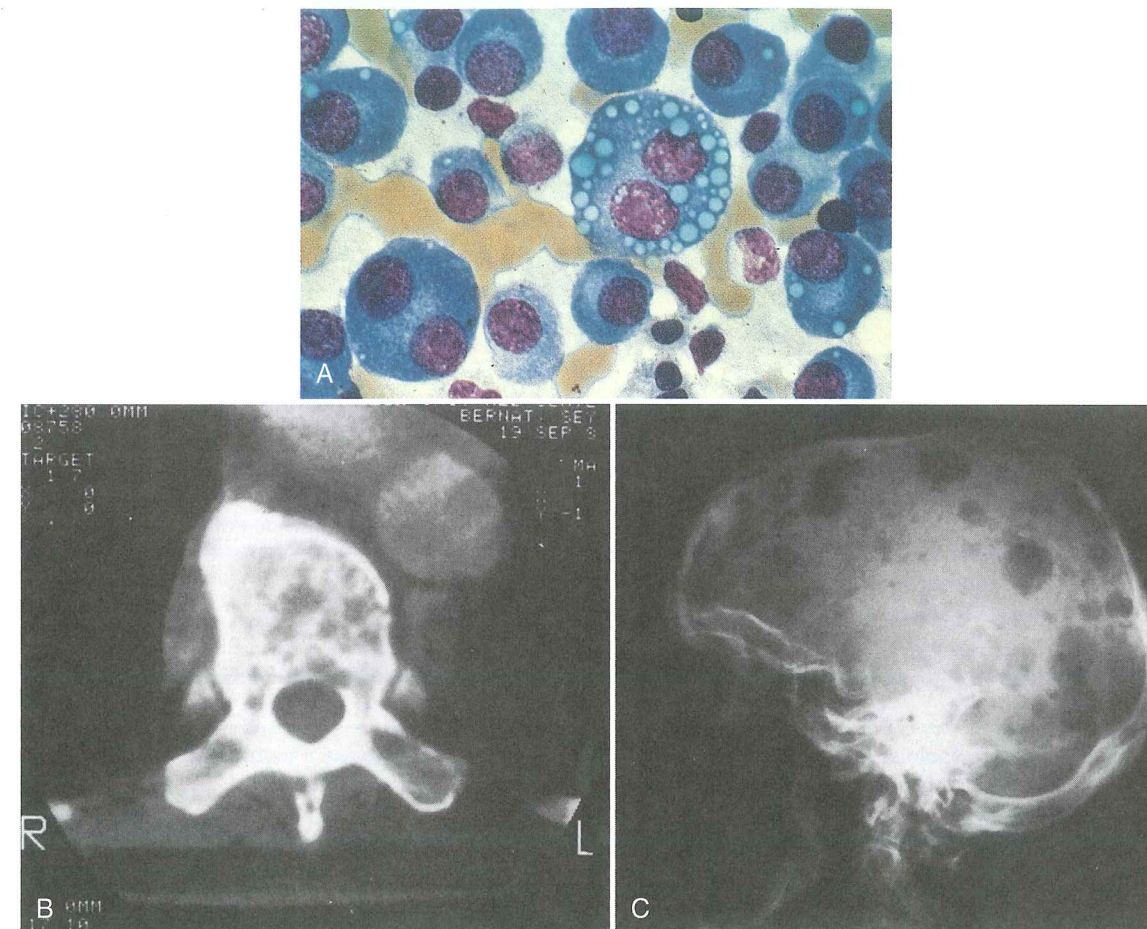


FIGURE 10-24 A, Bone marrow aspirate from a patient with multiple myeloma showing a large number of abnormal plasma cells with multiple nuclei and cytoplasmic droplets. (From Kumar V, et al, editors: Robbins Basic Pathology, ed 8, Philadelphia, 2007, Saunders, p 455.) Vertebral body (B) and skull (C) radiographs showing the characteristic "honeycomb" appearance of demineralized bone associated with multiple myeloma. (Courtesy Marvin J. Stone, MD, Sammons Cancer Center, Baylor University Medical Center, Dallas. From Copstead LE, Banasik J: Pathophysiology, ed 5, St. Louis, 2013, Mosby.)

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

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