HEMATOLOGIC DISEASES

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THE PROCESS OF HEMATOPOIESIS

Hematopoiesis is the formation of cellular components of the blood from a small population of pluripotential stem cells, which are formed in embryonic life and persist thereafter through self-regeneration. When stimulated by hematopoietic growth factors such as cytokines, these precursor cells give rise to progenitor cells committed to development along specific pathways. These progenitor cells, through a series of divisions and maturational changes, give rise to myeloid or lymphoid mature cells in the circulating blood. The earliest recognizable erythroid progenitors are the burst-forming units–erythroid (BFU-E) and the less primitive colony-forming units–erythroid (CFU-E). Erythropoietin, produced by the kidney, circulates to the bone marrow, where it stimulates the erythroid progenitor cells to differentiate and mature into erythrocytes.1

RED BLOOD CELL DISORDERS

Polycythemia
Anemia

WHITE BLOOD CELL DISORDERS

Quantitative Disorders
Qualitative Leukocyte Disorders
Leukemia

LYMPHOMA
Hodgkin’s Disease
Non-Hodgkin’s Lymphoma
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Oral and Dental Considerations

MULTIPLE MYELOMA
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RED BLOOD CELL DISORDERS

Polycythemia

Polycythemia may be defined as an abnormal increase in the erythrocyte count in the peripheral blood, usually accompanied by an increase in hemoglobin and hematocrit. Polycythemia is divided into absolute erythrocytosis (a true increase in red-cell mass) and relative erythrocytosis (the red-cell mass is normal, but the plasma volume is reduced). Relative polycythemia is caused by the loss of tissue and intravascular fluid, which may be the result of such diverse conditions as diabetic ketoacidosis, postsurgical dehydration, prolonged vomiting or diarrhea, or rapid diuresis secondary to treatment for congestive heart failure. In relative polycythemia, the hemoglobin rarely rises more than 25%, and there are no appreciable oral changes.
Three main groups of polycythemia are recognized: primary proliferative polycythemia (polycythemia rubra vera), secondary polycythemia resulting from changes in erythropoietin concentration, and apparent polycythemia. The latter condition lacks a true increase in red-cell mass.

**POLYCYTHEMIA VERA**

Polycythemia vera (PV) is a myeloproliferative disorder characterized by excessive proliferation of erythroid elements along with granulocytic and megakaryocytic cells; it usually begins after 50 years of age. The etiology of PV is unknown; however, it is likely a result of acquired genetic changes in the stem cell leading to disturbances of normal cellular growth.

The red blood cell (RBC) volume increases to an erythrocyte count of 6 to 12 million/mm³ with a hemoglobin concentration of 18 to 24 g/dL, leading to increased blood viscosity and thrombosis. Seventy percent of cases also have high white blood cell and platelet counts. Patients with PV develop episodes of thrombosis and hemorrhage in the later stages of the disease. Hyperuricemia and hyperuricosuria are seen in 40% of the cases at diagnosis. Serum iron and ferritin are low owing to excessive iron use, and the leukocyte alkaline phosphatase is elevated. Erythropoietin levels are decreased. PV may progress to myelofibrosis or acute myeloid leukemia in 5 to 50% of cases, with a median survival of 10 to 16 years.

A characteristic clinical picture of ruddy cyanosis is seen on the face and extremities, owing to the presence of deoxygenated blood in cutaneous vessels. Patients complain of headache, dizziness, tinnitus, fullness of the head and face, and pruritus. Splenomegaly is a common finding on physical examination. Frequently, coronary thrombosis is diagnosed, and complications known as “erythromelalgia” may manifest as paresthesias involving the cranial nerves.

**Oral Manifestations.** A purplish red discoloration of the oral mucosa is visible on the tongue, cheeks, and lips. The gingivae are red and may bleed spontaneously. Petechiae and ecchymoses are observed in patients with platelet abnormalities. Varicosities in the ventral tongue, a frequent normal finding, are exaggerated in cases of polycythemia.

**Treatment.** The major therapy for PV involves repeated phlebotomy. Patients with severe disease and elderly patients receive myelosuppressive agents to reduce the hematocrit to its upper limit of 50%. Alkylation agents and radioactive phosphorus (³²P) have been shown to increase the risk of leukemia and should be avoided. Chemotherapy with agents such as busulfan, chlorambucil, cyclophosphamide, and melphalan may also be beneficial. Hydroxyurea is now being widely used when myelosuppressive therapy is indicated because of the established leukemogenic potential of other agents. Treatment with hydroxyurea also decreases the thrombotic complications.

**Oral and Dental Considerations.** Dental treatment presents a risk because of the possibility of bleeding or thrombosis. Patients should have a complete blood count prior to treatment. To prevent complications, it is recommended that the hemoglobin be reduced below 16 g/dL and the hematocrit to below 47% as these are the thresholds at which medical management is instituted. Patients with this disease require special attention to local hemostasis. Preoperative myelosuppressive treatment should be considered prior to dental treatment when the blood counts are not controlled with phlebotomy alone.

**SECONDARY POLYCYTHEMIA: ERYTHROCYTOSIS**

Secondary polycythemia is due to an increase in erythropoietin production to compensate for hypoxia. This reactive erythrocytosis has been described in people who live at high altitudes with low atmospheric pressure and in people with chronic pulmonary disease, congenital heart disease (right-to-left shunt), and renal disease (hydronephrosis). Pheochromocytoma and other endocrine disorders also have been described as possible causes of erythrocytosis.

Secondary polycythemia also may occur with some tumors, particularly brain, renal, and lung carcinomas that produce an erythropoietin-like substance. The increased blood viscosity may lead to thrombosis or coagulation defects. When the elevated erythrocyte volume becomes dangerously high, it may be treated by phlebotomy to reduce viscosity.

**APPARENT POLYCYTHEMIA**

Apparent polycythemia, characterized by an increased hemoglobin concentration and packed-cell volume but normal RBC mass, is caused by a reduction in plasma volume. Apparent polycythemia most commonly affects middle-aged obese men with hypertension and a significant social history of smoking and high alcohol consumption. Some cases are associated with diuretic therapy. Treatment is usually geared toward the underlying disorder; however, more aggressive measures may be taken in patients with definite cardiovascular risks.

**Anemia**

Anemia is present whenever there is a decrease in the normal amount of circulating hemoglobin. This reduction in hemoglobin may result from blood loss, as in common iron deficiency anemia; from increased destruction of red blood cells, as in the hemolytic anemias; from decreased production of red cells, as in pernicious and folic acid deficiency anemias; or from combinations of these three. When there is a combination of causes, one mechanism usually predominates.

Anemias also may be classified according to their pathophysiologic basis: size (microcytic, normocytic, or macrocytic) of the red cells or their hemoglobin concentration (hypochromic, normochromic). The term “hyperchromic” is seldom used, but it refers to a macrocytic cell with normal hemoglobin concentration that, because of its large size, has an increased hemoglobin content. General symptoms of all anemias include pallor of the skin, palpebral conjunctiva, and nail beds; dyspnea; and easy fatigability. The more common anemias or those with common oral manifestations are discussed in this chapter.
ANEMIA OWING TO BLOOD LOSS: IRON DEFICIENCY

Iron deficiency anemia (blood loss anemia, hypochromic microcytic anemia) is the most common of all anemias, affecting approximately 30% of the world’s population and accounting for up to 500 million cases worldwide.4 Iron deficiency anemia may result from chronic blood loss, such as occurs in menstrual or menopausal bleeding, parturition, bleeding hemorrhoids, or a bleeding malignant lesion or ulcer in the gastrointestinal tract. It also may develop in patients from a variety of causes that may decrease the rate of absorption of iron, such as subtotal or complete gastrectomy, or a habit of clay eating, or as part of malabsorption syndromes.5

Iron deficiency anemia will have low serum iron concentrations and a markedly reduced.6 There is a characteristic absence of stainable iron in the bone marrow, which is an early finding in the disease. The physician must perform a thorough search for the source of bleeding, including using radiologic surveys of the gastrointestinal tract, sigmoidoscopy, a gynecologic examination, and a complete menstrual and dietary history.

Dental Considerations. Dental patients presenting with symptoms of anemia or oral signs suggestive of this condition should have a complete blood count (CBC) with differential. If significantly lowered hemoglobin values are obtained, the patient should be referred to his or her physician for a more thorough medical history, laboratory diagnosis, and treatment. Elective oral surgical or periodontal procedures should not be performed on patients with marked anemia because of the potential for increased bleeding and impaired wound healing. When hemoglobin levels fall below 10 g/dL, the low oxygen tension affects the rheologic interactions between the cellular components of blood, mainly platelets and endothelium, decreasing their ability to clot effectively. General anesthesia should not be administered unless the hemoglobin is at least 10 g/dL. The patient should never be treated with iron until the cause of the microcytic hypochromic anemia is found and corrected or until a thorough search for the cause has proved fruitless.

Treatment. The diagnosis of iron deficiency anemia is made either by demonstration of an iron deficient state or by evaluation of the response to therapeutic iron replacement. The single most important aspect of treatment is identification of the cause, especially a source of occult blood loss.7

Plummer-Vinson Syndrome. First described by Plummer and Vinson, this syndrome is characterized by dysphagia and a microcytic hypochromic anemia. A smooth and sore tongue, dry mouth, spoon-shaped nails, and angular stomatitis are common findings. There is atrophy of the tongue papillae, but it is less severe than in pernicious anemia. There are atrophic changes in the oral mucosa, the pharynx, the upper esophagus, and the vulva. These tissues are dry, inelastic, and glazed in appearance. In addition, general symptoms include listlessness, pallor, ankle edema, and dyspnea, all related to the anemia.

Many patients with this syndrome are edentulous, having lost their teeth early in life. Complaints of a sore mouth and an inability to wear dentures are frequent. In addition, patients with Plummer-Vinson syndrome often complain of a “spasm in the throat” or “food sticking in the throat.” The dysphagia, which represents an important feature of this condition, appears to be the result of muscular degeneration in the esophagus, and stenoses or webs of the esophageal mucosa.

The diagnosis of this syndrome can be made on the basis of the history and hematologic findings. The esophageal lesions are demonstrable radiologically (barium swallow) or by esophagoscopy. Relative degrees of achlorhydria are usually present. Because many of the symptoms in this syndrome are similar to those observed in vitamin B complex deficiency and
simple hypochromic anemias, these conditions should be treated. A variable and apparently unpredictable response to therapy can be expected. At times, the dysphagia improves following iron therapy.

Plummer-Vinson syndrome is potentially serious because pharyngeal and intraoral carcinoma are more common in these patients. Patients with symptoms of this syndrome should be followed up at short intervals and checked for the development of lesions that raise the suspicion of malignancy.

ANEMIA OWING TO HEMOLYSIS

The hemolytic anemias result from decreased survival of erythrocytes, either episodically or continuously, resulting from intracorpuscular defects in the erythrocytes (often hereditary) or from extracorpuscular factors. Some of the more common causes are summarized in Table 16-1.

The bone marrow has the capacity to increase production of erythrocytes by up to eightfold in response to reduced erythrocyte survival, and considerable hemolysis can take place before anemia results. This mechanism is overcome when the RBC survival is extremely short or when the ability of the marrow to compensate is impaired. Similarly, a small amount of hemolysis can take place without resulting in jaundice because of the normal liver's ability to excrete increased amounts of bilirubin.

**Diagnosis.** Laboratory findings common to all hemolytic anemias are decreased hemoglobin, increased reticulocytes (young red cells released into the circulation as a result of the marrow's producing more red cells to compensate for the excessive destruction), and increases in serum bilirubin, mostly in the indirect (unconjugated, prehepatic) fraction. Other diagnostic tests that may be useful in certain of the hemolytic anemias are outlined below.

To measure red cell survival time, a small amount of the patient's red cells may be tagged with radioactive chromium ($^{51}$Cr) and re-injected. If the hemolysis is caused by an extracorpuscular factor, a compatible donor's red cells, similarly tagged and injected into the patient, should disappear as quickly as the patient's own red cells. If the hemolysis is caused by intracorpuscular defects, the compatible donor's red cells should survive longer than do the patient's red cells when injected into the veins of the patient.

Most hemolytic anemias are accompanied by a decrease in the serum haptoglobins, which are globulins with a marked affinity to bind hemoglobin. When hemoglobin is released into the blood by hemolysis, it is quickly bound by haptoglobins, and the haptoglobin-hemoglobin complex is rapidly removed from the circulation by the reticuloendothelial system, thus resulting in a lowered serum haptoglobin level.

Although the hemolytic anemias are usually characterized by normocytic normochromic morphology on a blood smear with normal red cell indices, the cells in hereditary spherocytosis and hereditary elliptocytosis may exhibit an abnormal spheric or elliptic shape. This may be more apparent in wet preparations than in dried smears.

The cells in hereditary spherocytosis show increased hemolysis (osmotic fragility) in hypotonic solutions. The Coombs test is useful in demonstrating antibodies to the erythrocytes. The direct Coombs test demonstrates incomplete antibodies attached to the erythrocytes, which require a substance such as antihuman globulin to produce hemolysis. The indirect Coombs test detects antibodies to the red cells, which are present in the patient's serum, usually immunoglobulin IgG1 and IgG3, both of which activate complement.

Hemoglobin electrophoresis is a versatile and broadly effective procedure for the detection of pathologic hemoglobin proteins.

**Oral Manifestations.** There are certain oral and physical findings that are common to all hemolytic anemias. When sufficient hemolysis has taken place to produce anemia, pallor results. This is most easily observed in the nail beds and palpebral conjunctiva. Pallor of the oral mucosa—especially evident in the soft palate, tongue, and sublingual tissues—also is observable as the anemia progresses. In contrast to the anemias produced by bleeding or by factor deficiencies, the hemolytic anemias produce jaundice caused by the hyperbilirubinemia secondary to erythrocyte destruction. This is best seen in the sclera, but the skin, soft palate, and tissues of the floor of the mouth also become icteric as the serum bilirubin increases. The erythroid elements of the bone marrow are hyperplastic in an attempt to compensate for the anemia. This hyperplasia produces a characteristic appearance on the dental radiograph. Because of the enlargement of the medullary spaces, the trabeculae become more prominent, creating increased bone radiolucency with prominent lamellar striations.

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**TABLE 16-1 Common Causes of Hemolytic Anemia**

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<td>Rh factor incompatibility (hemolytic disease of newborn, erythroblastosis fetalis)</td>
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<td>Folic acid and vitamin B12 deficiency anemias</td>
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  - Cardiac valvular protheses
  - Hyppersplenism
  - Rh factor incompatibility (hemolytic disease of newborn, erythroblastosis fetalis)
  - Chronic liver disease
  - Autoimmune hemolytic disease (eg, as in systemic lupus erythematosus)
  - Transfusion reactions

- Intra-corpuscular defects
  - Abnormal shape of the erythrocytes
  - Hereditary spherocytosis
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  - Paroxysmal nocturnal hemoglobinuria
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  - Abnormal hemoglobins (hemoglobinopathies)
  - Sickle cell anemia and sickle cell trait
  - Thalassemia
  - Other hemoglobinopathies (eg, hemoglobin C and F)
  - Erythrocyte defects associated with other disease
    - CGL
    - Folic acid and vitamin B12 deficiency anemias
**Hematologic Diseases**

**Paroxysmal Nocturnal Hemoglobinuria.** This intracorporeal defect is an acquired clonal stem cell disorder that results in abnormal sensitivity of the RBC membrane to lysis by complement. Patients present with variable degrees of anemia, mild granulocytopenia, and thrombocytopenia. Complications include venous thromboses, hemoglobinuria, and hemosiderinuria. Patients complain of back pain, abdominal pain, and headaches that result from ischemia. This diagnosis should be suspected in confusing cases of hemolytic anemia or pancytopenia. Diagnosis is made by tests that demonstrate the increased sensitivity of the erythrocytes to complement, such as the sucrose hemolysis test. Most patients with this rare disease survive for less than 10 years, owing to complications of thrombosis or renal failure. Treatment with corticosteroids or androgens brings some degree of improvement in the anemia. Blood transfusions are necessary prior to surgical intervention, and some patients are treated with anticoagulants.

**Glucose-6-Phosphate Dehydrogenase Deficiency.** Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a hereditary enzyme defect that causes episodic hemolysis because of a reduced capacity of RBCs to deal with oxidative stresses. Patients with an enzymatic defect, such as the one found in the hexose monophosphate shunt, do not maintain the required level of reduced glutathione in their RBCs. As a result, hemoglobin sulfhydryl groups and the cell membranes themselves are oxidized, leading to hemoglobin precipitation in the cell and eventual cell lysis. This X-linked hereditary deficiency is the most common metabolic disorder of the RBCs. More than 400 variants of the enzyme have been described.

Anemia is the most frequent sign of this deficiency because the erythrocyte is the most sensitive cell to the oxidative processes. The highest incidence of G6PD deficiency has been found among people of Mediterranean and African descent.

In the G6PD deficient erythrocyte, the denatured hemoglobin with stromal proteins forms particles, called Heinz bodies, as a result of an oxidative process. These cells circulate with difficulty through the spleen and liver and are removed from the circulation, resulting in hemolytic anemia. No treatment is necessary except avoidance of known oxidant drugs such as dapsone.

**Dental Considerations.** The severity of anemia and its correction should be evaluated before major dental interventions because the decline in hemoglobin can reach 3 to 4 g/dL during hemolytic episodes. Blood transfusions may be used prior to dental treatment in severe cases. Drugs that might induce hemolysis, such as dapsone, sulfasalazine, and phenacetin, should be avoided. Analgesics and antibiotics can be given safely in therapeutic doses, provided special attention is given to the written recommendations of the manufacturer.

The hemolytic episodes are self-limited, and most patients with drug- or infection-induced hemolysis recover fully following treatment.

**Hemoglobinopathies.** The hemoglobinopathies, exemplified by sickle cell disease and thalassemia, are caused by defects in the globin portion of the hemoglobin molecule. These defects render the erythrocyte containing the abnormal hemoglobin more susceptible to hemolysis. A normal hemoglobin molecule consists of two pairs of amino acid chains, the α and β chains. This normal hemoglobin, hemoglobin A, may be represented by the formula $\alpha_2\beta_2$, indicating that there are two α and two β chains. In the hemoglobinopathies, abnormal hemoglobins are produced either in the form of abnormal chains (eg, γ, δ) or of small alterations in the α or β chain. Fetal hemoglobin, normal in the fetus but abnormal if persisting into adult life, is designated hemoglobin F and is represented by the formula $\alpha_2\gamma_2$, indicating that it differs from hemoglobin A in that the β chains are replaced by two γ chains. Sickle cell disease involves a single amino acid abnormality: the glutamic acid normally found in position 6 of the β chain is replaced by valine. Thus, the formula for hemoglobin S is $\alpha_2\beta_2^{V^6}$.

More than 30 different hemoglobins have been identified. Identification is made possible by the use of serum electrophoresis. Many of the abnormal hemoglobins show slower or faster electrophoretic mobility than does hemoglobin A. Specific identification of the exact biochemical abnormality depends on more sophisticated analysis of the molecule. At present, the specific molecular abnormality in many of the hemoglobinopathies has not been identified.

**Sickle Cell Disease.** In sickle cell disease, an autosomal recessive disorder, an abnormality in the β chain of hemoglobin is present in which valine is substituted for the normal glutamic acid residue on position 6. This relatively minor biochemical change results in profound undesirable physical characteristics in the hemoglobin. In the presence of either a lowered blood oxygen tension or an increased blood pH, the hemoglobin forms a sickle-shaped crystal (a tactoid) within the erythrocyte. This sickling of the erythrocyte leads to stasis and hemolysis of the red cells, especially in end-capillary circulation. The stasis then results in an even lower oxygen tension, an increased pH, and further sickling. The disease is hereditary and may manifest itself as the sickle cell trait or as sickle cell anemia.

In sickle cell anemia, 75 to 100% of the hemoglobin is S hemoglobin S, and the remainder is hemoglobin F; in sickle cell trait, only 20 to 45% of the hemoglobin is hemoglobin S, and the rest is normal hemoglobin A. In sickle cell trait (heterozygous), only one of the β chains is thought to be abnormal, whereas in sickle cell anemia (homozygous), both β chains are abnormal.

Patients with sickle cell trait an estimated 9% of African Americans are not anemic and have no symptoms of their disease unless they are placed in situations where there is abnormally low oxygen, such as in an unpressurized airplane or under injudicious administration of general anesthesia. On the other hand, patients with sickle cell anemia (approximately 0.15% of the African descent population), usually exhibit marked clinical manifestations.
CLINICAL MANIFESTATIONS. Patients with sickle cell anemia show marked underdevelopment and often die before 40 years of age. The clinical manifestations are the results of the basic anemia and hemolytic process (jaundice, pallor, and cardiac failure) or of necrosis following stasis of blood and vaso-occlusion. This latter phenomenon is manifested by splenic infarction, chronic leg ulcers, priapism, cerebral vascular thromboses (“strokes”), and painful attacks of abdominal and bone pain (pain crises). The long bones may present radiodense sclerotic areas as a residual of small infarcts.

Aplastic crises sometimes develop from infection, hypersensitivity reactions, or unknown causes. In these aplastic crises, the patient becomes acutely ill, red cell production virtually stops, and the hemoglobin drops precipitously. It has been suggested that folic acid deficiency may develop in these patients because of the increased demand for folic acid as a result of increased erythropoiesis. The folic acid deficiency may play a part in the genesis of the aplastic crisis.

ORAL MANIFESTATIONS. Other than the jaundice and pallor of the oral mucosa, patients often show delayed eruption and hypoplasia of the dentition secondary to their general underdevelopment. Because of the chronic increased erythropoietic activity and marrow hyperplasia, which are attempts to compensate for the hemolysis, increased radiolucency resulting from the decreased number of trabeculae is seen on dental radiographs. This change is noted especially in the alveolar bone between the roots of the teeth, where the trabeculae may appear as horizontal rows, creating a ladderlike effect (Figure 16-1). By contrast, the lamina dura appears dense and distinct. In skull films, the diploë is thickened, and the trabeculae are coarse and tend to run perpendicular to the inner and outer tables, giving a radiographic appearance of “hair on end” (Figure 16-2). The teeth do not present undue mobility. Areas of sclerosis or increased radiopacity represent areas of past thromboses with subsequent bony infarction.

Patients with sickle cell anemia are particularly prone to developing osteomyelitis, probably because of hypovascularity of the bone marrow secondary to thromboses. Inasmuch as the initial radiographic changes in vascular thrombosis and osteomyelitis are quite similar, confusion often results in the differential diagnosis of these two conditions, and other supporting data must be used to differentiate the two.

Hays study of the nuclear characteristics of the buccal mucosa cells in sickle cell anemia showed that, in those who were folate deficient, there was an increased number of cells with enlarged nuclei. This is not a surprising finding because it also is found in patients who have generalized megaloblastic changes, as in those with pernicious anemia or folic acid deficiency anemia.

Patients presenting with temporary anesthesia of the mental nerve, thought to be secondary to vascular occlusion involving the nerve’s blood supply, have been reported.

DIAGNOSIS. A smear of peripheral blood usually shows normochromic normocytic cells. Sickling does not often occur until the oxygen tension is lowered. To this end, a special preparation was formerly used for diagnosis: fresh blood was sealed in a small chamber of a microscopic slide with sodium metabisulfite (a reducing agent) for 1 hour and then observed for sickling. Hemoglobin electrophoresis is less expensive, more accurate, and more definitive in the diagnosis of sickle cell disease as it detects hemoglobin S\(^{10}\).

TREATMENT. There is no treatment for sickle cell disease other than symptomatic treatment. Antibiotics should be used early in the treatment of infection, and analgesic drugs should be used if necessary but with caution to prevent...

![Figure 16-1](image1.png) Radiograph of a patient with sickle cell anemia, demonstrating horizontal trabeculation creating a ladderlike effect. (Courtesy of Dr. Eisa Mozaffari, Philadelphia, PA).

![Figure 16-2](image2.png) Lateral skull film demonstrating thinned cortex with wavy lines, called “hair on end.” (Courtesy of Dr. Eisa Mozaffari, Philadelphia, PA).
iatrogenic addiction. Neither splenectomy nor antianemic drugs (except possibly folic acid) are of any value. Transfusions are avoided unless the patient has an aplastic crisis with a resulting extremely low hemoglobin level, because the transfusion effects are transitory, and the patients tend to develop antibodies, making it difficult to find suitable donors for future transfusions. Also there is an ever-present risk of hepatitis transmission with transfusions, and because these patients do not lose the iron portion of the hemoglobin molecule, transfusion can result in iron overload and eventual hemosiderosis.

Many physicians routinely use folic acid dietary supplements for patients with sickle cell anemia, increasing levels to therapeutic doses to treat an aplastic crisis. There is no good evidence that folic acid treatment increases the blood hemoglobin level.

Cytotoxic agents such as hydroxyurea have been shown to increase hemoglobin F and reduce the frequency of painful episodes; they are indicated in patients whose quality of life is disrupted by frequent painful episodes. Allogeneic stem cell transplantation is being studied as a possible curative option for severely affected young patients.11

**DENTAL CONSIDERATIONS.** Elective dental procedures involving the soft tissues should not be performed in patients with poorly controlled disease unless absolutely necessary because of increased risk of complications secondary to chronic anemia and delayed wound healing. Elimination of oral sources of infection should be instituted since infection can precipitate an aplastic crisis. General anesthesia should be used with caution in patients with sickle cell trait or sickle cell anemia; when used, it is imperative to avoid episodes of hypoxia because cerebral or myocardial thrombosis can result.

**Thalassemias.** The thalassemias are a group of congenital disorders characterized by a deficient synthesis of either the α or the β chains of globin in the hemoglobin molecule. As a result, the red blood cells are microcytic and hypochromic with an aberrant morphology. Thalassemias are often considered among the hypoproliferative anemias, the hemolytic anemias, and the anemias related to abnormal hemoglobin.

In α-thalassemia (deficient or reduced α chain) intracellular inclusions, Heinz bodies are formed by the precipitation of the α chains that accumulate in excess following the impaired chain production. In the most severe form of this disease, the fetus’s red blood cells contain hemoglobin composed of γ chains only. This condition is incompatible with life, due to the hemoglobin’s lack of oxygen-carrying capacity. Clinical signs in α-thalassemia depend on the severity of the α-chain production deficiency.

β-Globin synthesis is impaired in β-thalassemia with mutations in the sequences of the β-globin gene, leading to errors in the splicing of messenger ribonucleic acid (mRNA). In some cases, reduced amounts of β chains are produced (β+–thalassemia); in others, no normal β chains are produced (β–thalassemia).

Affected individuals are either heterozygotes, homozygotes, or double heterozygotes for the β-chain genes. The heterozygous individual has the β-thalassemia trait; the homozygous state is known as β-thalassemia major or Cooley’s anemia. The frequency of the disease approaches 0.1% in the Mediterranean basin, the Middle East, Africa, Asia, and the South Pacific. In India and Thailand, it is particularly prevalent.

Reduced erythropoiesis and hemolysis are characteristic of the disease as a result of an imbalance in β-chain production. In the major type, there is a relative excess of β chains that eventually aggregate and form inclusion bodies. Due to this defect, the RBCs that show abnormalities in membrane permeability are entrapped and removed from circulation by phagocytosis or lysis. As a compensatory process, an erythropoietic stimulus follows, causing an expansion of the red cell compartments of the marrow and extramedullary hematopoiesis. Another compensatory process increases the synthesis of γ chains that are able to combine with the free α chains and form a stable tetramer (fetal hemoglobin). This minimizes the severity of the clinical manifestations.

Clinical signs are minimal in β-thalassemia minor (β-thalassemia trait); most of the affected individuals are never diagnosed and have only a mild, clinically insignificant microcytic anemia. No treatment is needed, but genetic counseling should be offered and the opportunity for prenatal diagnosis discussed with at-risk couples.

β-thalassemia major or Cooley’s anemia is the most severe congenital hemolytic anemia.12 At 4 to 6 months of life, with the change from fetal XX chain to adult XX chain hemoglobin production, the first clinical manifestations appear. The hematocrit decreases to less than 20, the degree of anemia can reach a hemoglobin level of 2 to 3 g/dL, and the hemolysis is extensive, as is the iron overload. Growth and development in children is slow. In adolescence, secondary sex characteristics are delayed. The skin color becomes ashen-gray due to the combination of pallor, jaundice, and hemosiderosis. Patients also present with cardiomegaly, hepatomegaly, and splenomegaly.

**DIAGNOSIS.** Hemolytic anemia with hypochromic microcytic red blood cells that vary in size and shape is characteristic of thalassemia major. The hemoglobin electrophoresis shows increased amounts of fetal hemoglobin and variable amounts of normal adult hemoglobin. In patients homozygous for β-thalassemia, there is no detectable hemoglobin A. Prenatal diagnosis of thalassemia is facilitated by deoxyribonucleic acid (DNA) analysis of amniotic fluid cells, and it plays an important role in genetic counseling.

**TREATMENT.** Patients with mild thalassemia (α trait or β minor) are clinically normal and require no treatment. In other cases, the patient’s survival depends on blood transfusions. Prevention of a hemoglobin concentration decrease to under 10 g/dL improves the chances of normal development and survival into adulthood. This hypertransfusion treatment results in iron overload with hemosiderosis and iron deposition in all body tissues. As a result, patients may develop abnormalities in cardiac, endocrine, and hepatic functions, with car-
dian insufficiency, diabetes, pituitary hypofunction, and a possible bleeding tendency due to liver disease.

If regular blood transfusions are given to children with thalassemia to maintain the hemoglobin level between 10 and 14 g/dL, the children develop normally, without the marked skeletal changes. Some patients with thalassemia undergo splenectomy in an attempt to prolong RBC survival. Folic acid supplement also seems to be of some benefit. The iron overload is treated with continuous injections of a chelator, deferoxprine, which mobilizes and excretes the excess iron. Hematopoietic stem cell transplantation constitutes a future hope for the treatment of thalassemia.13

ORAL MANIFESTATIONS. Bimaxillary protrusion and other occlusal abnormalities are frequent in thalassemia major cases. Dental and facial abnormalities include poor spacing of teeth, a marked opened bite, prominent malar bones, and a saddle nose. In addition, the pneumatization of the maxillary sinuses is delayed. As a result of these skeletal changes, the upper lip is retracted, giving the child a “chipmunk facies.”

The radiographic changes seen in the jaws include generalized rarefaction of the alveolar bone, thinning of cortical bone, enlarged marrow spaces, and coarse trabeculae, which are similar to the changes observed in sickle cell disease patients. In the parietal bones, the thin cortex covering the coarse vertical trabeculae and the enlarged diploë produce a “hair on end” picture (see Figure 16-2).

Cranial nerve palsies have been described in thalassemia due to the extramedullary hematopoiesis resulting in pressure on the nerves.

In β-thalassemia major, there is no correlation between the chronologic, skeletal, and dental developmental age. The skeletal retardation increases with age due to hypoxia from severe anemia, endocrine hypofunction secondary to iron deposition, or the toxic action of iron enzyme systems leading to tissue injury.

The dentin and enamel are indicators of iron deposition, and deciduous and permanent teeth of patients with thalassemia contain up to five times the iron concentration measured in normal patients. The high concentration of iron explains the discoloration of teeth in patients with β-thalassemia major.

DENTAL MANAGEMENT. As in any patient with a chronic anemia, poor healing may ensue after surgical dental procedures. The possibility always exists of exacerbating the symptoms of cerebral or cardiac hypoxia if substantial bleeding occurs in a patient who is already anemic. Surgery has been used successfully to treat the facial deformities.

ANEMIA OWING TO DECREASED PRODUCTION OF RED CELLS

Megaloblastic Anemias. The term “megaloblastic anemia” is used to describe a group of disorders characterized by a distinct morphologic pattern in hemapoietic cells. These cells have small immature nuclei and large mature cytoplasmic loops. Microscopically, this nuclear-cytoplasmic asynchrony is described as “megaloblastic.” This group of disorders chiefly affects cells with rapid turnover. In addition to the hematopoietic cells, epithelial cells, gastrointestinal mucosa, and oral mucosa are involved. Deficiencies of vitamin B₁₂ (cobalamin) or folic acid are the major causes of megaloblastic anemia.14

Vitamin B₁₂ (Cobalamin) Deficiency/Pernicious Anemia. The development of a vitamin B₁₂ deficiency is a slow process and is most frequently due to impaired absorption rather than dietary deficiency. Conditions that can lead to cobalamin deficiency include pernicious anemia, gastrectomy, small-bowel bacterial overgrowth, diverticulosis, blind intestinal loops, scleroderma, tapeworm, tropical sprue, alcoholism, and medications such as neomycin and colchicine. The major manifestations are anemia, gastrointestinal disorders, and neurologic complications.

The most common form of vitamin B₁₂ deficiency is pernicious anemia, which is due to atrophy of the gastric mucosa resulting in a lack of intrinsic factor secretion. Intrinsic factor acts by binding to the vitamin B₁₂ molecule, forming a complex that crosses the ileal mucosa and protects the vitamin from proteolysis. The disease can be the result of an autoimmune reaction to either the gastric parietal cells or intrinsic factor and is often seen in connection with other autoimmune diseases such as Graves’ disease.

ORAL MANIFESTATIONS. Glossitis and glossodynia are the classic oral symptoms of pernicious anemia (Figure 16-3). The tongue is “beefy red” and inflamed, with small erythematous areas on the tip and margins. There is a loss of filiform papillae, and, in advanced disease, the papillary atrophy involves the entire tongue surface together with a loss of the normal muscle tone. The erythematous macular lesions also can involve the buccal and labial mucosa.15 Patients may complain of dysphagia and taste aberrations. Discomfort described by denture wearers who have pernicious anemia is probably due to the weakened mucosal tissues. Although the “burning mouth” sensation diagnosed in pernicious anemia can be due to a neuropathy, other causes of oral burning, including candidiasis, should be considered.

FIGURE 16-3 Atrophic glossitis in a patient with vitamin B₁₂ deficiency. (Courtesy of Dr. Thomas P. Sollecito, University of Pennsylvania School of Dental Medicine, Philadelphia, PA)
Oral mucosa biopsy results from patients with pernicious anemia show epithelial atrophy, enlarged basal cell nuclei, increased mitoses in the basal epithelium, epithelial dysplasia, and a nonspecific infiltrate of lymphocytes, plasma cells, and polymorphonuclear leukocytes in the lamina propria.

Following treatment with vitamin B₁₂, the tongue undergoes complete healing with cessation of the symptoms and reversal of the morphologic alterations.

**DIAGNOSIS.** Pernicious anemia should be suspected in any anemic patient with neurologic symptoms. The first definitive clue that one is dealing with pernicious anemia, however, is the finding of macrocytic normochromic red cells on the blood smear. The mean corpuscular volume is increased, the mean corpuscular hemoglobin increased, and the mean corpuscular hemoglobin concentration normal. In addition, the shape of the red cells varies considerably, the platelets are abnormally large, and the neutrophils often are hypersegmented, having as many as six lobes to their nuclei instead of the usual three. A bone marrow examination will confirm these morphologic changes by revealing the presence of megaloblastic marrow changes. Because folic acid deficiency also may produce these hematologic changes, further studies are necessary to pinpoint vitamin B₁₂ deficiency as the cause. A serum assay for vitamin B₁₂ and folate should be performed using a microbiologic or radioisotope technique. Once vitamin B₁₂ deficiency has been established, the cause of the deficiency must be determined.

To diagnose pernicious anemia, the Schilling test is used. In the Schilling test, the patient is given a measured small amount of radioactive vitamin B₁₂ by mouth, followed shortly by a large flushing dose of parenteral nonradioactive vitamin B₁₂. Because the total dose of vitamin B₁₂ far exceeds the renal threshold for this vitamin, the excess appears in the urine within the next 24 hours. The amount of radioactivity in the urine is proportional to the amount of the orally administered vitamin B₁₂ that has been absorbed. The normal patient excretes 7 to 30% of the radioactive B₁₂ in 24 hours, whereas the patient with pernicious anemia excretes no more than 3%. Further studies may be necessary to determine that intestinal disease is not responsible for the malabsorption, and these studies involve administration of a complex of radioactive B₁₂ and intrinsic factor. The patient with pernicious anemia will exhibit normal absorption and urine excretion of vitamin B₁₂.

Serum antibodies to gastric parietal cells are found in 90% of the patients; antibodies to the intrinsic factor are found in 60%. These antibodies also have been found in saliva.†,†,17

**TREATMENT.** Management consists of administration of parenteral cyanocobalamin. Large oral doses may be used when intramuscular injection is contraindicated. This treatment corrects the hematologic changes but will only arrest, not correct, the neurologic changes. It should be given by the patient’s physician and must be continued for the rest of the patient’s life. Patients who have a history of being treated for anemia for “a while” with B₁₂ shots, who no longer take the injections, and who are not anemic, almost certainly do not have pernicious anemia. Almost 100% of patients with pernicious anemia have a relapse within 6 months after discontinuation of B₁₂ therapy.

Because the hematologic changes of pernicious anemia may be reversed by oral folic acid therapy without arrest of the neurologic changes, patients who are anemic should never be given folic acid therapy without the possibility of pernicious anemia first being ruled out. Folic acid removes a valuable diagnostic sign (low hemoglobin) and allows the neurologic changes, which are mostly irreversible even with B₁₂ therapy, to progress. It is best when prescribing therapeutic vitamins to choose one without folic acid or to ensure that the hemoglobin is normal before instituting vitamin therapy.

**Folic Acid Deficiency Anemia.** Folic acid deficiency causes severe anemia but does not cause the neurologic abnormalities seen in pernicious anemia. Folate deficiency is prevalent in patients whose diet is devoid of leafy vegetables, such as alcoholics and drug abusers, and in patients with an increased requirement for folate, such as pregnant women and young children. Drugs used for cancer chemotherapy treatment, such as methotrexate, azathioprine, 6-mercaptopurine, 5-fluorouracil, and cytosine arabinoside, are known to cause folate deficiency by interfering with DNA synthesis.

Diagnosis is made by detection of hematologic changes (the same as those in pernicious anemia) with a normal Schilling test and serum vitamin B₁₂ assays, but low serum assays of folic acid. Treatment of folic acid deficiency consists of oral folic acid tablets. Oral doses of 1 mg/d are adequate for most patients, and a 5 mg tablet suffices to treat even a patient with intestinal malabsorption.

Oral manifestations may include angular cheilitis and, with severe cases, ulcerative stomatitis and pharyngitis.

**Aplastic Anemia.** Aplastic anemia is a normochromic normocytic anemia caused by bone marrow failure. Although the cause is frequently unknown, approximately half of the cases are suspected to be caused by chemical substances (eg, paint solvents, benzol, chloramphenicol) or exposure to high levels of x-ray radiation. The term “anemia” is, in a sense, a misnomer since all three cellular elements of the marrow are often involved (pancytopenia).

Fanconi’s anemia is an inherited aplastic anemia that manifests in early childhood. It is associated with brown skin pigmentation, hypoplasia of the kidney and spleen, absent or hypoplastic thumb or radius, microcephaly, and mental and sexual retardation.

**Dental Considerations.** There are two major problems in the dental management of patients with aplastic anemia: infection and bleeding. Local infections and bacteremias originating in the oral region can have a fatal course. A thorough oral examination of teeth, periodontium, soft tissues, and salivary glands should be conducted once the diagnosis of aplastic anemia is established. Gingival bleeding can be reduced by the use of systemic antifibrinolytic agents, such as aminocaproic acid or tranexamic acid, as well as local hemostatic measures.
Tranexamic acid is given in a dosage of 20 mg/kg body weight four times a day starting 24 hours before oral procedures and continuing for 3 to 4 days afterward. Oral rinses with chlorhexidine 0.2% in an aqueous solution will reduce the amount of plaque and the number of microorganisms in the oral cavity. However, intramuscular injections and nerve block anesthesias are to be avoided because of the risk of thrombocytopenia and the bleeding tendency. Intraligamentary anesthesia can be used safely in these cases.

**WHITE BLOOD CELL DISORDERS**

Leukocytes protect against foreign invaders such as fungi, bacteria, viruses, and parasites. Recent advances have expanded our understanding of the cellular and molecular basis of both normal and neoplastic leukocyte function. To understand leukocyte disease, several aspects of normal function must be appreciated. Leukocytes originate from pluripotent hematopoietic stem cells in either the bone marrow or lymphoid tissue; under various external influences and regulating mechanisms, including cytokines and matrix proteins, stem cells develop into progenitor cells of various lineages. Granulocytes and monocytes are derived from the same stem cell precursors in the bone marrow, whereas lymphocytes originate in the lymph nodes. The majority of leukocytes are produced and stored in the bone marrow in several “pools.” The mitotic pool consists of immature precursors, the maturing pool consists of white blood cells (WBCs) undergoing maturation, and the storage pool consists of functional WBCs that can be released when needed.

The three types of granulocytes are neutrophils, eosinophils, and basophils. Neutrophils are the most dominant of all circulating phagocytes. They provide the first line of defense against bacterial invasion of the mucous membranes and skin, and comprise greater than half of all leukocytes. Three cellular functions must be intact for neutrophils to provide this protection against infection. They must respond to chemotactic stimuli and migrate to the site of tissue damage, they must be capable of phagocytosis, and they must destroy bacteria through enzymatic activity. The risk of infection is increased if insufficient numbers of neutrophils are present or if one of the three actions of neutrophils is not intact. Neutrophil function is aided by the presence of immunoglobulins, complement, and fibronectin, which help the neutrophils attach to the surface of microorganisms. If these proteins are not present, neutrophil function decreases. The largest number of neutrophils (90%) can be found in the bone marrow. However, neutrophils are released into the circulation into two pools: circulating and marginal. Cells in the marginal pool adhere to vessel walls and are readily available to help fight invading organisms.

The function of the other granulocytes, eosinophils, and basophils is not as well understood. Eosinophils have a weak ability to phagocytize foreign substances and cannot kill bacteria. They function in immune-related antigen-antibody reactions, such as asthmatic attacks and allergic reactions. In addition, levels are increased in parasitic infections. Basophils migrate to tissues carrying heparin and histamine- and platelet-activating factors, and they act as mast cells in allergic reactions. Monocytes are immature cells when in the bloodstream, and they use the bloodstream briefly as a transportation system. Once in the tissues, they mature to macrophages, which have a number of vital functions, including processing antigens to initiate lymphocyte response; secretion of lysosome, complement components, and interleukin-1; and activation and mobilization of other leukocytes.

Lymphocytes are the primary cells involved in immunity. They appear to originate from pluripotent stem cells in the bone marrow and migrate to other lymphoid tissues, including lymph nodes, spleen, thymus, and mucosal surfaces of the gastrointestinal tract. There are two types of lymphocytes: thymus-dependent T lymphocytes and non-thymus-dependent B lymphocytes. Both B and T lymphocytes are seen in the peripheral blood. A description of lymphocyte function is contained in Chapter 18, “Immunologic Diseases.”

Peripheral blood contains approximately 4,000 to 11,000 WBCs per cubic millimeter. The hematology laboratory also reports the differential WBC count, which reports the proportion of cell types by percentages. When interpreting the differential WBC count, the clinician should not rely on the percentage to decide whether a cell type is increased or deficient because this number may be misleading. The clinician should determine the absolute number of each cell type by multiplying the total WBC count by the percentage. Automated laboratory systems count the cells directly. The absolute number is a more accurate reflection of disease because it maintains the relationship of the total to the differential count. The normal range of the absolute number of WBCs is summarized in Table 16-2.

<table>
<thead>
<tr>
<th>Cell</th>
<th>Percent</th>
<th>Number</th>
<th>High Count</th>
<th>Low Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>50–70 (segments), 3–5 (bands)</td>
<td>3,000–7,000</td>
<td>Infection, drugs</td>
<td>Viral disease, drugs, agranulocytosis</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20–40</td>
<td>1,000–3,500</td>
<td>Viral disease, mononucleosis</td>
<td>HIV, AIDS</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0–7</td>
<td>0–700</td>
<td>Infection, SBE</td>
<td>—</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0–5</td>
<td>0–500</td>
<td>Parasitic disease, allergy</td>
<td>—</td>
</tr>
<tr>
<td>Basophils</td>
<td>0–1</td>
<td>0–100</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; SBE = subacute bacterial endocarditis.

(Lymphocyte disorders are described in Chapter 18,
“Immunologic Diseases.”) Diseases of granulocytes are divided into three major types: quantitative, qualitative, and myeloproliferative. Quantitative disorders result from an abnormal number of white cells, qualitative disorders result from poorly functioning cells, and myeloproliferative disease results from acquired clonal abnormalities of hematopoietic stem cells. The leukemias are the myeloproliferative diseases described in this chapter.

**Quantitative Leukocyte Disorders**

**GRANULOCYTOSIS**

Increases in the number of white blood cells may result from infection, tissue necrosis, allergic reactions, neoplastic diseases, inflammatory diseases, or any activity, such as stress or exercise, that increases epinephrine release. A persistent elevation of the WBC count with the absolute neutrophil count remaining above 30,000/mm\(^3\) with a pronounced left shift and the presence of myelocytes, metamyelocytes, and band forms is called a “leukemoid reaction.” In response to increased demand, an increased number of immature neutrophils called “bands” enter the circulation, a process called a “left shift.” This reaction, often secondary to a severe viral infection, is distinguished from acute leukemia because, in leukemoid reactions, there is an orderly maturation and proliferation of all normal myeloid elements in the bone marrow.

**GRANULOCYTOPENIA AND AGRANULOCYTOSIS**

Granulocytopenia may occur alone or as part of a generalized suppression of the bone marrow also affecting the erythrocytes and platelets (aplastic anemia). A decrease in granulocytes chiefly results from a decrease in neutrophils, and most cases of granulocytopenia are known as neutropenia. The degree of neutropenia predicts the risk of serious bacterial infections.

Neutropenia is defined as an absolute neutrophil count of more than two standard deviations below a normal mean value. The normal absolute number of neutrophils in the peripheral blood is 3,000/mm\(^3\) to 6,000/mm\(^3\). Mild neutropenia occurs when 1,000/mm\(^3\) to 2,000/mm\(^3\) neutrophils are present, moderate neutropenia occurs when 500/mm\(^3\) to 1,000/mm\(^3\) neutrophils are present, and severe neutropenia occurs when fewer than 500/mm\(^3\) neutrophils are present in the peripheral blood. The term “agranulocytosis” is used when no neutrophils are seen on a peripheral blood smear. Agranulocytosis is a serious condition characterized by an extremely low leukocyte count and the absence of neutrophils; it most often is caused by a drug or medication that interferes with cell formation or enhances cell destruction.

Neutropenia, like anemia, is not a disease but a sign of an underlying disorder; it has a wide range of underlying causes. Decreased production of neutrophils is associated with deficiencies of vitamin B\(_12\) and folic acid. Certain infections decrease the number of neutrophils in the circulating blood because of increased migration of neutrophils into the tissues, sequestration of neutrophils, or the direct toxic effect of the microorganism and its toxins on the blood marrow. Infections with viruses, particularly hepatitis A and B viruses, parvovirus, human immunodeficiency virus (HIV-1), and Cytomegalovirus, are associated with neutropenia. Overwhelming bacterial infection, particularly septicemia, can be accompanied by neutropenia because the cells are used at rapid rate to overcome the infection. Diseases causing sequestration of neutrophils include systemic lupus erythematosus and Felty’s syndrome.\(^{21}\) The most common cause of neutropenia is a drug reaction. A large number of drugs can cause neutropenia or aplastic anemia. Neutropenia secondary to a drug reaction results from either a toxic (ie, dose-related) or an idiosyncratic phenomenon. Toxic neutropenia occurs predictably in all people who take the offending drugs at sufficient doses for a sufficient time. These drugs interfere with DNA synthesis, protein synthesis, or mitosis. Drugs that cause toxic neutropenia include those used in cancer chemotherapy, benzene, and alcohol. Increasingly, more commonly used drugs, such as analgesics, antibiotics, and antihistamines, have been identified as potential causes of severe neutropenia or agranulocytosis. Neutropenia secondary to ionizing radiation also results from a direct toxic effect on the division of bone marrow cells.

Idiosyncratic reactions are not dose related and occur only in a small percentage of individuals taking the drug. Idiosyncratic drug reactions causing neutropenia are thought to be either an immunologic reaction affecting the bone marrow or an inherited inability to metabolize the drug properly. Drugs that have an increased risk of causing idiosyncratic neutropenia include phenothiazides, phenylbutazone, sulfonamides, and chloramphenicol.\(^{22}\)

**Clinical Manifestations.** Along with feelings of general malaise (headache, discomfort, and muscle aches), the most common complication of neutropenia and agranulocytosis is infection.\(^{20}\) The clinician must be aware that the localizing clinical signs of infection may be few or absent owing to a decreased inflammatory reaction. Swelling and pus will be minimal. The most common sign of infection in neutropenic patients is fever. Other common manifestations include mucosal ulcers, tachycardia, acute pharyngitis, and lymphadenopathy. Common sites of infection include the lungs, urinary tract, skin, rectum, and mouth. Acute bacterial infections are the most common and usually are caused by *Staphylococcus aureus* or gram-negative bacilli, such as *Klebsiella, Pseudomonas,* and *Proteus.*

**Treatment.** The cause of neutropenia must be determined. All drugs should be discontinued and the patient carefully observed for signs of infection. At the first sign of infection, cultures must be taken and the patient started on a regimen of combined often broad-spectrum antibiotics. A combination of antibiotics is commonly used because of the broad coverage against most organisms known to cause infection in neutropenic patients, such as those in *Staphylococcus* species and enteric gram-negative bacteria. Some medical centers use reverse isolation or sterile environments, such as laminar flow beds, to reduce the risk of infection. Third-generation cephalosporins such as ceftazidime are effective single-agent therapies.\(^{23}\)
Patients with antibodies to neutrophils benefit from corticosteroids; those with neutropenia associated with Felty’s syndrome, a disease in which neutrophils sequester in the spleen, benefit from splenectomy. Hematopoietic stem cell transplantation has been used to treat patients with severe aplastic anemia when a suitable donor is available. The myeloid growth factors granulocyte colony-stimulating factor (G-CSF) (filgrastim) and granulocyte-macrophage colony-stimulating factor (sargramostim) may be useful in shortening the duration of neutropenia associated with chemotherapy.

**Oral and Dental Considerations.** The most common oral sign of neutropenia is ulceration of the oral mucosa (Figure 16-4). Neutropenic ulcers differ from other oral ulcers in that they usually lack surrounding inflammation and are characterized by necrosis. Because the bacteria are poorly opposed by neutrophils, the ulcers become large irregular deep lesions that are extremely painful. The necrotic tissue is often foul smelling, a characteristic of fusospirochetal organisms, although invasion by species of *Staphylococcus* or gram-negative bacilli is common.

Oral ulcers, advanced periodontal disease, pericoronitis, and pulpal infections in patients with severe neutropenia should be considered potentially life threatening because they can lead to bacteremia and septicemia. The infection must be cultured to determine the predominant organism, and the patient should be placed on the appropriate combination of parenteral broad-spectrum antibiotics. Topical application of antibacterial mouth rinses also may be helpful for ulcers. Also useful is an individualized soft splint made from a maxillary study cast that covers palatal lesions and carries medication in a well that continually bathes the oral ulcers. A combination of topical neomycin, bacitracin, and nystatin has been used to reduce the risk of severe infection. Chlorhexidine oral rinses are usually ordered, although their chronic use may be controversial because chlorhexidine use is accompanied by increased gram-negative rods in the oral flora. The pain of the ulcers is reduced by the use of topical anesthetic mouth rinses. A solution containing 5% diphenhydramine hydrochloride mixed with magnesium hydroxide or kaolin with pectin is useful for this purpose. Dental treatment for neutropenic patients is discussed in detail in the section below entitled “Leukemia.”

**CYCLIC NEUTROPENIA**

Cyclic neutropenia is a rare disorder that occurs secondary to a periodic failure of the stem cells in the bone marrow. This failure results from an abnormality in the regulation of bone marrow precursor cells or an inhibitor of neutrophils released from monocytes. It is characterized by transient severe neutropenia that occurs approximately every 21 days. The nadir neutrophil count lasts 3 to 7 days and is occasionally associated with elevations in monocytes. One-third of cases are inherited as an autosomal dominant trait, and two-thirds arise spontaneously during the first few years of life. The disease is frequently present during infancy or childhood.
although there is an adult-onset form of the disease, and both sexes appear to be equally affected. The patient is healthy between neutropenic episodes, but at regular intervals the absolute neutrophil count falls quickly below 500/mm$^3$; in some patients, the neutrophil count falls to 0. Normal hematopoiesis is not constant in the bone marrow of patients with cyclic neutropenia, causing fluctuations in marrow platelet and erythrocyte precursors and granulocytes.

**Clinical Manifestations.** The major signs and symptoms of cyclic neutropenia are related to infection occurring during neutropenic episodes. The most common signs are fever, stomatitis, pharyngitis, and skin abscesses. The severity of the infections is related to the severity of the neutropenia. Some patients with severe periodic neutropenia experience few infections owing to a compensatory increase in monocytes, which act as phagocytes to prevent the spread of bacterial infection. Less frequently, patients experience lung and urinary tract infections and rectal and vaginal ulcers. Life expectancy is good for patients who receive careful monitoring.

**Treatment.** The universally accepted treatment for most cases of cyclic neutropenia is careful monitoring of the patient for infection during neutropenic periods and vigorous early management of infection. In some patients, use of corticosteroids, adrenocorticotropic, or testosterone modulates the sharp reduction in marrow function. Unfortunately, these drugs are not successful for all patients. The use of granulocyte colony-stimulating factor (G-CSF) has been employed to boost neutrophil levels. Unlike with congenital agranulocytosis, G-CSF therapy in cyclic neutropenia is not associated with the development of acute myeloid leukemia or myelodyplasia.

**Oral and Dental Considerations.** Oral lesions are common in cyclic neutropenia and may be the major clinical manifestation of the disease. The two most common oral manifestations are oral mucosal ulcers and periodontal disease. The oral ulcers recur with each new bout of neutropenia and resemble the large deep scarring ulcers seen in major aphthous stomatitis. The periodontal manifestations range from marginal gingivitis to rapidly advancing periodontal bone loss caused by bacterial infection of the dental supporting structures (Figures 16-5 and 16-6). In patients with major aphthous ulcers or generalized rapidly advancing periodontal disease that cannot be explained by local factors alone, cyclic neutropenia should be ruled out as a possible cause. Suspicion of cyclic neutropenia should be particularly high when either of these oral diseases is seen in children.

Clinicians must remember that a single WBC count is not a sufficient test to rule out the diagnosis of cyclic neutropenia because the examination may be performed as the peripheral neutrophils are being replenished. A series of three total and differential WBC counts per week for 4 to 6 weeks is necessary to rule out this disease. Patients with known cyclic neutropenia require frequent dental treatment to minimize advancing periodontal disease. Routine treatment should be confined to the periods when the absolute neutrophil count is above 2,000/mm$^3$. A white cell count taken the day of a dental procedure is a wise precaution because the neutrophil count can change rapidly. Oral hygiene must be carefully maintained, and patients should be recalled for oral hygiene every 2 to 3 months. The use of colony-stimulating factor has reduced oral ulcers and periodontal disease in these patients.

**Qualitative Leukocyte Disorders**

**CHÉDIAK–HIGASHI SYNDROME**

First described just more than 30 years ago, Chédiak-Higashi syndrome is a rare autosomal recessive defect characterized by oculocutaneous albinism, progressive neurologic abnormalities, and large blue-grey granules in the cytoplasm of neutrophils, eosinophils, basophils, and platelets. Abnormal granules also have been observed in renal tubular cells, nerve cells, and fibroblasts. The abnormal granules seen in all blood granulocytes result in neutrophils with decreased chemotactic and bactericidal ability, although phagocytosis remains intact. The abnormality in bactericidal activity is thought to be caused by an inefficient use of lysosomal enzymes resulting from a mutation in the lysosomal trafficking regulator, or $LYST$ gene. This leads to defective T-cell signaling and the potential for an associated lymphoproliferative syndrome. Patients develop severe neutropenia as a result of ineffective granulopoiesis, and most die in childhood from infections or advanced lymphoproliferative syndrome.

**Clinical Manifestations.** Hypopigmentation resulting from the pigment dilution is noted in skin and hair during infancy. The hair will have gray streaks. Neuropathy and ataxis are prominent features in some patients. The degranulation defect

**FIGURE 16-5** Full-mouth radiographs of a 4-year-old boy with cyclic neutropenia, showing resorption of the alveolar and supporting bone. (Reproduced with permission from Cohen DW, Morris AL. J Periodontol;32:159.)
of neutrophils causes recurrent bacterial infections of the skin and respiratory tract, chiefly by gram-positive organisms, such as *Staphylococcus aureus* and β-hemolytic *Streptococcus*. This differs from the infections seen in patients who are neutropenic from leukemia or cancer chemotherapy, in whom gram-negative bacilli cause the majority of infections. Patients usually die of recurrent infections before the age of 10 years. Patients who survive the recurrent infections experience an accelerated phase of the disease that resembles lymphoma. The lymph nodes, spleen, liver, and bone marrow become infiltrated with lymphohistiocytic cells. Diagnosis of Chédiak-Higashi syndrome is based on the pathognomonic giant blue-gray granules seen in the cytoplasm of granulocytes when examining a peripheral blood smear.

**Treatment.** Medical management of Chédiak-Higashi syndrome in infants centers on rigorous treatment of infections as soon as they occur. Because gram-positive organisms cause a majority of infections, the infections respond well to antibiotics. Treatment of neutrophils with ascorbate has enhanced the function of neutrophils in some patients, and hematopoietic stem cell transplantation (HSCT) has been helpful in others. Approximately 50% of these patients are cured by HSCT when it is applied early in the course of the disease. Chemotherapy has been used to treat the accelerated lymphoproliferative phase of the disease.

**Oral and Dental Considerations.** Gingival and periodontal disease are common findings in patients with Chédiak-Higashi syndrome, and early loss of teeth owing to periodontal disease and caries is frequently reported in the literature.31

**CHRONIC IDIOPATHIC NEUTROPENIA**

Reports of long-standing severe neutropenia with few associated abnormalities have appeared in the literature under a variety of names, including familial neutropenia, chronic benign neutropenia, chronic neutropenia, and hypoplastic neutropenia. Chronic idiopathic neutropenia (CIN) refers to neutropenias whose characteristics do not fit into other categories. The etiology of this group of disorders is unknown, but it is characterized by a decreased production of neutrophils in the bone marrow. Some patients have antineutrophil antibodies detectable in the serum and comprise a subset of patients with so-called chronic immunoneutropenia. The bone marrow of patients with CIN shows a normal number of immature cells but a decreased number of mature neutrophils. This phenomenon has been called “maturation arrest,” but the reason for this problem is unclear. Increased margination of neutrophils has been noted in some cases.

**Clinical Manifestations.** Many patients with CIN are asymptomatic and are free from infections, even though their absolute neutrophil count may be below 500/mm³. This is caused by a compensatory monocytosis, which accounts for a normal number of phagocytes present at the site of a tissue injury. A minority of patients experience recurrent bacterial infections, but these are rarely life threatening. The most common infections are recurring upper respiratory tract infections, otitis media, bronchitis, and furunculosis. Oral ulcers, periodontal disease, sinusitis, and perirectal infections also occur.

**Treatment.** When managing CIN, the clinician must refrain from overtreating patients who are asymptomatic. G-CSF is
now the therapy of choice for patients who have serious infections. Corticosteroids and cytotoxic agents have also been effective in increasing the neutrophil count.

**Oral and Dental Considerations.** There have been many isolated case reports of patients with CIN with oral signs and symptoms. The most distressing oral problem repeatedly reported in patients with CIN is severe rapidly advancing periodontal disease. The gingivae appear intensely red, despite the neutropenia, with granulomatous margins. Severe gingival recession is common, and early severe periodontal disease with advanced bone loss, mobility, denuded roots, and loss of teeth has been described. These patients may also report recurring oral ulcerations that may correspond to the neutrophil count (Figure 16-7).

The dental management of patients with CIN depends on their past history of infections. The dentist needs to remember that even a patient with CIN with severe neutropenia may not be highly susceptible to infection, owing to a compensatory monocytosis. If a patient with CIN has never experienced an infection, it would not be reasonable to take extraordinary precautions for routine dental procedures.

**Leukemia**

Leukemia, originally described by Virchow in 1874 as “white blood,” is a malignancy affecting the WBCs of the bone marrow. This neoplastic process is characterized by differentiation and proliferation of malignantly transformed hematopoietic stem cells, leading to suppression of normal cells. The malignant cells replace and turn off the normal marrow elements, causing anemia, thrombocytopenia, and a deficiency of normally functioning leukocytes. In time, the leukemic cells infiltrate other body organs, destroying normal tissue. The most widely accepted classification system of leukemia is the French-American-British (FAB) classification. Although further subclassifications have been added, this system is a morphologic classification based on the differentiation and maturation of predominant leukemic cells in the bone marrow and on cytochemical analysis.

Leukemia is classified as either acute or chronic and by cell type. The etiology of leukemia, in most cases, is unknown (see below), but several factors that increase the risk of the disease are well established. Genetic factors play a role in some cases of leukemia, and families with a high incidence of the disease have been reported. Genetic disorders, such as Down, Klinefelter’s, and Fanconi’s syndromes, also are associated with an increased risk of leukemia. Familial leukemias are rare, but there seems to be a higher incidence of leukemia in siblings of affected children. Individuals with chromosomal abnormalities like those in Down syndrome have a 20-fold increased incidence of acute leukemia. Radiation in doses over 1 Gy is known to significantly increase the risk of leukemia. For example, a high incidence of leukemia was observed in survivors of atomic blasts as well as in early radiologists. Patients with a past history of radiotherapy also have an increased rate of leukemia.

Exposure to certain chemicals and drugs has been related to an increased risk of leukemia. Benzene has been related to leukemia incidence, and acute leukemia has been reported to occur after the use of the arthritis drug phenylbutazone and the antibiotic chloramphenicol. Patients treated with certain anticancer drugs have an increased risk of developing leukemia; particularly susceptible are patients treated for lymphoma with chemotherapy and radiation.

**ACUTE LEUKEMIA**

The acute leukemias are malignancies of hematopoietic progenitor cells, which consequently fail to mature and differentiate. They are divided into two major groups: acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) (Table 16-3). The common type of ALL, which comprises 65% of cases, is derived from B lymphocytes or their precursors. The T-cell type comprises 20% of cases, and 15% of AMLs are classified as null cell leukemia because they originate from the T or B cells.

In older patients, AML may be preceded by a preleukemic or myelodysplastic syndrome, with generalized bone marrow abnormalities affecting RBCs, leukocytes, and platelets. Leukemia preceded by these syndromes responds poorly to therapy.32

**Clinical Manifestations.** Acute leukemia can occur at any age, but ALL is commonly found in children, whereas AML occurs more frequently in adults.33 The symptoms and signs of acute leukemia result from either bone marrow suppression or infiltration of leukemic cells into other organs and tissues. The bone marrow changes cause anemia, thrombocytopenia, and a decrease in normally functioning neutrophils. The anemia results in pallor, shortness of breath, and fatigue, which is the most common presenting symptom.

Thrombocytopenia causes spontaneous bleeding, such as petechiae, ecchymoses, epistaxis, melena, increased menstrual bleeding, and gingival bleeding, when the platelet count falls below 25,000/mm³. Approximately 50% of patients have some complaint of purpura or bleeding at the time of diagnosis.
Although most bleeding results from decreased numbers of platelets, disseminated intravascular coagulation (DIC) can result from substances released from leukemic cells that activate coagulation. These patients, who usually have promyelocytic leukemia, have the ironic combination of thrombosis and hemorrhage owing to depletion of coagulation factors.

Although leukemic patients often present with a greatly increased number of leukocytes, these leukemic cells do not function normally, resulting in defective migration, phagocytosis, or bactericidal action. Infection is therefore a frequent complication of the disease and is the most common cause of morbidity and mortality. Fever is an early sign of disease owing to recurrent infections of the lungs, urinary tract, skin, mouth, rectum, and upper respiratory tract. Infiltration of organs and tissues by leukemic cells causes lymphadenopathy, hepatomegaly, and splenomegaly. Cells may infiltrate the central nervous system or peripheral nerves, leading to cranial nerve palsy, paresthesia, anesthesia, and paralysis. Localized tumors consisting of leukemic cells are called “chloromas.” The surface of these tumors turns green when exposed to light because of the presence of myeloperoxidase.

The diagnosis of acute leukemia is made with laboratory examination of the peripheral blood and bone marrow. The peripheral WBC count is usually elevated, but some cases present with normal or decreased counts. These cases are called subleukemic or aleukemic leukemia. In most cases, significant numbers of immature granulocytic or lymphocytic precursors or even stem cells are present in the peripheral blood, accompanied by a significant anemia and thrombocytopenia. Microscopic examination of a bone marrow aspirate finalizes the diagnosis.

**Treatment.** The first step in treatment is to obtain complete remission, which is characterized by normal peripheral blood with resolution of cytopenias, normal marrow with normal blasts, and normal clinical status. This, however, is not synonymous with a cure, and the leukemia will return without additional therapy. Combination chemotherapy, including daunorubicin and cytarabine, is the treatment of choice for patients with acute leukemia. The cytotoxic drugs are used in doses that kill more than 99.9% of leukemic cells. Chemotherapy is divided into three stages: (1) induction, an intense myelosuppressing regimen of a combination of toxic drugs attempting to achieve remission; (2) consolidation, involving a second course of intensive therapy in an attempt to prevent relapse; and (3) maintenance chemotherapy using a lower dose of drugs, which may be continued periodically from months to years.

The chemotherapy used depends on the type of leukemia. The treatment of ALL in children is one of the dramatic success stories of the use of cancer chemotherapy. Previously, patients with ALL died within months of diagnosis, but now more than 90% of children achieve remission after induction and consolidation chemotherapy, and 50% of these remissions are prolonged enough to be considered cures. The term “remission” is used when the patient is asymptomatic, peripheral blood counts are normal, and fewer than 5% of cells in the marrow are blasts. A combination of drugs has been found to be more effective than a single agent.

The treatment of AML has not been as successful, and most patients die within a few years of diagnosis. A major reason for the high mortality is the toxicity of the combination of drugs used to treat AML. Cytogenetic studies have emerged as great predictors in AML survival. Favorable cytogenetics in AML include t(8;21), t(15;17), and inv(16)(p13;q22) and result in both short-term and long-term disease control.34

In addition to chemotherapy, treatment of acute leukemia includes supportive care during the severe bone marrow aplasia. The use of platelet transfusions has significantly reduced the mortality from hemorrhage. Packed red blood cells are widely used to decrease the signs and symptoms of anemia, and heparin is administered to patients with DIC to prevent thrombosis along with the malignant leukemic cells.

Infection, especially with bacteria and fungi, is the major cause of death in leukemic patients because of their increased susceptibility to infection from the disease process and from the bone marrow aplasia caused by toxic chemotherapy. Infections with gram-negative bacilli such as *Pseudomonas,*
Klebsiella, and Proteus are common, as are fungal infections with Candida, Aspergillus, and Phycomyces. Early diagnosis and prompt treatment of infections of the urinary tract, respiratory tract, rectum, skin, and mouth are necessary. Generalized viral infections, especially with herpes simplex virus (HSV), varicella-zoster virus, and Cytomegalovirus, also are common complications (see Figure 16-6).

The transplantation of hematopoietic stem cells, previously known as “bone marrow transplantation,” has been used to treat acute leukemia and other hematologic malignancies, genetic diseases of the immune and blood systems, and, more recently, solid tumors. The purpose of HSCT in leukemia is to eradicate all malignant cells and replace them with normal progenitor cells from the marrow. Stem cell transplantation in solid tumors, such as in breast cancer, is used to treat patients with extremely high doses of toxic chemotherapy, which would normally be fatal due to bone marrow failure.

Stem cell grafts may be syngeneic (from a genetically identical twin); allogeneic (from a donor who is genetically similar but not identical); or autologous (a portion of the patient’s own marrow is removed prior to chemotherapy, screened, preserved, and reimplanted after therapy).

Stem cell transplantation is preceded by a combination of high-dose chemotherapy and, in some cases, total body radiation. The pluripotent stem cells engraft up to 4 weeks after transplantation, and during this period, the patient is highly susceptible to infection and hemorrhage and therefore must be carefully supported in medical centers that have skilled experienced oncology teams.

After engraftment, complications include acute and chronic graft-versus-host disease (GVHD) caused by T lymphocytes from the graft that destroy normal vital host tissues and organs. Acute GVHD occurs within the first 100 days after transplantation, causing mild to severe skin, liver, intestinal, and immunologic disease. Chronic GVHD begins more than 100 days after transplantation and resembles autoimmune diseases such as lupus and scleroderma. This complication frequently is treated successfully with immunosuppressives. Hematopoietic stem cell transplantation is discussed in further detail in Chapter 19.

**CHRONIC LEUKEMIA**

Chronic leukemias are characterized by the presence of large numbers of well-differentiated cells in the bone marrow, peripheral blood, and tissues and a prolonged clinical course even without therapy. This distinguishes chronic leukemia from acute leukemia, in which immature cells predominate, and the untreated clinical course leads to death in months. The two major types of chronic leukemia are chronic granulocytic leukemia (CGL, or chronic myelocytic leukemia [CML]) and chronic lymphocytic leukemia (CLL), which differ in natural history, clinical presentation, prognosis, and treatment.

**Chronic Myelocytic Leukemia.** CGL was the first type of leukemia identified by physicians in the 1840s, when macroscopic changes in the blood were noted in patients with splenomegaly. More commonly called CML, it is the form of leukemia most closely related to exposure to ionizing radiation and toxic chemicals. The disease is identified by genetic changes seen in the patient’s chromosomes; 90% of CML patients have the Philadelphia chromosome, an acquired genetic defect resulting from translocation of genetic material from chromosome 22 to chromosome 9. This chromosomal abnormality affects the hematopoietic stem cell and thus is present in the myeloid and some lymphoid cell lines. Another change is the deletion of leukocyte alkaline phosphatase. These two biochemical abnormalities are not present in the other forms of leukemia.

CML has two phases: chronic and blastic. During the chronic phase, large numbers of granulocytes are present in the bone marrow and peripheral blood, but the cells retain normal functions. It takes between 5 and 8 years after the formation of the first CML cell for clinical signs and symptoms to develop. The blastic phase, which takes place 2 to 4 years after diagnosis, is characterized by further malignant transformation to immature cells, which act similarly to cells in acute leukemia.

**Clinical Manifestations.** CML occurs most frequently in patients between the ages of 30 and 30 years. No symptoms are noted by the patient during the first few years, and the disease may be discovered during a routine examination when splenomegaly or an elevated WBC count is noted. Early signs and symptoms are usually secondary to anemia or the packing of leukocytes into the spleen and bone marrow. The anemia causes weakness, fatigue, and dyspnea on exertion, while bone pain or abdominal pain in the upper left quadrant results from the spleen and bone marrow changes. As the disease progresses, thrombocytopenia can cause petechiae, ecchymoses, and hemorrhage.

Laboratory tests taken during this stage show a markedly elevated WBC count that may reach several hundred thousand leukocytes per cubic millimeter. The bone marrow is hypercellular. Diagnosis is confirmed by the presence of the Philadelphia chromosome in 90% of cases and the absence of leukocyte alkaline phosphatase. The patient often survives for years before the disease enters the blastic phase. Transformation of the blastic phase may occur suddenly or develop slowly over months. The symptoms caused by splenomegaly worsen, and other organs, particularly the liver, lymph nodes, and skin, become involved. Death occurs within months after the blastic phase begins.

**Treatment.** Control of the chronic phase of CML is often successful. If the disease is discovered while the patient is asymptomatic, only careful monitoring is necessary. When symptoms begin, the most common treatment is the use of busulfan or other alkylating agents. The disease is controlled during the chronic phase with chemotherapy and radiation, but true remissions are rare unless bone marrow transplantation from a histocompatible donor is performed during the chronic phase. The blastic phase of the disease is refractory to treatment. Life may occasionally be prolonged by use of the chemotherapy protocols used in the treatment of acute leukemia.
Chronic Lymphocytic Leukemia. CLL results from a slowly progressing malignancy involving the lymphocytes. More than 90% of cases involve the B lymphocytes, which are responsible for immunoglobulin synthesis and antibody response, rather than T lymphocytes, which account for only 5% of cases. The CLL B lymphocytes do not carry out their normal immunologic function and do not differentiate into normal immunoglobulin-producing plasma cells when exposed to antigen. One reason the disease progresses slowly is that, unlike the cells in other forms of leukemia, the CLL cells do not turn off normal marrow cells until late in the course of the disease. Occasional cases of T-lymphocytic CLL have been reported.

Clinical Manifestations. CLL occurs most frequently in males older than 40 years, with 60 years being the most common age of onset. As a result of the slow natural history, it is not uncommon for the disease to be detected incidentally by routine hematology before any signs or symptoms are apparent. The peripheral blood shows many small well-differentiated lymphocytes; hundreds of thousands, even millions, of cells per cubic millimeter may be present in the peripheral blood. The asymptomatic phase of the disease may last for years, but eventually signs and symptoms of infiltration of leukemic cells in the bone marrow, lymph nodes, or other tissues appear. Bone marrow infiltration causes anemia and thrombocytopenia, resulting in pallor, weakness, dyspnea, and purpura. Infiltration of other tissues causes lymphadenopathy, splenomegaly, hepatomegaly, and leukemic infiltrates of skin or mucosa. Cervical lymphadenopathy and tonsillar enlargement are frequent head and neck signs of CLL.

Patients with CLL exhibit some degree of hypogammaglobulinemia, with an increased susceptibility to bacterial infection. Infection with varicella-zoster virus also is common. Late in the disease, massive lymphadenopathy may cause intestinal or urethral obstruction and obstructive jaundice. Leukemic infiltrates result in skin masses, liver dysfunction, intestinal malabsorption, pulmonary obstruction, or compression of the central or peripheral nervous system. Abnormal immunoglobulins may cause hemolytic anemia or thrombocytopenia.

Treatment. Most oncologists do not treat asymptomatic CLL patients with chemotherapy because there is no convincing evidence that early treatment enhances survival. Indications for treatment include progressive fatigue, troublesome lymphadenopathy, or the development of anemia or thrombocytopenia. The standard treatment for CLL used to be chlorambucil; however, fludarabine has been shown to produce a higher response rate.

Hairy cell leukemia is a distinct variant of CLL characterized by leukemic B lymphocytes with cytoplasmic projections and a striking 5:1 male predominance. Common signs and symptoms include splenomegaly, vasculitis, and erythema nodosum. The treatment of choice is cladribine. This nontoxic drug produces benefit in 95% of cases and complete remission in more than 80%. Interferon and splenectomy are rarely used.

ORAL AND DENTAL CONSIDERATIONS

Dentists in clinical practice and research have become increasingly interested in leukemia because the oral complications are common throughout the clinical course of the disease, dental management is complex, and the mouth is a potential source of morbidity and mortality.

Because oral signs and symptoms are common, the dentist may be the first clinician to suspect the disease. Head and neck signs result from leukemic infiltrates or marrow failure. These include cervical lymphadenopathy, oral bleeding, gingival infiltrates, oral infections, and oral ulcers.

Thrombocytopenia and anemia caused by marrow suppression from disease and chemotherapy result in pallor of the mucosa, petechiae, and ecchymoses, as well as gingival bleeding (Figures 16-8 and 16-9). The extent of gingival bleeding depends on the severity of the thrombocytopenia and the extent of local irritants. Spontaneous gingival bleeding is common when the platelet count falls below 20,000/mm³; severe gingival bleeding may often be managed successfully with local treatment, reducing the need for platelet transfusions. The dentist should always weigh the risk of platelet transfusions against their benefit before recommending their use for treatment of oral bleeding. The risks of platelet transfusion include hepatitis, HIV infection, transfusion reactions, and the formation of antiplatelet antibodies, which reduce the usefulness of platelet transfusions during future hemorrhagic episodes. Oral hemorrhage also may result from DIC, causing hypofibrinogenemia.

Topical treatment to stop gingival bleeding should always include removal of obvious local irritants, and direct pressure. Helpful is the use of absorbable gelatin or collagen sponges, topical thrombin, or the placement of microfibrillar collagen held in place by packing or splints. Some have reported successful management of gingival bleeding with oral rinses of antifibrinolytic agents such as tranexamic acid or...
e-aminocaproic acid. If these local measures are not successful in stopping significant gingival hemorrhage, platelet transfusions are necessary.

Oral Ulcers. Oral mucosal ulcers are common findings in leukemic patients taking chemotherapy and are frequently caused by the direct effect of chemotherapeutic drugs on the oral mucosal cells. Lockhart and Sonis have reported that ulcers secondary to chemotherapy begin approximately 7 days following the start of treatment. Bacterial invasion secondary to severe neutropenia also plays a role in the formation of oral ulcers, and these lesions may be seen as an early sign of disease (see Figure 16-4). The ulcers are characteristically large, irregular, and foul smelling, and are surrounded by pale mucosa caused by anemia and a lack of normal inflammatory response.

The most common cause of oral ulcers in leukemic patients receiving chemotherapy is recurrent HSV infections. These infections involve the intraoral mucosa and the lips. The lesions frequently begin with the classic cluster of vesicles typical of recurrent HSV and quickly spread, causing large ulcers that often have a raised white border (Figure 16-10). However, they can often appear atypical. In all patients receiving immunosuppressive doses of chemotherapy, HSV should be ruled out as a cause of oral ulcers with a cytology smear stained with fluorescent antibody to HSV antibody (direct fluorescent antibody) and a viral culture. The lesions respond well to parenteral acyclovir administered intravenously or by mouth, although acyclovir-resistant HSV strains have been reported.

The management of non-HSV oral ulcers in leukemic patients should prevent the spread of localized infection, minimize bacteremia, promote healing, and reduce pain. The ulcers in hospitalized leukemic patients taking chemotherapy may be infected with organisms not commonly associated with oral infection, particularly gram-negative enteric bacilli. Topical antibacterial treatment can be attempted with povidone-iodine solutions, bacitracin-neomycin ointments, or chlorhexidine rinses. Kaolin and pectin plus diphenhydramine oral rinses can be used to reduce pain. Other oral preparations containing sucralfate suspensions have been advocated for their ability to bind to and protect ulcers.

Oral Infections. Oral infection is a serious potentially fatal complication in neutropenic leukemic patients. Candidiasis is a common oral fungal infection, but infections with other fungi, such as Histoplasma, Aspergillus, or Phycomycetes, fungi, also may begin on the oral tissues. When these lesions are suspected, a biopsy specimen, a fine-needle aspiration, or a cytology smear must be obtained because a culture alone is not a reliable test for these organisms.

Diagnosis of dental infection, particularly periodontal and pericoronal infections, is difficult in neutropenic leukemic patients because normal inflammation is absent. The early diagnosis of oral infection is imperative because it has been demonstrated that oral flora is a significant source of potentially life-threatening infections with gram-positive and gram-negative bacilli. It is a dentist’s obligation to carry out screening examinations and eliminate obvious sources of potential
acute infection or bacteremia before chemotherapy is instituted, although platelet transfusions and intravenous combinations of antibiotics may be required before dental treatment. With the newer broad-spectrum antibiotics now employed by hematology-oncology teams, the rate of infection and septicemia from odontogenic sources is unknown, but it may be less than previously reported.

Oral signs also may result from the presence of leukemic infiltrates. These are most frequently reported as gingival infiltrates in patients with myelomonocytic and monoblastic leukemia (M4,5) or acute promyelocytic leukemia (M3) (Figures 16-11, 16-12, and 16-13). Leukemic infiltrates involving the palate, alveolar bone, and dental pulp also have been reported. Leukemic infiltrates may cause oral signs and symptoms because of the involvement of the fifth and seventh cranial nerves. Disorders of the fifth and seventh cranial nerves also have been reported in leukemic patients as a result of the use of vincristine, a drug commonly used to treat ALL.

Children with ALL receive radiation to the cranium and chemotherapy to prevent a relapse of the disease in the brain. Craniofacial deformities and dental anomalies are common in patients who receive this therapy as children, particularly if given before age 5 years. The most common anomalies reported are deficient mandibular development, dental agenesis, arrested root development, microdontia, and enamel dysplasia.

Oral lesions are common complications of HSC transplant patients. Lesions occur in approximately 80% of patients with GVHD. Lichenoid lesions, including desquamative gingivitis, keratotic lesions, atrophy, and ulceration, may be present (Figure 16-14). The lesions appear clinically and histologically similar to lichen planus or discoid lupus. Patients with GVHD also develop xerostomia. Biopsy results of minor salivary glands of GVHD patients show changes compatible with those in Sjögren’s syndrome.

▼LYMPHOMA

The lymphomas are a group of malignant solid tumors involving cells of the lymphoreticular or immune system, such as B lymphocytes, T lymphocytes, and monocytes. The etiology is unknown, but identified risk factors include immunodeficiency states, viral infections, and chemical exposure. The initial tumor formation in lymphoma is in the secondary lymphatic tissues, where normal tissue is replaced by malignant lymphocytes. Lymphomas are divided into two major categories: Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL). These diseases usually begin in the lymph nodes but may be first diagnosed in extranodal lymphoid tissue.

Hodgkin’s Disease

Hodgkin’s Disease (HD), a malignant lymphatic disease, was first described by British pathologist Thomas Hodgkin in 1832. The etiology remains unknown, but it is probably the culmination of diverse pathologic processes such as viral infections, environmental exposures, and a genetically determined host response.

HD used to be a uniformly fatal disease, but modern modes of diagnosis and treatment have given a newly diagnosed patient a more than 70% chance of cure. One reason for this advance is improved methods of classifying and staging
the disease; this improves the opportunity for the patient to be managed properly. Accurate classification of the disease clinically and histologically is essential because treatment is determined by stage. Staging must include lymph node biopsy, chest radiography, computed tomography scan of the abdomen and pelvis, bone marrow biopsy, and laboratory evaluation of liver, kidney, and bone. In selected cases, lymphography, exploratory laparotomy, radionuclide scans, and magnetic resonance imaging are indicated.

HD is classified histologically according to the Rye system, which lists four major subgroups: lymphocyte predominance type, nodular sclerosis type, mixed cellularity type, and lymphocyte depletion type. The lymphocyte predominance type has the best prognosis, and the lymphocyte depleted type has the worst. The disease also is staged clinically according to the criteria established at the Ann Arbor conference of 1971 and modified by Cotswolds (Table 16-4). Stage I has the best prognosis, and stage IV has the worst. The presence or absence of significant systemic symptoms is indicated by the suffixes “A” (symptoms absent) or “B” (symptoms present). The suffix “E” indicates extralymphatic disease, and “X” indicates the presence of bulky disease.

### TABLE 16-4 Staging of Hodgkin’s Disease: Ann Arbor Staging Classification with Cotswolds Modification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Extent of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of one lymph node region or single extranodal site</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of multiple lymph node regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>Stage III (1 and 2)</td>
<td>Involvement of lymph nodes on both sides of the diaphragm</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Generalized involvement</td>
</tr>
</tbody>
</table>

Subclassifications include the following: A = no symptoms; B = fever, night sweats, >10% weight loss in prior 6 mo; X = bulky disease; E = involvement of single extranodal site; CS = clinical stage; PS = pathologic stage (determined by laparotomy).

Males have an increased incidence of HD (male-to-female ratio is 3:2), and the disease has two peaks of highest incidence. The first peak occurs during the second and third decades of life, and the second occurs after the fifth decade. Differences in clinical presentation in the two age groups have led some to speculate that these peaks may represent distinct disease entities.

### CLINICAL MANIFESTATIONS

The most common presentation of HD is a painless enlargement of the lymph nodes in a patient without other symptoms of disease. The cervical lymph nodes are the initial sites of detection in more than 50% of cases. Early involvement of the axillary, inguinal, and mediastinal nodes also is common. Other patients may seek medical attention because of constitutional symptoms, such as fever, weight loss, pruritus, or night sweats. On examination, the involved peripheral nodes are nontender and feel rubbery. The presentation of asymptomatic enlarged lymph nodes is most common in younger patients with HD and is consistent with a histologic classification of lymphocyte predominance or nodular sclerosis. In older patients with increased risk of developing lymphocyte depleted or mixed cellularity histologic pattern, systemic symptoms, such as malaise, fever, and night sweats, may precede noticeable lymphadenopathy.

As the disease progresses, signs and symptoms arise from pressure and obstruction caused by enlarging nodes. Enlarged mediastinal nodes cause dysphagia, whereas retroperitoneal nodes can cause ureteral obstruction. Further progression of the disease leads to invasion of the bone marrow, lungs, liver, bones, and spinal cord.

Characteristic clinical features of HD include the Pel-Ebstein fever, a cyclic spiking of high fever, and generalized severe pruritus of unknown etiology. Pruritus is a symptom seen most frequently in young women with HD. Many investigators of HD have demonstrated a defective functioning of T lymphocytes that results in a faulty delayed-type hypersensitivity reaction. Early in the course of HD, this immunodeficiency can be demonstrated by a decreased reaction to skin tests and prolonged survival of grafts from noncompatible donors. When the disease is generalized, the immunodeficiency leads to increased susceptibility to viral and fungal infections. Diagnosis of HD is always finalized by an adequate biopsy of enlarged lymphoid tissue. A needle biopsy does not provide sufficient tissue for this purpose. Demonstration of the characteristic Reed-Sternberg cells is diagnostic, but the nature of this cell’s involvement is still controversial.

### TREATMENT

The management of HD consists of radiotherapy, chemotherapy, or a combination of both, depending on the stage of the disease at time of diagnosis. Radiation therapy is used as initial treatment only for patients with low-risk stage IA and IIA disease. Currently, combination chemotherapy of doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) is used for most HD patients. The combination of radiotherapy and chemotherapy is used for advanced disease, but it increases the...
chance of complications such as bone marrow aplasia and acute leukemia.\textsuperscript{43} Five-year survival of patients with localized (IA or IIA) disease exceeds 80%, and the mean 5-year survival exceeds 50% for all stages of the disease.

Radiation commonly consists of 3,500 to 4,500 cGy delivered to the involved lymph node chain and contiguous areas. Three distinct radiation fields have been developed to treat HD: the mantle, para-aortic, and pelvic fields. The mantle field includes the submandibular region, neck, axillae, and mediastinum.

**Non-Hodgkin's Lymphoma**

The group of malignant disorders known as non-Hodgkin's lymphoma (NHL) arises from B or T lymphocytes. There are several classification systems in use for NHL. The disorders are variable in clinical presentation and course. The classification of the lymphomas is a controversial area undergoing evolution. The National Cancer Institute uses monoclonal antibody immunophenotyping to characterize NHL according to biologic behavior. Low-grade NHL has a favorable prognosis, may respond to radiotherapy alone, and is localized in 10 to 25% of cases. Intermediate- and high-grade NHLs are treated with intensive chemotherapy regimens.

**CLINICAL MANIFESTATIONS**

The most common presentation of NHL is a painless persistent enlargement of the lymph nodes, but extranodal lesions occur more commonly than in HD, especially in the intermediate- and high-grade forms of the disease. NHL lesions may be detected in Waldeyer’s ring, the gastrointestinal tract, the spleen, the skin, and bone marrow. NHL is more common in patients older than age 40 years but can occur at any age. In children, NHL may enter a leukemic phase, with malignant lymphocytes pouring into the peripheral blood. Signs and symptoms depend on the site of involvement and result from the pressure of enlarged lymph nodes or infiltration. Renal obstruction, neurologic impairment, liver or skin infiltration, and bone marrow involvement commonly occur during the course of the disease.

**TREATMENT**

Indolent lymphomas are usually not curable and are treated with palliative therapy. Within 1 to 3 years, the disease usually progresses and requires therapy. Radiation and chemotherapy are the most successful modes of treatment. Localized NHL is highly radiosensitive, so it is treated with 3,000 to 4,000 cGy to the involved area. Intensive combinations of chemotherapeutic drugs are the treatment of choice for intermediate- and high-grade NHL. The specific regimen used depends on the result of clinical staging and classification according to the Working Formulation of the National Cancer Institute. Cancer centers use several combinations of agents. Commonly used drug protocols include cyclophosphamide, vincristine, and prednisone (CVP); or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). A monoclonal antibody directed against the B-cell surface antigen CD20 has been shown to be effective for relapsed indolent lymphomas.\textsuperscript{44} High-dose chemotherapy with autologous stem cell transplantation is the treatment of choice for patients with relapsed disease.

**Burkitt's Lymphoma**

During the 1950s, Denis Burkitt described rapidly growing jaw and abdominal lymphoid tumors in East African children. This neoplasm had a strict geographic distribution and occurred in zones where malaria was endemic. The tumor, named Burkitt’s lymphoma (BL), is the human cancer most closely linked with a virus. Epstein-Barr virus is associated with 90% of African patients with BL, but this percentage is considerably lower for BL seen in other parts of the world. The reason for the association between BL and Epstein-Barr virus remains unknown. The virus may be a prime etiologic agent, a cocarcinogen, or just an innocent passenger. Since its original description by Burkitt, BL has been found in many countries outside Africa, including the United States. The primary tumor cell has been shown to be a poorly differentiated B lymphocyte.

**CLINICAL MANIFESTATIONS**

The African form of BL most frequently manifests itself as rapid-growing extranodal jaw tumors in young children, but it also may be first detected as an abdominal mass involving the kidneys or ovaries. Cases reported in the United States appear to follow a pattern that differs from the African disease. A majority of US cases involve abdominal lesions arising from Peyer’s patches or mesenteric lymph nodes. The tumor expands rapidly and may double in size every 1 to 3 days, making it the fastest growing human cancer. This rapid growth nullifies the usefulness of the Ann Arbor classification used for other NHLs. BL patients are divided into two categories: small tumor burden and large tumor burden.

**TREATMENT**

BL lesions have a dramatic response to chemotherapy, particularly cyclophosphamide. The tumor also has been shown to be sensitive to methotrexate, vincristine, and cytarabine. Combinations of drugs have achieved remissions in more than 90% of patients. Half of the patients relapse but may respond to bone marrow transplantation. Surgical debulking of large localized jaw or abdominal tumors is beneficial prior to chemotherapy.

**Oral and Dental Considerations**

Asymptomatic enlargement of the cervical lymph node chains is a common early sign of lymphoma, and the dentist should play a significant role in early detection by routine examination of the neck. Suspicion of lymphoma should increase when lymphadenopathy appears without signs of infection, more than one lymph node chain is involved, or a lymph node of 1 cm or greater in diameter persists for more than 1 month. It is uncommon for primary lesions of HD to begin in an extranodal site, so primary jaw lesions are uncommon but have been reported. More commonly, dental complications result from radiotherapy or chemotherapy administered to children with HD during tooth development. These abnormalities...
include agenesis, hypoplasia, and blunted or thin roots. Extranodal primary NHL is reported more frequently. One common site for extranodal NHL is the lymphoid tissue of Waldeyer’s ring; therefore, nontender enlargements of tonsillar tissue in adults should be referred for evaluation. NHL is more frequent in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS) and those receiving immunosuppressive drug therapy. NHL of the jaws and mouth, particularly the palate, has been reported by several authors. These palatal lesions have been described as slow-growing, painless, bluish, soft masses, and they have been confused with minor salivary gland tumors. Oral NHL also mimics inflammatory diseases and may present as a gingival mass, tongue mass, or intraosseous lesion. Isolated loose teeth, paresthesia of the face, and major salivary gland enlargement also may be presenting signs of NHL.

When lymphoma is included in the differential diagnosis of an oral lesion, a biopsy specimen which has not been traumatized should be taken from the center of the lesion and sent to an experienced pathologist. The pathologist should be informed of the possibility of lymphoma because NHL is easily confused with benign lymphoproliferative disorders. Special staining with Giemsa and periodic acid–Schiff and typing with immunohistochemistry are helpful in making the diagnosis of NHL. The use of these special studies has clarified the diagnosis of lesions that previously could not be properly classified. For example, midline lethal granuloma has recently been shown to be a form of NHL.

Oral lesions also have been described in patients with cutaneous T-cell lymphoma (mycosis fungoides). These lesions are often described as either indurated plaques with a red or white surface or ulcerated tumors. The most common site of involvement is the tongue and usually follow skin lesions.

**MULTIPLE MYELOMA**

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that is characterized by the production of pathologic M proteins, bone lesions, kidney disease, hyperviscosity, and hypercalcemia. Human leukocyte antigen studies suggest a genetic predisposition to the disease, which occurs equally in both sexes, most often in patients older than 50 years of age. Skeletal pain is the most common presenting symptom and is caused by bone lysis that may result either directly from accumulation of tumor cells or indirectly from osteoclast-activating factors secreted by the malignant myeloma cells. Approximately 80% of patients with MM have bone lesions, and pathologic fractures are a frequent complication. Often the disease is detected during radiologic examination for other purposes. The most common radiographic abnormality is the presence of “punched-out” radiolucent lesions (plasmacytomas), but generalized osteoporosis may occur in the absence of these discrete punched-out lesions (Figure 16-15).

Proliferation of abnormal plasma cells causes most of the manifestations of the disease. These plasma cells produce abnormal M proteins that are useful in the diagnosis of the disease due to their characteristic electrophoretic pattern but useless in functioning as normal antibodies. Hypogammaglobulinemia results in increased susceptibility to bacterial infections, particularly of the lungs and urinary tract.

Renal failure also is a common complication resulting from a combination of amyloidosis, hypercalcemia, and infiltration of malignant cells. Amyloid also may deposit in the heart, liver, nervous system, or other organs, interfering with normal function. Deposition of this amorphous protein under the skin or mucosa also is common. Clotting defects result from the abnormal myeloma (M) proteins coating platelets or interfering with the normal coagulation cascade.

Diagnosis is based on serum M proteins demonstrated with serum protein electrophoresis or immunoelectrophoresis, or on Bence Jones proteins, which are monoclonal immunoglobulin light chains detected in 24-hour urine specimens. Bone marrow biopsy results reveal atypical plasma cells.

**Treatment**

The alkylating agents, such as melphalan or cyclophosphamide, are the treatment of choice for patients with extensive bone lesions or rising levels of M proteins. Local symptomatic lesions are treated with radiotherapy. Average survival with treatment is 2 to 3 years, but with the introduction of newer chemotherapeutic agents, the time of survival is increasing; some patients have remissions of 6 years or more. A common cause of death is the myeloma kidney, caused by the accumulation of abnormal proteins in the renal tissue.\(^\text{45}\)

**Oral Manifestations**

Approximately 5 to 30% of myeloma patients have jaw lesions, and accidental discovery of lesions in the jaws may be the first evidence of this disease. The patient may experience pain, swelling, numbness of the jaws, epulis formation, or unexplained mobility of the teeth. Skull lesions are more common than jaw lesions. Multiple radiolucent lesions of varying size, with ill-defined margins and a lack of circumferential osteosclerotic activity, should suggest this diagnosis (see Figure 16-15).

The mandible is more frequently involved in MM because of its greater content of marrow. Lesions are most common in the region of the angle of the jaw, where red marrow generally is present. In most instances, the lesions appear unassociated with the apices of the teeth. Extrasosseous lesions also occur in a significant number of patients (Figure 16-16) although a majority of the lesions are asymptomatic.

Several authors have called attention to the development of oral amyloidosis as a complication of this disease. Tongue biopsy is an excellent method of diagnosis. Clinically, the tongue may be enlarged and studded with small garnet-colored enlargements, including nodes on the cheeks and lips. Amyloidosis occurs in 6 to 15% of patients with MM and may be detected in tissue specimens with use of a Congo red stain or electron microscopy. When a dentist is requested to take a biopsy specimen to detect amyloidosis, the specimen must include muscle tissue from the mucobuccal fold or tongue.
of renal failure or complications of hyperviscosity, such as heart or pulmonary failure.

▼REFERENCES


Dental Management

Hemorrhage and infection are the dentist’s major concerns when treating a patient with MM. Bleeding may result from several causes, including thrombocytopenia, abnormal platelet function, abnormal coagulation, or hyperviscosity. If surgery is necessary, recent results of platelet count, bleeding time, prothrombin time, and partial thromboplastin time should be obtained. If hyperviscosity is present, excess bleeding may occur even if these tests are normal, and a hematology consultation should be considered.

The dentist also should determine whether the patient has an increased susceptibility to bacterial infection due to hyper-gammaglobulinemia, bone marrow failure, or complications of cancer chemotherapy. A consultation with the managing oncologist is indicated to determine whether there is evidence of renal failure or complications of hyperviscosity, such as heart or pulmonary failure.

FIGURE 16-15 Radiograph of the skull discloses widely distributed lesions in multiple myeloma. (Reproduced with permission from Calman HI. Oral Surg. 5:1308.)

FIGURE 16-16 Intraoral radiographic series showing multiple involvement of the maxilla and the mandible in multiple myeloma. (Reproduced with permission from Calman HI. Oral Surg;5:1034.)