e11 Atlas of Hematology and Analysis of Peripheral Blood Smears

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Some of the relevant findings in peripheral blood, enlarged lymph nodes, and bone marrow are illustrated here. Systematic histologic examination of the bone marrow and lymph node are beyond the scope of a general medicine textbook. However, every internist should know how to examine a peripheral blood smear.

The examination of the peripheral blood smear is one of the most informative exercises a physician can perform. While advances in automated technology have made the examination of the peripheral blood smear by the physician seem less important, the technology is not a completely satisfactory replacement for blood smear interpretation by a trained medical professional who also knows the patient's clinical history, family history, social history, and physical findings. It is useful to ask the laboratory to generate a Wright's-stained peripheral blood smear and to examine it.

The best place to examine blood cell morphology is the feathered edge of the blood smear where red cells lie in a single layer, side by side, just barely touching each other but not overlapping. My own approach is to look at the smallest cellular elements first, the platelets, and work my way up in size to red cells and then white cells.

Using an oil immersion lens that magnifies the cells 100-fold, one first counts the platelets in five to six fields, averages the number per field, and multiplies by 20,000 to get a rough estimate of the platelet count. The platelets are usually 1–2 μm in diameter and have a blue granulated appearance. There is usually 1 platelet for every 20 or so red cells. Of course, the automated counter is much more accurate, but gross disparities between the automated and manual counts should be assessed. Large platelets may be a sign of rapid platelet turnover, as young platelets are often larger than old platelets; alternatively, certain rare inherited syndromes can produce large platelets. Platelet clumping visible on the smear can be associated with falsely low automated platelet counts. Similarly, neutrophil fragmentation can be a source of falsely elevated automated platelet counts.

Next one examines the red blood cells. One can gauge their size by comparing the red cell to the nucleus of a small lymphocyte. Both are normally about 8 μm wide. Red cells that are smaller than the small lymphocyte nucleus may be microcytic; those larger than the small lymphocyte nucleus may be macrocytic. The automated mean corpuscular volume (MCV) can assist in making a classification. However, some patients may have both iron and vitamin B_{12} deficiency, which will produce an MCV in the normal range but wide variation in red cell size. When the red cells vary greatly in size, *anisocytosis* is said to be present. When the red cells vary greatly in shape, *poikilocytosis* is said to be present.

After red cell size is assessed, one examines the hemoglobin content of the cells. They are either normal in color (*normochromic*) or they are pale in color (*hypochromic*). They are never "hyperchromic." If more than the normal amount of hemoglobin is made, the cells get larger—they do not become darker. In addition to hemoglobin content, the red cells are examined for inclusions. Red cell inclusions are the following:

1. *Basophilic stippling*—diffuse fine or coarse blue dots in the red cell representing usually RNA residue—especially common in lead poisoning
2. *Howell-Jolly bodies*—dense blue circular inclusions that represent nuclear remnants—their presence implies defective splenic function
3. *Nuclei*—red cells may be released or pushed out of the marrow prematurely before nuclear extrusion—often implies a myelophthisic process
4. *Parasites*—red cell parasites include malaria and babesia (**Chap. e18**)
5. *Polychromatophilia*—the red cell cytoplasm has a bluish hue, reflecting the persistence of ribosomes still actively making hemoglobin in a young red cell

Vital stains are necessary to see precipitated hemoglobin called *Heinz bodies*.

Red cells can take on a variety of different shapes. All abnormally shaped red cells are *poikilocytes*. Small red cells without the central pallor are *spherocytes*; they can be seen in hereditary spherocytosis, hemolytic anemias of other causes, and clostridial sepsis. *Dacrocytes* are teardrop-shaped cells that can be seen in hemolytic anemias, severe iron deficiency, thalassemias, myelofibrosis, and myelodysplastic syndromes. *Schistocytes* are helmet-shaped cells that reflect microangiopathic hemolytic anemia or fragmentation on an artificial heart valve. *Echinocytes* are spiculated red cells with the spikes evenly spaced; they can represent an artifact of abnormal drying of the blood smear or reflect changes in stored blood. They can also be seen in renal failure and malnutrition and are often reversible. *Acanthocytes* are spiculated red cells with the spikes irregularly distributed. This process tends to be irreversible and reflects underlying renal disease, abetalipoproteinemia, or splenectomy. *Elliptocytes* are elliptical-shaped red cells that can reflect an inherited defect in the red cell membrane, but they are also seen in iron deficiency, myelodysplastic syndrome, megaloblastic anemia, and thalassemias. *Stomatocytes* are red cells in which the area of central pallor takes on the morphology of a slit instead of the usual round shape. Stomatocytes can indicate an inherited red cell membrane defect and can also be seen in alcoholism. *Target cells* have an area of central pallor that contains a dense center, or bull's eye. These cells are seen classically in thalassemia, but they are also present in iron deficiency, cholestatic liver disease, and some hemoglobinopathies. They can also be generated artifactually by improper slide making.

One last feature of the red cells to assess before moving to the white blood cells is the distribution of the red cells on the smear. In most individuals, the cells lie side by side in a single layer. Some patients have red cell clumping (called *agglutination*) in which the red cells pile upon one another; it is seen in certain paraproteinemias and autoimmune hemolytic anemias. Another abnormal distribution involves red cells lying in single cell rows on top of one another like stacks of coins. This is called *rouleaux formation* and reflects abnormal serum protein levels.

Finally, one examines the white blood cells. Three types of granulocytes are usually present; neutrophils, eosinophils, and basophils, in decreasing frequency. Neutrophils are generally the most abundant white cell. They are round, 10–14 μm wide, and contain a lobulated nucleus with two to five lobes connected by a thin chromatin thread. Bands are immature neutrophils that have not yet completed nuclear condensation and have a U-shaped nucleus. Bands reflect a left shift in neutrophil maturation in an effort to make more cells more rapidly. Neutrophils can provide clues to a variety of conditions. Vacuolated neutrophils may be a sign of bacterial sepsis. The presence of 1- to 2-μm blue cytoplasmic inclusions, called *Dohle bodies*, can reflect infections, burns, or other inflammatory states. If the neutrophil granules are larger than normal and stain a darker blue, "toxic granulations" are said to be present, and they also suggest a systemic inflammation. The presence of neutrophils with more than five nuclear lobes suggests megaloblastic anemia. Large misshapen granules may reflect the inherited Chédiak-Higashi syndrome.

Eosinophils are slightly larger than neutrophils, have bilobed nuclei, and contain large red granules. Diseases of eosinophils are associated with too many of them rather than any morphologic or qualitative change. They normally total less than one-thirtieth the number of neutrophils. Basophils are even more rare than eosinophils in the blood. They have large dark-blue granules and may be increased as part of chronic myeloid leukemia,

Lymphocytes can be present in several morphologic forms. Most common in healthy individuals are the small lymphocytes with a small dark nucleus and scarce cytoplasm. In the presence of viral infections, more of the lymphocytes are larger, about the size of neutrophils, with abundant cytoplasm and a less condensed nuclear chromatin. These

are called *reactive lymphocytes*. About 1% of the lymphocytes are larger and contain blue granules in a light blue cytoplasm; these are called *large granular lymphocytes*. In chronic lymphoid leukemia, the small lymphocytes are increased in number, and many of them are ruptured in making the blood smear, leaving a smudge of nuclear material without a surrounding cytoplasm or cell membrane; these are called *smudge cells* and are rare in the absence of chronic lymphoid leukemia.

Monocytes are the largest white blood cells, ranging from 15–22 μm in diameter. The nucleus can take on a variety of shapes but usually appears to be folded; the cytoplasm is gray.

Abnormal cells may appear in the blood. Most often the abnormal cells originate from neoplasms of bone marrow–derived cells including lymphoid cells, myeloid cells, and occasionally red cells. More rarely, other types of tumors can get access to the blood stream, and rare epithelial malignant cells may be identified. The chances of seeing such abnormal cells is increased by examining blood smears made from buffy coats, the layer of cells that is visible on top of sedimenting red cells when blood is left in the test tube for an hour. Smears made from finger sticks may include rare endothelial cells.

ACKNOWLEDGMENT

Figures in this e-chapter were borrowed from Williams Hematology, *7th edition, M Lichtman et al (eds). New York, McGraw-Hill, 2005;* Hematology in General Practice, *4th edition, RS Hillman, KA Ault, New York, McGraw-Hill, 2005.*

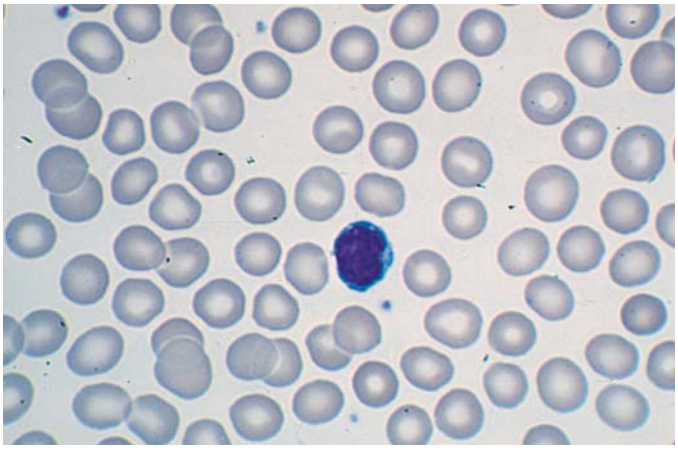

FIGURE e11-1 Normal peripheral blood smear. Small lymphocyte in center of field. Note that the diameter of the red blood cell is similar to the diameter of the small lymphocyte nucleus.

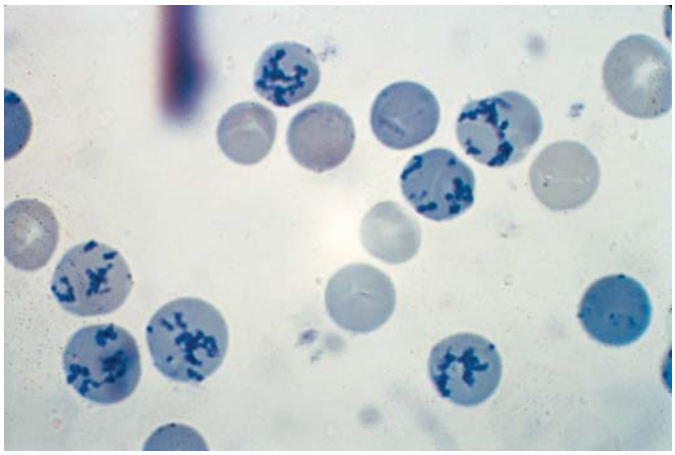

FIGURE e11-2 Reticulocyte count preparation. This new methylene blue–stained blood smear shows large numbers of heavily stained reticulocytes (the cells containing the dark blue–staining RNA precipitates).

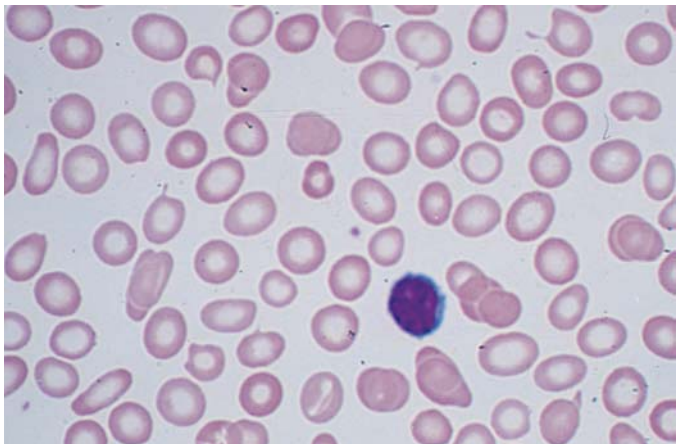

FIGURE e11-3 Hypochromic microcytic anemia of iron deficiency. Small lymphocyte in field helps assess the red blood cell size.

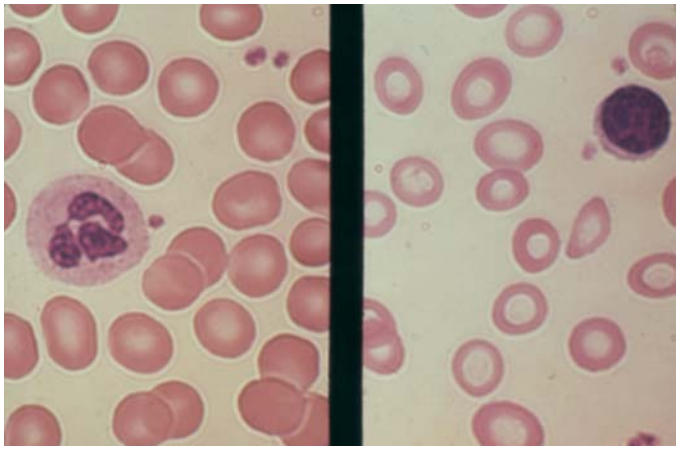

FIGURE e11-4 Iron deficiency anemia next to normal red blood cells. Microcytes (*right panel*) are smaller than normal red blood cells (cell diameter < 7 μm) and may or may not be poorly hemoglobinized (hypochromic).

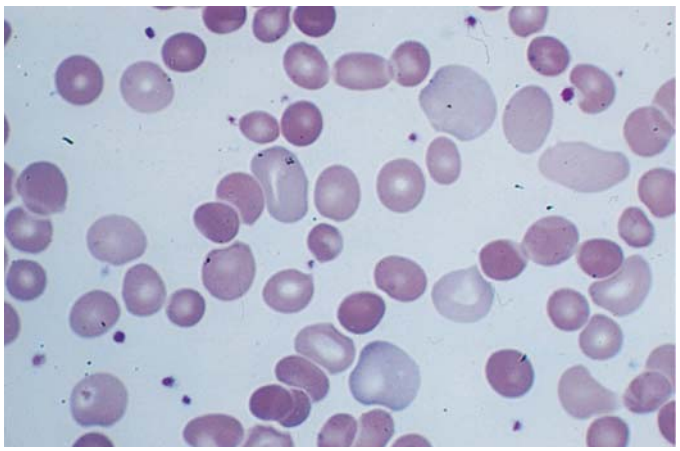

FIGURE e11-5 Polychromatophilia. Note large red cells with light purple coloring.

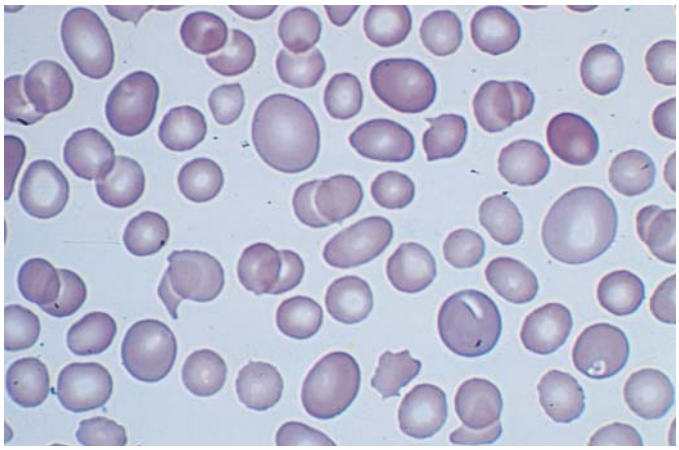

FIGURE e11-6 Macrocytosis. These cells are both larger than normal (mean corpuscular volume > 100) and are somewhat oval in shape. Some morphologists call these cells "macroovalocytes."

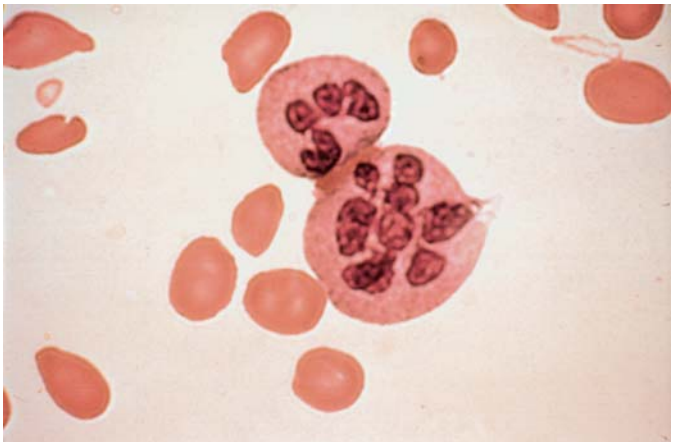

FIGURE e11-7 Hypersegmented neutrophils. Hypersegmented neutrophils (multilobed polymorphonuclear leukocytes) are larger than normal neutrophils with five or more segmented nuclear lobes. They are commonly seen with folic acid or vitamin B_{12} deficiency.

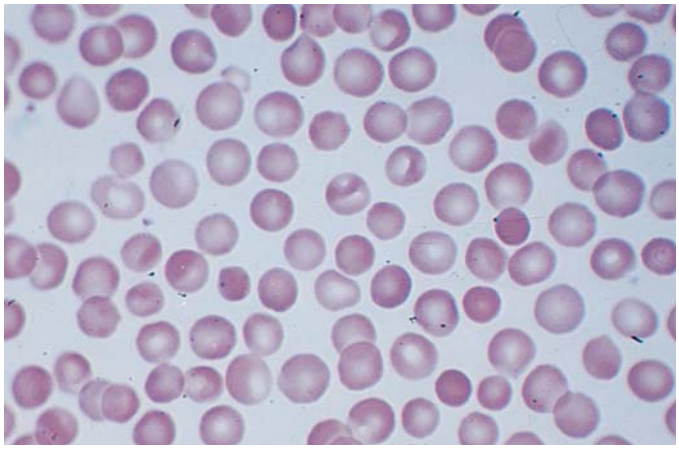

FIGURE e11-8 Spherocytosis. Note small hyperchromatic cells without the usual clear area in the center.

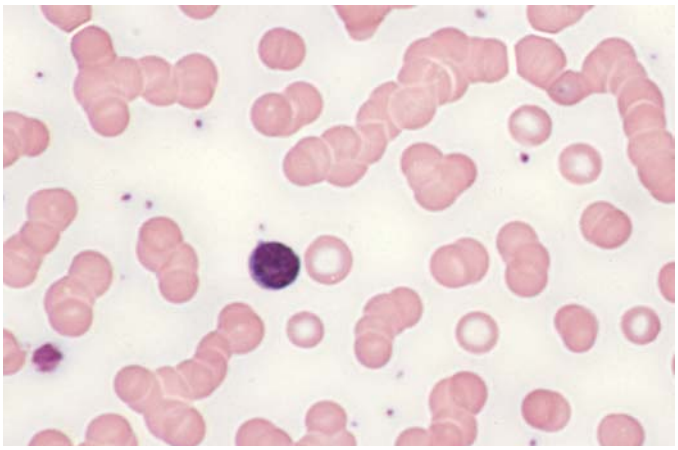

FIGURE e11-9 Rouleaux formation. Small lymphocyte in center of field. These red cells align themselves in stacks and are related to increased serum protein levels.

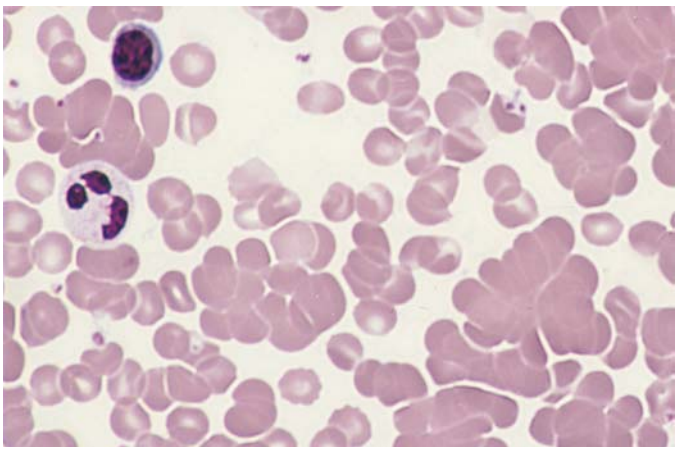

FIGURE e11-10 Red cell agglutination. Small lymphocyte and segmented neutrophil upper left center. Note irregular collections of aggregated red cells.

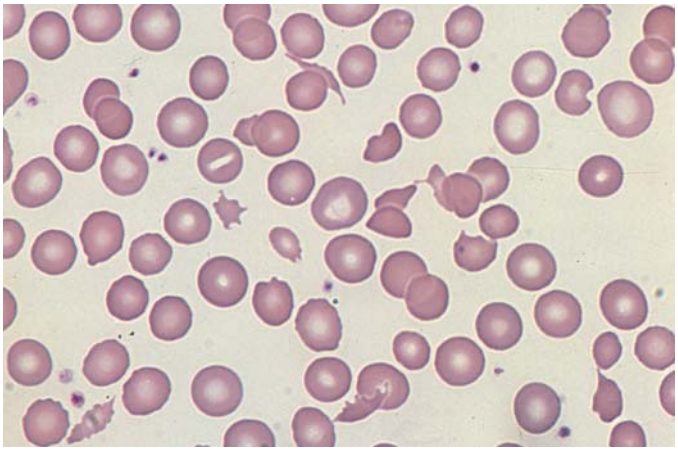

FIGURE e11-11 Fragmented red cells. Heart valve hemolysis.

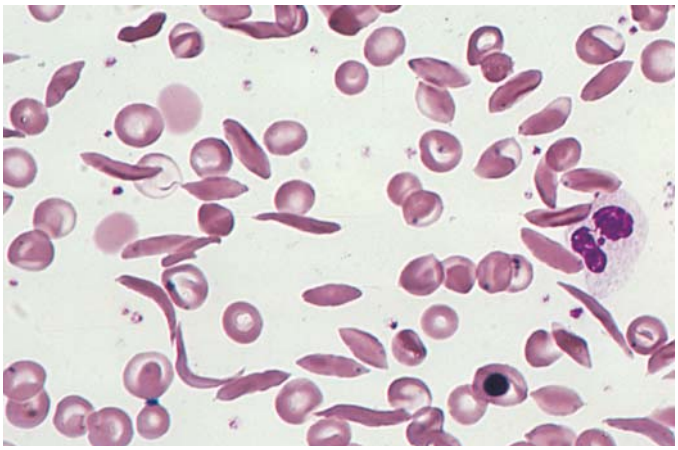

FIGURE e11-12 Sickle cells. Homozygous sickle cell disease. A nucleated red cell and neutrophil are also in the field.

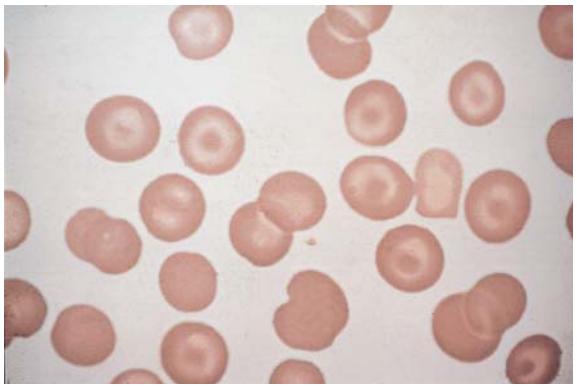

FIGURE e11-13 Target cells. Target cells are recognized by the bull's-eye appearance of the cell. Small numbers of target cells are seen with liver disease and thalassemia. Larger numbers are typical of hemoglobin C disease.

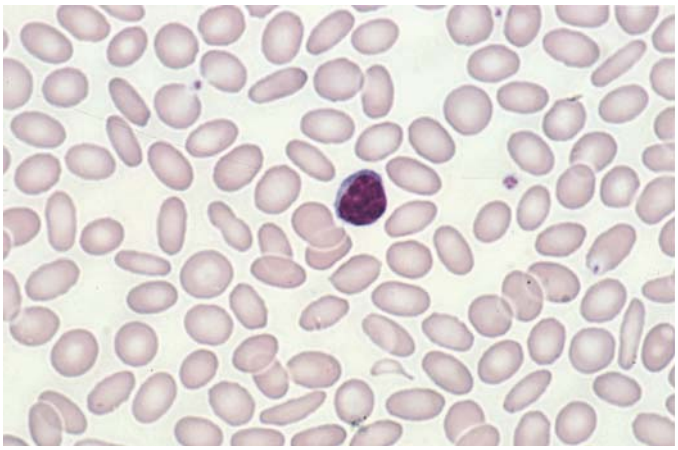

FIGURE e11-14 Elliptocytosis. Small lymphocyte in center of field. Elliptical shape of red cells related to weakened membrane structure, usually due to mutations in spectrin.

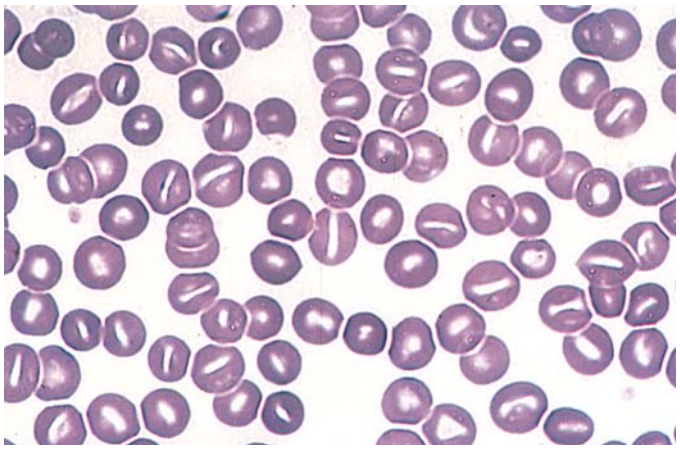

FIGURE e11-15 Stomatocytosis. Red cells characterized by a wide transverse slit or stoma. This is often seen as an artifact in a dehydrated blood smear. These cells can be seen in hemolytic anemias and in conditions in which the red cell is overhydrated or dehydrated.

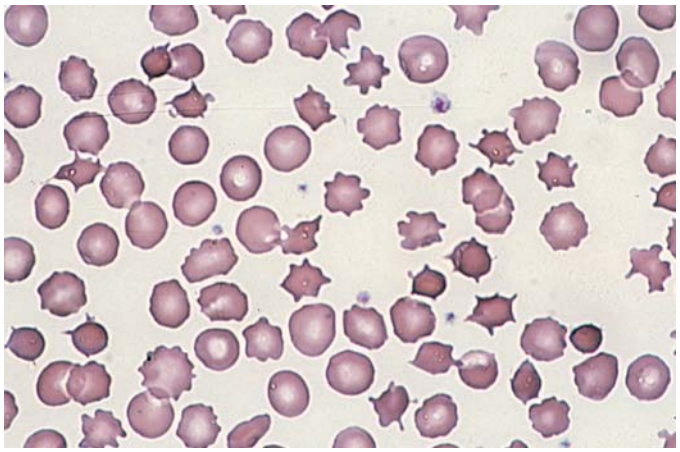

FIGURE e11-16 Acanthocytosis. Spiculated red cells are of two types: *acanthocytes* are contracted dense cells with irregular membrane projections that vary in length and width; *echinocytes* have small, uniform, and evenly spaced membrane projections. Acanthocytes are present in severe liver disease, in patients with abetalipoproteinemia, and in rare patients with McLeod blood group. Echinocytes are found in patients with severe uremia, in glycolytic red cell enzyme defects, and in microangiopathic hemolytic anemia.

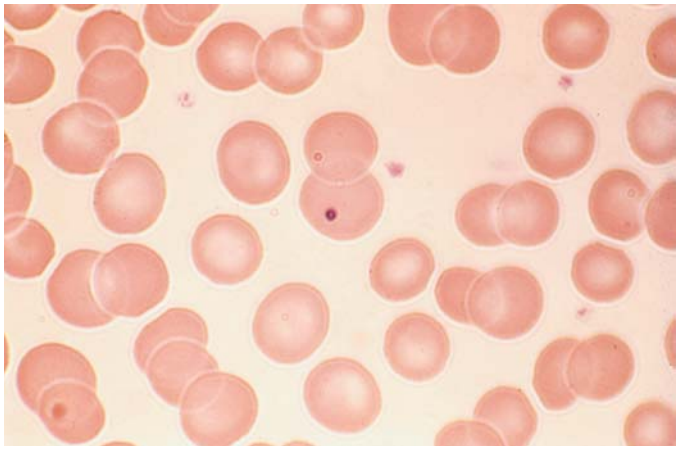

FIGURE e11-17 Howell-Jolly bodies. Howell-Jolly bodies are tiny nuclear remnants that are normally removed by the spleen. They appear in the blood after splenectomy (defect in removal) and with maturation/dysplastic disorders (excess production).

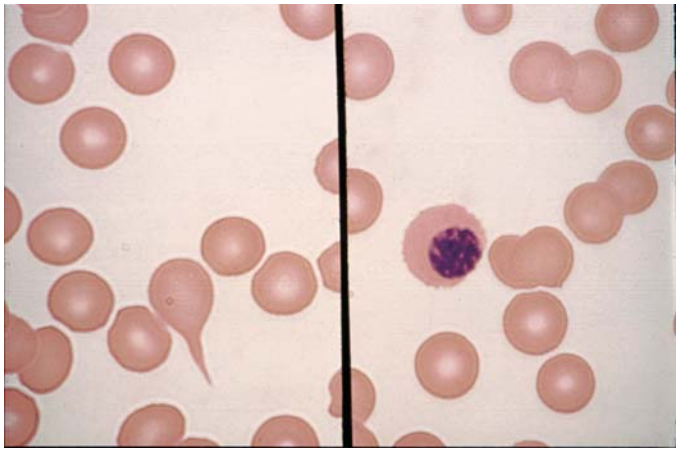

FIGURE e11-18 Teardrop cells and nucleated red blood cells characteristic of myelofibrosis. A teardrop-shaped red blood cell (*left panel*) and a nucleated red blood cell (*right panel*) as typically seen with myelofibrosis and extramedullary hematopoiesis.

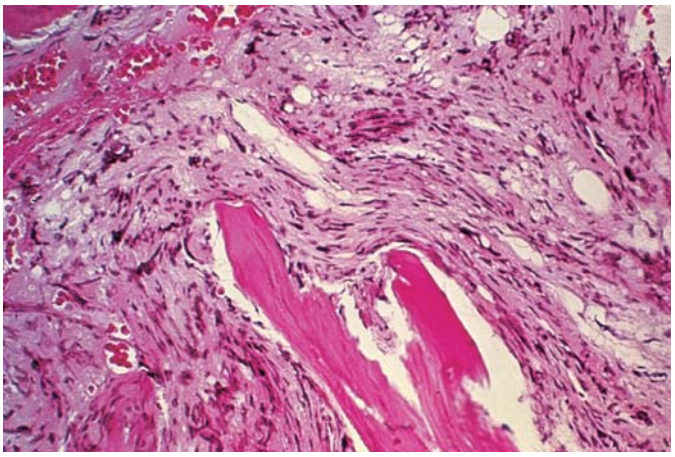

FIGURE e11-19 Myelofibrosis of the bone marrow. Total replacement of marrow precursors and fat cells by a dense infiltrate of reticulin fibers and collagen (H&E stain).

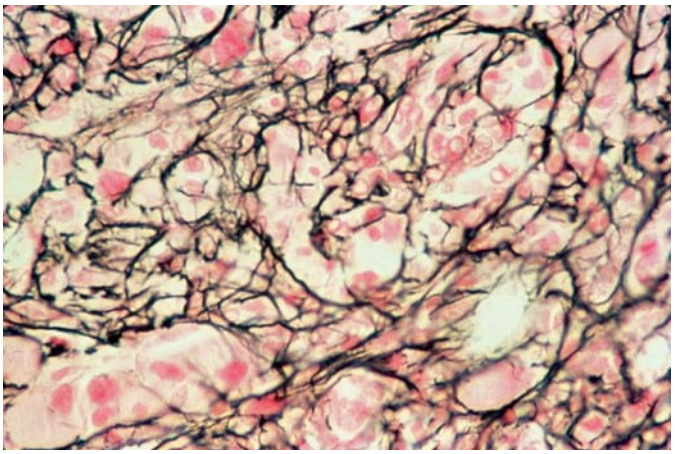

FIGURE e11-20 Reticulin stain of marrow myelofibrosis. Silver stain of a myelofibrotic marrow showing an increase in reticulin fibers (black-staining threads).

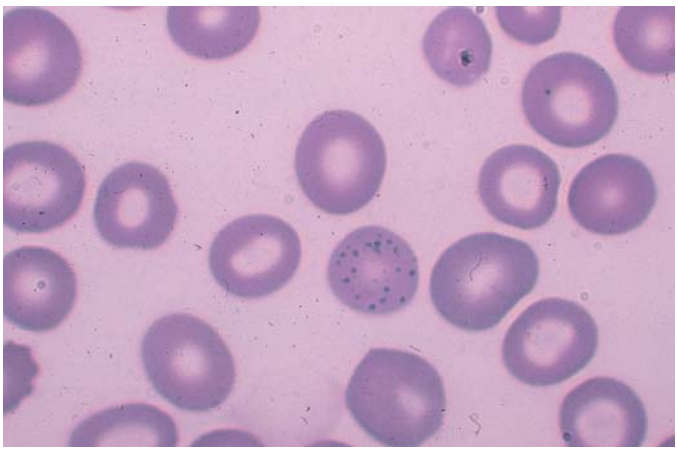

FIGURE e11-21 Stippled red cell in lead poisoning. Mild hypochromia. Coarsely stippled red cell.

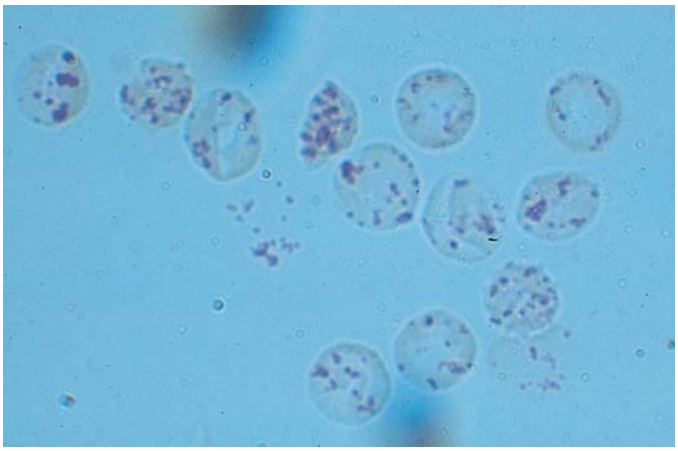

FIGURE e11-22 Heinz bodies. Blood mixed with hypotonic solution of crystal violet. The stained material is precipitates of denatured hemoglobin within cells.

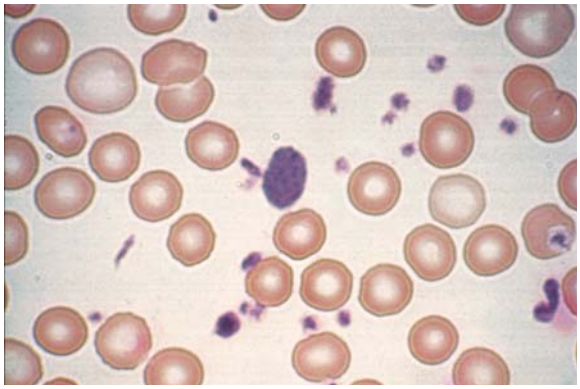

FIGURE e11-23 Giant platelets. Giant platelets, together with a marked increase in the platelet count, are seen in myeloproliferative disorders, especially primary thrombocythemia.

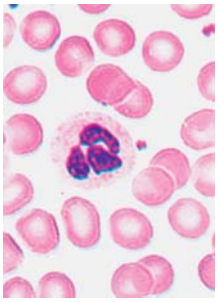

FIGURE e11-24 Normal granulocytes. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm.

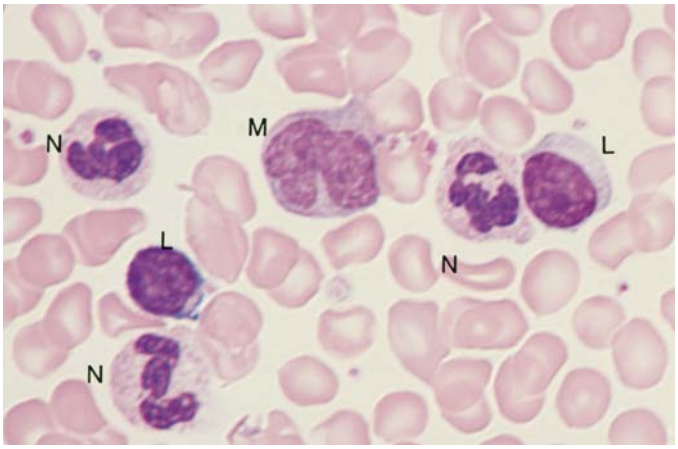

FIGURE e11-25 Normal monocytes. The film was prepared from the buffy coat of the blood from a normal donor. L, lymphocyte; M monocyte; N, neutrophil.

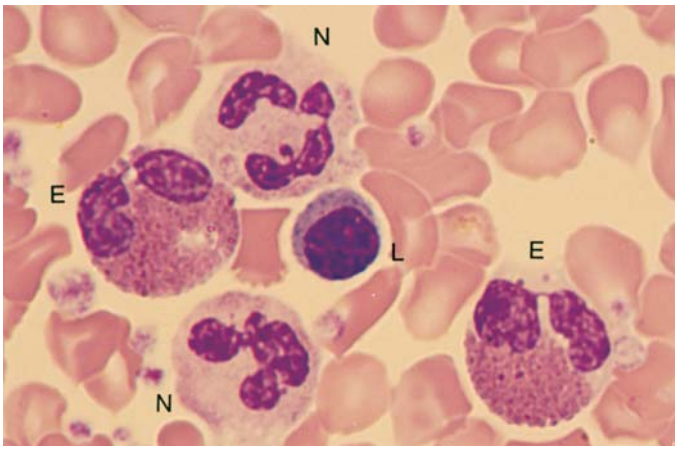

FIGURE e11-26 Normal eosinophils. The film was prepared from the buffy coat of the blood from a normal donor. N, neutrophil; E, eosinophil.

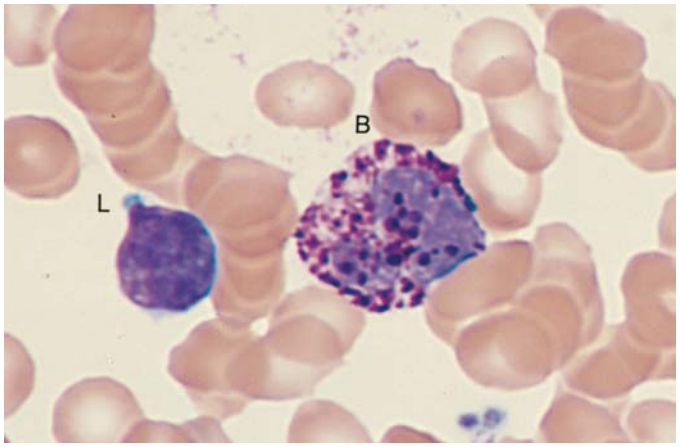

FIGURE e11-27 Normal basophil. The film was prepared from the buffy coat of the blood from a normal donor. L, lymphocyte; B, basophil.

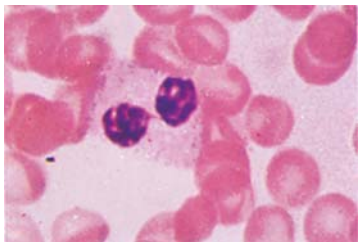

FIGURE e11-28 Pelger-Hüet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez" configuration.

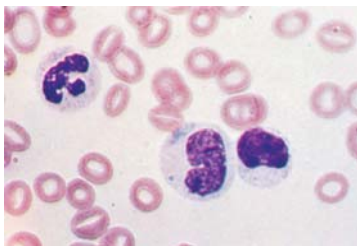

FIGURE e11-29 Döhle body. Neutrophil band with Döhle body. The neutrophil with a sausage-shaped nucleus in the center of the field is a band form. Döhle bodies are discrete, blue-staining nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum.

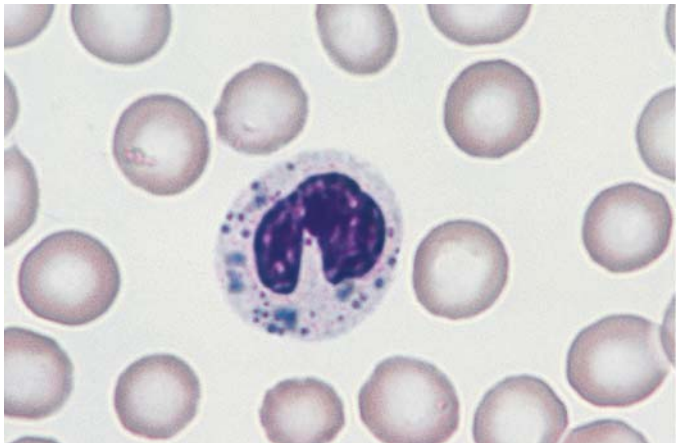

FIGURE e11-30 Chédiak-Higashi disease. Note giant granules in neutrophil.

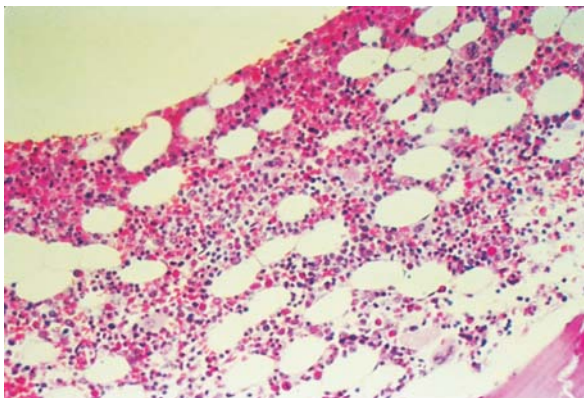

FIGURE e11-31 Normal bone marrow. Low-power view of normal adult marrow (H&E stain), showing a mix of fat cells (clear areas) and hematopoietic cells. The percentage of the space that is hematopoietic cells is referred to as *marrow cellularity*. In adults, normal marrow cellularity is 35–40%. If demands for increased marrow production occur, cellularity may increase to meet the demand. As we age, the marrow cellularity decreases and the marrow fat increases. Patients >70 years may have a 20–30% marrow cellularity.

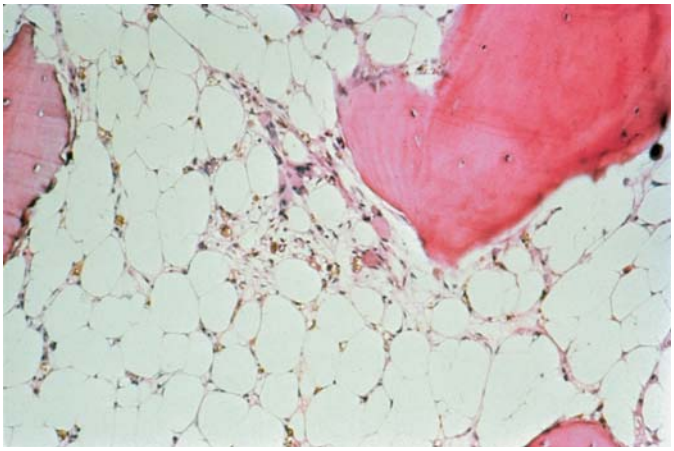

FIGURE e11-32 Aplastic anemia bone marrow. Normal hematopoietic precursor cells are virtually absent, leaving behind fat cells, reticuloendothelial cells, and the underlying sinusoidal structure.

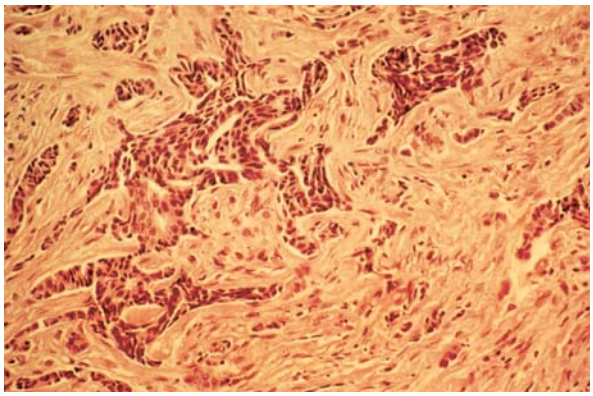

FIGURE e11-33 Metastatic cancer in the bone marrow. Marrow biopsy specimen infiltrated with metastatic breast cancer and reactive fibrosis (H&E stain).

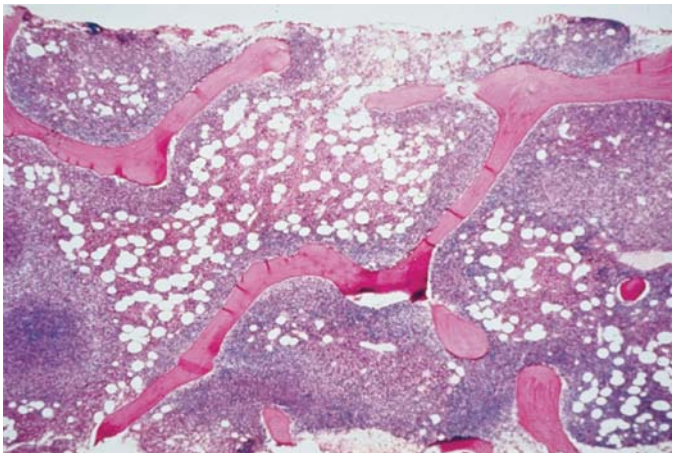

FIGURE e11-34 Lymphoma in the bone marrow. Nodular (follicular) lymphoma infiltrate in a marrow biopsy specimen. Note the characteristic paratrabecular location of the lymphoma cells.

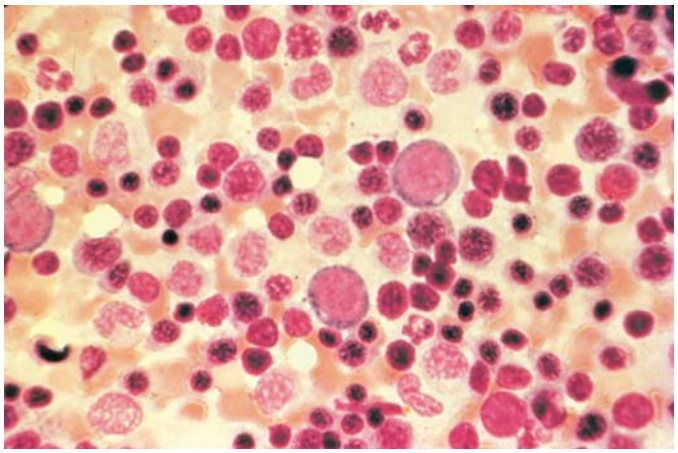

FIGURE e11-35 Erythroid hyperplasia of the marrow. Marrow aspirate specimen with a myeloid/erythroid ratio (M/E ratio) of 1:1–2, typical for a patient with a hemolytic anemia or recovering from blood loss.

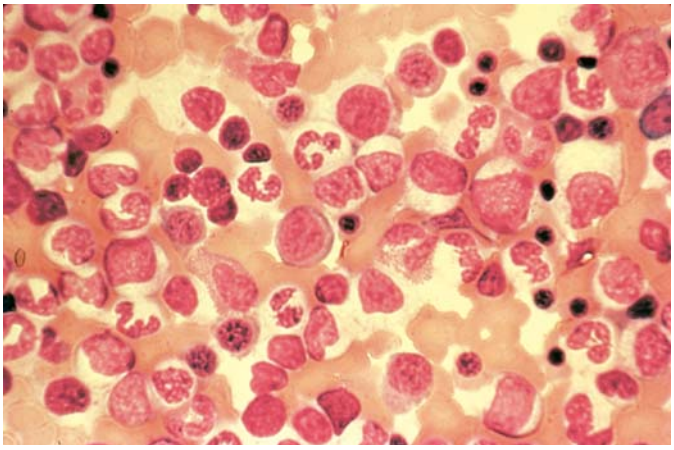

FIGURE e11-36 Myeloid hyperplasia of the marrow. Marrow aspirate specimen showing a myeloid/erythroid ratio of ≥3:1, suggesting either a loss of red blood cell precursors or an expansion of myeloid elements.

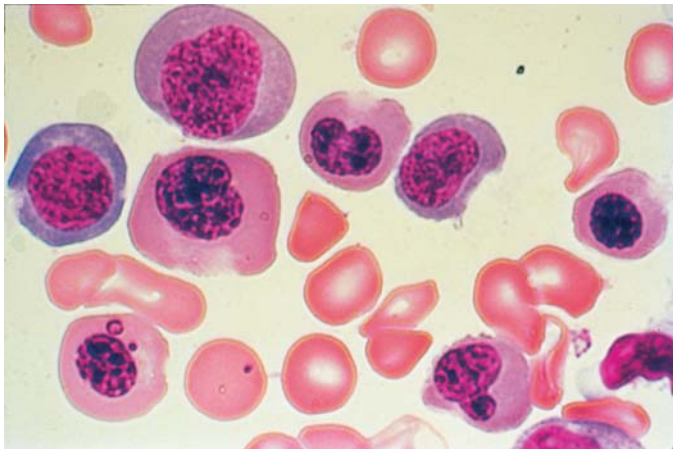

FIGURE e11-37 Megaloblastic erythropoiesis. High-power view of megaloblastic red blood cell precursors from a patient with a macrocytic anemia. Maturation is delayed with late normoblasts showing a more immature appearing nucleus with a lattice-like pattern with normal cytoplasmic maturation.

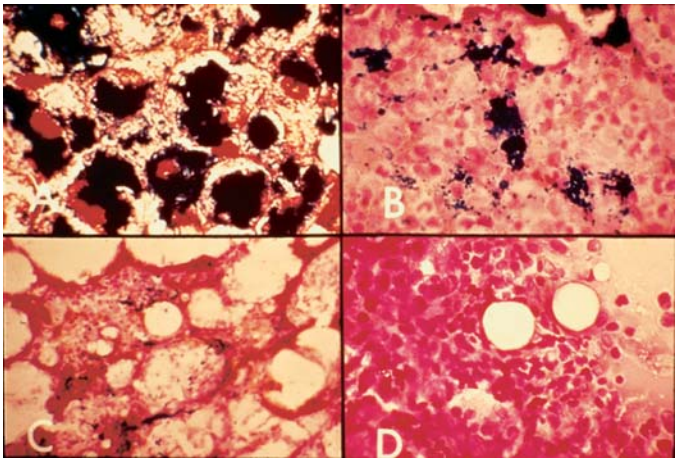

FIGURE e11-38 Prussian blue staining of marrow iron stores. Iron stores can be graded on a scale of 0 to 4+. ***A:*** a marrow with excess iron stores (>4+); ***B:*** normal stores (2–3+); ***C:*** minimal stores (1+); and ***D:*** absent iron stores (0).

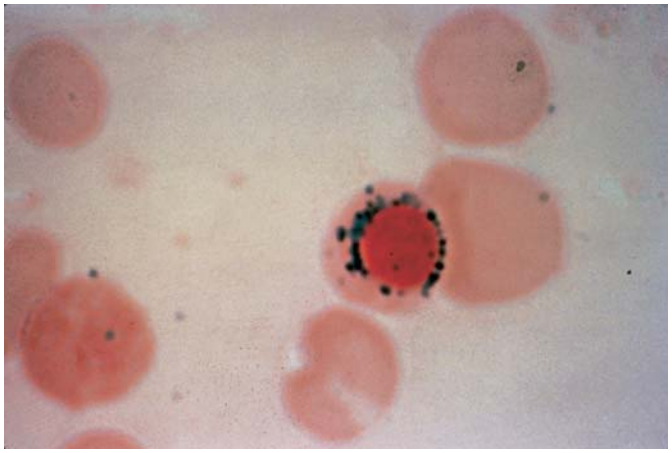

FIGURE e11-39 Ringed sideroblast. An orthochromatic normoblast with a collar of blue granules (mitochondria encrusted with iron) surrounding the nucleus.

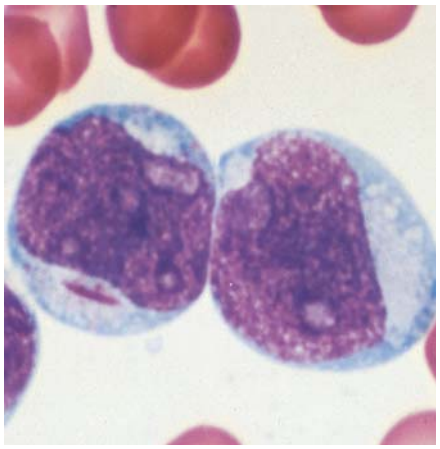

FIGURE e11-40 Acute myeloid leukemia. Leukemic myeloblast with an Auer rod. Note two to four large, prominent nucleoli in each cell.

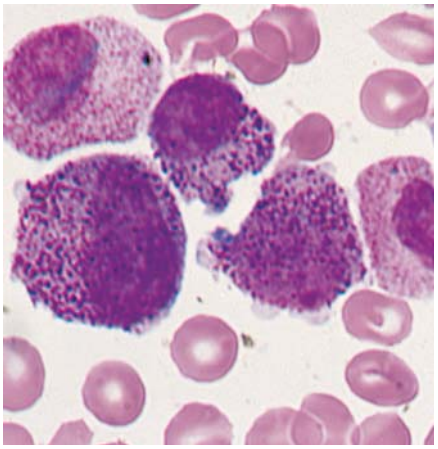

FIGURE e11-41 Acute promyelocytic leukemia. Note prominent cytoplasmic granules in the leukemia cells.

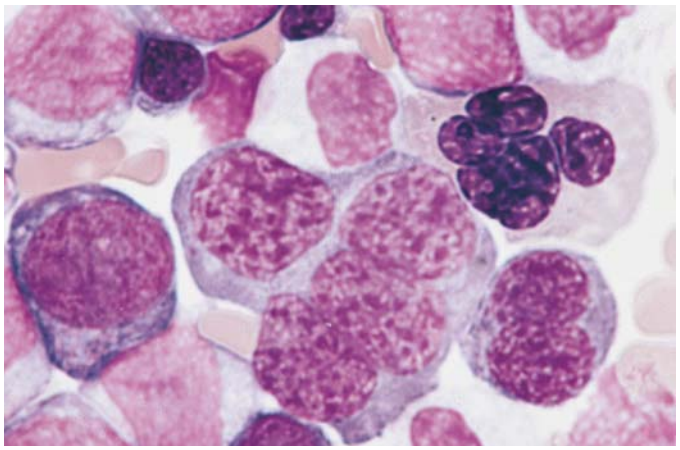

FIGURE e11-42 Acute erythroleukemia. Note giant dysmorphic erythroblasts, two are binucleate and one is multinucleate.

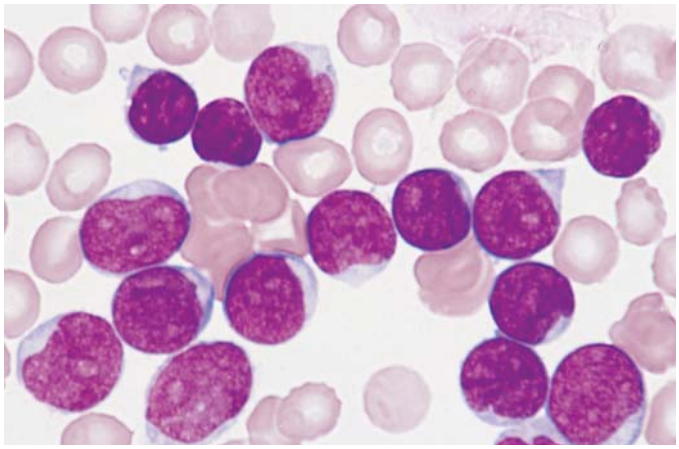

FIGURE e11-43 Acute lymphoblastic leukemia.

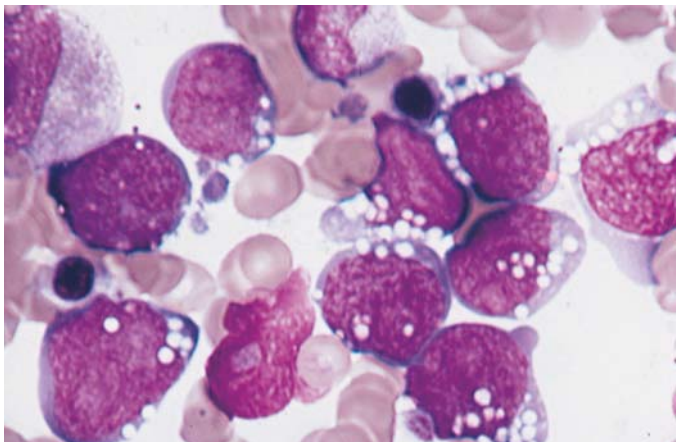

FIGURE e11-44 Burkitt's leukemia, acute lymphoblastic leukemia.

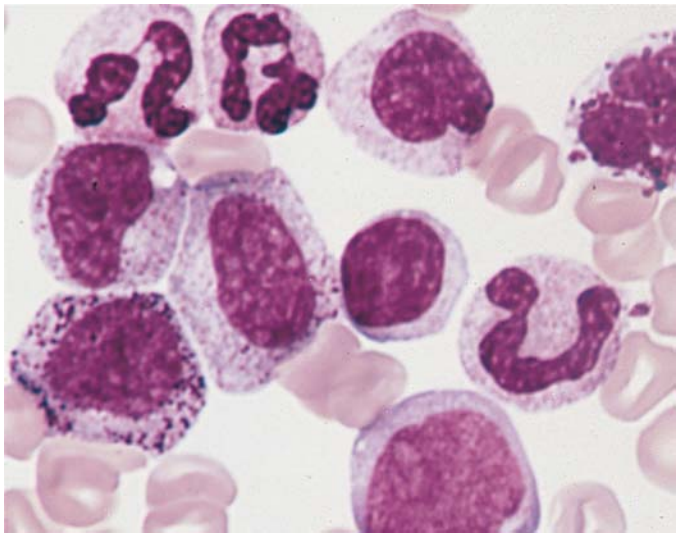

FIGURE e11-45 Chronic myeloid leukemia in the peripheral blood.

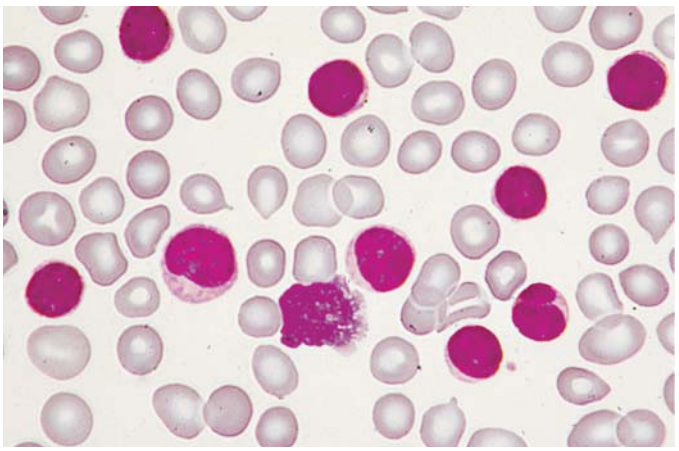

FIGURE e11-46 Chronic lymphoid leukemia in the peripheral blood.

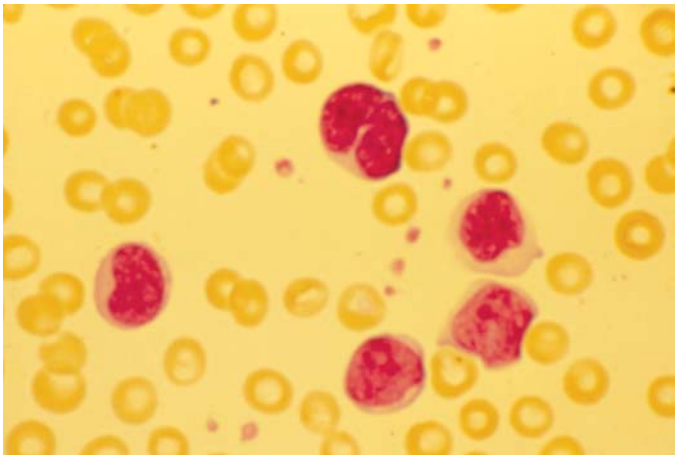

FIGURE e11-47 **Sézary's syndrome.** Lymphocytes with frequently convoluted nuclei (Sézary cells) in a patient with advanced mycosis fungoides.

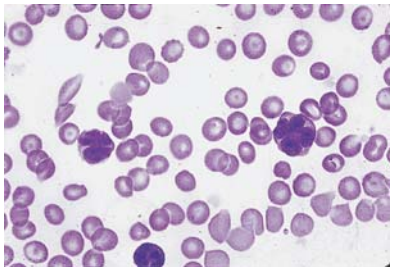

FIGURE e11-48 **Adult T cell leukemia.** Peripheral blood smear showing leukemia cells with typical "flower-shaped" nucleus.

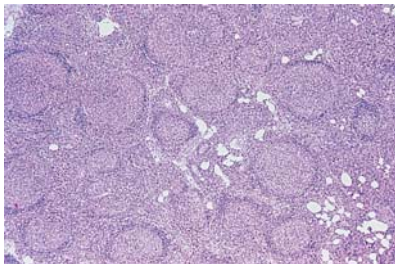

FIGURE e11-49 **Follicular lymphoma in a lymph node.** The normal nodal architecture is effaced by nodular expansions of tumor cells. Nodules vary in size and contain predominantly small lymphocytes with cleaved nuclei along with variable numbers of larger cells with vesicular chromatin and prominent nucleoli.

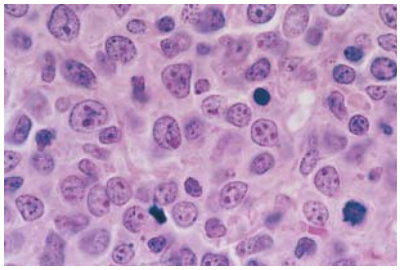

FIGURE e11-50 Diffuse large B cell lymphoma in a lymph node. The neoplastic cells are heterogeneous but predominantly large cells with vesicular chromatin and prominent nucleoli.

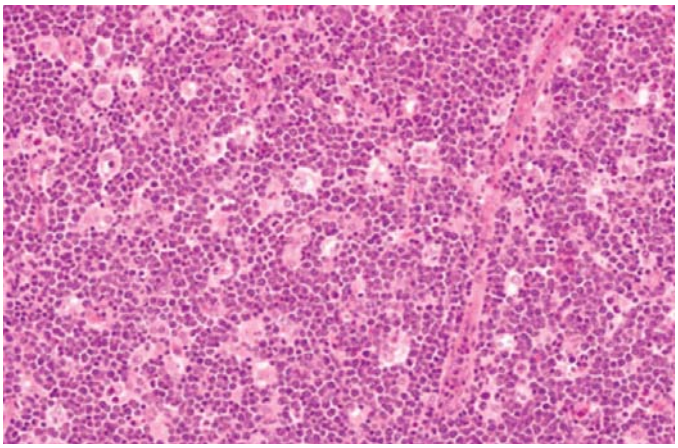

FIGURE e11-51 Burkitt's lymphoma in a lymph node. Burkitt's lymphoma with starry-sky appearance. The lighter areas are macrophages attempting to clear dead cells.

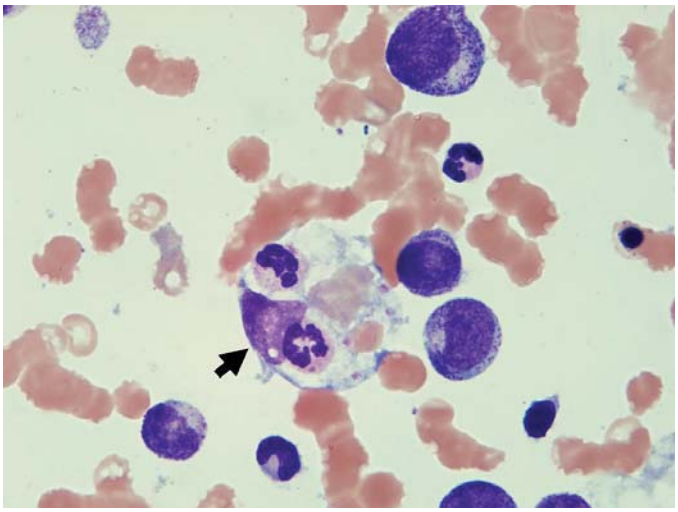

FIGURE e11-52 Erythrophagocytosis accompanying aggressive lymphoma. The central macrophage is ingesting red cells, neutrophils, and platelets. *(Courtesy of Dr. Kiyomi Tsukimori, Kyushu University, Fukuoka, Japan.)*

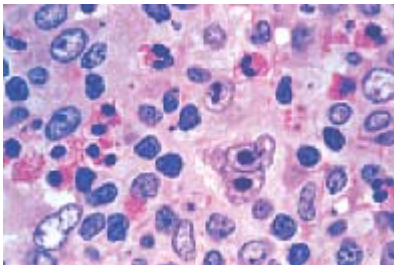

FIGURE e11-53 Hodgkin's disease. A Reed-Sternberg cell is present near the center of the field; a large cell with a bilobed nucleus and prominent nucleoli giving an "owl's eyes" appearance. The majority of the cells are normal lymphocytes, neutrophils, and eosinophils that form a pleiomorphic cellular infiltrate.

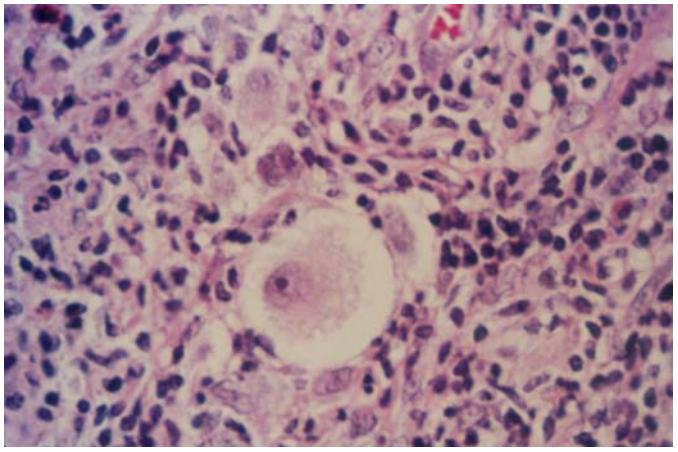

FIGURE e11-54 Lacunar cell; Reed-Sternberg cell variant in nodular sclerosing Hodgkin's disease. High-power view of single mononuclear lacunar cell with retracted cytoplasm in a patient with nodular sclerosing Hodgkin's disease.

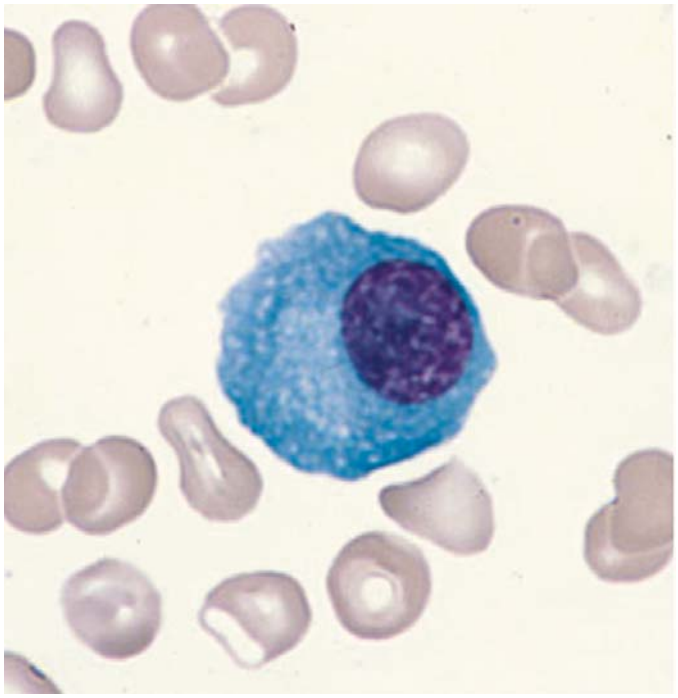

FIGURE e11-55 Normal plasma cell.

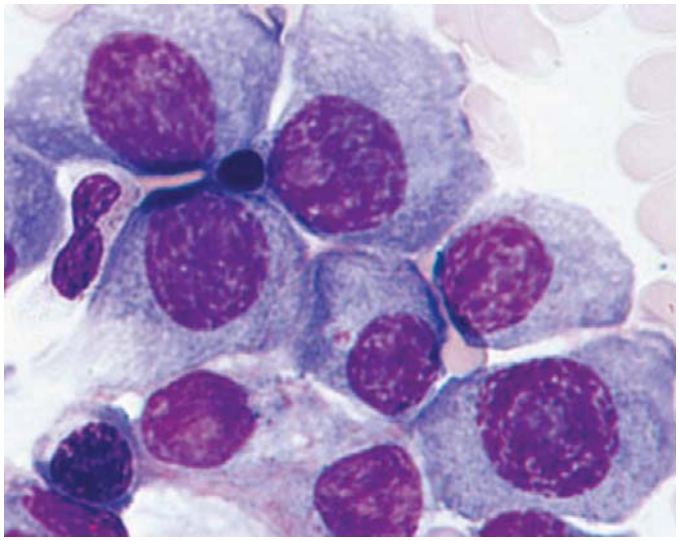

FIGURE e11-56 Multiple myeloma.

FIGURE e11-57 Color serum in hemoglobinemia. The distinctive red coloration of plasma (hemoglobinemia) in a spun blood sample in a patient with intravascular hemolysis.