common than warm antibody immunohemolytic anemia, accounting for 16% to 32% of cases of immunohemolytic anemia. Such antibodies appear *acutely* during the recovery phase of certain infectious disorders, such as mycoplasma pneumonia and infectious mononucleosis. In these settings, the disorder is self-limited and rarely induces clinical manifestations of hemolysis. Other infectious agents associated with this form of anemia include cytomegalovirus, influenza virus, and human immunodeficiency virus (HIV). *Chronic* cold agglutinin immunohemolytic anemias occur in association with certain lymphoid neoplasms or as an idiopathic condition. Clinical symptoms result from binding of IgM to red cells at sites such as exposed fingers, toes, and ears where the temperature is below 30°C. IgM binding agglutinates red cells and rapidly fixes complement on their surface. As the blood recirculates and warms, IgM is rapidly released, usually before complement-mediated hemolysis can occur. However, the transient interaction with IgM is sufficient to deposit sublytic quantities of C3b, an excellent opsonin, leading to rapid removal of affected red cells by mononuclear phagocytes in the liver and spleen. The hemolysis is of variable severity. Vascular obstruction caused by red cell agglutinates results in pallor, cyanosis of the body parts exposed to cold temperatures, and Raynaud phenomenon (Chapter 11).

Cold Hemolysin Hemolytic Anemia.

Cold hemolysins are autoantibodies responsible for an unusual entity known as *paroxysmal cold hemoglobinuria,* characterized by acute intermittent massive intravascular hemolysis, frequently with hemoglobinuria, after exposure to cold temperatures. This is the least common form of immunohemolytic anemia. Lysis is clearly complement dependent. The autoantibodies are IgGs that bind to the P blood group antigen on the red cell surface at low temperatures. Complement-mediated intravascular lysis does not occur until the cells recirculate to warm central regions, as the enzymes of the complement cascade function more efficiently at 37°C. The antibody, also known as the Donath-Landsteiner antibody, was first recognized in association with syphilis. Today, most cases of paroxysmal cold hemoglobinuria follow infections such as mycoplasma pneumonia,

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measles, mumps, and ill-defined viral and "flu" syndromes. The mechanisms responsible for production of such autoantibodies in these settings are unknown.

Hemolytic Anemia Resulting from Trauma to Red Cells

Red blood cells can be disrupted by physical trauma in a variety of circumstances. Of these, *hemolytic anemias caused by cardiac valve prostheses, or narrowing or obstruction of the microvasculature, are most important clinically*. Severe traumatic hemolytic anemia is more frequently associated with artificial mechanical valves than bioprosthetic porcine valves. Hemolysis in both instances stems from shear stresses produced by turbulent blood flow and abnormal pressure gradients. Microangiopathic hemolytic anemia, on the other hand, occurs when red cells are forced to squeeze through abnormally narrowed small vessels. Narrowing is most often caused by fibrin deposition in association with disseminated intravascular coagulation (discussed later in this chapter). Other causes of microangiopathic hemolytic anemia include malignant hypertension, systemic lupus erythematosus, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and disseminated cancer, most of which are discussed elsewhere in this book. The common feature among all these disorders is a microvascular lesion that causes mechanical injury to circulating red cells. This damage is evident in peripheral blood smears in the form of red cell fragments (schistocytes), "burr cells," "helmet cells," and "triangle cells" (Fig. 13-17). Except for TTP and HUS, hemolysis is not a major clinical problem in most instances.

Figure 13-17 Microangiopathic hemolytic anemia. A peripheral blood smear from a patient with hemolytic-uremic syndrome shows several fragmented red cells. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

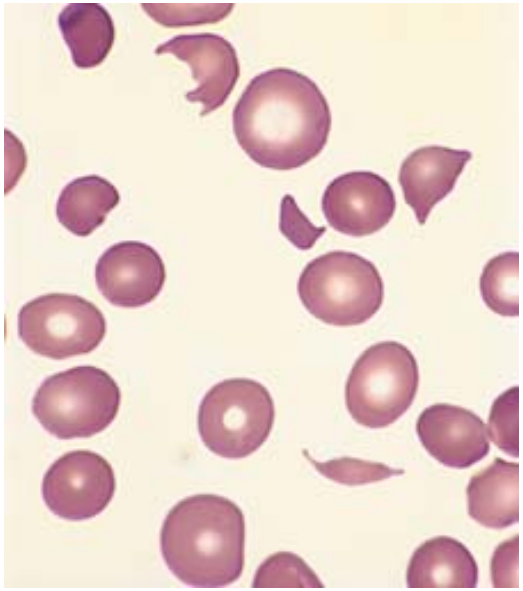


Figure 13-18 Megaloblastic anemia. A peripheral blood smear shows a hypersegmented neutrophil with a six-lobed nucleus. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

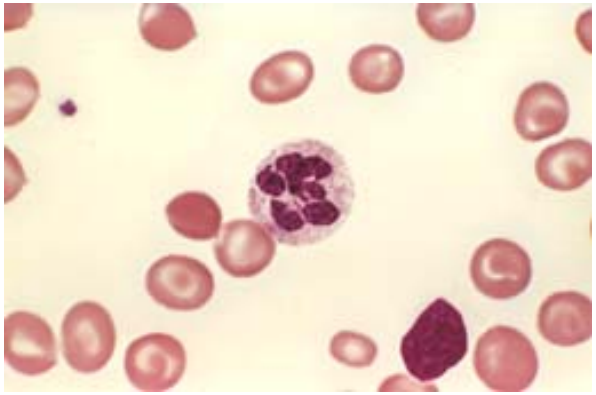


Figure 13-19 Megaloblastic anemia (bone marrow aspirate). *A* to *C*, Megaloblasts in various stages of differentiation. Note that the orthochromatic megaloblast *(B)* is hemoglobinized (as revealed by cytoplasmic color), but in contrast to normal orthochromatic normoblasts, the nucleus is not pyknotic. The granulocytic precursors are also large and have abnormally "immature" chromatin. *(Courtesy of Dr. Jose Hernandez, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

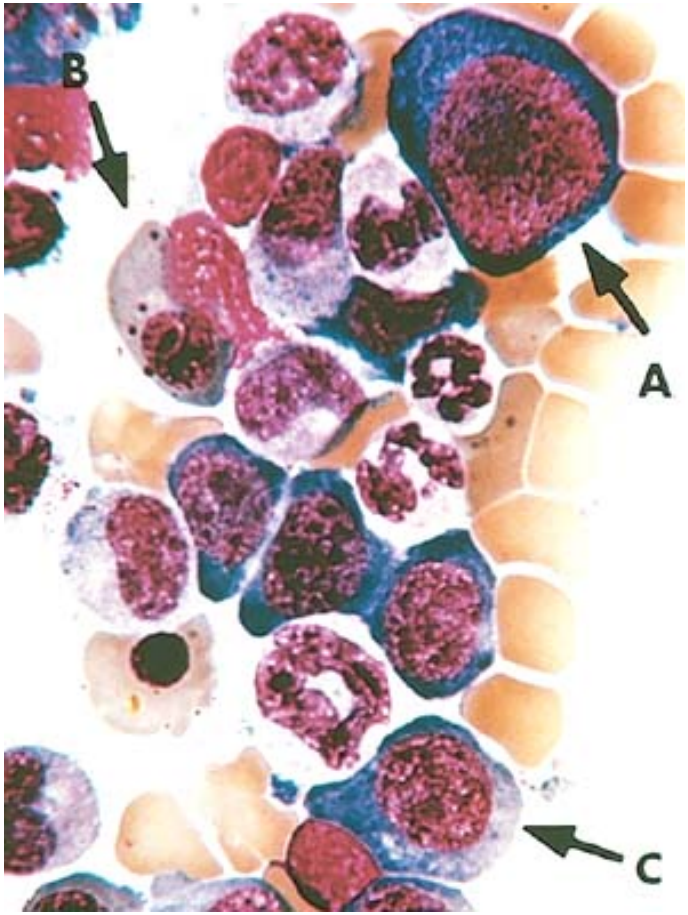


TABLE 13-5 -- Causes of Megaloblastic Anemia

Vitamin B_{12} Deficiency
Decreased intake
••Inadequate diet, vegetarianism
Impaired absorption
••Intrinsic factor deficiency
••••Pernicious anemia
••••Gastrectomy
••Malabsorption states
••Diffuse intestinal disease, e.g., lymphoma, systemic sclerosis
••Ileal resection, ileitis

••Competitive parasitic uptake
••••Fish tapeworm infestation
••Bacterial overgrowth in blind loops and diverticula of bowel
Increased requirement
••••Pregnancy, hyperthyroidism, disseminated cancer
Folic Acid Deficiency
Decreased intake
••Inadequate diet—alcoholism, infancy
Impaired absorption
••Malabsorption states
••Intrinsic intestinal disease
••Anticonvulsants, oral contraceptives
Increased loss
••Hemodialysis
Increased requirement
••Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
Impaired use
••Folic acid antagonists
Unresponsive to Vitamin B_{12} or Folic Acid Therapy
Metabolic inhibitors of DNA synthesis and/or folate metabolism, e.g., methotrexate
Modified from Beck WS: Megaloblastic anemias. In Wyngaarden JB, Smith LH (eds): Cecil Textbook of Medicine, 18th ed. Philadelphia, WB Saunders, 1988, p. 900.

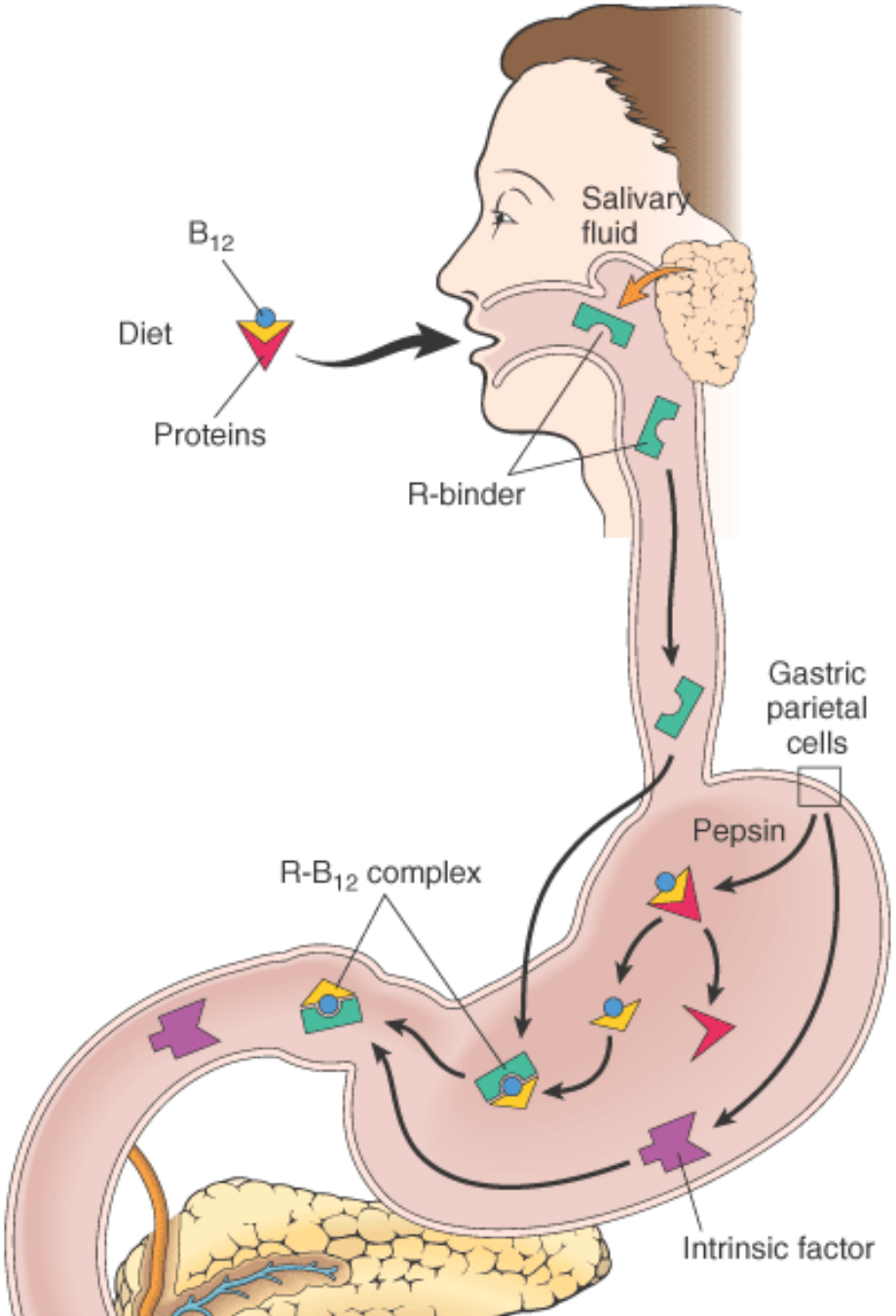
marrow and mucosal lining of the gastrointestinal tract. In addition to the intrinsic-factor dependent pathway, evidence also supports the existence of an alternative mechanism that is not dependent on availability of intrinsic factor or intact terminal ileum. The mechanism involved is not entirely clear but up to 1% of a large oral dose can be absorbed by this pathway, thus making it feasible to treat pernicious anemia by oral vitamin B_{12} therapy.[33]

Etiology of Vitamin B_{12} Deficiency.

With this background, we can consider the various causes of vitamin B_{12} deficiency (see Table 13-5). Inadequate diet is obvious but must be present for many years to deplete reserves. The absorption of vitamin B_{12} can be impaired by disruption of any one of the steps outlined earlier. With achlorhydria and loss of pepsin secretion (which occurs in some elderly individuals), vitamin B_{12} is not readily released from proteins in food. With gastrectomy and pernicious anemia, intrinsic factor is not available for transport to the ileum. With loss of exocrine pancreatic function, vitamin B_{12} cannot be released from R-binder-vitamin B_{12} complexes. Ileal resection or diffuse ileal disease can remove or damage the site of intrinsic factor-

vitamin B_{12} complex absorption. Tapeworm infestation, by competing for the nutrient, can induce a deficiency state. Under some circumstances, for example, pregnancy, hyperthyroidism, disseminated cancer, and chronic infections,

Figure 13-20 Schematic illustration of vitamin B_{12} absorption.



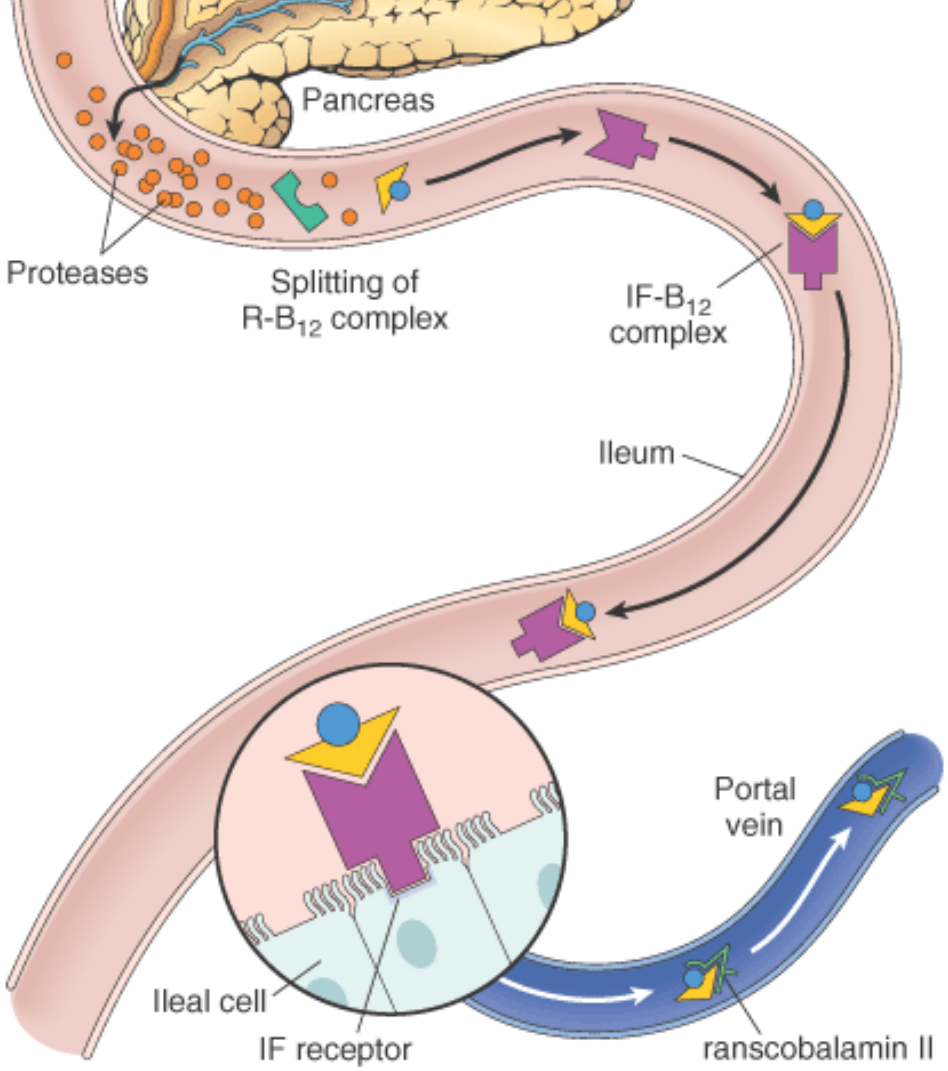


Figure 13-21 Relationship of N^5 -methyl FH_4 , methionine synthase, and thymidylate synthetase. In cobalamin deficiency, folate is sequestered as N^5 -methyl FH_4 . This ultimately deprives thymidylate synthetase of its folate coenzyme ($N^{5,10}$ -methylene FH_4), thereby impairing DNA synthesis.

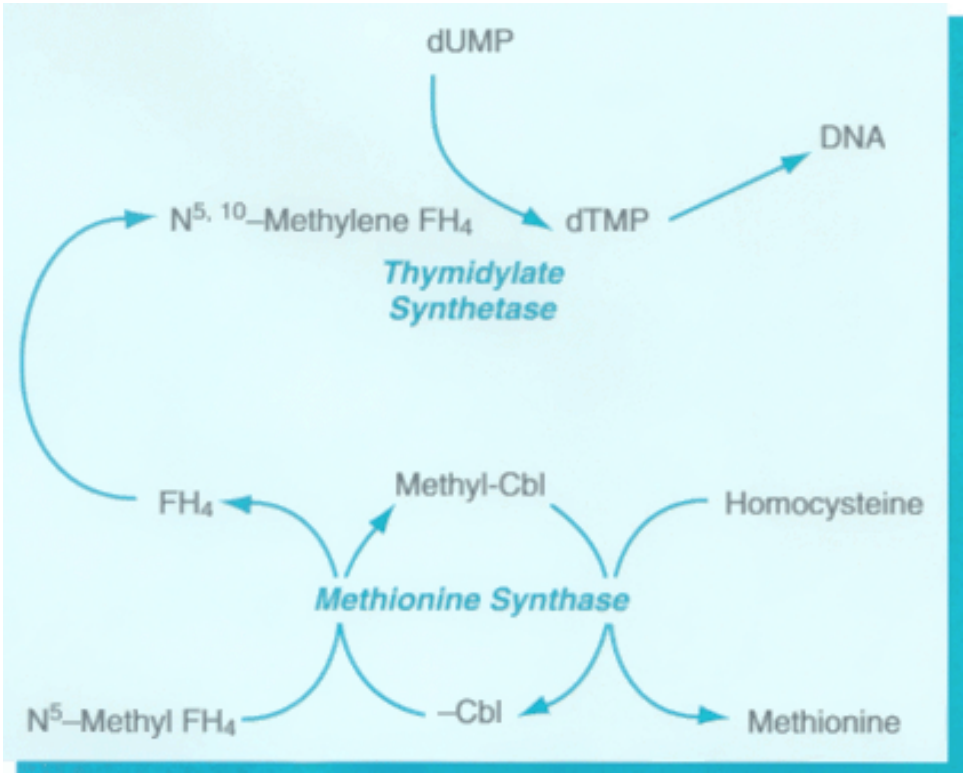


Figure 13-22 Role of folate derivatives in the transfer of one-carbon fragments for synthesis of biologic macromolecules. FH_4 , tetrahydrofolic acid; FH_2 , dihydrofolic acid; FIGlu, formiminoglutamate; dTMP, deoxythymidylate monophosphate. *Synthesis of methionine also requires vitamin B_{12} .

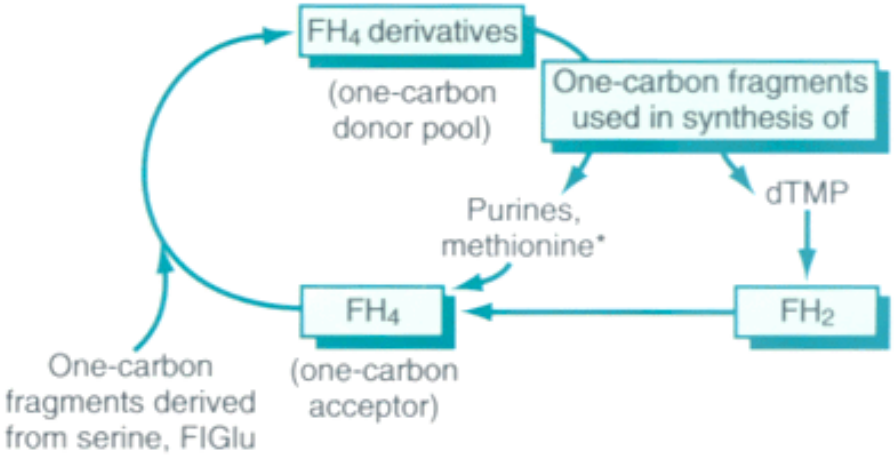


TABLE 13-6 -- Iron Distribution in Healthy Young Adults (mg)

Pool	Men	Women

Total	3450	2450
Functional		
••Hemoglobin	2100	1750
••Myoglobin	300	250
••Enzymes	50	50
Storage		
••Ferritin, hemosiderin	1000	400

Free iron is highly toxic, and the pool of storage iron is tightly bound to either ferritin or hemosiderin.[40] *Ferritin is a protein-iron complex* found in all tissues but particularly in liver, spleen, bone marrow, and skeletal muscles. In the liver, most ferritin is stored within the parenchymal cells; in other tissues, such as spleen and bone marrow, it is mainly in the mononuclear phagocytic cells. Hepatocytic iron is derived from plasma transferrin, whereas storage iron in the mononuclear phagocytic cells (Kupffer cells) is derived from the breakdown of red cells (Fig. 13-23). Intracellular ferritin is located in both the cytosol and lysosomes, in which partially degraded protein shells of ferritin aggregate into *hemosiderin* granules. With a hematoxylin and eosin stain, hemosiderin appears in cells as golden yellow granules. The iron in hemosiderin is chemically reactive and turns blue-black when exposed to potassium ferrocyanide, which is the basis for the Prussian blue stain. With normal iron stores, only trace amounts of hemosiderin are found in the body, principally in mononuclear phagocytic cells in the bone marrow, spleen, and liver. In iron-overloaded cells, most iron is stored in hemosiderin.

Very small amounts of ferritin normally circulate in the plasma. *Since plasma ferritin is derived largely from the storage pool of body iron, its levels correlate well with body iron stores.* In iron deficiency, serum ferritin is always below 12 µg/L, whereas in iron overload, high values approaching 5000 µg/L can be seen. Of physiologic importance, the storage iron pool can be readily mobilized if iron requirements increase, as may occur after loss of blood.

Iron is transported in plasma by an iron-binding glycoprotein called *transferrin* (see Fig. 13-23), which is synthesized in the liver. In normal individuals, transferrin is about 33% saturated with iron, yielding serum iron levels that average 120 µg/dL in men and 100 µg/dL in women. Thus, the total

Figure 13-23 The internal iron cycle. Plasma iron bound to transferrin is transported to the marrow, where it is transferred to developing red cells and incorporated into hemoglobin. Mature red blood cells are released into the circulation and, after 120 days, are ingested by macrophages in the reticuloendothelial system (RES). Here iron is extracted from hemoglobin and returned to the plasma, completing the cycle. *(From Wyngaarden JB, et al [eds]: Cecil Textbook of Medicine, 19th ed. Philadelphia, WB Saunders, 1992, p. 841.)*

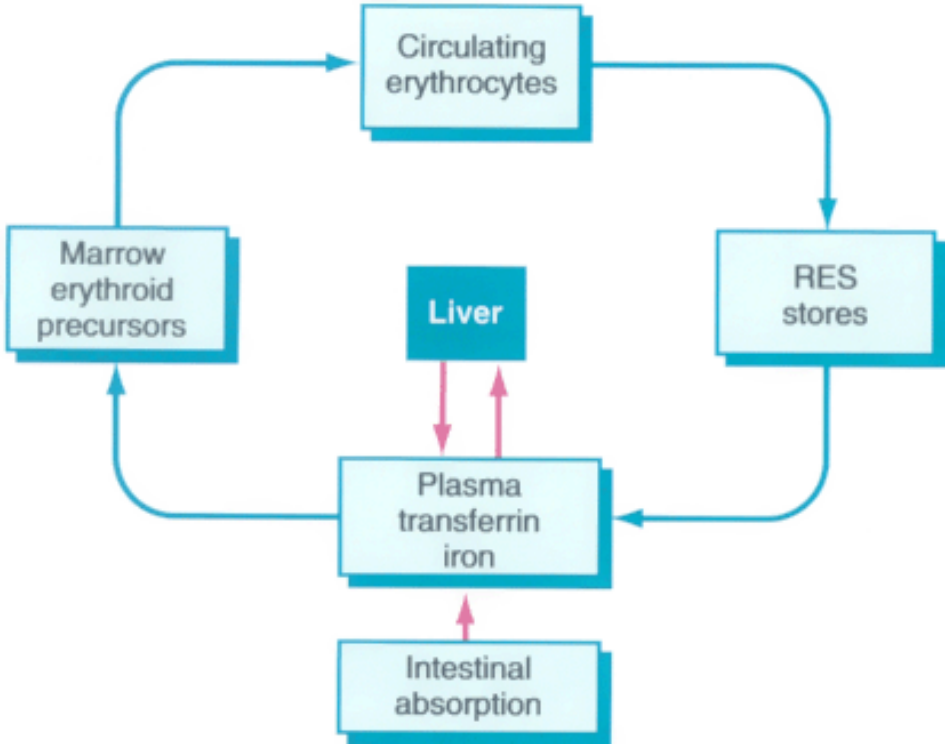


Figure 13-24 Diagrammatic representation of iron absorption. Mucosal uptake of heme and nonheme iron is depicted. When the storage sites of the body are replete with iron and erythropoietic activity is normal, most of the absorbed iron is lost into the gut by shedding of the epithelial cells. Conversely, when body iron needs increase or when erythropoiesis is stimulated, a greater fraction of the absorbed iron is transferred into plasma transferrin, with a concomitant decrease in iron loss through mucosal ferritin.

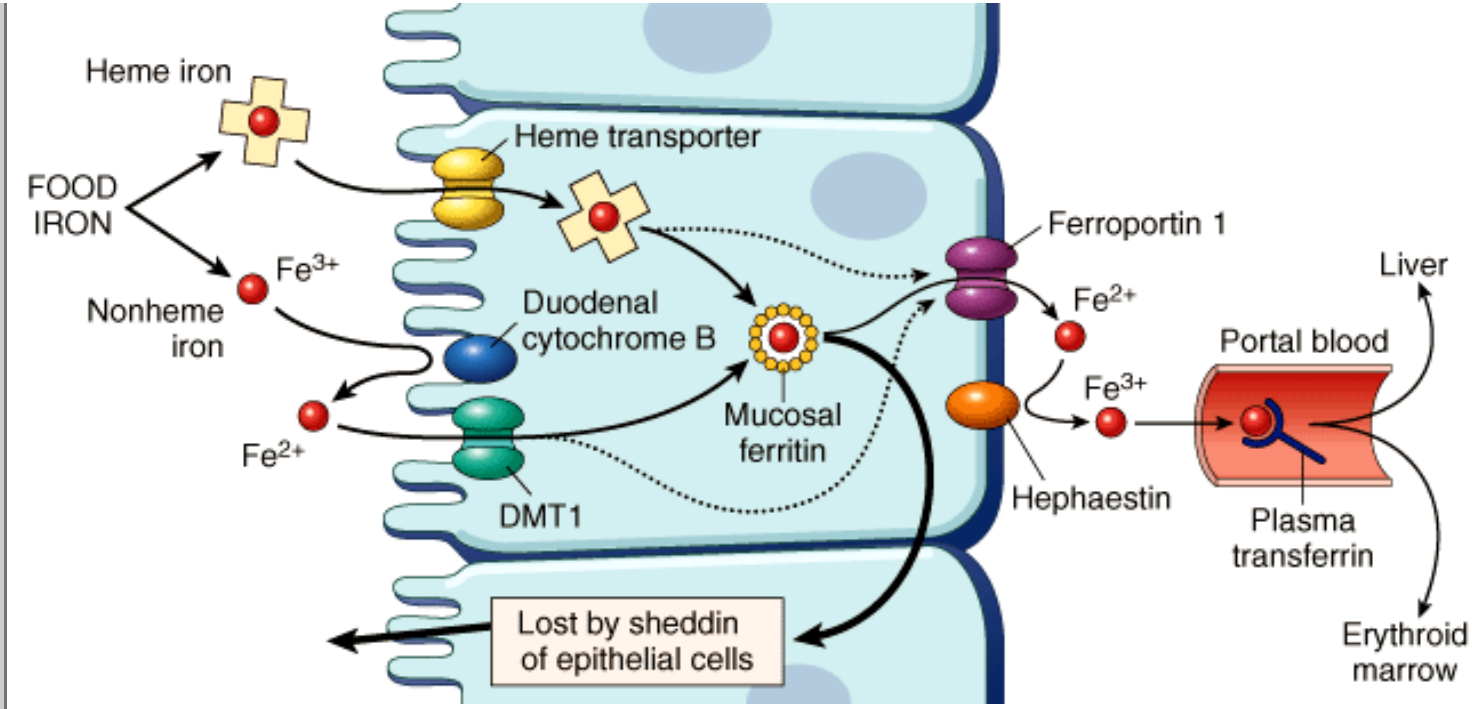


Figure 13-25 Hypochromic microcytic anemia of iron deficiency (peripheral blood smear). Note the small red cells containing a narrow rim of peripheral hemoglobin. Scattered fully hemoglobinized cells, present due to recent blood transfusion, stand in contrast. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

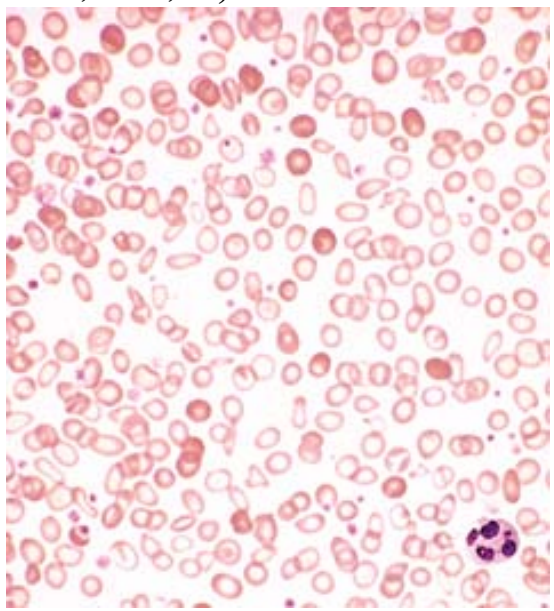


TABLE 13-7 -- Major Causes of Aplastic Anemia

Acquired
Idiopathic
••Primary stem cell defect
••Immune mediated
Chemical agents
••Dose related
••••Alkylating agents
••••Antimetabolites
••••Benzene
••••Chloramphenicol
••••Inorganic arsenicals
••Idiosyncratic
••••Chloramphenicol
••••Phenylbutazone
••••Organic arsenicals
••••Methylphenylethylhydantoin
••••Streptomycin
••••Chlorpromazine
••••Insecticides (e.g., DDT, parathion)
Physical agents (e.g., whole-body irradiation)
Viral infections
••Hepatitis (unknown virus)
••Cytomegalovirus infections
••Epstein-Barr virus infections
••Herpes varicella-zoster
Miscellaneous
••Infrequently, many other drugs and chemicals
Inherited
Fanconi anemia

required for DNA repair[45] (Chapter 7). Marrow hypofunction in Fanconi anemia becomes evident early in life and is accompanied by multiple congenital anomalies, such as hypoplasia of the kidney and spleen and hypoplastic anomalies of bone, often involving the thumbs or radii.

Despite all these possible causes, no provocative factor can be identified in fully 65% of the cases, which are lumped into the *idiopathic* category.

Pathogenesis.

The pathogenesis of aplastic anemia is not fully understood. Indeed, it is unlikely that a single mechanism underlies all cases. Two major etiologies have been invoked: an immunologically mediated suppression and an intrinsic abnormality of stem cells (Fig. 13-26).

Recent studies suggest that aplastic anemia results most commonly from suppression of stem cell function by activated T cells.[46] It is postulated that stem cells are first antigenically altered by exposure to drugs, infectious agents, or other unidentified environmental insults. This evokes a cellular immune response, during which activated T cells produce cytokines such as interferon-γ and TNF that prevent normal stem cell growth and development. This scenario is supported by several observations. Immunosuppressive therapy with antithymocyte globulin combined with drugs such as cyclosporine produces responses in 60% to 70% of patients, and successful bone marrow transplantation requires "conditioning" with high doses of myelotoxic drugs or radiation. In both instances, it is hypothesized these therapies work by suppressing or killing autoreactive T-cell clones. The target antigens for T-cell attack are not well defined. In some instances GPI-linked proteins may be the targets of sensitized T cells,

Figure 13-26 Pathophysiology of aplastic anemia. Damaged stem cells can produce progeny expressing neo-antigens that evoke an autoimmune reaction, or give rise to a clonal population with reduced proliferative capacity. Either pathway could lead to marrow aplasia.

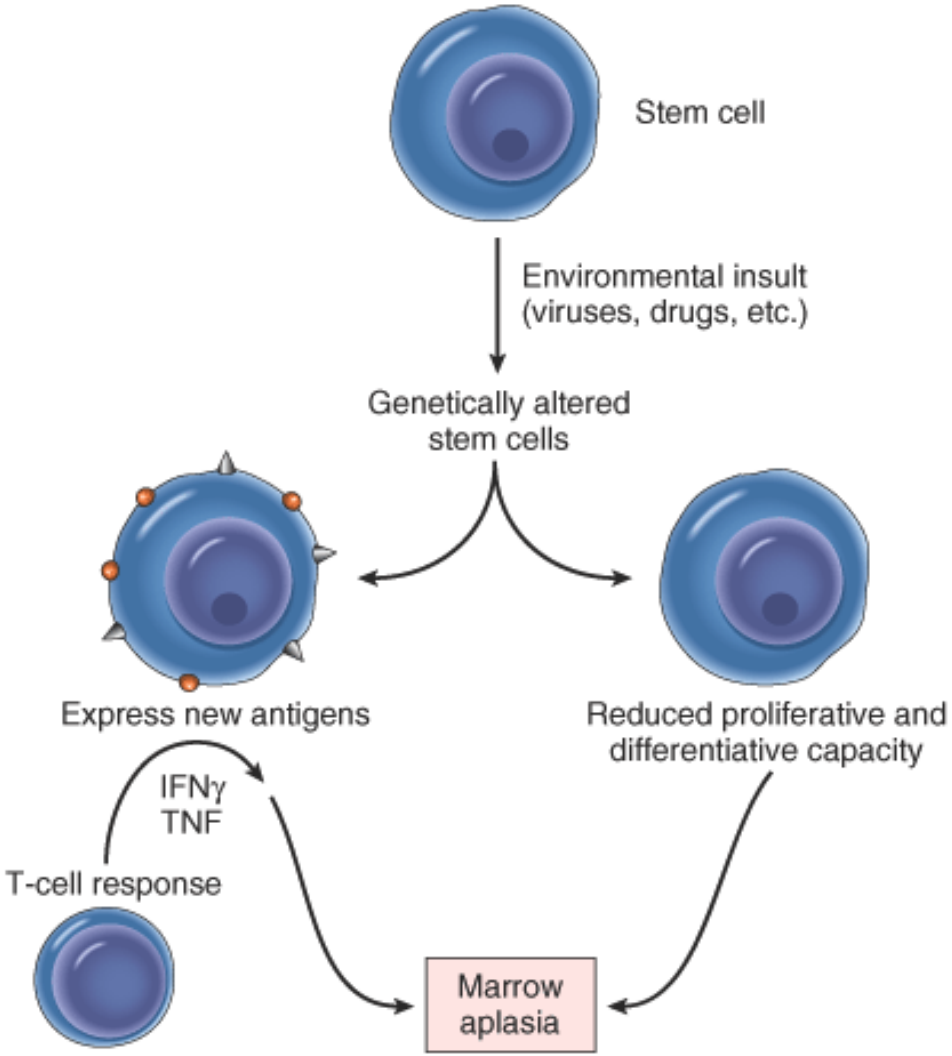


Figure 13-27 Aplastic anemia (bone marrow biopsy). Markedly hypocellular marrow contains mainly fat cells. *A*, Low power. *B*, High power. *(Courtesy of Dr. Steven Kroft, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

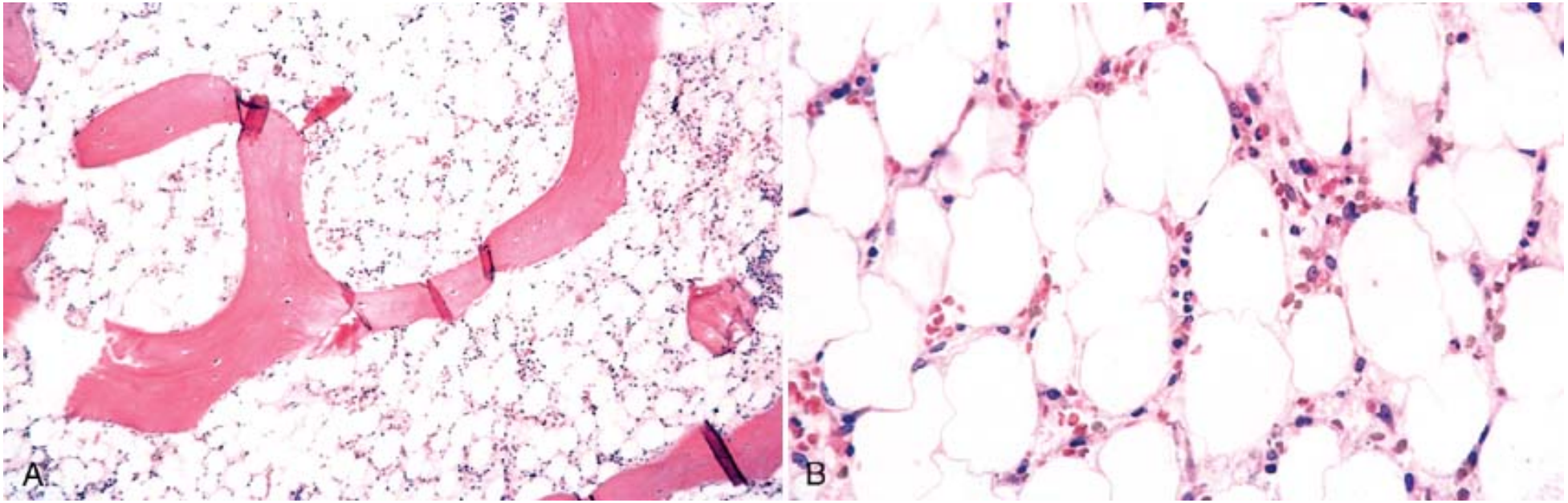


TABLE 13-8 -- Pathophysiologic Classification of Polycythemia

Relative	Reduced plasma volume (hemoconcentration)
Absolute	
Primary	Polycythemia vera, rare erythropoietin receptor mutations (low erythropoietin)
Secondary	High erythropoietin
	Appropriate: lung disease, high-altitude living, cyanotic heart disease
	Inappropriate: erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma)

More specialized tests are available to measure the levels of specific clotting factors, fibrinogen, fibrin split products, the presence of circulating anticoagulants, and platelet function. With this overview, we can turn to the various categories of bleeding disorders.

BLEEDING DISORDERS CAUSED BY VESSEL WALL ABNORMALITIES

Disorders within this category, sometimes called *nonthrombocytopenic purpuras,* are relatively common but do not usually cause serious bleeding problems. Most often, they induce small hemorrhages (petechiae and purpura) in the skin or mucous membranes, particularly the gingivae. On occasion, however, more significant hemorrhages can occur into joints, muscles, and subperiosteal locations or take the form of menorrhagia, nosebleeds, gastrointestinal bleeding, or hematuria. *The platelet count, bleeding time, and results of the coagulation tests (PT, PTT) are usually normal.*

The varied clinical conditions in which hemorrhages can be related to abnormalities in the vessel wall include the following:

- Many *infections* induce petechial and purpuric hemorrhages, but especially implicated are meningococcemia, other forms of septicemia, infective endocarditis, and several of the

rickettsioses. The involved mechanism is presumably microbial damage to the microvasculature (vasculitis) or disseminated intravascular coagulation (DIC). Failure to recognize meningococcemia as a cause of petechiae and purpura can be catastrophic for the patient.

• *Drug reactions* sometimes induce cutaneous petechiae and purpura without causing thrombocytopenia. In many instances, the vascular injury is mediated by drug-induced antibodies and deposition of immune complexes in the vessel walls, leading to hypersensitivity (leukocytoclastic) vasculitis (Chapter 11).

• *Scurvy and the Ehlers-Danlos syndrome* are associated with microvascular bleeding resulting from impaired formation of collagens needed for support of vessel walls. The same mechanism may account for spontaneous purpura commonly seen in the very elderly. The predisposition to skin hemorrhages in *Cushing syndrome,* in which the protein-wasting effects of excessive corticosteroid production cause loss of perivascular supporting tissue, has a similar etiology.

• *Henoch-Schönlein purpura* is a systemic hypersensitivity disease of unknown cause characterized by a purpuric rash, colicky abdominal pain (presumably due to focal hemorrhages into the gastrointestinal tract), polyarthralgia, and acute glomerulonephritis (Chapter 20). All these changes result from the deposition of circulating immune complexes within vessels throughout the body and within the glomerular mesangial regions.

• *Hereditary hemorrhagic telangiectasia* is an autosomal dominant disorder characterized by dilated, tortuous blood vessels with thin walls that bleed readily. Bleeding can occur anywhere in the body but is most common under the mucous membranes of the nose (epistaxis), tongue, mouth, and eyes and throughout the gastrointestinal tract.

• *Amyloid infiltration of blood vessels.* Systemic amyloidosis is associated with perivascular deposition of amyloid and consequent weakening of blood vessel wall. This is most commonly observed in plasma cell dyscrasias (Chapter 14) and is manifested as mucocutaneous petechiae.

Bleeding in these conditions is rarely life threatening with the exception of some cases of hereditary telangiectasia. Recognition of the presenting symptoms should prompt further studies to establish a specific diagnosis.

BLEEDING RELATED TO REDUCED PLATELET NUMBER: THROMBOCYTOPENIA

Reduction in platelet number constitutes an important cause of generalized bleeding. Normal platelet counts range from 150,000 to 300,000/μL. A count below 100,000/μL is generally considered to constitute thrombocytopenia. However, spontaneous bleeding does not become evident until the count falls below 20,000/μL. Platelet counts in the range of 20,000 to 50,000/μL can aggravate post-traumatic bleeding. Bleeding resulting from thrombocytopenia alone is associated with a prolonged bleeding time and normal PT and PTT.

The important role of platelets in hemostasis is discussed in Chapter 4 . It hardly needs reiteration that these cells are critical for hemostasis, as they form temporary plugs that quickly stop bleeding and promote key reactions in the clotting cascade. Spontaneous bleeding associated with thrombocytopenia most often involves small vessels. The common sites of such hemorrhage are the skin and the mucous membranes of the gastrointestinal and genitourinary tracts. Intracranial bleeding is a threat to any patient with a markedly depressed platelet count.

The many causes of thrombocytopenia can be classified into the four major categories listed in Table 13-9 .

• *Decreased production of platelets.* This can accompany generalized diseases of bone marrow such as aplastic anemia and leukemias or result from diseases that affect the megakaryocytes somewhat selectively. In vitamin B_{12} or folic acid deficiency, there is poor development and accelerated destruction of megakaryocytes within the bone marrow (ineffective megakaryopoiesis) because DNA synthesis is impaired.

• *Decreased platelet survival.* This important cause of thrombocytopenia can have an *immunologic* or *nonimmunologic* etiology. In the immune conditions, platelet destruction is caused by circulating antiplatelet antibodies or, less often, immune complexes. The antiplatelet antibodies can be directed against a self-antigen on the platelets (autoantibodies) or against platelet antigens that differ among different individuals (alloantibodies). Common antigenic targets of both autoantibodies and alloantibodies are the platelet membrane glycoprotein complexes IIb-IIIa and Ib-IX. Autoimmune thrombocytopenias include idiopathic thrombocytopenic purpura, certain drug-induced thrombocytopenias, and HIV-associated thrombocytopenias. All of these are discussed later. Alloimmune thrombocytopenias arise when an individual is exposed to platelets

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of another person, as may occur after blood transfusion or during pregnancy. In the latter case, neonatal or even fetal thrombocytopenia occurs by a mechanism analogous to

erythroblastosis fetalis.[52]

Nonimmunologic destruction of platelets may be caused by *mechanical injury*,in a manner analogous to red cell destruction in microangiopathic hemolytic anemia. The underlying conditions are also similar, including prosthetic heart valves and diffuse narrowing of the microvessels (e.g., malignant hypertension).

• *Sequestration.* Thrombocytopenia, usually moderate in severity, may develop in any patient with marked splenomegaly, a condition sometimes referred to as *hypersplenism* (Chapter 14). The spleen normally sequesters 30% to 40% of the body's platelets, which remain in equilibrium with the circulating pool. When necessary, hypersplenic thrombocytopenia can be ameliorated by splenectomy.

• *Dilutional.* Massive *transfusions* can produce a dilutional thrombocytopenia. Blood stored for longer than 24 hours contains virtually no viable platelets; thus, plasma volume and red cell mass are reconstituted by transfusion, but the number of circulating platelets is relatively reduced.

TABLE 13-9 -- Causes of Thrombocytopenia

Decreased production of platelets
Generalized diseases of bone marrow
••Aplastic anemia: congenital and acquired (see Table 13-7)
••Marrow infiltration: leukemia, disseminated cancer
Selective impairment of platelet production
••Drug-induced: alcohol, thiazides, cytotoxic drugs
••Infections: measles, human immunodeficiency virus (HIV)
Ineffective megakaryopoiesis
••Megaloblastic anemia
••Myelodysplastic syndromes
Decreased platelet survival
Immunologic destruction
••Autoimmune: idiopathic thrombocytopenic purpura, systemic lupus erythematosus
••Isoimmune: post-transfusion and neonatal
••Drug-associated: quinidine, heparin, sulfa compounds
••Infections: infectious mononucleosis, HIV infection, cytomegalovirus
Nonimmunologic destruction
••Disseminated intravascular coagulation
••Thrombotic thrombocytopenic purpura
••Giant hemangiomas
••Microangiopathic hemolytic anemias
Sequestration

Hypersplenism
Dilutional

Immune Thrombocytopenic Purpura (ITP)

ITP can occur in the setting of a variety of conditions and exposures (secondary ITP) or in the absence of any known risk factors (primary or idiopathic ITP). There are two clinical subtypes of primary ITP, acute and chronic; both are autoimmune disorders in which platelet destruction results from the formation of antiplatelet autoantibodies. We first discuss the more common chronic form of primary ITP; acute ITP, a self-limited disease of children, is discussed later.

Immunologically mediated destruction of platelets (immune thrombocytopenia) occurs in many different settings, including systemic lupus erythematosus, acquired immunodeficiency syndrome (AIDS), after viral infections, and as a complication of drug therapy. These *secondary forms of immune thrombocytopenia can sometimes mimic the idiopathic autoimmune variety*, and hence the diagnosis of this disorder should be made only after exclusion of other known causes of thrombocytopenia. Particularly important in this regard is systemic lupus erythematosus, a multisystem autoimmune disease (Chapter 6) that can present with thrombocytopenia.

Pathogenesis.

Chronic ITP is caused by the formation of autoantibodies against platelet membrane glycoproteins, most often IIb-IIIa or Ib-IX.[53] Antibodies reactive with these membrane glycoproteins can be demonstrated in the plasma as well as bound to the platelet surface (platelet-associated immunoglobulins) in approximately 80% of patients. In the overwhelming majority of cases, the antiplatelet antibodies are of the IgG class.

The mechanism of platelet destruction is similar to that seen in autoimmune hemolytic anemias. Opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system. About 75% to 80% of patients are remarkably improved after splenectomy, indicating that the spleen is the major site of removal of sensitized platelets. Since it is also an important site of autoantibody synthesis, the beneficial effects of splenectomy may in part derive from removal of the source of autoantibodies. Although destruction of sensitized platelets is the major mechanism responsible for thrombocytopenia, there is some evidence that megakaryocytes may be damaged by autoantibodies, leading to impairment of platelet production. In most cases, however, megakaryocyte injury is not significant enough to deplete their numbers.

Morphology.

The principal morphologic lesions of thrombocytopenic purpura are found in the spleen and bone marrow but they are not diagnostic. Secondary changes related to the bleeding diathesis may be found in any tissue or structure in the body.

The spleen is normal in size. On histologic examination, there is congestion of the sinusoids and hyperactivity and enlargement of the splenic follicles, manifested by the formation of prominent germinal centers. In many instances, scattered megakaryocytes are found within the sinuses and sinusoidal walls. This may represent a very mild form of extramedullary hematopoiesis driven by elevated levels of thrombopoietin. These splenic findings are not sufficiently distinctive to be considered diagnostic.

Bone marrow reveals a modestly increased number of megakaryocytes. Some are apparently immature, with large, nonlobulated, single nuclei. These findings are not specific for autoimmune thrombocytopenic purpura but merely reflect accelerated thrombopoiesis, being found in most forms of thrombocytopenia resulting from increased platelet destruction. The importance of bone marrow examination is to rule out thrombocytopenias resulting from bone marrow failure. A decrease in the number of megakaryocytes argues against the diagnosis of ITP. The secondary changes relate to the hemorrhages that are dispersed throughout the body.

Clinical Features.

Chronic ITP occurs most commonly in adult women younger than age 40 years. The female-to-male ratio is 3:1. This disorder is often insidious in onset and is characterized by bleeding into the skin and mucosal surfaces. Cutaneous bleeding is seen in the form of *pinpoint hemorrhages* (petechiae), especially prominent in the dependent areas where the capillary pressure is higher. Petechiae can become confluent, giving rise to *ecchymoses*. Often there is a history of easy bruising, nosebleeds, bleeding from the gums, and hemorrhages into soft tissues from relatively minor trauma. The disease may manifest first with melena, hematuria, or excessive menstrual flow. Subarachnoid hemorrhage and intracerebral hemorrhage are serious consequences of thrombocytopenic purpura but, fortunately, are rare in treated patients. Splenomegaly and lymphadenopathy are uncommon in primary ITP, and their presence should lead one to consider other possible diagnoses.

The clinical signs and symptoms associated with ITP are not specific for this condition but rather reflective of thrombocytopenia. Destruction of platelets as the cause of thrombocytopenia is supported by the findings of a low platelet count and normal or increased megakaryocytes in the bone marrow. Accelerated thrombopoiesis often leads to the formation of abnormally large platelets (megathrombocytes), detected easily in a blood smear. The bleeding time is prolonged, but PT and PTT are normal. Tests for platelet autoantibodies are not widely available. *Therefore, a diagnosis of ITP should be made only after other causes of platelet deficiencies, such as those listed in Table 13-9 , have been ruled out.*

Almost all patients respond to immunosuppressive doses of glucocorticoids, but many eventually relapse and come to splenectomy. Most maintain safe platelet counts postsplenectomy and require no further therapy. A significant minority, however, have refractory forms of ITP that can be very difficult to treat. Various immunosuppressive approaches may be effective in such patients.

Acute Immune Thrombocytopenic Purpura

Like chronic ITP, this condition is caused by antiplatelet autoantibodies, but its clinical features and course are distinct. Acute ITP is a disease of childhood occurring with equal frequency in both sexes. The onset of thrombocytopenia is abrupt and is preceded in many cases by a viral illness. The usual interval between the infection and onset of purpura is 2 weeks. Unlike the adult chronic form of ITP, the childhood disease is self-limited, usually resolving spontaneously within 6 months. Steroid therapy is indicated only if thrombocytopenia is severe. Approximately 20% of the children, usually those without a viral prodrome, have persistent low platelet counts beyond 6 months and appear to have chronic ITP similar in most respects to the adult disease.

Drug-Induced Thrombocytopenia: Heparin-Induced Thrombocytopenia

Like hemolytic anemia, thrombocytopenia can result from immunologically mediated destruction of platelets after drug ingestion.[54] The drugs most commonly involved are quinine, quinidine, sulfonamide antibiotics, and heparin. Heparin-induced thrombocytopenia (HIT) is of particular importance because this anticoagulant is used widely and failure to make a correct diagnosis can have severe consequences. Thrombocytopenia occurs in approximately 5% of patients receiving heparin. Most develop so-called type I thrombocytopenia, which occurs rapidly after onset of therapy, is modest in severity and clinically insignificant, and may resolve despite continuation of heparin therapy. It most likely results from a direct platelet-aggregating effect of heparin.

Type II thrombocytopenia is more severe. It occurs 5 to 14 days after commencement of therapy (or sometimes sooner if the patient has been previously sensitized to heparin) and can, paradoxically, lead to life-threatening venous and arterial thrombosis.[54] HIT is caused by an immune reaction directed against a complex of heparin and platelet factor 4, a normal component of platelet granules that binds tightly to heparin. It appears that heparin binding modifies the conformation of platelet factor 4, making it susceptible to immune recognition. [55] *Binding of antibody to platelet factor 4 produces immune complexes that activate platelets, promoting thrombosis even in the setting of marked thrombocytopenia.* The mechanism of platelet activation is not understood. Unless therapy is immediately discontinued, clots within large arteries may lead to vascular insufficiency and limb loss, and emboli from deep venous thrombosis can cause fatal pulmonary thromboembolism.

HIV-Associated Thrombocytopenia

Thrombocytopenia is perhaps the most common hematologic manifestation of HIV infection. Both impaired platelet production and increased destruction are responsible. CD4, the receptor for HIV on T cells, has also been demonstrated on megakaryocytes, making it possible for these cells to be infected by HIV.[56] Infected megakaryocytes are prone to apoptosis and are impaired in terms of platelet production. HIV infection also causes hyperplasia and dysregulation of B cells, which predispose to the development of immune-mediated thrombocytopenia. Antibodies directed against platelet membrane glycoprotein IIb-III complexes are detected in some patients' sera. These autoantibodies, which sometimes cross-react with HIV-associated gp120, are believed to act as opsonins, thus promoting the phagocytosis of platelets by splenic phagocytes. Some studies also implicate nonspecific deposition of immune complexes on platelets as a factor in their premature destruction by the mononuclear phagocyte system.

Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic-Uremic Syndrome (HUS)

The term *thrombotic microangiopathy* encompasses a spectrum of clinical syndromes that includes TTP and HUS. TTP, as originally defined, is associated with the pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits, and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished from TTP by the absence of neurologic symptoms, the prominence of acute renal failure, and frequent affliction of children. Recent studies, however, have tended to blur these clinical distinctions. Many adult patients with "TTP" lack one or more of the five criteria, and some patients with "HUS" have fever and neurologic dysfunction. The common fundamental feature in both of these conditions is widespread formation of hyaline thrombi, comprised primarily of platelet aggregates, in the

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microcirculation. Consumption of platelets leads to *thrombocytopenia*, and the intravascular thrombi provide a likely mechanism for the *microangiopathic hemolytic anemia* and widespread organ dysfunction. It is believed the varied clinical manifestations of TTP and HUS are related to differing proclivities for thrombus formation in specific microvascular beds.

For many years, the pathogenesis of TTP was enigmatic, although treatment with plasma exchange (initiated in the early 1970s) changed an almost uniformly fatal condition into one that is successfully treated in more than 80% of cases. Recently, the underlying cause of many, but not all, cases of TTP has been elucidated. In brief, symptomatic patients are often deficient in an enzyme called ADAMTS 13. This enzyme is designated "vWF metalloprotease" and it normally degrades very high molecular weight multimers of von Willebrand factor (vWF).[57] (ADAMTS 13 is unrelated to the other tissue metalloproteases that cleave extracellular matrix.) In the absence of this enzyme, very high molecular weight multimers of vWF accumulate in plasma and, under some circumstances, promote platelet microaggregate formation throughout the microcirculation, leading to the symptoms of TTP. Superimposition of endothelial cell injury (caused by some other condition) may further predispose a patient to microaggregate formation, thus initiating or exacerbating clinically evident TTP.

The deficiency of ADAMTS 13 may be inherited or acquired.[58] In many patients an antibody that inhibits vWF metalloprotease is detected.[57] Much less commonly the patients have inherited an inactivating mutation in the gene encoding this enzyme. Despite these advances, it is clear that factors other than vWF metalloprotease deficiency must be involved in triggering full-blown TTP, because symptoms are episodic even in those with hereditary deficiency of vWF metalloprotease. It is important to consider the possibility of TTP in any patient presenting with thrombocytopenia and microangiopathic hemolytic anemia, as any delay in diagnosis and treatment can be fatal. Plasma exchange can be life saving by providing the missing enzyme.

In contrast to TTP, most patients with HUS have normal levels of vWF metalloprotease, indicating that HUS usually has a different pathogenesis. [59] One important cause of HUS in children and the elderly is infectious gastroenteritis caused by *E. coli* strain 0157:H7.[60] This strain elaborates a Shiga-like toxin that is absorbed from the inflamed gastrointestinal mucosa. It binds to and damages endothelial cells in the glomerulus and elsewhere, thus initiating platelet activation and aggregation. Affected children present with bloody diarrhea, and a few days later HUS makes its appearance. With appropriate supportive care, affected children often recover completely, but irreversible renal damage and death can occur in more severe cases. HUS can also be seen in adults following exposures that damage endothelial cells (e.g., certain drugs, radiation therapy). The prognosis of adults with HUS is guarded, as it is most often seen in the setting of other chronic, life-threatening conditions.

While DIC and thrombotic microangiopathies share features such as microvascular occlusion and microangiopathic hemolytic anemia, they are pathogenetically distinct. In TTP and HUS (unlike DIC), activation of the coagulation cascade is not of primary importance, and hence results of laboratory tests of coagulation, such as PT and PTT, are usually normal.

BLEEDING DISORDERS RELATED TO DEFECTIVE PLATELET FUNCTIONS

Qualitative defects of platelet function can be congenital or acquired. Several congenital disorders characterized by prolonged bleeding time and normal platelet count have been described. A brief discussion of these rare diseases is warranted by the fact that they provide excellent models for investigating the molecular mechanisms of platelet function.[61]

Congenital disorders of platelet function can be classified into three groups on the basis of the specific functional abnormality: (1) *defects of adhesion,* (2) *defects of aggregation,* and (3) *disorders of platelet secretion (release reaction).*

- Bleeding resulting from defective adhesion of platelets to subendothelial matrix is best illustrated by the autosomal recessive disorder *Bernard-Soulier syndrome*, which is caused by an inherited deficiency of the platelet membrane glycoprotein complex Ib-IX. This glycoprotein is a receptor for vWF and is essential for normal platelet adhesion to subendothelial matrix (Chapter 4).
- Bleeding due to *defective platelet aggregation* is exemplified by *Glanzmann's thrombasthenia,* which is also transmitted as an autosomal recessive trait. Thrombasthenic platelets fail to aggregate in response to adenosine diphosphate (ADP), collagen, epinephrine, or thrombin owing to deficiency or dysfunction of glycoprotein IIb-IIIa, a protein complex that participates in the formation of "bridges" between platelets by binding fibrinogen and vWF.
- *Disorders of platelet secretion* are characterized by normal initial aggregation with collagen or ADP, but subsequent responses, such as secretion of thromboxanes and release of granule-bound ADP, are impaired. The underlying biochemical defects of these so-called *storage pool disorders* are varied, complex, and beyond the scope of our discussion.

Among the *acquired defects* of platelet function, two are clinically significant.[62] The first is *ingestion of aspirin* and other nonsteroidal anti-inflammatory drugs, which significantly prolongs the bleeding time. Aspirin is a potent, irreversible inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A_2 and prostaglandins (Chapter 2). These mediators play important roles in platelet aggregation and subsequent release reactions (Chapter 4). The antiplatelet effects of aspirin form the basis for its use in the prophylaxis of thrombosis (Chapter 12). *Uremia* (Chapter 20) is the second condition exemplifying an acquired defect in platelet function. Although the pathogenesis of bleeding in uremia is complex and not fully understood, several abnormalities of platelet function are found.

HEMORRHAGIC DIATHESES RELATED TO ABNORMALITIES IN CLOTTING FACTORS

A deficiency of every clotting factor has been reported to be the cause of a bleeding disorder, with the exception of factor XII deficiency, which does not cause bleeding. The bleeding in factor deficiencies differs from platelet deficiencies in that spontaneous petechiae or purpura are uncommon. Rather, *the bleeding is manifested by large post-traumatic ecchymoses or hematomas, or prolonged bleeding after a laceration or any form of surgical procedure*. Bleeding into the gastrointestinal and urinary tracts, and particularly into weight-bearing joints, is common. Typical stories include the patient who continues to

ooze for days after a tooth extraction or who develops a hemarthrosis after relatively trivial stress on a knee joint. The course of history may have been changed by a hereditary coagulation defect present in the intermarried royal families of Great Britain and other parts of Europe. Clotting abnormalities can also be acquired in many different conditions.

Acquired disorders are usually characterized by multiple clotting abnormalities. Vitamin K deficiency (Chapter 9) results in impaired synthesis of factors II, VII, IX, and X and protein C.

Since the liver makes virtually all the clotting factors, severe parenchymal liver disease can be associated with a hemorrhagic diathesis. Disseminated intravascular coagulation produces a deficiency of multiple coagulation factors.

Hereditary deficiencies have been identified for each of the clotting factors. Deficiencies of factor VIII (hemophilia A) and of factor IX (Christmas disease, or hemophilia B) are transmitted as sex-linked recessive disorders. Most others follow autosomal patterns of transmission. *These hereditary disorders typically involve a single clotting factor.*

Deficiencies of Factor VIII-vWF Complex

Hemophilia A and von Willebrand disease, two of the most common inherited disorders of bleeding, are caused by qualitative or quantitative defects involving the factor VIII-vWF complex. Before we can discuss these disorders, it is essential to review the structure and function of these proteins.[63] [64]

Plasma factor VIII-vWF is a complex made up of two separate proteins (factor VIII and vWF) that can be characterized according to functional, biochemical, and immunologic criteria. Factor VIII procoagulant protein, or factor VIII (Fig. 13-28 ;

Figure 13-28 Structure and function of factor VIII-von Willebrand factor (vWF) complex. Factor VIII is synthesized in the liver and kidney, and vWF is made in endothelial cells and megakaryocytes. The two associate to form a complex in the circulation. vWF is also present in the subendothelial matrix of normal blood vessels and the alpha granules of platelets. Following endothelial injury, exposure of subendothelial vWF causes adhesion of platelets, primarily via glycoprotein lb platelet receptor. Circulating vWF and vWF released from the alpha granules of activated platelets can bind exposed subendothelial matrix, further contributing to platelet adhesion and activation. Activated platelets form hemostatic aggregates; fibrinogen (and possibly vWF) participate in aggregation through bridging interactions with the platelet receptor GpIIb/III. Factor VIII takes part in the coagulation cascade as a cofactor in the activation of factor X on the surface of activated platelets.

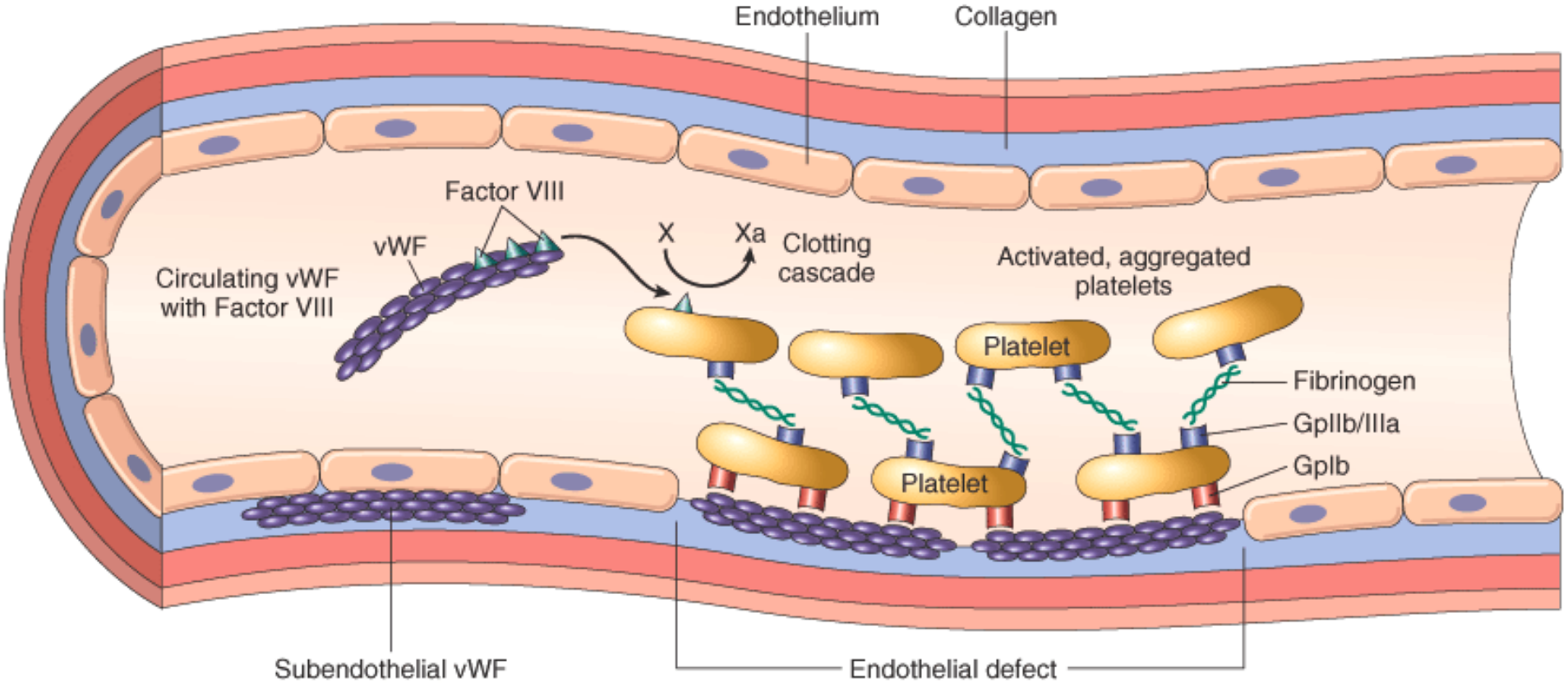

TABLE 13-10 -- Major Disorders Associated with Disseminated Intravascular Coagulation

Obstetric Complications
Abruptio placentae
Retained dead fetus
Septic abortion
Amniotic fluid embolism
Toxemia
Infections
Gram-negative sepsis
Meningococcemia
Rocky Mountain spotted fever
Histoplasmosis

Aspergillosis
Malaria
Neoplasms
Carcinomas of pancreas, prostate, lung, and stomach
Acute promyelocytic leukemia
Massive Tissue Injury
Traumatic
Burns
Extensive surgery
Miscellaneous
Acute intravascular hemolysis, snakebite, giant hemangioma, shock, heat stroke, vasculitis, aortic aneurysm, liver disease

increase the expression of tissue factor on endothelial cell membranes and simultaneously decrease the expression of thrombomodulin.[72] The net result is a shift in balance toward procoagulation.

Endothelial injury, the other major trigger, can initiate DIC by causing release of tissue factor, promoting platelet aggregation, and activating the intrinsic coagulation pathway. TNF is an extremely important mediator of endothelial cell inflammation and injury in septic shock. In addition to the effects previously mentioned, TNF up-regulates the expression of adhesion molecules on endothelial cells and thus favors adhesion of leukocytes, which in turn damage endothelial cells by releasing oxygen-derived free radicals and preformed proteases.[72] Even subtle endothelial injury can unleash procoagulant activity by enhancing membrane expression of tissue factor. Widespread endothelial injury may be produced by deposition of antigen-antibody complexes (e.g., systemic lupus erythematosus), temperature extremes (e.g., heat stroke, burns), or microorganisms (e.g., meningococci, rickettsiae).

Several disorders associated with DIC are listed in Table 13-10 . Of these, DIC is most likely to follow *obstetric complications, malignant neoplasia, sepsis,* and *major trauma*. The initiating factors in these conditions are often multiple and interrelated. For example, particularly in infections caused by gram-negative bacteria, released endotoxins can activate both the intrinsic and extrinsic pathways by producing endothelial cell injury and release of thromboplastins from inflammatory cells; furthermore, endotoxins inhibit the anticoagulant activity of protein C by suppressing thrombomodulin expression on endothelium. Endothelial cell damage can also be produced directly by meningococci, rickettsiae, and viruses. Antigen-antibody complexes formed during the infection can activate the classical complement pathway, and complement fragments can secondarily activate both platelets and granulocytes. Endotoxins as well as other bacterial products are also capable of directly activating factor XII. In *massive trauma, extensive surgery,* and *severe burns,* the major mechanism of DIC is believed to be the release of tissue thromboplastins. In *obstetric* conditions, thromboplastins derived from the placenta, dead retained fetus, or amniotic fluid may enter the circulation. However, hypoxia, acidosis, and shock, which often coexist with the surgical and obstetric conditions, also cause widespread endothelial injury. Supervening infection can complicate the problems further. Among cancers, acute promyelocytic leukemia and carcinomas of the lung, pancreas, colon, and stomach are most frequently associated with DIC. These tumors release of a variety of thromboplastic substances, including tissue factors, proteolytic enzymes, mucin, and other undefined tumor products.

The consequences of DIC are twofold. First, there is *widespread deposition of fibrin* within the microcirculation. This can lead to ischemia of the more severely affected or more vulnerable organs and to a *hemolytic anemia* resulting from fragmentation of red cells as they squeeze through the narrowed microvasculature (microangiopathic hemolytic anemia). Second, a *hemorrhagic diathesis* can dominate the clinical picture. This results from consumption of platelets and clotting factors as well as activation of plasminogen. Plasmin can not only cleave fibrin, but also digest factors V and VIII, thereby reducing their concentration further. In addition, fibrinolysis leads to the formation of fibrin degradation products, which inhibit platelet aggregation and fibrin polymerization and have antithrombin activity. All these influences lead to the hemostatic failure seen in DIC (Fig. 13-29).

Morphology.

In general, thrombi are found in the following sites in decreasing order of frequency: brain, heart, lungs, kidneys, adrenals, spleen, and liver. However, no tissue is spared, and thrombi are occasionally found in only one or several organs without affecting others. In giant hemangiomas, for example, thrombi are localized to the neoplasm, where they are believed to form due to local stasis and recurrent trauma to fragile blood vessels. The affected kidneys can reveal small thrombi in the glomeruli that may evoke only reactive swelling of endothelial cells or, in severe cases, microinfarcts or even bilateral renal cortical necrosis. Numerous fibrin thrombi may be found in alveolar capillaries, sometimes associated with pulmonary edema and fibrin exudation, creating "hyaline membranes" reminiscent of acute respiratory distress syndrome (Chapter 15). In the central nervous system, fibrin thrombi can cause microinfarcts, occasionally complicated by simultaneous hemorrhage. Such changes are the basis for the bizarre neurologic signs and symptoms sometimes observed in DIC. The manifestations of DIC in the endocrine glands are of considerable interest. In meningococcemia, fibrin thrombi within the microcirculation of the adrenal cortex are the likely basis for the massive adrenal hemorrhages seen in Waterhouse-Friderichsen syndrome (Chapter 24). Similarly, Sheehan postpartum pituitary necrosis (Chapter 24) is a form of DIC complicating labor and delivery. In toxemia of pregnancy (Chapter 22), the placenta exhibits widespread microthrombi, providing a plausible

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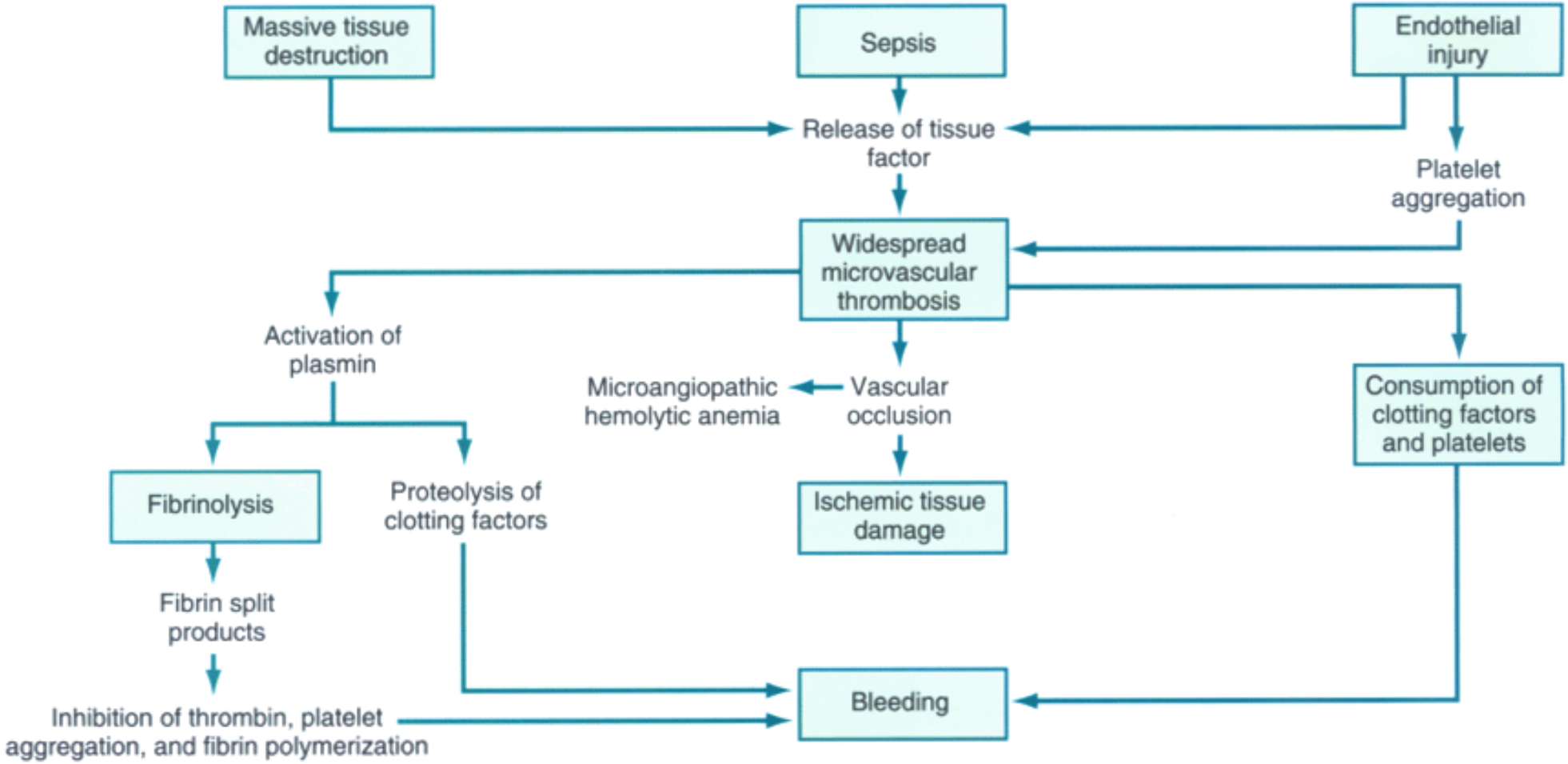
Figure 13-29 Pathophysiology of disseminated intravascular coagulation.



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Chapter 14 - Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus

Jon C. Aster MD, PhD

White Blood Cells and Lymph Nodes

Normal

The origin and differentiation of white blood cells (granulocytes, monocytes, and lymphocytes) were briefly discussed in Chapter 13 . Lymphocytes and monocytes not only circulate in the blood and lymph but also accumulate in discrete, organized masses within lymph nodes, thymus, spleen, tonsils, adenoids, and Peyer patches. Less discrete collections of lymphoid cells occur in the bone marrow, lungs, gastrointestinal tract, and other tissues. Lymph nodes are the most widely distributed and easily accessible component of the lymphoid tissue and hence are frequently examined for diagnosis of lymphoreticular disorders. Before discussing these pathologic states, we will briefly review the normal morphology of lymph nodes (shown in Fig. 6-3 , Chapter 6).

Lymph nodes are discrete structures surrounded by a capsule composed of connective tissue and a few elastic fibrils. The capsule is perforated by multiple afferent lymphatics that empty into a fenestrated subcapsular peripheral sinus. Lymph extravasates from this sinus and slowly percolates through the node, eventually collecting in medullary sinusoids and exiting through a single efferent lymphatic vessel in the hilus, which is the point of penetration by a single small artery and vein. Situated in the cortex subjacent to the peripheral sinus are spherical or egg-shaped aggregates of small lymphocytes, the so-called primary *follicles*, which contain numerous immunologically naïve B cells. The paracortical region lying between primary follicles is populated by numerous evenly dispersed small T lymphocytes. Deep to the cortex lies the medulla, which contains variable numbers of plasma cells and relatively few lymphocytes.

This morphologic description reflects the static organization of a lymph node that is not responding to a foreign invader. As secondary lines of defense, lymph nodes constantly respond to stimuli, particularly infectious microbes, even in the absence of clinical disease. Within several days of antigenic stimulation, primary follicles enlarge and are transformed into palestaining *germinal centers*, highly dynamic structures in which B cells acquire the capacity to make high-affinity antibodies against specific antigens. Normal germinal centers are surrounded by a dark-staining mantle zone, which contains mainly small naïve B cells. In some reactive conditions, a rim of B cells with slightly more cytoplasm accumulates outside of the mantle zone; cells occupying this region are called *marginal zone B cells*. The paracortical T-cell zones also frequently undergo hyperplasia in immune reactions in which cellular immunity is particularly important, such as viral infections.

The degree and pattern of morphologic change are dependent on the inciting stimulus and the intensity of the immune response. Trivial injuries and infections induce subtle changes in lymph node histology, while more significant infections inevitably produce enlargement of nodes and sometimes leave residual scarring. For this reason, lymph nodes in adults are almost never "normal" or "resting," and it is often necessary to distinguish morphologic changes secondary to past experience from those related to present disease.

Pathology

Disorders of white blood cells can be classified into two broad categories: *proliferative disorders*, in which there is an expansion of leukocytes, and *leukopenias*, which are defined as a deficiency of leukocytes. Proliferations of white cells can be *reactive* or *neoplastic*. Since the major function of leukocytes is host defense, reactive proliferation in response to an underlying primary, often microbial, disease is fairly common. Neoplastic disorders, although less frequent, are much more important clinically. In the following discussion, we shall first

describe the leukopenic states and summarize the common reactive disorders and then consider in some detail malignant proliferations of white cells.

Leukopenia

The number of circulating white cells may be markedly decreased in a variety of disorders. An abnormally low white cell count *(leukopenia)* usually results from reduced numbers of neutrophils *(neutropenia, granulocytopenia). Lymphopenia* is less common; in addition to congenital immunodeficiency diseases (see Chapter 6), it is most commonly observed in specific settings, such as advanced HIV infection, following therapy with glucocorticoids or cytotoxic drugs, autoimmune disorders, malnutrition, and certain acute viral infections. Only the more common leukopenias involving granulocytes will be discussed further here.

NEUTROPENIA, AGRANULOCYTOSIS

Reduction in the number of granulocytes in the peripheral blood *(neutropenia)* can be seen in a wide variety of circumstances. A marked reduction in neutrophil count, referred to as *arganulocytosis*, has serious consequences by making individuals susceptible to infections.

Pathogenesis.

A reduction in circulating granulocytes will occur if there is (1) reduced or ineffective production of neutrophils or (2) accelerated removal of neutrophils from the circulating blood. *Inadequate or ineffective granulopoiesis* is observed in the setting of:

- Suppression of myeloid stem cells, as occurs in aplastic anemia (see Chapter 13) and a variety of infiltrative marrow disorders (tumors, granulomatous disease, etc.); in these conditions, granulocytopenia is accompanied by anemia and thrombocytopenia.
- Suppression of committed granulocytic precursors due to exposure to certain drugs, as discussed below.

- Disease states associated with ineffective granulopoiesis, such as megaloblastic anemias due to vitamin B_{12} or folate deficiency (see Chapter 13) and myelodysplastic syndromes, where defective precursors are susceptible to death in the marrow.
- Rare inherited conditions (such as Kostmann syndrome) in which genetic defects in specific genes result in impaired granulocytic differentiation.

Accelerated removal or destruction of neutrophils occurs with:

- Immunologically mediated injury to the neutrophils, which may be idiopathic, associated with a well-defined immunologic disorder (e.g., systemic lupus erythematosus), or produced by exposure to drugs.
- Splenic sequestration, in which excessive destruction occurs secondary to enlargement of the spleen, usually associated with increased destruction of red cells and platelets as well.
- Increased peripheral utilization, as may occur in overwhelming bacterial, fungal, or rickettsial infections.

Drugs are responsible for most of the significant neutropenias (agranulocytoses). Certain drugs, such as alkylating agents and antimetabolites used in cancer treatment, produce agranulocytosis in a predictable, dose-related fashion. Because such drugs cause a generalized suppression of the bone marrow, production of erythrocytes and platelets is also affected. Agranulocytosis can also occur as an idiosyncratic reaction to a large variety of agents. The roster of implicated drugs includes aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, thiouracil, and phenylbutazone. The neutropenia induced by chlorpromazine and related phenothiazines may result from a toxic effect on granulocytic precursors in the bone marrow. In contrast, agranulocytosis following administration of aminopyrine, thiouracil, and certain sulfonamides likely stems from immunologically mediated destruction of mature

neutrophils through mechanisms similar to those involved in drug-induced hemolytic anemias (see Chapter 13).

In some patients with acquired idiopathic neutropenia, autoantibodies directed against neutrophil-specific antigens are detected.[1] Severe neutropenia can also occur in association with monoclonal proliferations of large granular lymphocytes (so-called LGL leukemia).[2] The mechanism of this neutropenia is not clear; suppression of marrow granulocytic progenitors is considered most likely.

Morphology.

The anatomic alterations in the bone marrow vary according to the underlying cause. When neutropenia is caused by excessive destruction of mature neutrophils, the marrow is usually hypercellular owing to the presence of increased numbers of granulocytic precursors. Hypercellularity is also the rule in neutropenias associated with ineffective granulopoiesis, as occurs in megaloblastic anemias and myelodysplastic syndromes. Agranulocytosis caused by agents that suppress or destroy granulocytic precursors is understandably associated with marrow hypocellularity.

Infections (most often bacterial or fungal) are a common consequence of agranulocytosis. Ulcerating necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa, pharynx, or anywhere within the oral cavity (agranulocytic angina) are quite characteristic. These ulcers are typically deep, undermined, and covered by gray to green-black necrotic membranes from which numerous bacteria or fungi can be isolated. Less frequently, similar ulcerative lesions occur in the skin, vagina, anus, or gastrointestinal tract. Severe life-threatening invasive bacterial or fungal infections can occur in the lungs, urinary tract, and kidneys. The neutropenic patient is at particularly high risk for deep fungal infections caused by organisms such as *Candida* and *Aspergillus*. Sites of infection often show a massive growth of organisms with little leukocytic response. In the most dramatic instances, bacteria grow in colonies (botryomycosis) resembling those seen on nutrient media. The regional lymph nodes draining these infections are enlarged and inflamed.

Clinical Course.

The symptoms and signs of neutropenias are related to bacterial or fungal infections. They include malaise, chills, and fever, followed in sequence by marked weakness and fatigability. In severe agranulocytosis with virtual absence of neutrophils, these infections can be overwhelming and cause death within a few days.

A neutrophil count of less than 1000 cells per mm^3 of blood is worrisome, but most serious infections occur with counts below 500 per mm^3 . Because infections are often fulminant, broad-spectrum antibiotics are given expeditiously whenever signs or symptoms appear. In some instances, such as following myelosuppressive chemotherapy, neutropenia is treated with granulocyte colony-stimulating factor (G-CSF), a growth factor that stimulates the production of granulocytes from marrow precursors.

Reactive (Inflammatory) Proliferations of White Cells and Lymph Nodes

LEUKOCYTOSIS

Leukocytosis refers to an increase in the number of blood leukocytes. It is a common reaction to a variety of inflammatory states and is sometimes the first indication of neoplastic growth of leukocytes.

Pathogenesis.

The peripheral blood leukocyte count is influenced by several factors, including:

- The size of the myeloid (for granulocytes and monocytes) and lymphoid (for lymphocytes) precursor and storage cell pools in the bone marrow, circulation, and peripheral tissues
- The rate of release of cells from the storage pool into the circulation

- The proportion of cells that are adherent to blood vessel walls at any time (the marginating pool)
- The rate of extravasation of cells from the blood into tissues

As was discussed in Chapter 2 and Chapter 13 , leukocyte homeostasis is maintained by cytokines, growth factors, and adhesion molecules through their effects on the commitment, proliferation, differentiation, and extravasation of leukocytes and their progenitors. The mechanisms of leukocytosis vary

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Figure 14-1 (Figure Not Available) Mechanisms of neutrophilic leukocytosis. Neutrophils and their precursors are distributed in five pools: a bone marrow precursor pool; a bone marrow storage pool, consisting of mature and slightly immature neutrophils (band forms); a peripheral blood marginating pool; a peripheral blood circulating pool; and a tissue pool. Sampling of the peripheral blood assesses only the circulating pool, which can be enlarged by increased release of neutrophils and band forms from the marrow storage pool, decreased margination, diminished extravasation into tissues, or expansion of the marrow precursor cell pool. Diverse stimuli that increase the circulating pool through various mechanisms are listed. It should be noted that certain stimuli (e.g., acute infection) cause changes in flux between multiple pools simultaneously.

depending on the affected leukocyte pool and the particular factor. In acute infection, there is a rapid increase in the egress of mature granulocytes from the bone marrow pool, which is roughly 50 times the size of the peripheral blood marginal pool. The release of IL-1, TNF, and other inflammatory cytokines stimulates bone marrow stromal cells and T cells to produce increased amounts of colony-stimulating factors (CSFs), which enhance the proliferation and differentiation of committed granulocytic progenitors and, over several days, cause a sustained increase in neutrophil production. Figure 14-1 (Figure Not Available) summarizes the major mechanisms of neutrophilic leukocytosis and their causes.

TABLE 14-1 -- Causes of Leukocytosis

Neutrophilic leukocytosis	Acute bacterial infections, especially those caused by pyogenic organisms; sterile inflammation caused by, for example, tissue necrosis (myocardial infarction, burns)
Eosinophilic leukocytosis (eosinophilia)	Allergic disorders such as asthma, hay fever, allergic skin diseases (e.g., pemphigus, dermatitis herpetiformis); parasitic infestations; drug reactions; certain malignancies (e.g., Hodgkin disease and some non-Hodgkin lymphomas); collagen vascular disorders and some vasculitides; atheroembolic disease (transient)
Basophilic leukocytosis (basophilia)	Rare, often indicative of a myeloproliferative disease (e.g., chronic myelogenous leukemia)
Monocytosis	Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis and malaria; collagen vascular diseases (e.g., systemic lupus erythematosus) and inflammatory bowel diseases (e.g., ulcerative colitis)
Lymphocytosis	Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis); viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); *Bordetella pertussis* infection

Other growth factors preferentially stimulate other types of leukocytosis. For example, IL-5 causes eosinophilia by enhancing the growth, survival, and differentiation of eosinophils, while IL-7 plays a central role in lymphopoiesis. Such factors are differentially produced in response to various pathogenic stimuli, and as a result, the five principal types of leukocytosis (neutrophilic, eosinophilic, and basophilic leukocytosis, monocytosis, and lymphocytosis) each tend to be observed in particular clinical settings (summarized in Table 14-1).

In sepsis or severe inflammatory disorders (such as Kawasaki disease), leukocytosis is often accompanied by morphologic

changes in the neutrophils, such as toxic granulations, Döhle bodies, and cytoplasmic vacuoles (Fig. 14-2). *Toxic granules* are coarse and darker than the normal neutrophilic granules and are believed to represent abnormal azurophilic (primary) granules. *Döhle bodies* are patches of dilated endoplasmic reticulum that appear as sky-blue cytoplasmic "puddles" in smears stained with Wright-Giemsa stain.

In most instances, it is not difficult to distinguish reactive leukocytosis from leukocytosis caused by flooding of the peripheral blood by neoplastic white blood cells (leukemia), but uncertainties may arise in two settings. Particularly in children, acute viral infections can produce the appearance of activated lymphocytes in the peripheral blood and marrow that resemble neoplastic lymphoid cells. At other times, particularly in inflammatory states and severe chronic infections, many immature granulocytes appear in the blood, simulating a picture of myelogenous leukemia *(leukemoid reaction)*. Special laboratory studies (discussed later) are helpful in distinguishing reactive and neoplastic leukocytoses.

In addition to causing leukocytosis, infections and inflammatory stimuli often elicit immune reactions within lymph nodes. The infections that lead to lymphadenitis are numerous. Some that produce distinctive morphologic patterns are described in other chapters. Most, however, cause stereotypic patterns of lymph node reaction designated acute and chronic nonspecific lymphadenitis.

ACUTE NONSPECIFIC LYMPHADENITIS

Lymph nodes undergo reactive changes whenever they are challenged by microbiologic agents, cell debris, or foreign matter introduced into wounds or into the circulation. Acute lymphadenitis is most often seen in the cervical region due to microbial drainage from infections of the teeth or tonsils and in the axillary or inguinal regions secondary to infections in the extremities. Similarly, acute lymphadenitis often occurs in mesenteric lymph nodes draining acute appendicitis. Unfortunately, other self-limited infections can also cause mesenteric

Figure 14-2 Reactive changes in neutrophils. Neutrophils containing coarse purple cytoplasmic granules (toxic granulations) and blue cytoplasmic patches of dilated endoplasmic reticulum (Döhle bodies, *arrow*) are observed in this peripheral blood smear taken from a patient with bacterial sepsis.

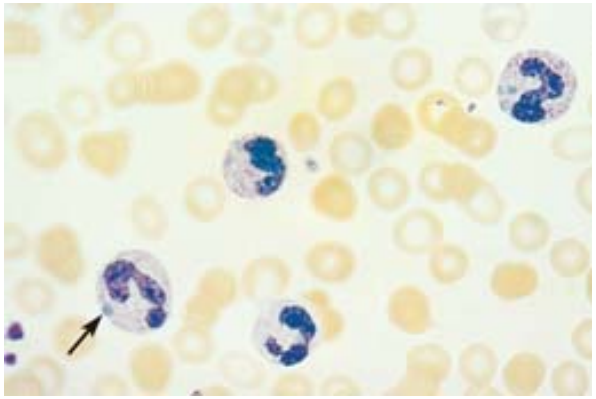

Figure 14-3 Follicular hyperplasia. *A*, Low-power view showing a reactive follicle and surrounding mantle zone. The dark-staining mantle zone is polarized, being much more prominent adjacent to the germinal center light zone in the left half of the follicle. The right half of the follicle consists of the dark zone. *B*, High-power view of the dark zone shows several mitotic figures and numerous macrophages containing phagocytosed apoptotic cells (tingible bodies).

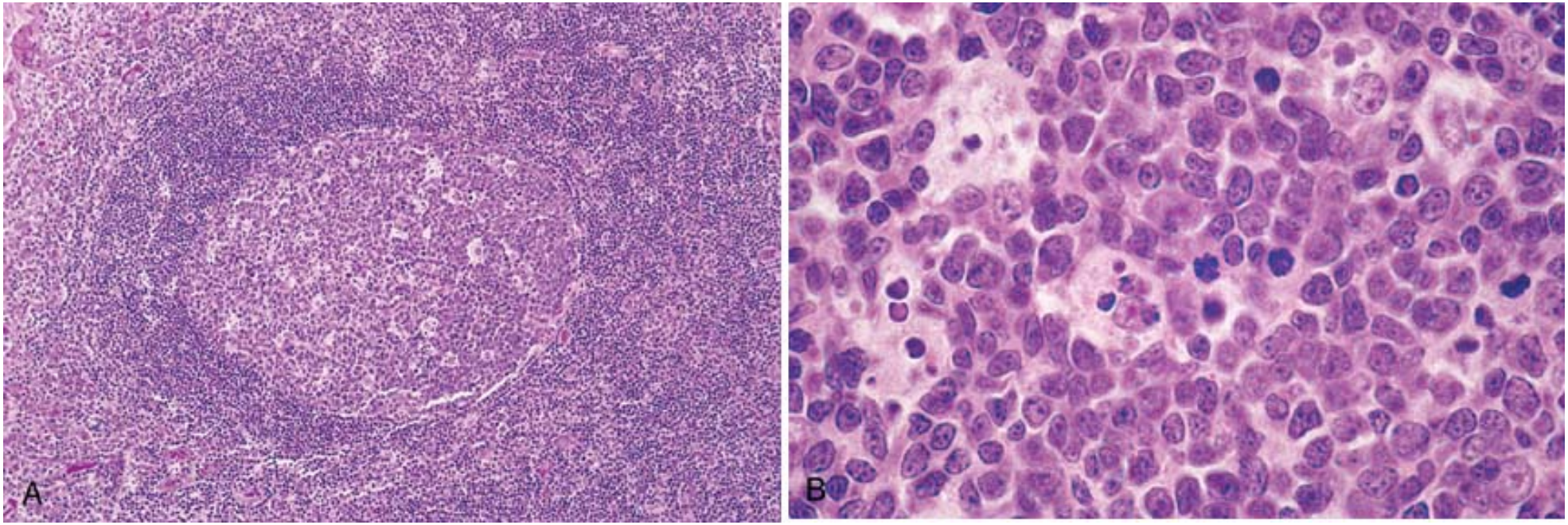

TABLE 14-2 -- The WHO Classification of the Lymphoid Neoplasms

I. Precursor B-Cell Neoplasms
Precursor-B lymphoblastic leukemia/lymphoma
II. Peripheral B-Cell Neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic and nodal marginal zone lymphomas
Extranodal marginal zone lymphoma
Mantle cell lymphoma
Follicular lymphoma
Marginal zone lymphoma
Hairy cell leukemia
Plasmacytoma/plasma cell myeloma
Diffuse large B-cell lymphoma
Burkitt lymphoma

III. Precursor T-Cell Neoplasms
Precursor-T lymphoblastic leukemia/lymphoma
IV. Peripheral T-Cell and NK-Cell Neoplasms
T-cell prolymphocytic leukemia
Large granular lymphocytic leukemia
Mycosis fungoides/Sézary syndrome
Peripheral T-cell lymphoma, unspecified
Anaplastic large cell lymphoma
Angioimmunoblastic T-cell lymphoma
Enteropathy-associated T-cell lymphoma
Panniculitis-like T-cell lymphoma
Hepatosplenic γδ T-cell lymphoma
Adult T-cell leukemia/lymphoma
NK/T-cell lymphoma, nasal type
NK-cell leukemia
V. Hodgkin Lymphoma
Classical subtypes
••Nodular sclerosis
••Mixed cellularity
••Lymphocyte-rich
••Lymphocyte depletion
Lymphocyte predominance

hematopathologists, oncologists, and molecular biologists came together to create the *Revised European-American Classification of Lymphoid Neoplasms* (REAL).[8] Of importance, this classification scheme incorporated objective criteria, such as immunophenotype and genetic aberrations, together with morphologic and clinical features, to define distinct clinicopathologic entities. Experience has shown that most entities in the REAL classification can be diagnosed reproducibly by experienced pathologists and stratify patients into good and bad prognosis groups.[9] [10] More recently, an international group of hematopathologists and oncologists convened by the World Health Organization (WHO) reviewed and updated the REAL classification, resulting in the inclusion of a number of additional rare entities.[11] Presented here is the WHO classification (Table 14-2), which sorts the lymphoid neoplasms into five broad categories, based on their cell of origin:

1. Precursor B-cell neoplasms (neoplasms of immature B cells)
2. Peripheral B-cell neoplasms (neoplasms of mature B cells)
3. Precursor T-cell neoplasms (neoplasms of immature T cells)

4. Peripheral T-cell and NK-cell neoplasms (neoplasms of mature T cells and natural killer cells)
5. Hodgkin lymphoma (neoplasms of Reed-Sternberg cells and variants).

Before we discuss the specific entities described in the WHO classification, some important principles relevant to the lymphoid neoplasms need to be emphasized.

• Lymphoid neoplasia can be suspected from the clinical features, but *histologic examination of lymph nodes or other involved tissues is required for diagnosis*.
• As will be recalled from Chapter 6 , antigen receptor genes rearrange during normal B- and T-cell differentiation through a mechanism that ensures that each developing lymphocyte makes a single, unique antigen receptor. *In most lymphoid neoplasms, antigen receptor gene rearrangement*

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precedes transformation; hence, the daughter cells derived from the malignant progenitor share the same antigen receptor gene configuration and sequence and synthesize identical antigen receptor proteins(either immunoglobulins or T-cell receptors). In contrast, normal immune responses are polyclonal and thus comprise populations of lymphocytes expressing many different antigen receptors. As a result, analyses of antigen receptor genes and/or their protein products can be used to distinguish reactive and malignant lymphoid proliferations. In addition, each antigen receptor gene rearrangement produces a unique DNA sequence that constitutes a highly specific clonal marker that can be used to detect small numbers of residual malignant cells after therapy.[12]

• *The vast majority of lymphoid neoplasms (80% to 85%) are of B-cell origin, most of the remainder being T-cell tumors; only rarely are tumors of NK origin encountered.* Most lymphoid neoplasms resemble some recognizable stage of B- or T-cell differentiation (Fig. 14-4), a feature that is used in their classification. Markers recognized by antibodies that are helpful in the characterization of lymphomas and leukemias are listed in Table 14-3 .

• *As tumors of the immune system, lymphoid neoplasms often disrupt normal architecture and function of the immune system, leading to immune abnormalities.* Both a loss of vigilance (as evidenced by susceptibility to infection) and breakdown of tolerance (manifested by autoimmunity) can be seen, sometimes in the same patient. In a further, ironic twist, patients with inherited or acquired immunodeficiency are themselves at high risk of developing certain lymphoid neoplasms, particularly those caused by oncogenic viruses (e.g., EBV).

• *Neoplastic B and T cells tend to recapitulate the behavior of their normal counterparts.* Like normal lymphocytes, transformed B and T cells tend to home to particular tissue sites, leading to characteristic patterns of involvement. For example, follicular lymphomas proliferate in the B-cell areas of the lymph node, producing a nodular or follicular pattern of growth, whereas T-cell lymphomas typically grow in paracortical T-cell zones. As is true of their normal

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counterparts, lymph node homing of neoplastic lymphocytes is likely regulated by expression of particular chemokine receptors. Variable numbers of neoplastic B and T lymphoid cells also recirculate periodically through the lymphatics and peripheral blood to distant sites. Sensitive molecular techniques have shown that most lymphoid tumors are widely disseminated at the time of diagnosis. The most notable exception to this rule is Hodgkin lymphoma, which is sometimes restricted to one group of lymph nodes.

• *Hodgkin lymphoma spreads in an orderly fashion, and as a result staging is of importance in determining therapy.* In contrast, the spread of NHL is less predictable, and as was noted above, most patients are assumed to have systemic disease at the time of diagnosis. Hence, staging in particular NHLs provides useful prognostic information but is generally not as important in guiding therapy as is the case in Hodgkin lymphoma.

Figure 14-4 Origin of lymphoid neoplasms. Stages of B- and T-cell differentiation from which specific lymphoid tumors emerge are shown. Key: CLP, common lymphoid precursor; BLB, pre-B lymphoblast; NBC, naive B cell; MC, mantle B cell; GC, germinal center B cell; MZ, marginal zone B cell; DN, CD4/CD8 double negative pre-T cell; DP, CD4/CD8 double positive pre-T cell; PTC, peripheral T cell.

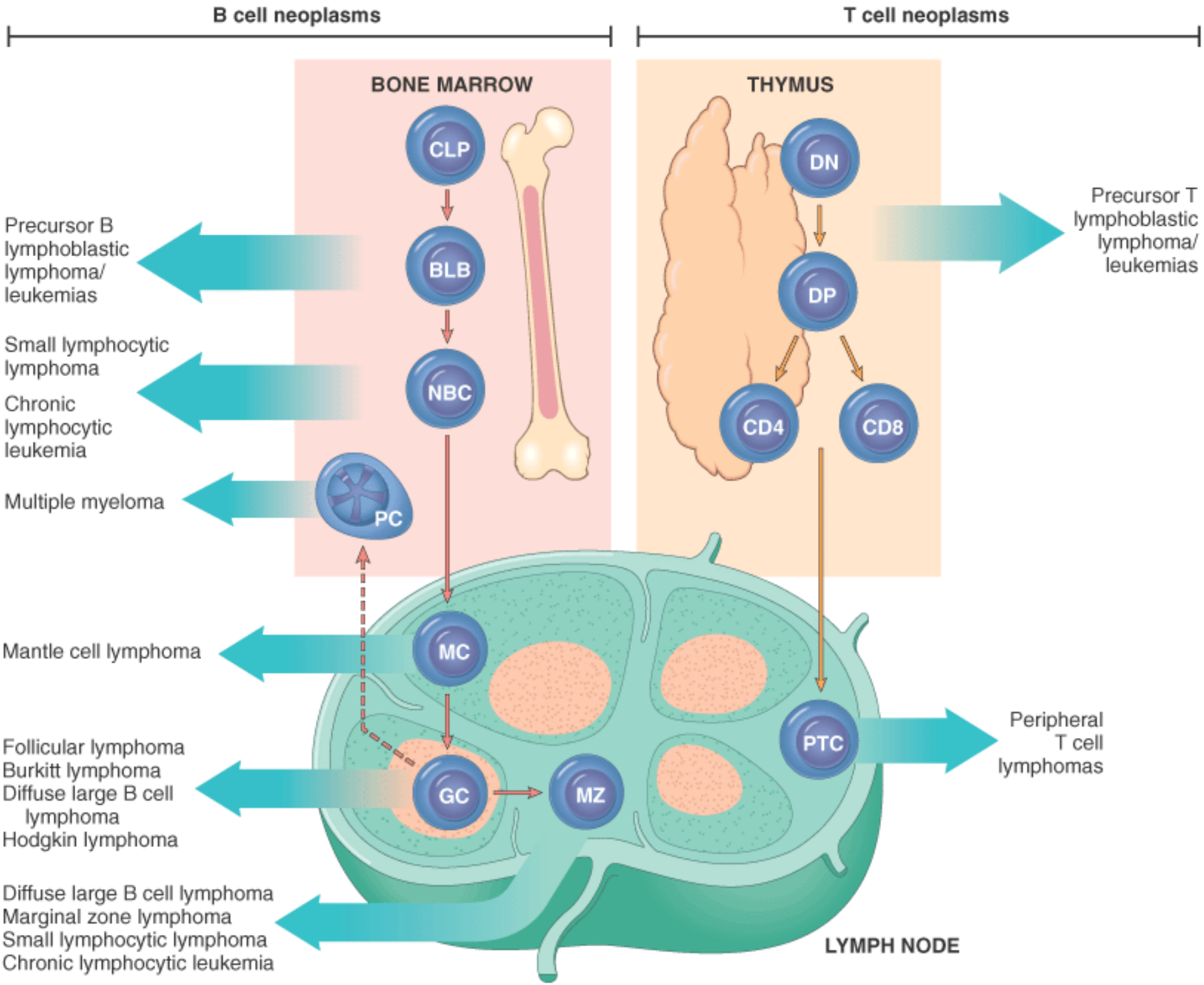

B cell neoplasms
T cell neoplasms
BONE MARROW
THYMUS
CLP
BLB
NBC
PC
DN
DP
CD4
CD8
Precursor B lymphoblastic lymphoma/ leukemias
Small lymphocytic lymphoma
Chronic lymphocytic leukemia
Multiple myeloma
Precursor T lymphoblastic lymphoma/ leukemias
Mantle cell lymphoma
Follicular lymphoma
Burkitt lymphoma
Diffuse large B cell lymphoma
Hodgkin lymphoma
Diffuse large B cell lymphoma
Marginal zone lymphoma
Small lymphocytic lymphoma
Chronic lymphocytic leukemia
MC
GC
MZ
PTC
Peripheral T cell lymphomas
LYMPH NODE

TABLE 14-3 -- Some Immune Cell Antigens Detected by Monoclonal Antibodies

Antigen Designation	Normal Cellular Distribution
Primarily T-Cell Associated	
CD1	Cortical thymocytes and Langerhans histiocytes
CD3	Thymocytes, peripheral T cells
CD4	Helper subset of peripheral T cells, single positive medullary thymocytes, and CD4/CD8 double positive thymocytes
CD5	T cells and a small subset of B cells
CD8	Cytotoxic subset of peripheral T cells, single positive medullary thymocytes, double positive cortical thymocytes, and some NK cells
Primarily B-Cell Associated	
CD10	Marrow pre-B cells and germinal center B cells; also called CALLA
CD19	Marrow pre-B cells and mature B cells but not plasma cells
CD20	Marrow pre-B cells after CD19 and mature B cells but not plasma cells
CD21	EBV receptor; present on mature B cells and follicular dendritic cells
CD23	Activated mature B cells
CD79a	Marrow pre-B cells and mature B cells.
Primarily Monocyte or Macrophage Associated	
CD11c	Granulocytes, monocytes, and macrophages; also expressed by hairy cell leukemias
CD13	Immature and mature monocytes and granulocytes
CD14	Monocytes
CD15	Granulocytes; also expressed by Reed-Sternberg cells and variants in classical Hodgkin lymphoma
CD33	Myeloid progenitors and monocytes
CD64	Mature myeloid cells
Primarily NK-Cell Associated	
CD16	NK cells and granulocytes
CD56	NK cells and a subset of T cells
Primarily Stem Cell and Progenitor Cell Associated	
CD34	Pluripotent hematopoietic stem cells and progenitor cells of many lineages
Activation Markers	
CD30	Activated B cells, T cells, and monocytes; also expressed by Reed-Sternberg cells and variants in classical Hodgkin lymphoma

Present on All Leukocytes	
CD45	All leukocytes; also known as leukocyte common antigen (LCA)
CD, cluster designation; NK, natural killer; CALLA, common acute lymphoblastic leukemia antigen; EBV, Epstein-Barr virus.	

We now turn to the specific entities of the WHO classification. In the discussion that follows, only the most salient immunophenotypic and karyotypic features are included; this information is summarized in Table 14-4 . We will begin with neoplasms of immature lymphoid cells and then move on to tumors of mature B cells, T cells, and NK cells. Within each immunophenotypic category, the most common (and thus most important) entities will be emphasized.

Precursor B- and T-Cell Neoplasms

Acute Lymphoblastic Leukemia/Lymphoma

Acute lymphoblastic leukemia/lymphoma (ALL) encompasses a group of neoplasms composed of immature, precursor B (pre-B) or T (pre-T) lymphocytes referred to as *lymphoblasts. The majority (~85%) of ALLs are precursor B-cell tumors that typically manifest as childhood acute "leukemias"* with extensive bone marrow and variable peripheral blood involvement. The less common *precursor T-cell ALLs tend to present in adolescent males as "lymphomas," often with thymic involvement*. It is worth noting, however, that there is considerable overlap in the clinical behavior of precursor B-cell and T-cell ALL; for example, pre-B cell tumors uncommonly present as "lymphomas," and many pre-T cell tumors evolve to a leukemic peripheral blood picture. Malignant pre-B and pre-T lymphoblasts are also morphologically indistinguishable, and subclassification of ALL is thus dependent on immunophenotyping. Because of their morphologic and clinical similarities, the various forms of ALL will be considered here together.

Approximately 2500 new cases of ALL are diagnosed each year in the United States, most cases occurring in individuals younger than 15 years of age. ALL is almost twice as common in whites as in nonwhites and is slightly more frequent in boys than in girls. The incidence of pre-B ALL is highest at about the age of 4, perhaps because the number of normal bone marrow pre-B lymphoblasts (the cell of origin) peaks in early childhood. Similarly, the peak incidence of pre-T ALL is in adolescence, the age when the thymus reaches its maximal size. Both pre-B and pre-T ALL occur in adults of all ages, but much less frequently than in children.

Morphology.

Because of different responses to chemotherapeutic agents, it is of great practical importance to distinguish ALL from acute myelogenous leukemia (AML), a neoplasm of immature myeloid cells that may cause identical signs and symptoms. Compared to myeloblasts, lymphoblasts have condensed chromatin, inconspicuous nucleoli, and scant agranular cytoplasm (Fig. 14-5*A*). However,

TABLE 14-4 -- Summary of Major Types of Lymphoid Neoplasms

Diagnosis	Cell of Origin	Genotype	Salient Clinical Features
Neoplasms of immature B and T cells			

Precursor B-cell acute lymphoblastic leukemia/ lymphoma	Bone marrow precursor B-cell expressing TdT and lacking surface Ig	Diverse chromosomal translocations; t(12;21) involving *CBFα* and *ETV6* most common rearrangement	Predominantly children with symptoms relating to pancytopenia secondary to marrow involvement; aggressive
Precursor T-cell acute lymphoblastic leukemia/ lymphoma	Precursor T-cell (often of thymic origin) expressing TdT	Diverse chromosomal translocations, many involving T-cell receptor loci; rearrangements of *TAL1* most common	Predominantly adolescent males with thymic masses; variable splenic, hepatic, and bone marrow involvement; aggressive
Neoplasms of mature B cells			
Burkitt lymphoma	Germinal center B-cell; CD10 expression usually seen	Translocations involving c-myc and Ig loci; usually t (8;14), but also t(2;8) or t(8;22). African (endemic) cases latently infected with EBV	Adolescents or young adults with jaw or extranodal abdominal masses; uncommonly presents as a "leukemia"; aggressive
Diffuse large B-cell lymphoma	Germinal center or postgerminal center B-cell	Diverse chromosomal aberrations; ~30% have rearrangements of *BCL6*; ~10% contain the t(14;18); c*REL* amplification in a subset	All ages, but most common in adults; often appears as a single rapidly growing mass; 30% extranodal; aggressive
Extranodal marginal zone lymphoma	Postgerminal center memory B-cell	Trisomy 18, t(11;18), t(1;14); latter create *MALT1-IAP2* and *BCL10-IgH* fusion genes, respectively	Arises at extranodal sites in adults with chronic inflammatory diseases; may remain localized; indolent
Follicular lymphoma	Germinal center B-cell; typically expresses CD10, BCL2, and BCL6	t(14;18) involving the *BCL2* gene	Older adults with generalized lymphadenopathy and marrow involvement; indolent
Hairy cell leukemia	Postgerminal center memory B-cell	No specific chromosomal abnormality	Older males with pancytopenia and splenomegaly; indolent
Mantle cell lymphoma	Naïve B-cell; expresses cyclin D1 and (usually) CD5	t(11;14) involving *BCL1* (cyclin D1) and *IgH*	Older males with disseminated disease; moderately aggressive
Multiple myeloma/solitary plasmacytoma	Plasma cell derived from a postgerminal center B-cell	Diverse rearrangements involving *IgH*	Myeloma: older adults with lytic bone lesions, pathologic fractures, hypercalcemia, renal failure, and primary amyloidosis. Plasmacytoma: isolated plasma cell masses in bone or soft tissue (e.g., oropharynx)
Small lymphocytic lymphoma/chronic lymphocytic leukemia	Naïve B-cell or postgerminal center memory B-cell; expresses CD5	Trisomy 12, deletions of 11q, 13q, and 17p	Older adults with bone marrow, lymph node, spleen and liver disease; most have peripheral blood involvement; autoimmune hemolysis and thrombocytopenia in a minority; indolent
Neoplasms of mature T-cells or NK-cells			
Adult T-cell leukemia/ lymphoma	Helper T-cell expressing CD25 (IL-2 receptor)	HTLV-1 provirus present in tumor cells	Adults with cutaneous lesions, marrow involvement, and hypercalcemia; Japan, West Africa, and the Caribbean; aggressive
Anaplastic large cell lymphoma	Cytotoxic T-cell	Rearrangements of *ALK*	Children and young adults, usually with lymph node and soft tissue disease; aggressive
Extranodal NK/T cell lymphoma	Natural killer cell (common) or cytotoxic T-cell (rare)	No specific chromosomal abnormality; uniformly EBV associated	Adults with destructive extranodal masses, most commonly sinonasal; often accompanied by hemophagocytic syndrome; aggressive

Mycosis fungoides/Sézary syndrome	Helper T-cell	No specific chromosomal abnormality	Adult patients with cutaneous patches, plaques, nodules, or generalized erythema; indolent
T-cell granular lymphocytic leukemia	Two types: (1) CD8+ T-cell, (2) NK-cell	No specific chromosomal abnormality	Adult patients with splenomegaly, neutropenia, and anemia, sometimes, accompanied by autoimmune disease
Hodgkin lymphoma			
Hodgkin lymphoma, lymphocyte-depletion subtype	Germinal center or postgerminal center B-cell	No specific chromosomal abnormality; >70% EBV associated	More common in the elderly and in HIV+ individuals; moderately aggressive
Hodgkin lymphoma, lymphocyte-predominance subtype	Germinal center B-cell	No specific chromosomal abnormality; not associated with EBV	Young to middle-aged males with cervical or axillary lymphadenophathy; indolent
Hodgkin lymphoma, lymphocyte-rich subtype	Germinal center or postgerminal center B-cell	No specific chromosomal abnormality; 40% EBV associated	More common in males, usually presents with lymphadenopathy; moderately aggressive
Hodgkin lymphoma, mixed cellularity subtype	Postgerminal center memory B-cell	No specific chromosomal abnormality; 70% EBV associated	More common in males, usually presents with lymphadenopathy; moderately aggressive
Hodgkin lymphoma, nodular sclerosing subtype	Germinal center or postgerminal center B-cell	No specific chromosomal abnormality; rarely EBV associated	Commonly presents as a mediastinal mass in young females; moderately aggressive

Figure 14-5 *A,* Acute lymphoblastic leukemia/lymphoma. Lymphoblasts with condensed nuclear chromatin, small nucleoli, and scant agranular cytoplasm. *B* and *C* represent the phenotype of the ALL shown in *A*, analyzed by flow cytometry. *B,* Note that the lymphoblasts represented by the red dots express TdT and the B-cell marker CD22. *C,* The same cells are positive for two other markers, CD10 and CD19, commonly expressed on pre-B lymphoblasts. Thus, this is a pre-B cell ALL. *(A, courtesy of Dr. Robert W. McKenna; B and C, courtesy of Dr. Louis Picker, Oregon Health Science Center, Portland, OR.)*

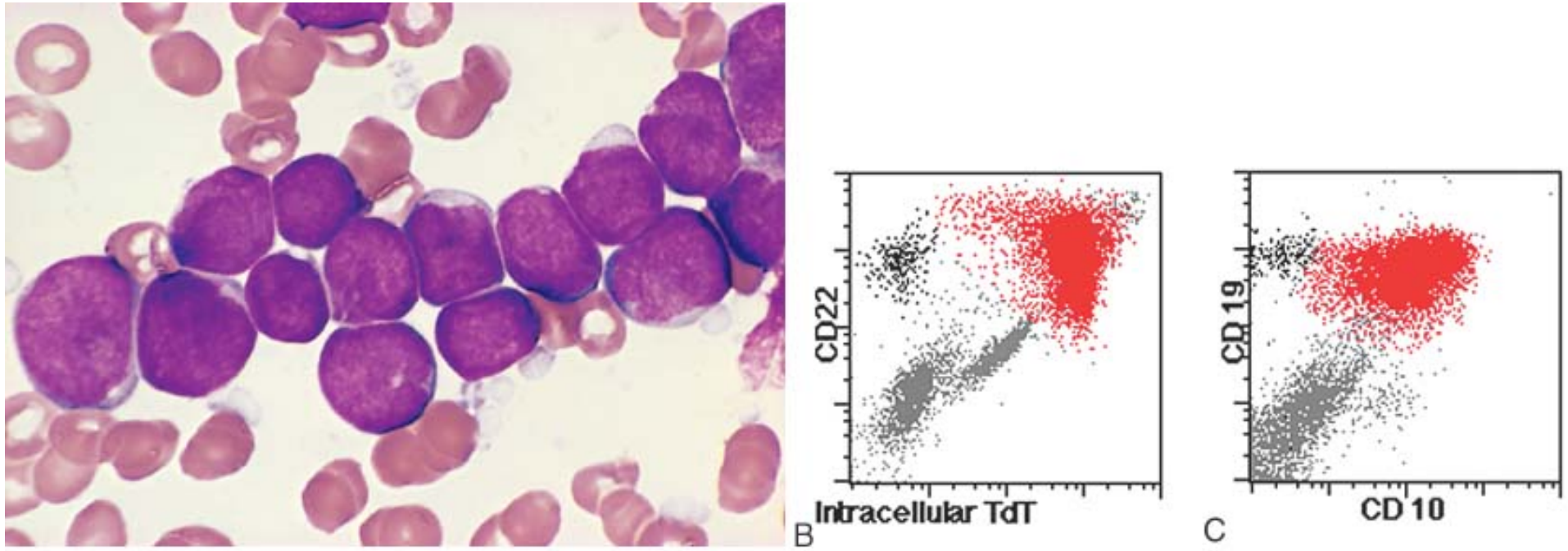


Figure 14-6 Small lymphocytic lymphoma/chronic lymphocytic leukemia (lymph node). *A,* Low-power view shows diffuse effacement of nodal architecture. *B,* At high power, the majority of the tumor cells are small round lymphocytes. A "pro-lymphocyte," a larger cell with a centrally placed nucleolus, is also present in this field (*arrow*). *(A, courtesy of Dr. José Hernandez, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

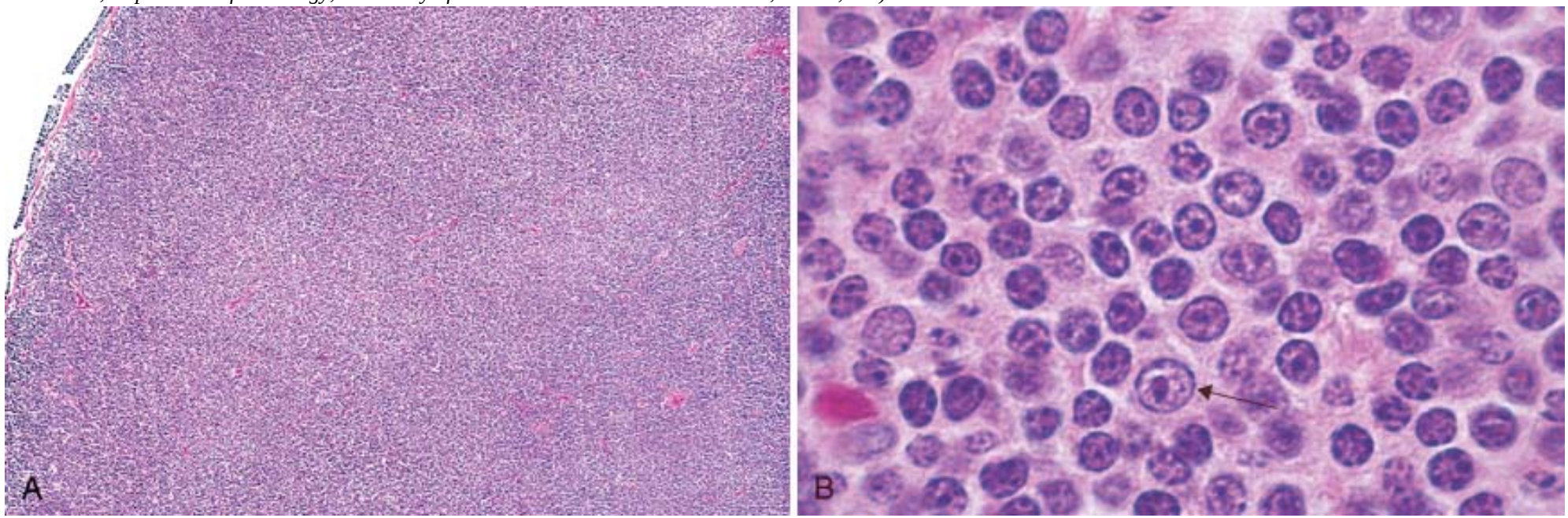


Figure 14-7 Chronic lymphocytic leukemia. This peripheral blood smear is flooded with small lymphocytes with condensed chromatin and scant cytoplasm. A characteristic finding is the

presence of disrupted tumor cells (smudge cells). A coexistent autoimmune hemolytic anemia (see Chapter 13) explains the presence of spherocytes (hyperchromatic, round erythrocytes). A nucleated erythroid cell is present in the lower left-hand corner of the field. In this setting, circulating nucleated red cells could stem from premature release of progenitors in the face of severe anemia, marrow infiltration by tumor (leukoerythroblastosis), or both. *(Courtesy of Dr. Jacqueline Mitus, Brigham and Women's Hospital, Boston, MA.)*

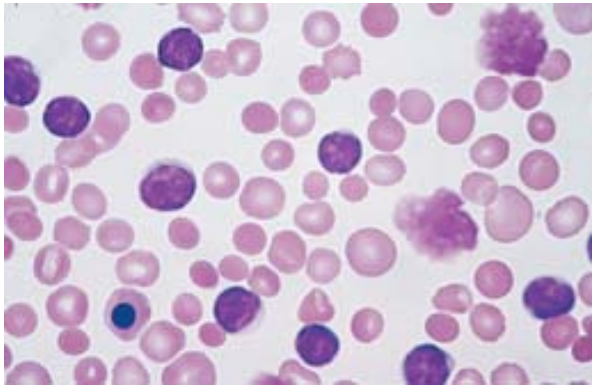


Figure 14-8 Small lymphocytic lymphoma/chronic lymphocytic leukemia (liver). Low-power view of a typical periportal lymphocytic infiltrate. *(Courtesy of Dr. Mark Fleming, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

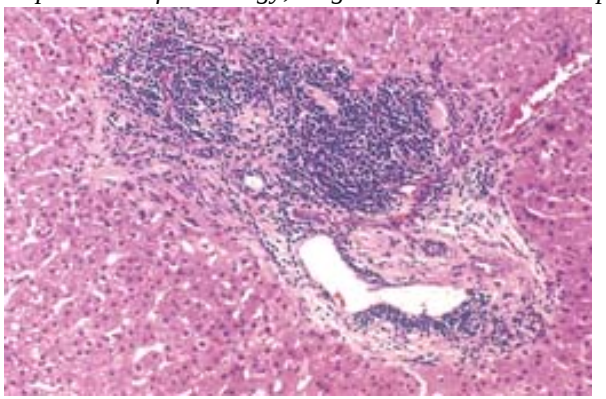


Figure 14-9 Follicular lymphoma (lymph node). *A*, Nodular aggregates of lymphoma cells are present throughout lymph node. *B*, At high magnification, small lymphoid cells with condensed chromatin and irregular or cleaved nuclear outlines (centrocytes) are mixed with a population of larger cells with nucleoli (centroblasts). *(A, courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

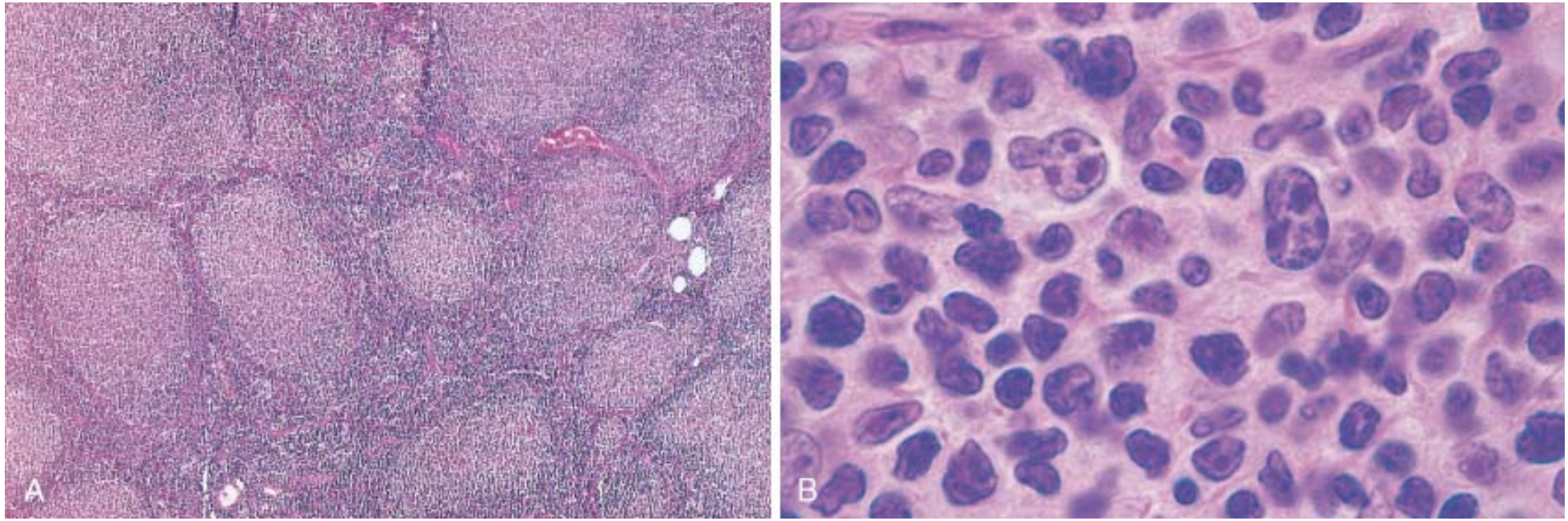


Figure 14-10 Follicular lymphoma (spleen). Prominent nodules represent white pulp follicles expanded by follicular lymphoma cells. Other indolent B-cell lymphomas (small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma) can produce an identical pattern of involvement. *(Courtesy of Dr. Jeffrey Jorgenson, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

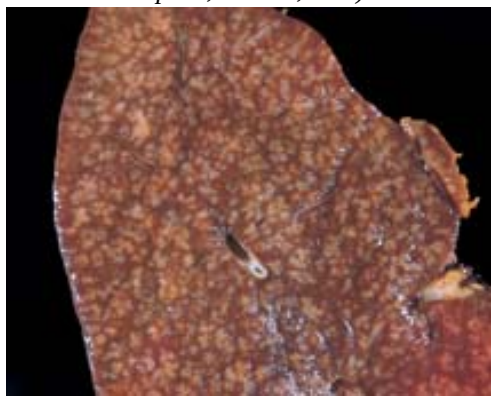


Figure 14-11 BCL2 expression in reactive and neoplastic follicles. BCL2 protein was detected by using an immunohistochemical technique that produces a brown stain. In reactive follicles (*A*), BCL2 is present in mantle zone cells but not follicular center B cells, whereas follicular lymphoma cells (*B*) exhibit strong BCL2 staining *(Courtesy of Dr. Jeffrey Jorgenson, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

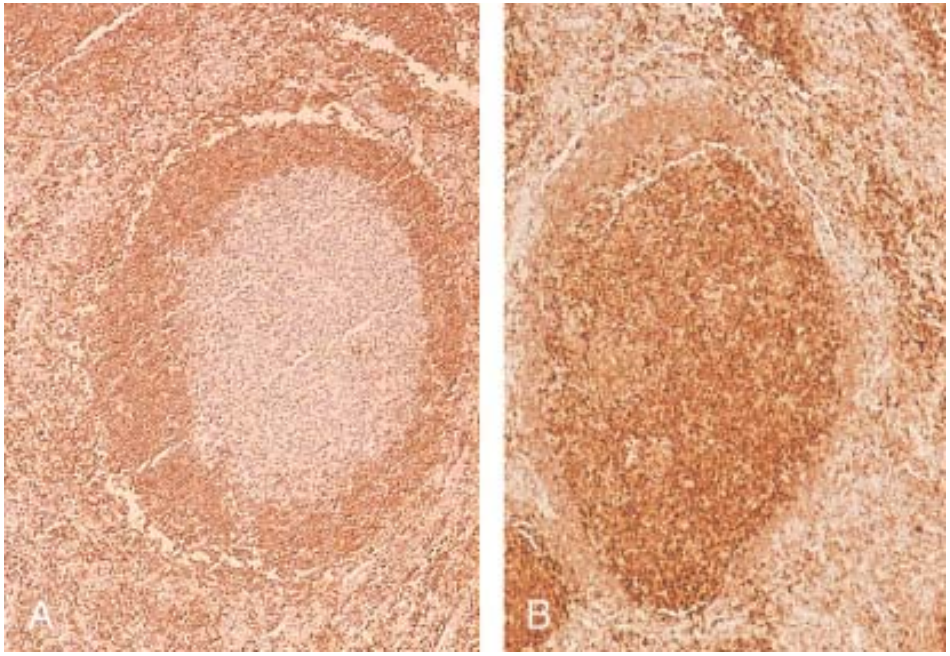


Figure 14-12 Diffuse large B-cell lymphoma. Tumor cells have large nuclei, open chromatin, and prominent nucleoli. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

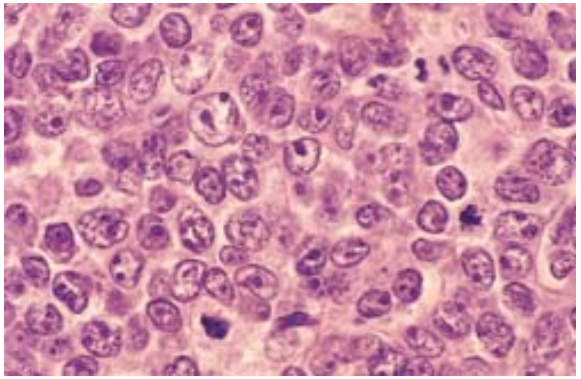


Figure 14-13 Diffuse large B-cell lymphoma (spleen). The presence of an isolated large mass is typical. In contrast, indolent B-cell lymphomas usually produce multifocal expansion of white pulp (see Fig. 14-10). *(Courtesy of Dr. Mark Fleming, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

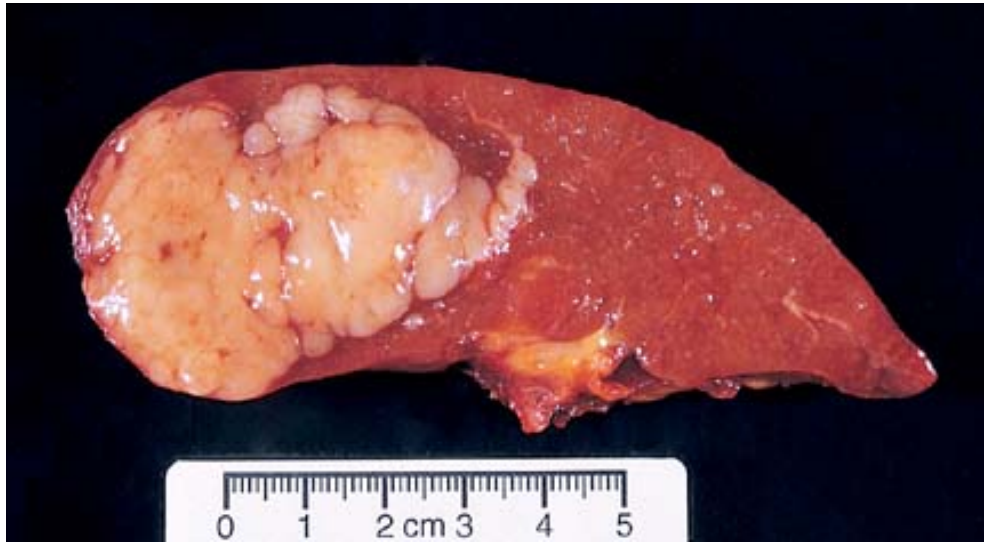


Figure 14-14 Burkitt lymphoma. *A,* At low power, numerous pale tingible body macrophages are evident, producing a "starry sky" appearance. *B,* At high power, tumor cells have multiple small nucleoli and high mitotic index. The lack of significant variation in nuclear shape and size lends a monotonous appearance. *(B, courtesy of Dr. José Hernandez, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

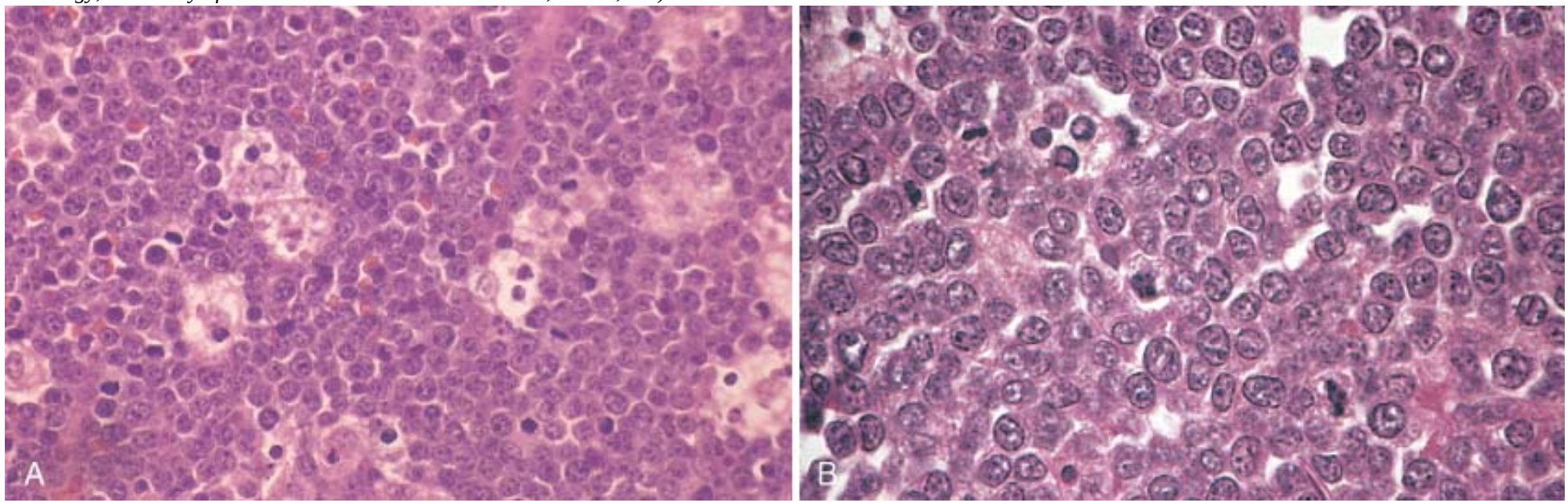


Figure 14-15 Multiple myeloma of the skull (radiograph, lateral view). The sharply punched-out bone lesions are most obvious in the calvarium.

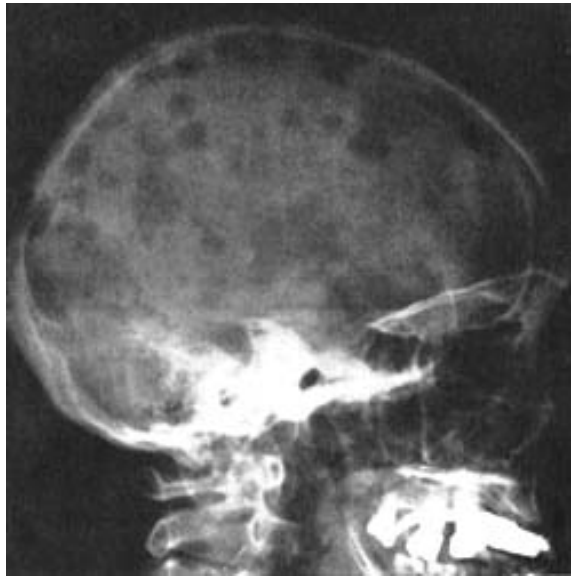


Figure 14-16 Multiple myeloma (bone marrow aspirate). Normal marrow cells are largely replaced by plasma cells, including forms with multiple nuclei, prominent nucleoli, and cytoplasmic droplets containing immunoglobulin.

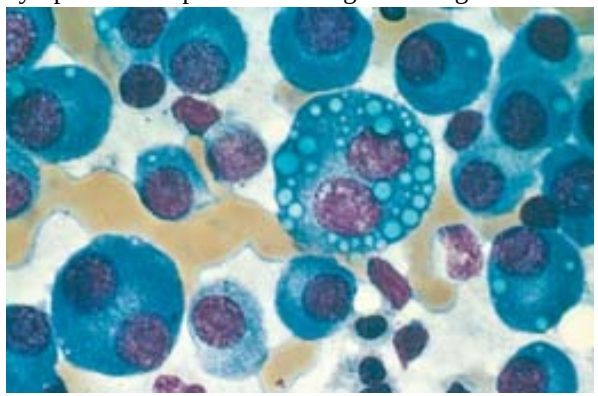


Figure 14-17 M protein detection, multiple myeloma. Serum protein electrophoresis (SP) is used to screen for a monoclonal immunoglobulin (M protein). Polyclonal IgG in normal serum (denoted by the *arrow*) appears as a broad band; in contrast, serum from a patient with multiple myeloma contains a single sharp protein band in this region of the electropherogram. The suspected monoclonal immunoglobulin is confirmed and characterized by immunofixation. In this procedure, proteins separated by electrophoresis within a gel are reacted with specific antisera. After extensive washing of the gel, only proteins that are cross-linked by antisera are retained. These are detected with a protein stain. Note the sharp band in the immunoglobulin region of the patient SP that is recognized by antisera against IgG heavy chain (G) and kappa light chain (κ), indicating the presence of a IgGκ M protein. Levels of polyclonal IgG, IgA (A), and lambda light chain (λ) are also decreased in the patient serum relative to normal, a common finding in multiple myeloma. *(Courtesy of Dr. David Sacks, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

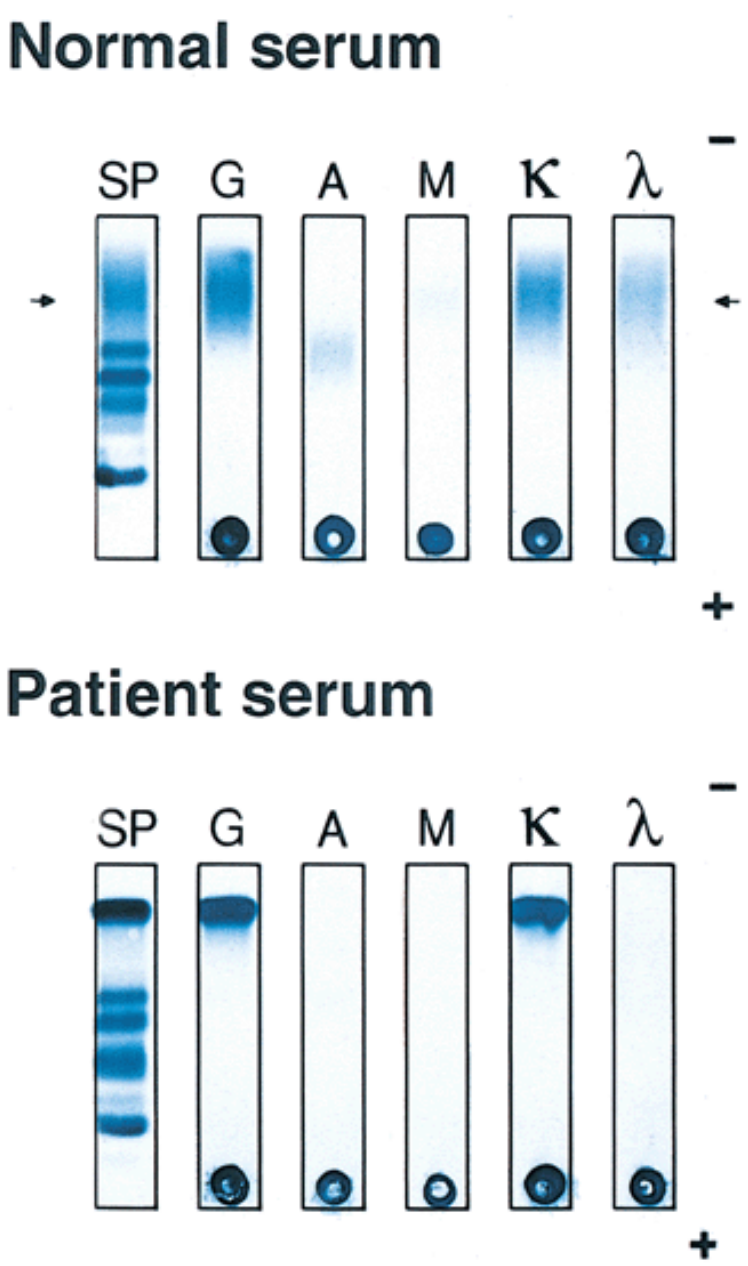


Figure 14-18 Lymphoplasmacytic lymphoma. Bone marrow biopsy shows a characteristic mixture of small lymphoid cells exhibiting various degrees of plasma cell differentiation. In addition, a mast cell with purplish-red cytoplasmic granules is present at the left-hand side of the field.

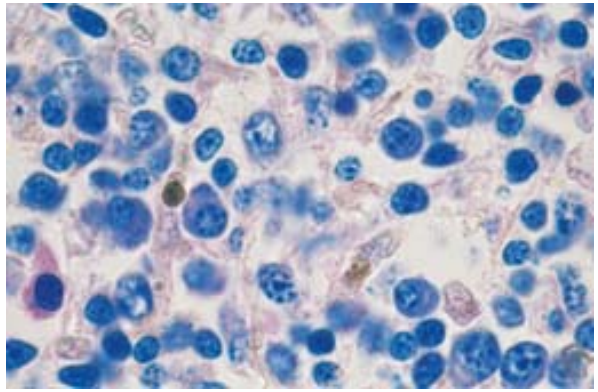


Figure 14-19 Mantle cell lymphoma. *A*, At low power, neoplastic lymphoid cells surround a small, atrophic germinal center, exhibiting a mantle zone pattern of growth. *B*, High-power view shows a homogeneous population of small lymphoid cells with somewhat irregular nuclear outlines, condensed chromatin, and scant cytoplasm. Large cells resembling prolymphocytes (seen in chronic lymphocytic leukemia) and centroblasts (seen in follicular lymphoma) are absent.

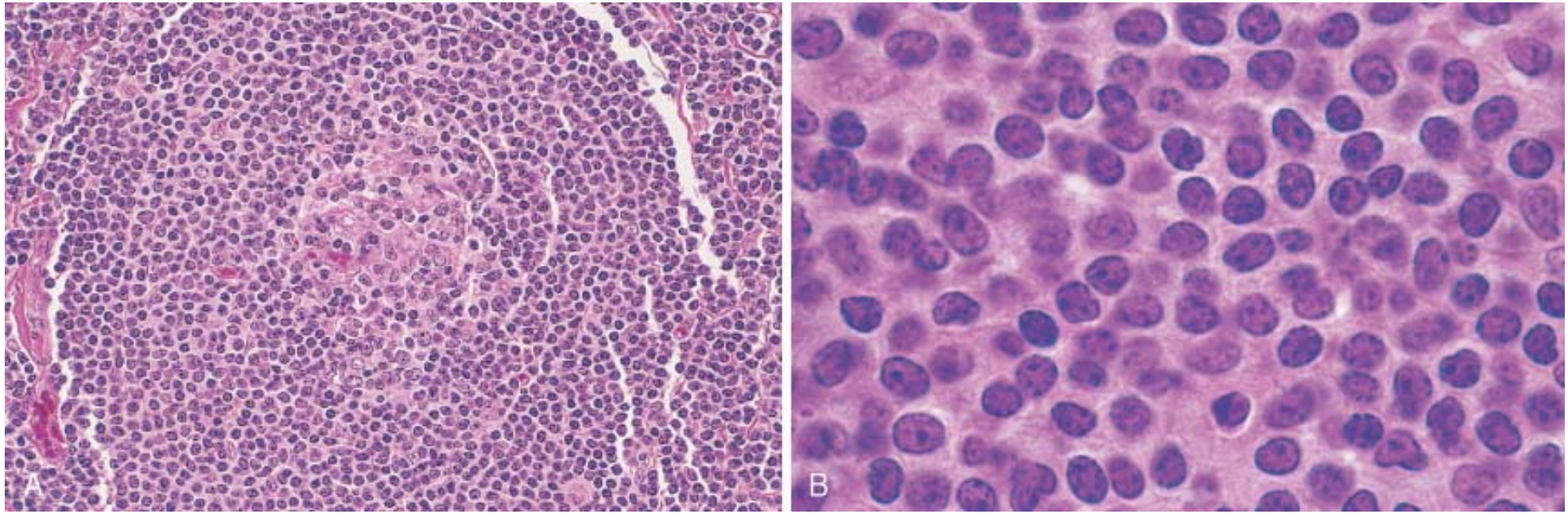


Figure 14-20 Hairy cell leukemia (peripheral blood smear). *A*, Phase-contrast microscopy shows tumor cells with fine hairlike cytoplasmic projections. *B*, In stained smears, these cells have round or folded nuclei and modest amounts of pale-blue, agranular cytoplasm. *(Courtesy of Dr. David Weinberg, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

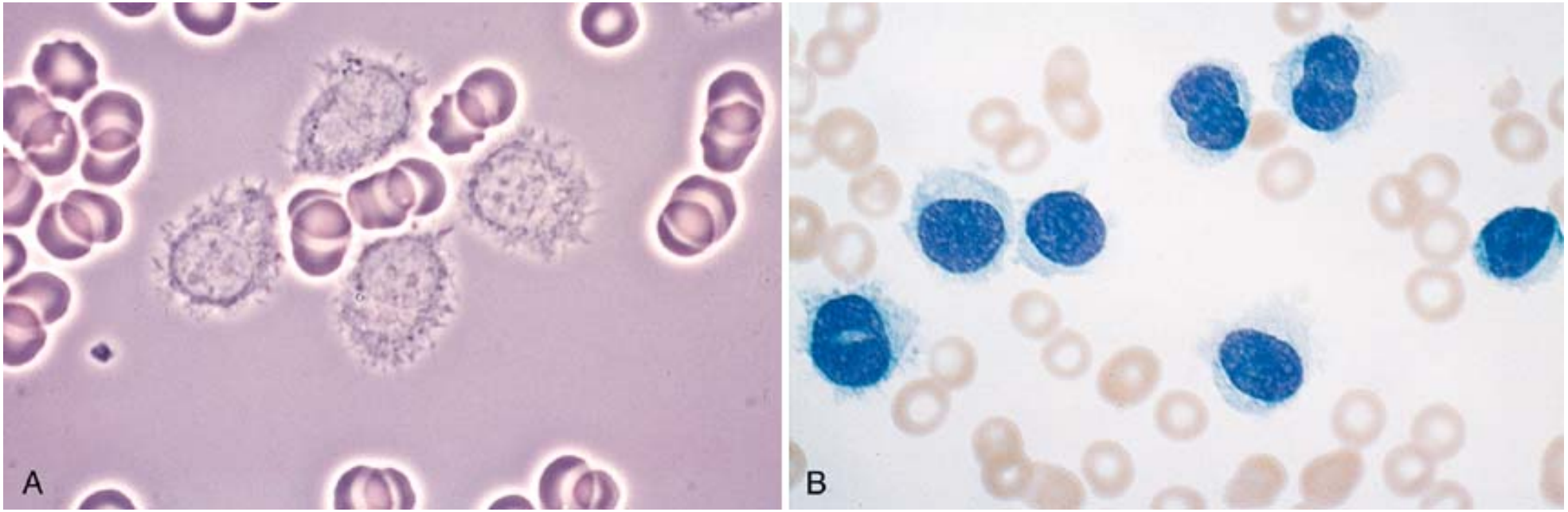


Figure 14-21 Peripheral T-cell lymphoma, unspecified (lymph node). A spectrum of small, intermediate, and large lymphoid cells, many with irregular nuclear contours, is seen.

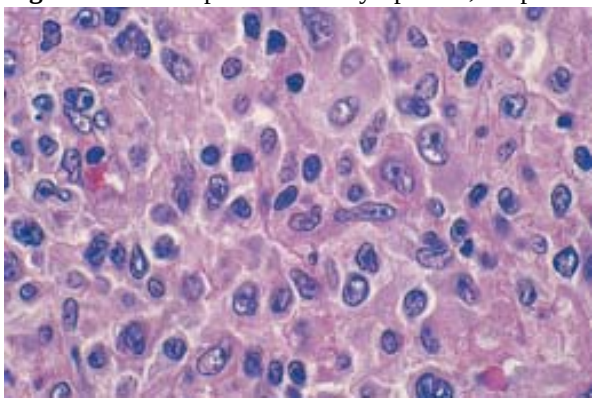


Figure 14-22 Anaplastic large cell lymphoma. *A,* Several "hallmark" cells with horseshoe-like or "embryo-like" nuclei and abundant cytoplasm lie near the center of the field. *B,* Immunohistochemical stain demonstrating expression of ALK protein. *(Courtesy of Dr. Jeffrey Kutok, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

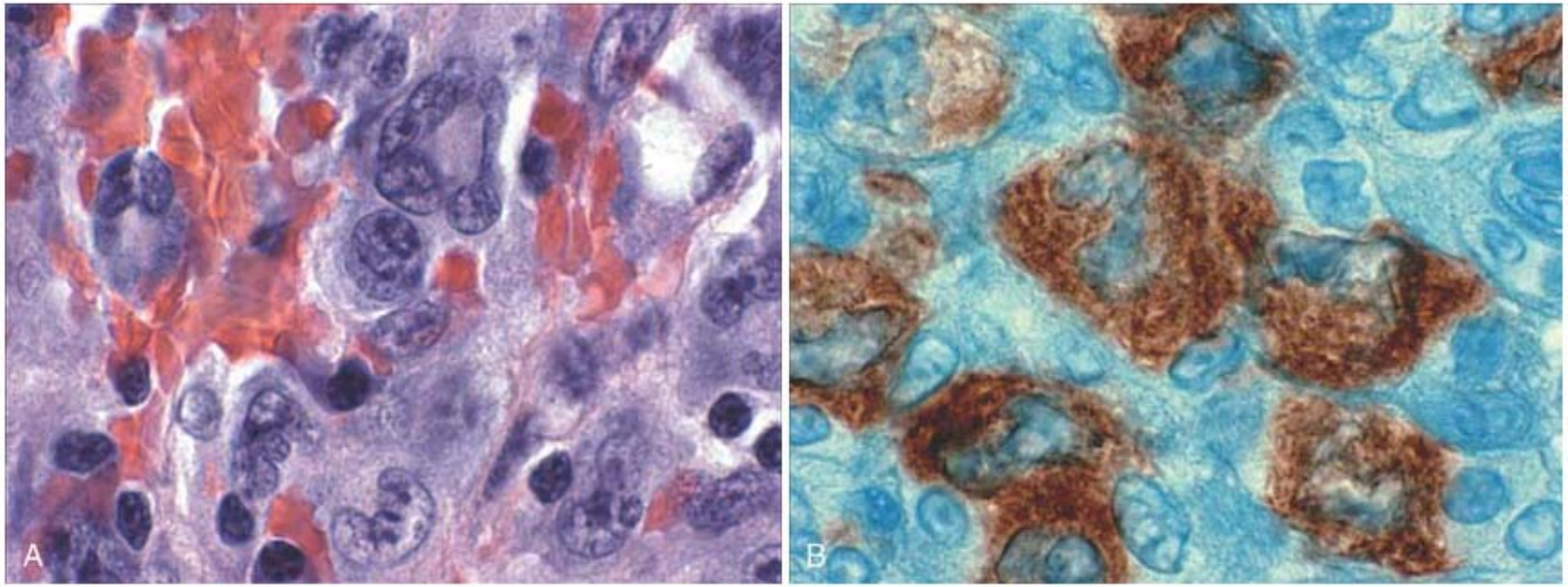


Figure 14-23 Reed-Sternberg cells and variants. *A*, Diagnostic Reed-Sternberg cell, with two nuclear lobes, large inclusion-like nucleoli, and abundant cytoplasm, surrounded by lymphocytes, macrophages, and an eosinophil. *B*, Reed-Sternberg cell, mononuclear variant. *C*, Reed-Sternberg cell, lacunar variant. This variant is characteristic of the nodular sclerosis subtype. It has a folded or multilobated nucleus lying within a clear space created by disruption of its cytoplasm during processing and cutting of the tissue. *D*, Reed-Sternberg cell, lymphohistiocytic (L&H) variant. Several such variants are present with complex nuclear irregularities, small nucleoli, fine chromatin, and abundant pale cytoplasm. *(A, courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

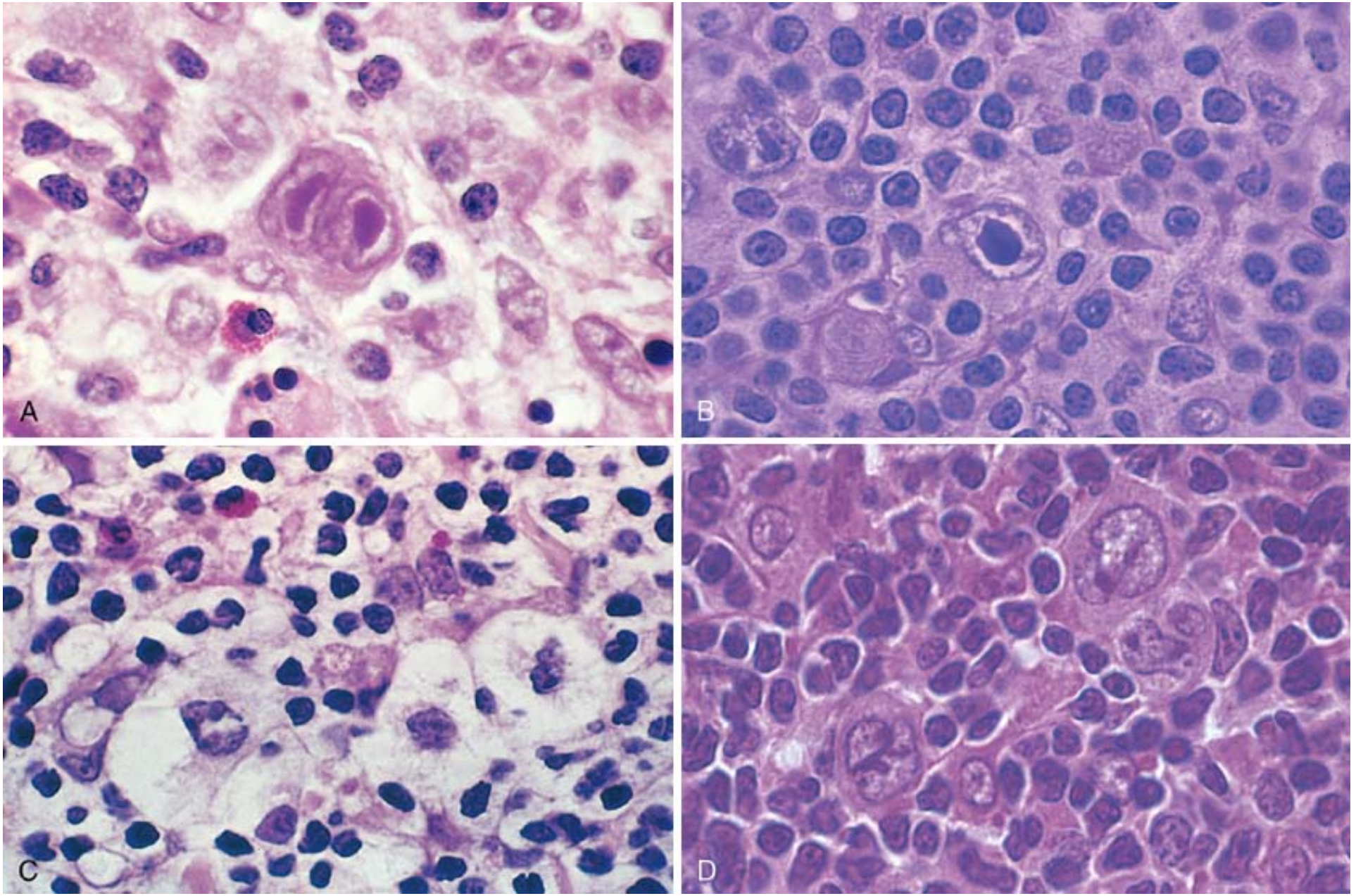


TABLE 14-5 -- Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification)

Stage	Distribution of Disease
I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE).

II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organ or tissue (IIE).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) and/or limited contiguous extralymphatic organ or site (IIIE, IIIES).
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement.
••All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: significant fever, night sweats, and/or unexplained weight loss of greater than 10% of normal body weight.	
Data from Carbone PT, et al: Symposium (Ann Arbor): Staging in Hodgkin's disease. Cancer Res 31:1707, 1971.	

eosinophils, plasma cells, and macrophages. Diagnostic Reed-Sternberg cells are less frequent than in the mixed cellularity and lymphocyte depletion types. The tumor cells have a characteristic immunophenotype: positive for CD15 and CD30 and negative for CD45 and B-cell and T-cell markers. As in other forms of HL, involvement of the spleen, liver, bone marrow,

TABLE 14-6 -- Classification of Hodgkin Lymphoma

Subtype	Morphology and Immunophenotype	Typical Clinical Features
Nodular sclerosis	Frequent lacunar cells and occasional diagnostic R-S cells; background infiltrate composed of T lymphocytes, eosinophils, macrophages and plasma cells; fibrous bands dividing cellular areas into nodules. R-S cells CD15+, CD30+; EBV-.	Stage 1 or 2 disease most common.
		Frequent mediastinal involvement.
		F = M, most patients young adults
Mixed cellularity	Frequent mononuclear and diagnostic R-S cells; background infiltrate rich in T lymphocytes, eosinophils, macrophages, plasma cells. R-S cells CD15+, CD30+; 70% EBV+.	More than 50% present as stage 3 or 4 disease. M > F. Biphasic incidence, peaking in young adults and again in adults older than 55.
Lymphocyte-rich	Frequent mononuclear and diagnostic R-S cells; background infiltrate rich in T lymphocytes. R-S cells CD15+, CD30+; 40% EBV+.	Uncommon. M > F. Tends to be seen in older adults.
Lymphocyte depletion	Reticular variant: Frequent diagnostic R-S cells and variants with a paucity of background reactive cells; diffuse fibrosis variant; hypocellular fibrillar background with scattered diagnostic R-S cells and variants and few reactive cells. R-S cells CD15+, CD30+; most EBV+.	Uncommon. More common in older males, HIV-infected individuals, and in developing countries. More likely to present with advanced disease.
Lymphocyte predominance	Frequent L&H (popcorn cell) variants in a background of follicular dendritic cells and reactive B cells. R-S cells CD20+, CD15-, C30-; EBV-.	Uncommon. Young males with cervical or axillary lymphadenopathy. Mediastinal.

and other organs and tissues can appear in due course and take the form of irregular tumor nodules resembling those present in the nodes.

The nodular sclerosis type occurs with equal frequency in males and females. It has a propensity to involve the lower cervical, supraclavicular, and mediastinal lymph nodes of adolescents or young adults and is only rarely associated with EBV. The prognosis is excellent.

Hodgkin Lymphoma, Mixed Cellularity Type.

This form of HL constitutes about 20% to 25% of cases. Lymph node involvement by the mixed cellularity type takes the form of **diffuse effacement** by a heterogeneous cellular infiltrate, which includes small lymphocytes, eosinophils, plasma cells, and benign macrophages admixed with the neoplastic cells (Fig. 14-25). **Diagnostic Reed-Sternberg cells and mononuclear variants are usually plentiful.** The immunophenotype is identical to that observed in the nodular sclerosis type. Small lymphocytes in the background are predominantly T cells, and early nodal disease preferentially involves paracortical T-cell zones.

Mixed cellularity HL is more common in males and strongly associated with EBV, as the Reed-Sternberg cells contain EBV genomes in at least 70% of cases. Compared to the lymphocyte predominance and nodular sclerosis subtypes, it is more likely to be associated with older age, systemic symptoms such as night sweats and weight loss, and advanced tumor stage. Nonetheless, the prognosis is very good.

Hodgkin Lymphoma, Lymphocyte-Rich Type.

This is an uncommon form of classical HL in which reactive

Figure 14-24 Hodgkin lymphoma, nodular sclerosis type. A low-power view shows well-defined bands of pink, acellular collagen that subdivide the tumor cells and associated reactive infiltrate into nodules. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

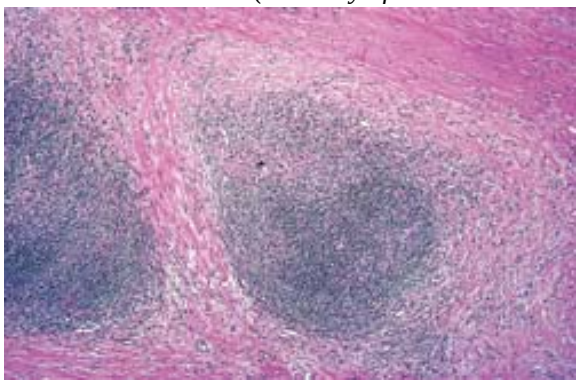


Figure 14-25 Hodgkin lymphoma, mixed cellularity type. A diagnostic, binucleate Reed-Sternberg cell is surrounded by reactive cells, including eosinophils (bright red cytoplasm), lymphocytes, and histiocytes. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

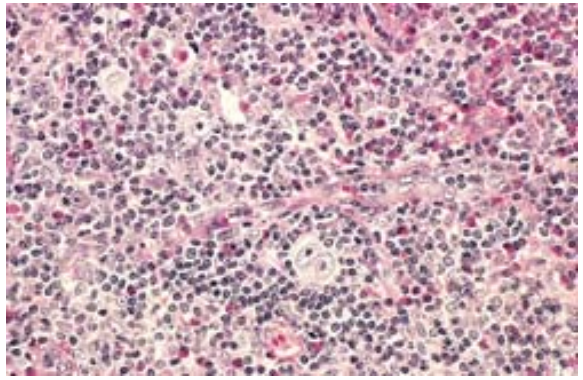


Figure 14-26 Hodgkin lymphoma, lymphocyte predominance type. Numerous mature-looking lymphocytes surround scattered, large, pale-staining L&H variants ("popcorn" cells). *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

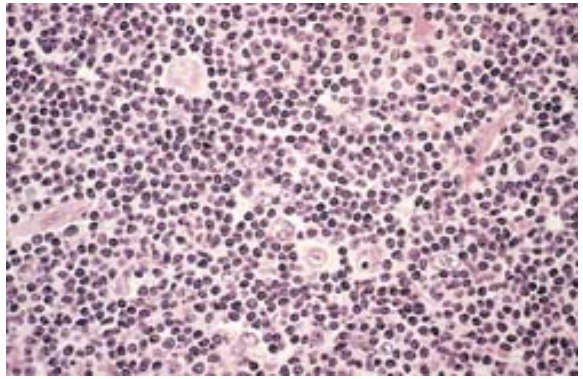


Figure 14-27 Proposed signals mediating "cross-talk" between Reed-Sternberg cells and surrounding normal cells in classical forms of Hodgkin lymphoma. bFGF, basic fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor (binds to the C-MET receptor); TNFβ, tumor necrosis factor β (lymphotoxin); TGFβ, transforming growth factor β.

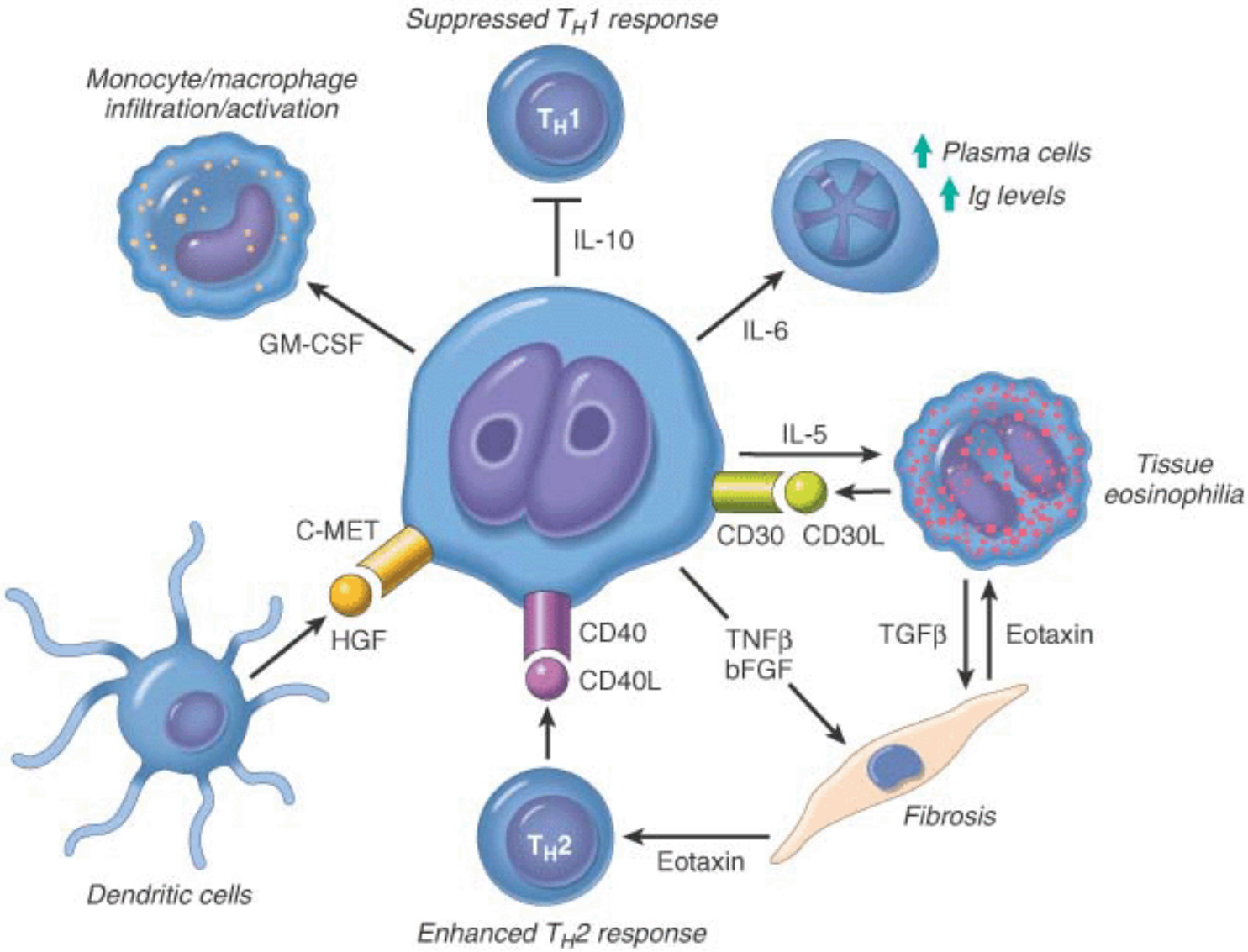


TABLE 14-7 -- Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Waldeyer ring and mesenteric nodes commonly involved
Extranodal involvement uncommon	Extranodal involvement common

myeloid series (erythrocytes, granulocytes, monocytes, and platelets). These diseases primarily involve the bone marrow and to a lesser degree the secondary hematopoietic organs (the spleen, liver, and lymph nodes) and present with altered hematopoiesis. Three broad categories of myeloid neoplasia exist:

- *Acute myelogenous leukemias*, characterized by the accumulation of immature myeloid forms in the bone marrow and the suppression of normal hematopoiesis
- *Myelodysplastic syndromes*, associated with ineffective hematopoiesis and associated cytopenias
- *Chronic myeloproliferative disorders*, usually associated with an increased production of terminally differentiated myeloid cells

The pathogenesis of myeloid neoplasms is best understood in the context of normal hematopoiesis, which (you will remember from Chapter 13) involves a hierarchy of hematopoietic progenitor cells. At the top of the hierarchy sits the pluripotent stem cell, which gives rise to multipotent progenitor cells committed to lymphoid or myeloid differentiation. The latter in turn produce more committed progenitors, which eventually give rise to terminally differentiated cells of a single type (e.g., erythrocyte, monocyte). In addition to giving rise to committed daughter cells, hematopoietic progenitor cells must also replicate themselves without differentiating (or else they would eventually disappear), a process known as self-renewal.

Normal hematopoiesis is finely tuned by homeostatic feedback mechanisms involving cytokines and growth factors that modulate the marrow output of red cells, granulocytes, and platelets. These mechanisms are deranged in marrows involved by myeloid neoplasms, which "escape" from normal homeostatic controls on growth and survival, and suppress the function of residual normal stem cells. The specific manifestations of the different myeloid neoplasms are further influenced by *(1) the position of the transformed cell within the hierarchy of progenitors* and *(2) the effect of the transforming events on differentiation programs, which may be blocked or preferentially shunted toward one lineage at the expense of others*. We will return to these themes as each type of myeloid neoplasm is discussed.

Given that all myeloid neoplasms originate from a transformed hematopoietic progenitor cell, it should come as no surprise that divisions between these neoplasms are sometimes blurred. Myeloid neoplasms, like other malignancies, tend to evolve over time to more aggressive forms of disease.

In particular, both the myelodysplastic syndromes and the chronic myeloproliferative disorders often "transform" to acute myelogenous leukemias. In the specific case of one of the myeloproliferative disorders, chronic myelogenous leukemia, transformation to acute lymphoblastic leukemia/lymphoma is also seen, indicating a likely origin from a transformed pluripotent stem cell.

Acute Myelogenous Leukemia

Acute myelogenous leukemias affect primarily adults, peaking in incidence between the ages of 15 and 39 years, but are also observed in older adults and children. AML is quite heterogeneous, reflecting the complexities of myeloid cell differentiation.

Pathophysiology.

Most AMLs are associated with acquired genetic alterations that inhibit terminal myeloid differentiation. As a result, normal marrow elements are replaced by relatively undifferentiated blasts exhibiting one or more types of early myeloid differentiation. The replication rate of these blasts is actually lower than that of normal myeloid progenitors, highlighting the pathogenic importance of blocked maturation and increased survival.

Specific recurrent chromosomal aberrations, including translocations, are seen in a high fraction of AMLs and tend to disrupt genes encoding transcription factors needed for normal myeloid differentiation. For example, the most common chromosomal rearrangements, t(8;21) and inv(16), involve genes that normally encode two subunits, CBF1α and CBF1β, of a single heterodimeric transcription factor. Both the t(8;21) and the inv(16) result in the formation of chimeric genes encoding fusion proteins with so-called dominant negative activity,

meaning they interfere with the function of the normal CBF1α/CBF1β heterodimer. Myeloid progenitors harboring such aberrations thus give rise to daughter cells exhibiting a partial or complete block in terminal differentiation. A deficit of CBF1α/CBF1β activity is not sufficient to cause leukemia, however, as "knockout" mice lacking either CBF1α or CBF1β, or "knock-in" mice expressing the fusion proteins created by the t(8;21) or inv(16),[66] succumb to hematopoietic failure. In such animals, the "blocked" progenitors die rather than undergoing transformation, indicating that other aberrations must collaborate with defects in critical transcription factors to produce AML.

An example of such a pathogenic collaboration underlies a form of AML, acute promyeloctyic leukemia, associated with a (15;17) chromosomal translocation. This translocation produces a fusion gene encoding a portion of a transcription factor, retinoic acid receptor-α (RARα), fused to a portion of another protein, PML. RARα normally activates transcription, but when fused to PML, it is converted to a repressor that turns off genes required for full and complete myeloid differentiation. In addition to the t(15;17), acute promyelocytic leukemia cells also frequently acquire point mutations in FLT3, a tyrosine kinase, that result in its constitutive activation.[67] As you will recall from Chapter 3 , tyrosine kinases produce signals that promote cellular proliferation and survival, activities that synergize with the block in differentiation produced by the RARα-PML fusion protein. This pathogenic collaboration has been proven in mouse models, in which coexpression of a RARα-PML fusion protein and activated forms of FLT3 produce the rapid onset of AML. It is believed that distinct, but pathogenically analogous, sets of synergistic genetic "hits" underlie other forms of AML.[68]

In all AMLs, the accumulation of proliferating neoplastic myeloid precursor cells in the marrow suppresses remaining normal hematopoietic progenitor cells by physical replacement as well as by other unknown mechanisms. The failure of normal hematopoiesis results in anemia, neutropenia, and thrombocytopenia, which cause most of the major clinical complications of AML. Therapeutically, the aim is to clear the bone marrow of the leukemic clone, thus permitting resumption of normal hematopoiesis. This can be accomplished by treatment with cytotoxic drugs or, in the specific case of acute promyelocytic leukemia, by overcoming the block in differentiation with pharmacologic doses of retinoic acid.

Classification.

In the most widely used system in current use, the revised FAB classification (Table 14-8*A*), AML is divided into eight (M0 to M7) categories.[69] This scheme takes into account both the degree of maturation (M0 to M3) and the lineage of the leukemic blasts (M4 to M7). Histochemical stains for peroxidase, specific esterase, and nonspecific esterase, and immunostains for myeloid specific antigens (see Table 14-8A) play important roles in defining the type of myeloid differentiation that blasts exhibit.

A recently proposed WHO classification for AML (Table 14-8*B*) retains the FAB categories M0 to M7 but also creates special categories for AMLs associated with particular chromosomal aberrations (e.g., the t(15;17), t(8;21), inv(16), or 11q23 rearrangements), which arise after prior chemotherapy or follow a myelodysplastic syndrome.[11] This classification thus attempts to define forms of AML according to molecular pathogenesis and outcome. Given the increasing role of cytogenetic and molecular features in directing therapy, a further shift toward molecular genetic classifications of AML seems inevitable and desirable.

Morphology.

The diagnosis of AML is based on finding that myeloid blasts make up more than 20% of the cells in the marrow. Several types of myeloid blasts are recognized, but more than one type of blast, or blasts with hybrid features, can be seen in individual patients. **Myeloblasts** have delicate nuclear chromatin, two to four nucleoli, and more voluminous cytoplasm than lymphoblasts (Fig. 14-28*A*). The cytoplasm often contains fine, azurophilic, peroxidase-positive granules. Distinctive red-staining peroxidase-positive structures called **Auer rods**, which represent abnormal azurophilic granules, are present in many cases and are particularly numerous in AML associated with the t(15;17) (acute promyelocytic leukemia) (Fig. 14-29*A*). The presence of Auer rods is taken to be definitive evidence of myeloid differentiation. **Monoblasts** (Fig. 14-29*B*) often have folded or lobulated nuclei, lack Auer rods, and are peroxidase negative and nonspecific esterase positive. In some AMLs, blasts exhibit megakaryocytic differentiation, which is often accompanied by marrow fibrosis caused by the release of fibrogenic cytokines. Rarely, the blasts of AML show evidence of erythroid differentiation (erythroblasts).

The number of leukemic cells in the peripheral blood is highly variable. Blast counts can be more than 100,000 cells per microliter but are under 10,000

TABLE 14-8A -- Revised FAB Classification of Acute Myelogenous Leukemias

Class	Incidence (% of AML)	Marrow Morphology/Comments
M0 Minimally differentiated AML	2–3%	Blasts lack definitive cytologic and cytochemical markers of myeloblasts (e.g., myeloperoxidase negative) but express myeloid lineage antigens and resemble myeloblasts ultrastructurally.
M1 AML without differentiation	20%	Very immature, but ≥3% of blasts are peroxidase positive; few granules or Auer rods and little maturation beyond the myeloblast stage.
M2 AML with maturation	30–40%	Full range of myeloid maturation through granulocytes; Auer rods present in most cases; often associated with the t (8;21).
M3 Acute promyelocytic leukemia	5–10%	Most cells are hypergranular promyelocytes, often with many Auer rods per cell; patients are younger (median age 35 to 40 years); high incidence of DIC; strong association with the t(15;17).
M4 Acute myelomonocytic leukemia	15–20%	Myelocytic and monocytic differentiation evident; myeloid elements show range of maturation; monoblasts are positive for nonspecific esterases; subset associated with the inv(16).
M5 Acute monocytic leukemia	10%	In M5a subtype, monoblasts (peroxidase-negative, nonspecific esterase-positive) and promonocytes predominate in marrow and blood; in M5b subtype, mature monocytes predominate in the peripheral blood; M5a and M5b occur in older patients; characterized by high incidence of organomegaly, lymphadenopathy, and tissue infiltration.
M6 Acute erythroleukemia	5%	Dysplastic erythroid precursors (some megaloblastoid, others with giant or multiple nuclei) predominate, and within the non-erythroid cells, >30% are myeloblasts; seen in advanced age; makes up 1% of de novo AML and 20% of therapy-related AML.
M7 Acute megakaryocytic leukemia	1%	Blasts of megakaryocytic lineage predominate; blasts react with platelet-specific antibodies directed against GPIIb/IIIa or vWF; myelofibrosis or increased marrow reticulin seen in most cases.

DIC, disseminated intravascular coagulation; vWF, von Willebrand factor.

TABLE 14-8B -- Proposed WHO Classification of Acute Myelogenous Leukemias

Class	Prognosis
I. AML with Recurrent Chromosomal Rearrangements	
AML with t(8;21)(q22;q22); *CBFα/ETO* fusion gene	Favorable
AML with inv(16)(p13;q22); *CBFβ/MYH11* fusion gene	Favorable
AML with t(15;17)(q22;11-12); *RARα/PML* fusion gene	Intermediate
AML with t(11q23;v); diverse *MML* fusion genes	Poor

II. AML with Multilineage Dysplasia	
With prior myelodysplastic syndrome	Very poor
Without prior myelodysplastic syndrome	Poor
III. AML, Therapy Related	
Alkylating agent related	Very poor
Epipodophyllotoxin related	Very poor
IV. AML, not Otherwise Specified	
Sub-classes defined by extent of differentiation and FAB classification (e.g., M0-M7)	Intermediate

cells per microliter in about 50% of the patients. **Occasionally, the peripheral smear might not contain any blasts** (aleukemic leukemia). For this reason, bone marrow examination is essential to exclude acute leukemia in pancytopenic patients.

Immunophenotype.

Because it is difficult to distinguish myeloblasts and lymphoblasts morphologically in some cases, the diagnosis of AML is typically confirmed by staining cells for myeloid-specific surface markers (Fig. 14-28*B*, *C*).

Chromosomal Abnormalities.

Special high-resolution banding techniques reveal chromosomal abnormalities in approximately 90% of all AML patients. In 50% to 70% of the cases, the karyotypic changes are detected by standard cytogenetic techniques.

Particular chromosomal abnormalities correlate with the clinical setting in which the tumor occurs. AML arising de novo in patients with no risk factors are often associated with balanced chromosomal translocations, particularly t(8;21), inv(16), and t(15;17). In contrast, AMLs following myelodysplastic syndromes or exposure to DNA-damaging agents (such as chemotherapy or radiation therapy) are commonly associated with deletions or monosomies involving chromosomes 5 and 7 and usually lack chromosomal translocations. The exception to this rule is AML occurring after treatment with topoisomerase II inhibitors, which is often associated with translocations involving the *MLL* gene on chromosome 11 at band q23.[70]

Clinical Features.

The clinical findings in AML are similar to those in acute lymphoblastic leukemia/lymphoma (ALL). *Most patients present within weeks or a few months of the onset of symptoms related to anemia, neutropenia, and thromobocytopenia*, most notably fatigue, fever, and spontaneous mucosal and cutaneous bleeding. Often, the bleeding diathesis caused by thrombocytopenia is the most striking clinical feature.

Figure 14-28 *A,* Acute myelogenous leukemia (FAB M1 subtype). Myeloblasts have delicate nuclear chromatin, prominent nucleoli, and fine azurophilic granules in the cytoplasm. *B,* In

the flow cytometric analysis shown, the myeloid blasts, represented by the red dots, express CD34, a marker of multipotent stem cells, but do not express CD64, a marker of mature myeloid cells. *C*, The same myeloid blasts express CD33, a marker of immature myeloid cells, and a subset express CD15, a marker of more mature myeloid cells. Thus, these blasts are minimally differentiated myeloid cells. *(A, courtesy of Dr. Robert W. McKenna Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX; B and C, courtesy of Dr. Louis Picker, Oregon Health Science Center, Portland, OR.)*

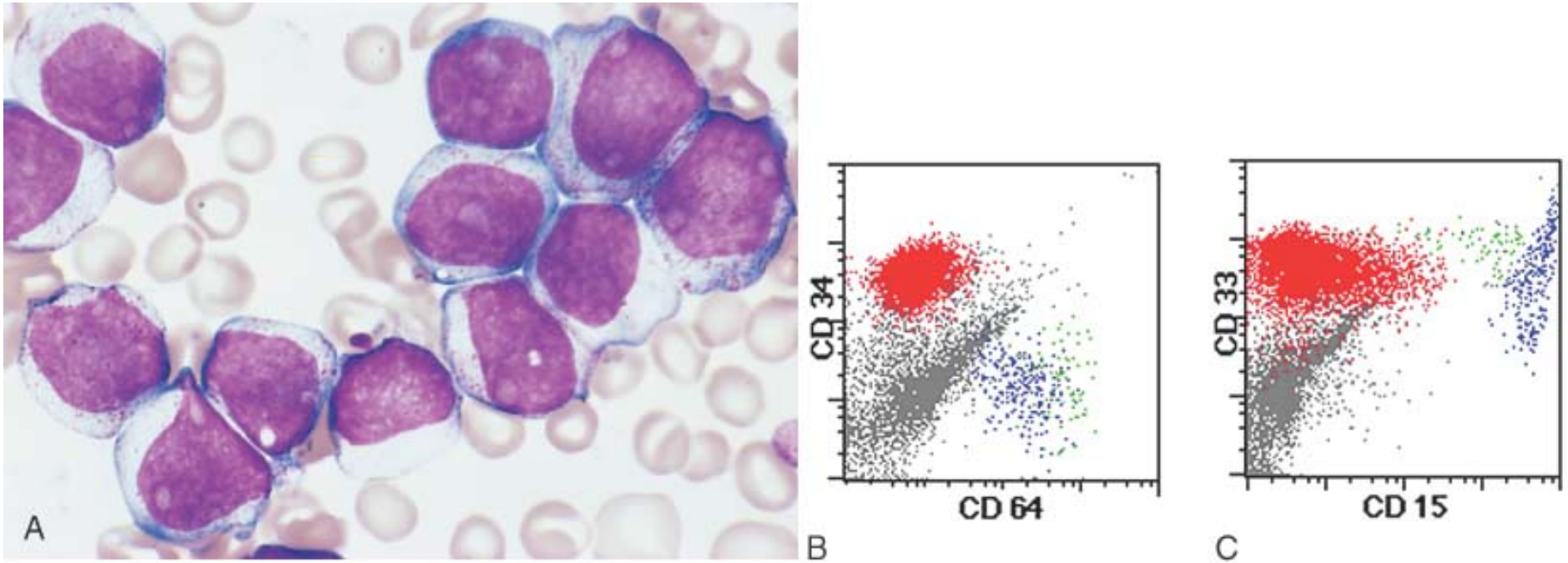


Figure 14-29 Acute myelogenous leukemia subtypes. *A*, Acute promyelocytic leukemia (FAB M3 subtype). Bone marrow aspirate shows neoplastic promyelocytes with abnormally coarse and numerous azurophilic granules. Other characteristic findings include the presence of several cells with bilobed nuclei and a cell in the center of the field that contains multiple needlelike Auer rods. *B*, Acute monocytic leukemia (FAB M5b subtype). Peripheral smear shows one monoblast and five promonocytes with folded nuclear membranes. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

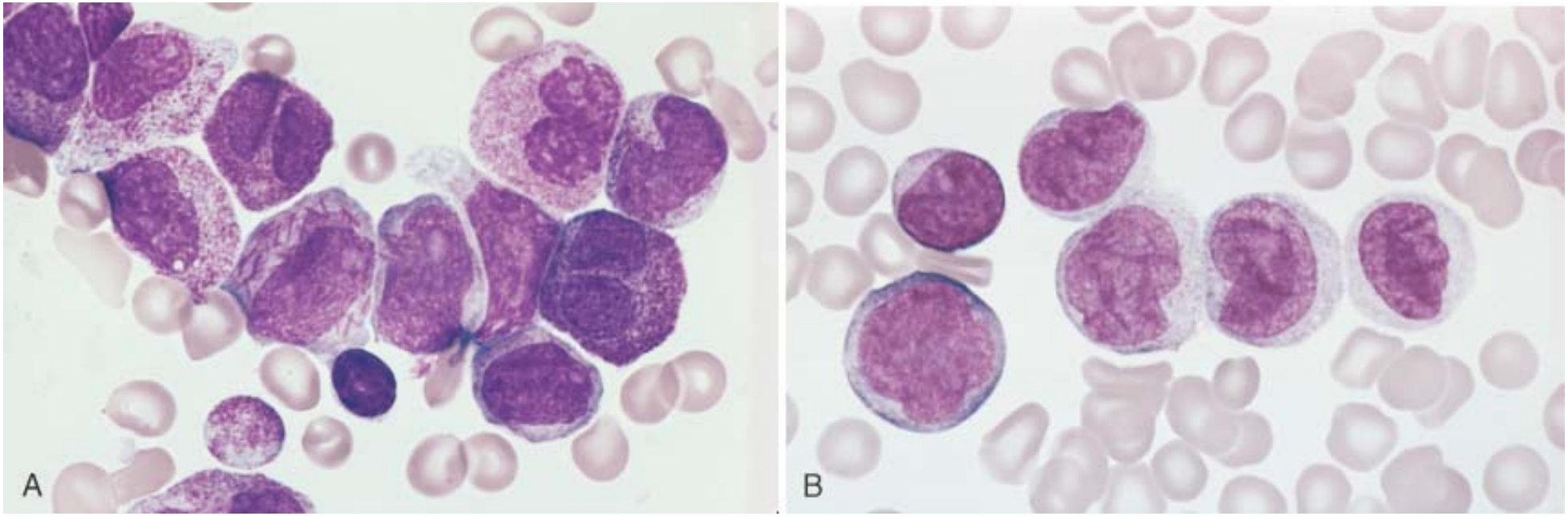


Figure 14-30 Myelodysplasia. Characteristic forms of dysplasia are shown. *A*, Nucleated red cell progenitors with multilobated or multiple nuclei. *B*, Ringed sideroblasts, erythroid progenitors with iron-laden mitochondria, seen as blue perinuclear granules (Prussian blue stain). *C*, Pseudo-Pelger-Hüet cells, neutrophils with only two nuclear lobes instead of the normal three to four, are observed at the top and bottom of this field. *D*, Megakaryocytes with multiple nuclei instead of the normal single multilobated nucleus. (*A*, *B*, *D*, marrow aspirates; *C*, peripheral blood smear.)

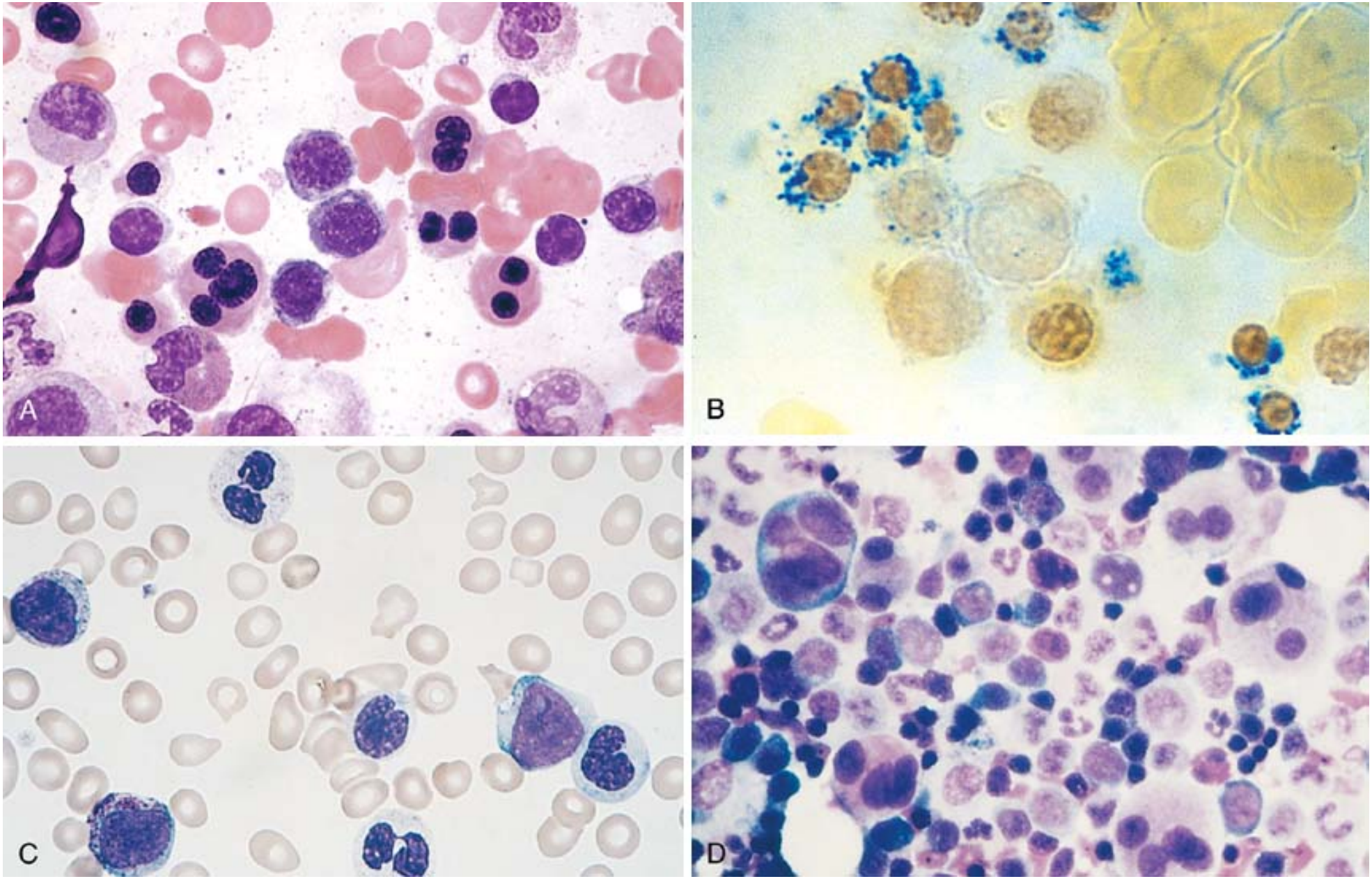
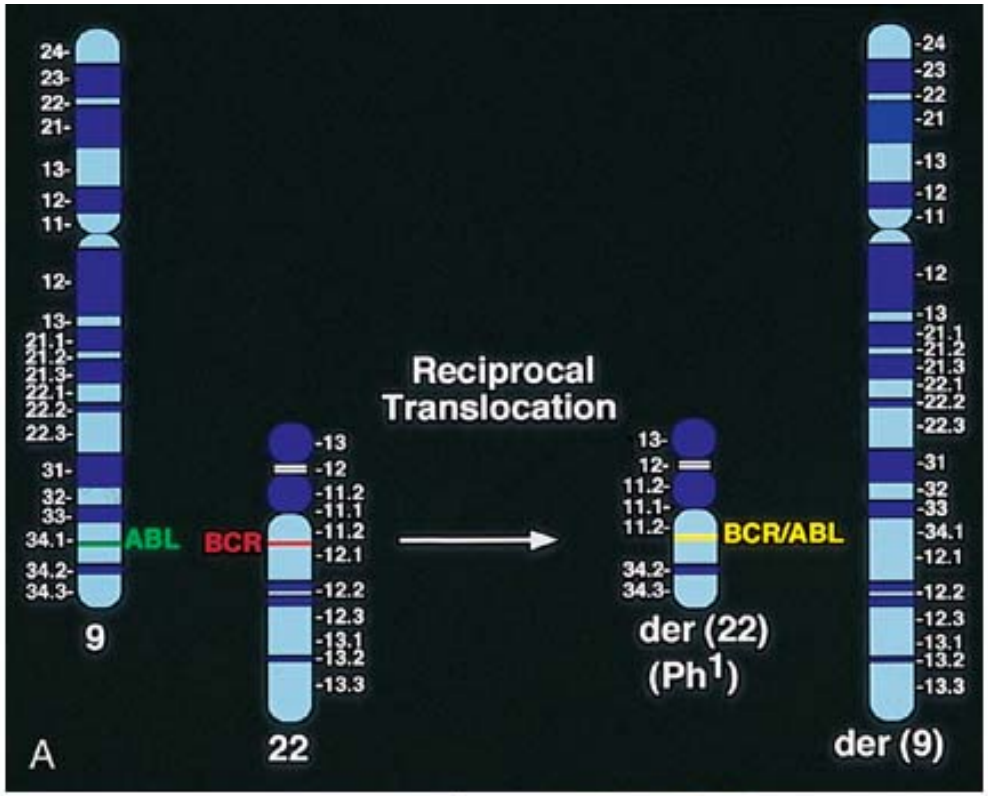
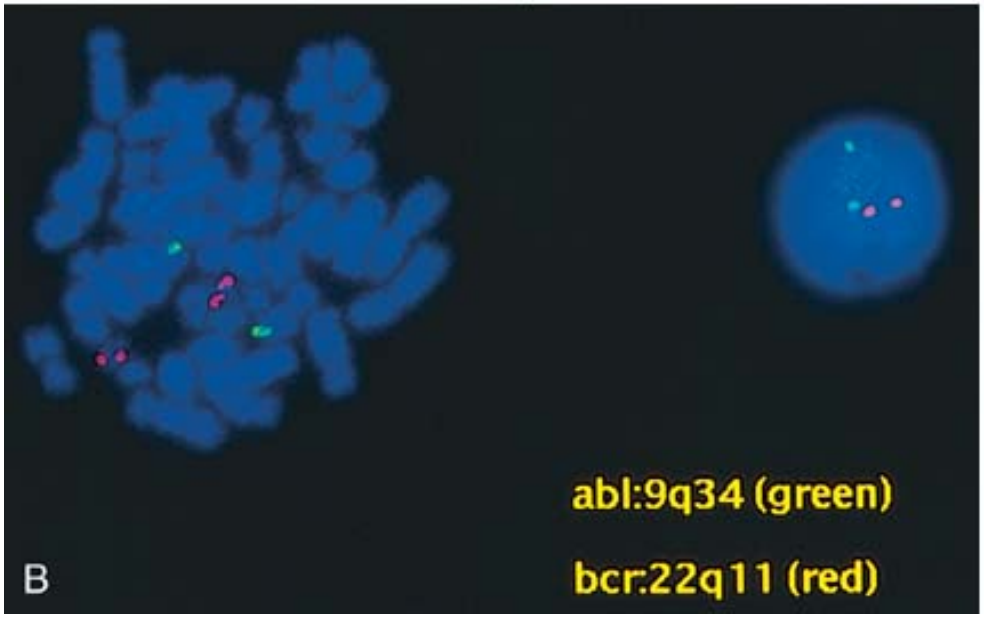


Figure 14-31 Detection of a *BCR-ABL* fusion gene by fluorescence in situ hybridization. *A,* An idiogram depicting chromosomes 9 and 22 and the position of the *ABL* and *BCR* genes. The Philadelphia chromosome (Ph) is created by a balanced chromosomal translocation that replaces the telomeric portion of 22q with the telomeric portion of 9q. At a molecular level, the breaking and rejoining of the DNA results in the formation of fusion gene on the Ph derived from the 5' end of *BCR* and the 3' end of *ABL* and hence brings *BCR* and *ABL* sequences that are normally far apart into close physical proximity. This abnormal colocalization of *BCR* and *ABL* can be detected by in situ hybridization with pairs of fluorescently tagged DNA probes complementary to genomic DNA sequences lying near the *BCR* and *ABL* breakpoints. *B,* A green *ABL* probe and a red *BCR* probe have been hybridized to metaphase chromosomes and interphase nuclei prepared from the peripheral blood cells of a normal individual. Because of the pairing of sister chromatids during mitosis, signals on metaphase chromosomes may be seen as a single dot or a pair of closely spaced dots. Two pairs of red signals and two green signals are seen on the metaphase chromosomes, while two red and two green signals are

present in the interphase nucleus, indicating the presence of normal, spatially distant copies of *ABL* and *BCR*, respectively. *C*, In contrast, metaphase chromosomes and an interphase nucleus prepared from the bone marrow cells of a patient with CML show one normal *ABL* signal, one normal *BCR* signal, and an abnormal yellow signal created by superimposition of one *BCR* and one *ABL* signal, a finding indicative of the presence of a *BCR-ABL* fusion gene. *(Courtesy of Dr. Cynthia Morton and Ms. Debbie Sandstrom, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*





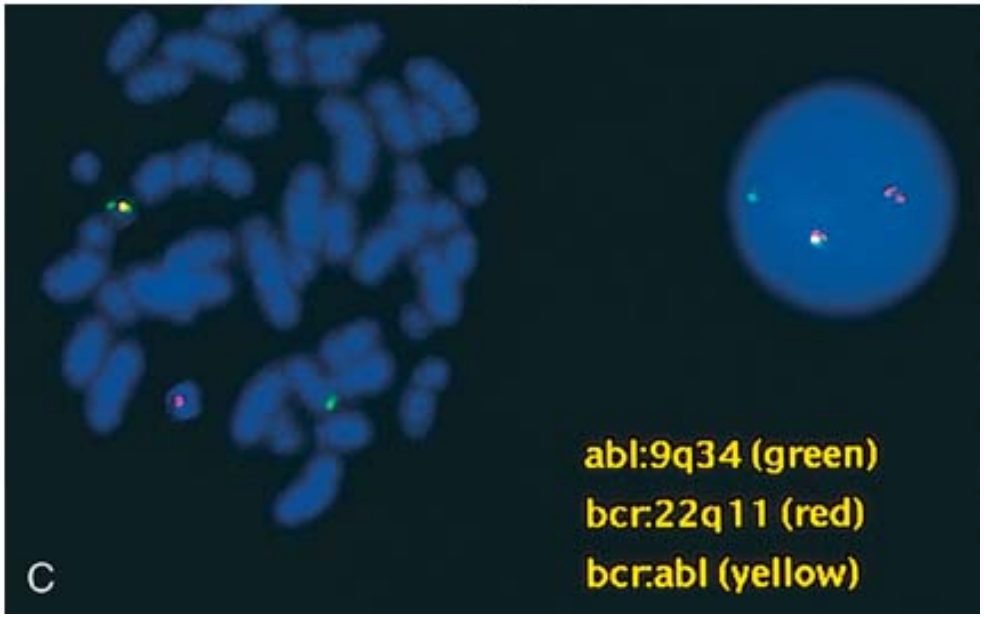


Figure 14-32 Chronic myelogenous leukemia. Peripheral blood smear shows many mature neutrophils, some metamyelocytes, and a myelocyte. *(Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)*

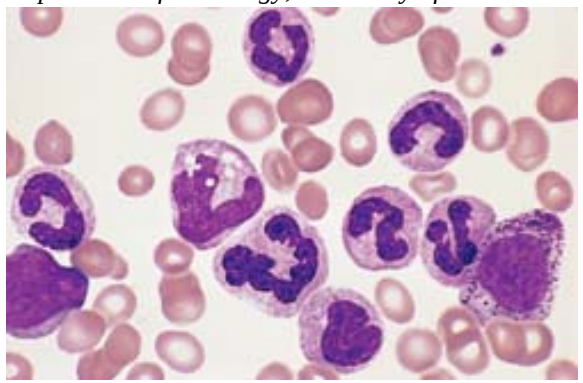


Figure 14-33 Chronic myelogenous leukemia (spleen). Enlarged spleen (2630 gm; normal: 150 to 200 gm) with greatly expanded red pulp stemming from neoplastic hematopoiesis. *(Courtesy of Dr. Daniel Jones, Department of Pathology, M.D. Anderson Cancer Center, Houston, TX.)*

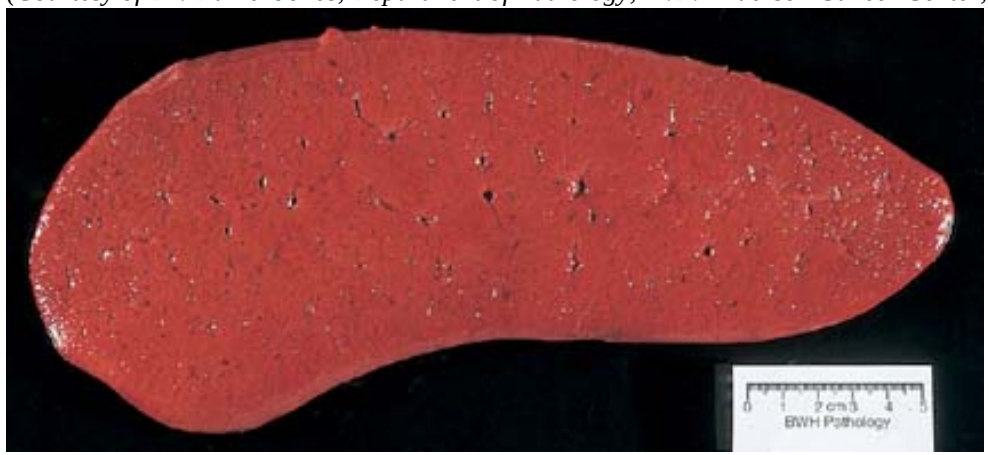


Figure 14-34 Polycythemia vera, spent phase. Massive splenomegaly (3020 gm; normal: 150 to 200 gm) largely owing to extramedullary hematopoiesis occurred in the setting of advanced marrow myelofibrosis. *(Courtesy of Dr. Mark Fleming, Department of Pathology, Brigham and Women's Hospital, Boston, MA.)*

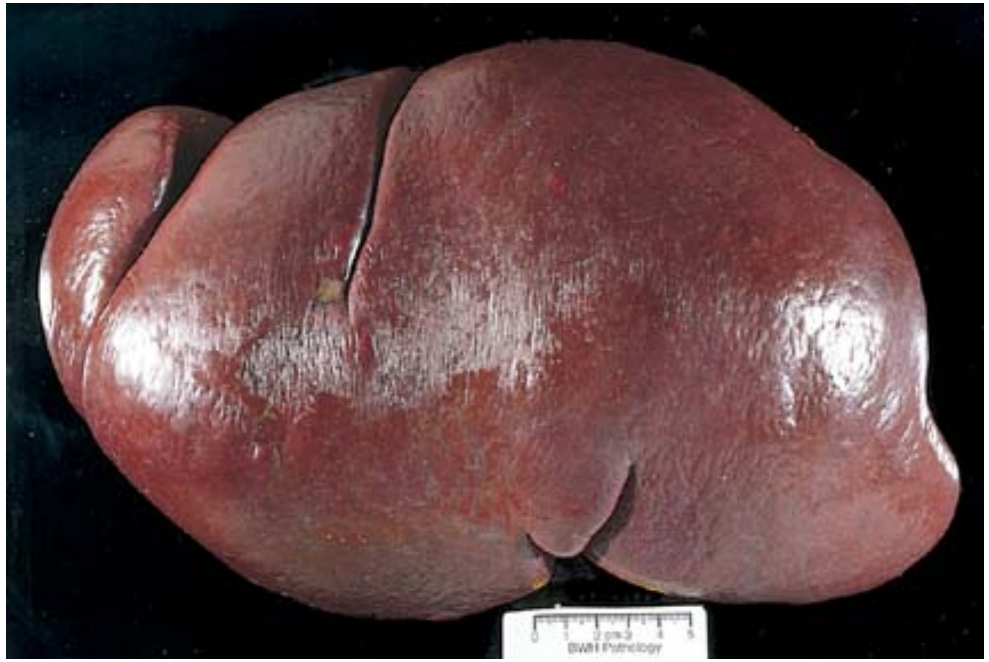


Figure 14-35 Essential thrombocytosis. Peripheral blood smear shows marked thrombocytosis, including giant platelets approximating the size of surrounding red cells. *(Courtesy of Dr. Jacqueline Mitus, Brigham and Women's Hospital, Boston, MA.)*

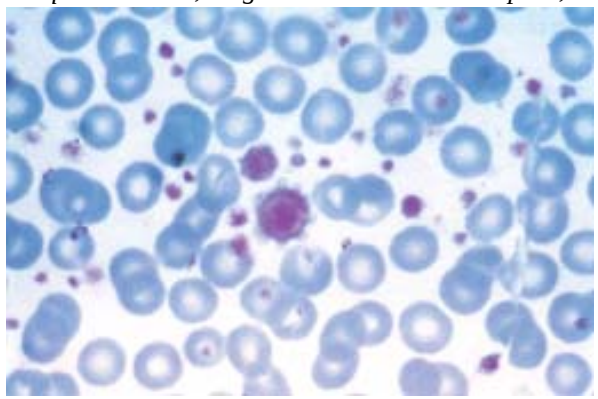


Figure 14-36 Primary myelofibrosis (peripheral blood smear). Two nucleated erythroid precursors and several teardrop-shaped red cells (dacryocytes) are evident. Immature myeloid cells were present in other fields. An identical picture can be seen in other diseases producing marrow distortion and fibrosis.

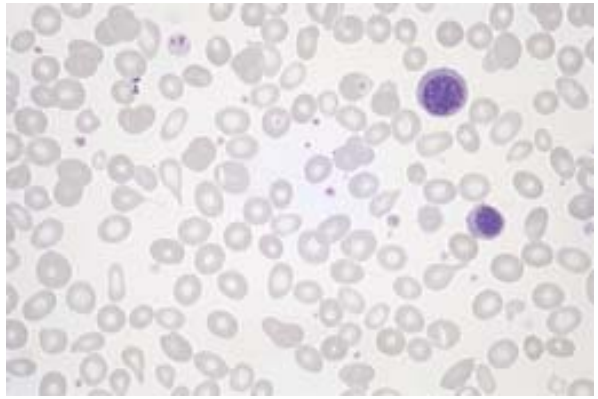


Figure 14-37 Langerhans cell histiocytosis. An electron micrograph shows rodlike Birbeck granules with characteristic periodicity and dilated terminal end. *(Courtesy of Dr. George Murphy, University of Pennsylvania School of Medicine, Philadelphia, PA.)*

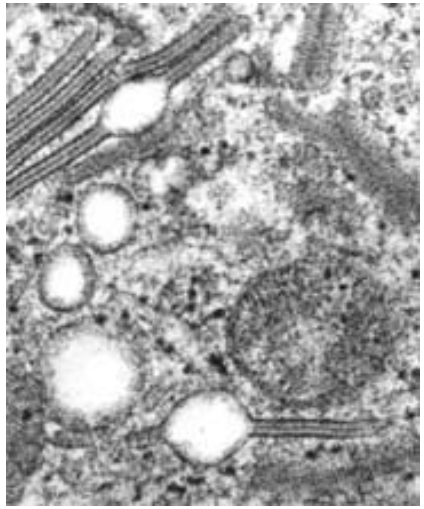


Figure 14-38 Normal splenic architecture. *(Modified from Faller DV: Diseases of the spleen. In Wyngaarden JB, Smith LH (eds): Cecil Textbook of Medicine, 18th ed. Philadelphia, WB Saunders, 1988, p. 1036.)*

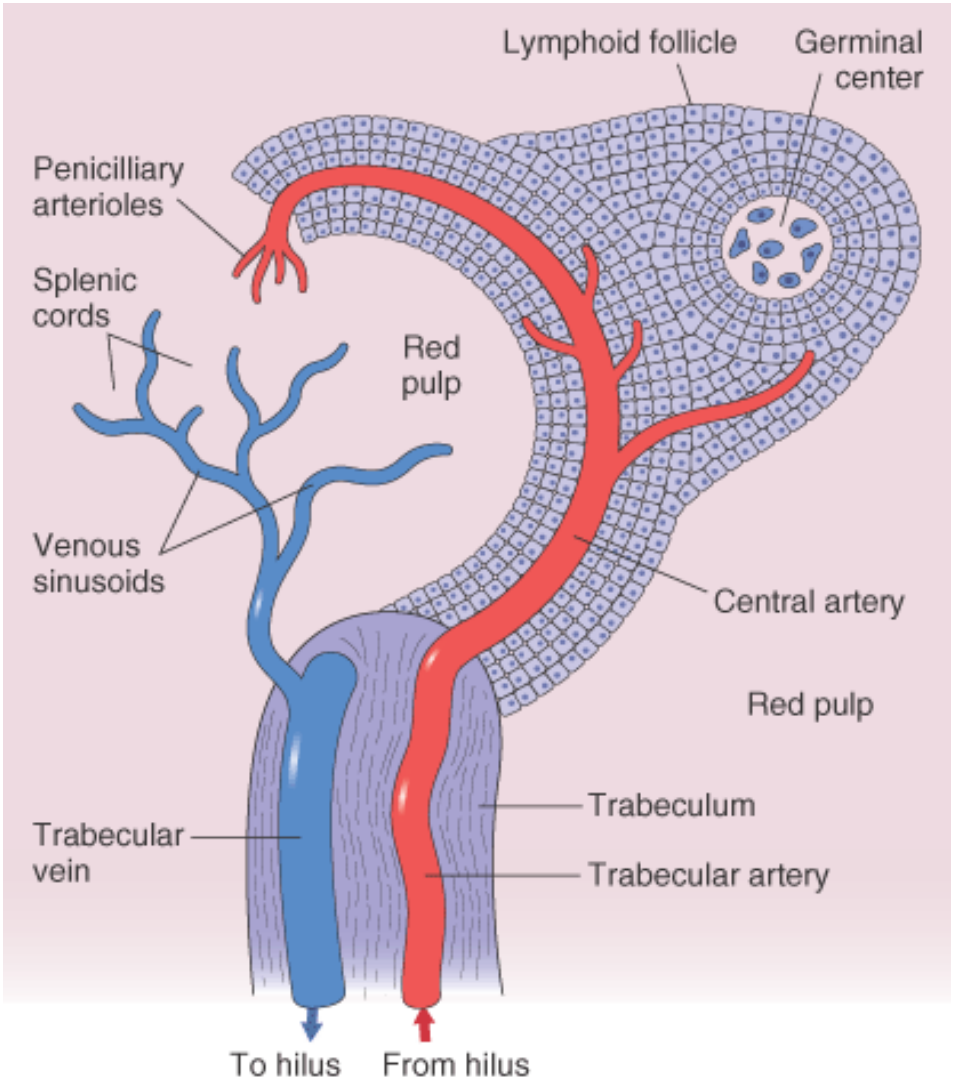


TABLE 14-9 -- Disorders Associated with Splenomegaly

I. Infections
Nonspecific splenitis of various blood-borne infections (particularly infective endocarditis)
Infectious mononucleosis
Tuberculosis
Typhoid fever
Brucellosis
Cytomegalovirus

Syphilis
Malaria
Histoplasmosis
Toxoplasmosis
Kala-azar
Trypanosomiasis
Schistosomiasis
Leishmaniasis
Echinococcosis
II. Congestive States Related to Portal Hypertension
Cirrhosis of the liver
Portal or splenic vein thrombosis
Cardiac failure
III. Lymphohematogenous Disorders
Hodgkin lymphoma
Non-Hodgkin lymphomas and lymphocytic leukemias
Multiple myeloma
Myeloproliferative disorders
Hemolytic anemias
Thromobocytopenic purpura
IV. Immunologic-Inflammatory Conditions
Rheumatoid arthritis
Systemic lupus erythematosus
V. Storage Diseases
Gaucher disease
Niemann-Pick disease
Mucopolysaccharidoses
VI. Miscellaneous
Amyloidosis
Primary neoplasms and cysts

Secondary neoplasms

NONSPECIFIC ACUTE SPLENITIS

Enlargement of the spleen occurs in any blood-borne infection. The nonspecific splenic reaction in these infections is caused both by the microbiologic agents themselves and by cytokines that are released as part of the immune response.

Morphology.

The spleen is enlarged (up to 200 to 400 gm) and soft. The splenic substance is often diffluent and can be so soft that it literally flows out from the cut surface. Microscopically, the major change is acute congestion of the red pulp, which can encroach on and sometimes virtually efface the lymphoid follicles. Neutrophils, plasma cells, and occasionally eosinophils are usually present throughout the white and red pulp. At times, there is acute necrosis of the centers of the splenic follicles, particularly when the causative agent is a hemolytic streptococcus. Rarely, abscess formation occurs.

CONGESTIVE SPLENOMEGALY

Chronic venous congestion can cause a form of splenic enlargement referred to as *congestive splenomegaly*. Venous congestion can be systemic in origin, caused by intrahepatic disorders that retard portal venous drainage, or may arise from extrahepatic disorders that directly obstruct the portal or splenic veins. All these disorders ultimately lead to portal or splenic vein hypertension. *Systemic, or central, venous congestion* is encountered in cardiac decompensation involving the right side of the heart, as can occur in tricuspid or pulmonic valvular disease, chronic cor pulmonale, or following left-sided heart failure. Systemic passive congestion produces only moderate enlargement of the spleen that rarely exceeds 500 gm in weight.

The only common causes of striking congestive splenomegaly are the various forms of cirrhosis of the liver. The "pipe-stem" hepatic fibrosis of schistosomiasis causes particularly severe congestive splenomegaly, while the diffuse fibrous scarring of alcoholic cirrhosis and pigment cirrhosis also evokes profound enlargements. Other forms of cirrhosis are less commonly implicated.

Congestive splenomegaly is also caused by obstruction of the extrahepatic portal vein or splenic vein. This can stem from *spontaneous portal vein thrombosis,* which is usually associated with some intrahepatic obstructive disease, or inflammation of the portal vein *(pylephlebitis),* such as follows intraperitoneal infections. Thrombosis of the splenic vein itself can be initiated by compression by tumors in neighboring organs, for example, carcinoma of the stomach or pancreas.

Morphology.

Long-standing congestion produces marked enlargement of the spleen (1000 gm or more); the organ is firm and becomes increasingly so the longer the congestion lasts. The weight can reach 5000 gm. The capsule is usually thickened and fibrous. The cut surface has a meaty appearance and varies from gray-red to deep red, depending on the amount of fibrosis. Often the white pulp is indistinct. Microscopically, the red pulp is congested in early chronic congestion but becomes increasingly more fibrous

and cellular with time. The increased portal venous pressure causes deposition of collagen in the basement membrane of the sinusoids, which appear dilated owing to the rigidity of their walls. The resultant slowing of blood flow from the cords to the sinusoids prolongs the exposure of the blood cells to the cordal macrophages, resulting in excessive destruction (hypersplenism). Foci of recent or old hemorrhage are often present. Organization of these focal hemorrhages gives rise to Gandy-Gamma nodules: foci of fibrosis containing iron and calcium salts deposited on connective tissue and elastic fibers.

SPLENIC INFARCTS

Splenic infarcts are common lesions. Caused by occlusion of the major splenic artery or any of its branches, in normal-sized spleens they are most often due to emboli that arise from thrombi in the heart. The spleen, along with kidneys and brain, ranks as one of the most frequent sites within which emboli lodge. The resulting infarcts can be small or large, single or multiple or can even involve the entire organ. They are usually bland but can be septic when associated with infectious endocarditis of mitral and aortic valves. Infarcts are also common in markedly enlarged spleens, presumably because the blood supply cannot keep up with the increased demands of the organ.

Morphology.

Bland infarcts are characteristically pale and wedge-shaped, with their bases at the periphery, where the overlying capsule is often covered with fibrin (Fig. 14-39). In septic infarcts, this appearance is modified by the development of suppurative necrosis. In the course of healing of splenic infarcts, large, depressed scars often develop.

Figure 14-39 Splenic infarcts. Multiple well-circumscribed infarcts are present in this spleen, which is massively enlarged (2820 gm; normal: 150 to 200) by extramedullary hematopoiesis secondary to a chronic myeloproliferative disorder (myelofibrosis). Recent infarcts are hemorrhagic, whereas older, more fibrotic infarcts are a pale yellow-gray color.

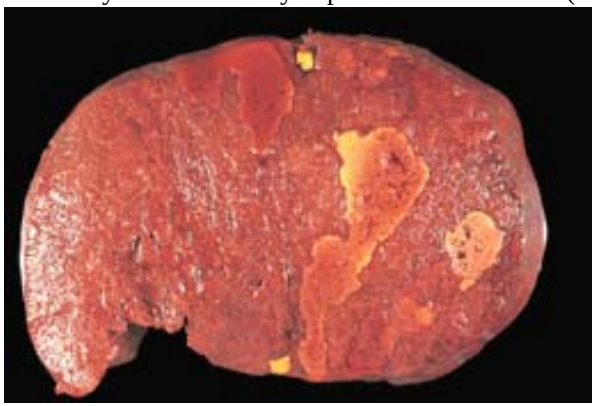
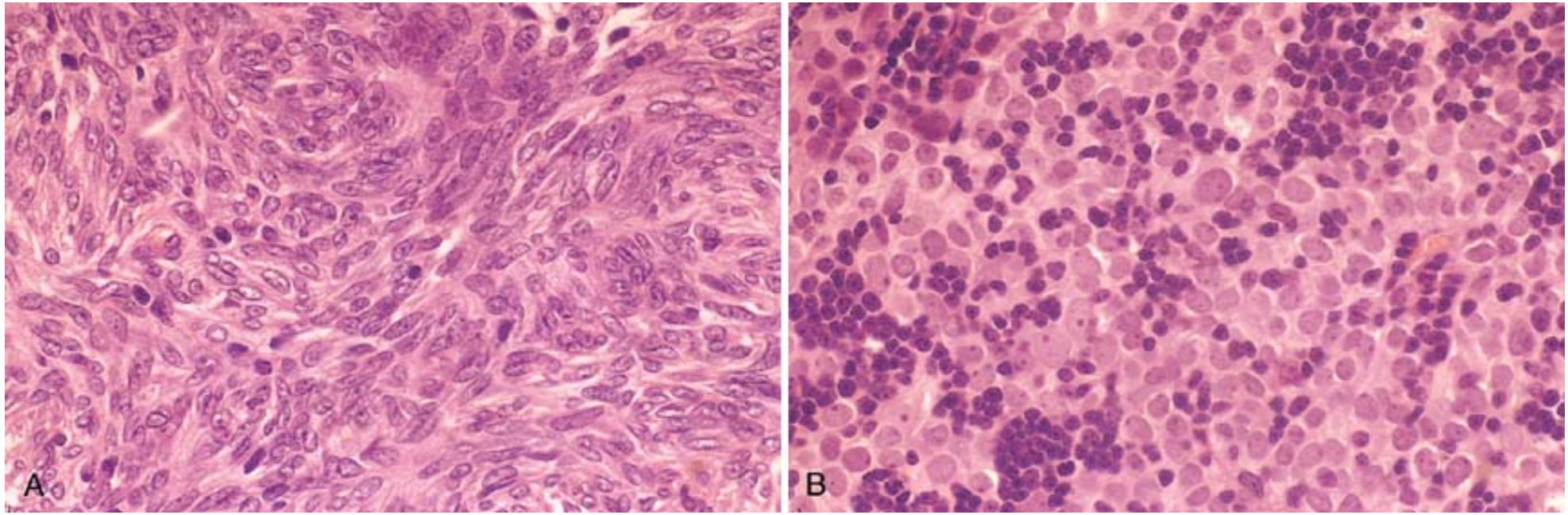


Figure 14-40 Thymoma. *A,* Benign thymoma (medullary type). The neoplastic epithelial cells are arranged in a swirling pattern and have bland, oval to elongated nuclei with inconspicuous nucleoli. Only a few small, reactive lymphoid cells are interspersed. *B,* Malignant thymoma, type I. The neoplastic epithelial cells are polygonal and have round to oval, bland nuclei with inconspicuous nucleoli. Numerous small, reactive lymphoid cells are interspersed. The morphologic appearance of this tumor is identical to that of benign thymomas of the cortical type. In this case, however, the tumor was locally aggressive, invading adjacent lung and pericardium.



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Chapter 15 - The Lung *

Aliya N. Husain MBBS
Vinay Kumar MD

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Normal Lung

The lungs are ingeniously constructed to carry out their cardinal function: the exchange of gases between inspired air and blood. Developmentally, the respiratory system is an outgrowth from the ventral wall of the foregut. The midline trachea develops two lateral outpocketings, the lung buds. The right lung bud eventually divides into three branches—the main bronchi—and the left into two main bronchi, thus giving rise to three lobes on the right and two on the left. The lingula on the left is the middle lobe equivalent; however, the left lung is smaller than the right. The right main stem bronchus is more vertical and more directly in line with the trachea than is the left. Consequently, aspirated foreign material, such as vomitus, blood, and foreign bodies, tends to enter the right lung rather than the left. The main right and left bronchi branch dichotomously, giving rise to progressively smaller airways. Accompanying the branching airways is the double arterial supply to the lungs, that is, the pulmonary and bronchial arteries. In the absence of significant cardiac failure, the bronchial arteries of aortic origin can often sustain the vitality of the pulmonary parenchyma when pulmonary arterial supply is blocked, as by emboli.

Progressive branching of the bronchi forms *bronchioles*, which are distinguished from bronchi by the lack of cartilage and submucosal glands within their walls. Further branching of bronchioles leads to the *terminal bronchioles*, which are less than 2 mm in diameter. The part of the lung distal to the terminal bronchiole is called the *acinus*; it is approximately spherical, with a diameter of about 7 mm. As illustrated in Figure 15-5*A* , an acinus is composed of *respiratory bronchioles* (emanating from the terminal bronchiole), which give off several alveoli from their sides. These bronchioles then proceed into the *alveolar ducts*, which immediately branch into *alveolar sacs*, the blind ends of the respiratory passages, whose walls are formed entirely of alveoli, which are the site of gas exchange. The alveoli open into the ducts through large mouths. In the correct plane of section, therefore, all alveoli are open and have incomplete walls. A cluster of three to five terminal bronchioles, each with its appended acinus, is usually referred to as the pulmonary *lobule*. As will be seen subsequently, this lobular architecture assumes importance in distinguishing the major forms of emphysema.

From the microscopic standpoint, except for the vocal cords, which are covered by stratified squamous epithelium, the entire respiratory tree, including the larynx, trachea, and bronchioles, is lined by pseudostratified, tall, columnar, ciliated epithelial cells, heavily admixed in the cartilaginous airways with mucus-secreting goblet cells. The bronchial mucosa also contains neuroendocrine cells that exhibit neurosecretory-type granules and contain serotonin, calcitonin, and gastrin-releasing peptide (bombesin). Numerous submucosal, mucus-secreting glands are dispersed throughout the walls of the trachea and bronchi (but not the bronchioles).

The microscopic structure of the alveolar walls (or alveolar septa) consists, from blood to air, of the following (Fig. 15-1):

- The *capillary endothelium* lining the intertwining network of anastomosing capillaries.
- A *basement membrane and surrounding interstitial tissue* separating the endothelial cells from the alveolar lining

epithelial cells. In thin portions of the alveolar septum, the basement membranes of epithelium and endothelium are fused, whereas in thicker portions, they are separated by an interstitial space (*pulmonary interstitum*) containing fine elastic fibers, small bundles of collagen, a few fibroblast-like interstitial cells, smooth muscle cells, mast cells, and, rarely, lymphocytes and monocytes.

- *Alveolar epithelium*, which contains a continuous layer of two principal cell types: flattened, platelike *type I pneumocytes* (or membranous pneumocytes) covering 95% of the alveolar surface and rounded *type II pneumocytes*. Type II cells are important for at least two reasons: (1) They are the source of *pulmonary surfactant*, contained in osmiophilic *lamellar bodies* seen with electron microscopy, and (2) they are the main cell type involved in the repair of alveolar epithelium after destruction of type I cells.
- *Alveolar macrophages*, loosely attached to the epithelial cells or lying free within the alveolar spaces, derived from blood monocytes and belonging to the mononuclear phagocyte system. Often, they are filled with carbon particles and other phagocytosed materials.

Figure 15-1 Microscopic structure of the alveolar wall. Note that the basement membrane (*yellow*) is thin on one side and widened where it is continuous with the interstitial space. Portions of interstitial cells are shown.

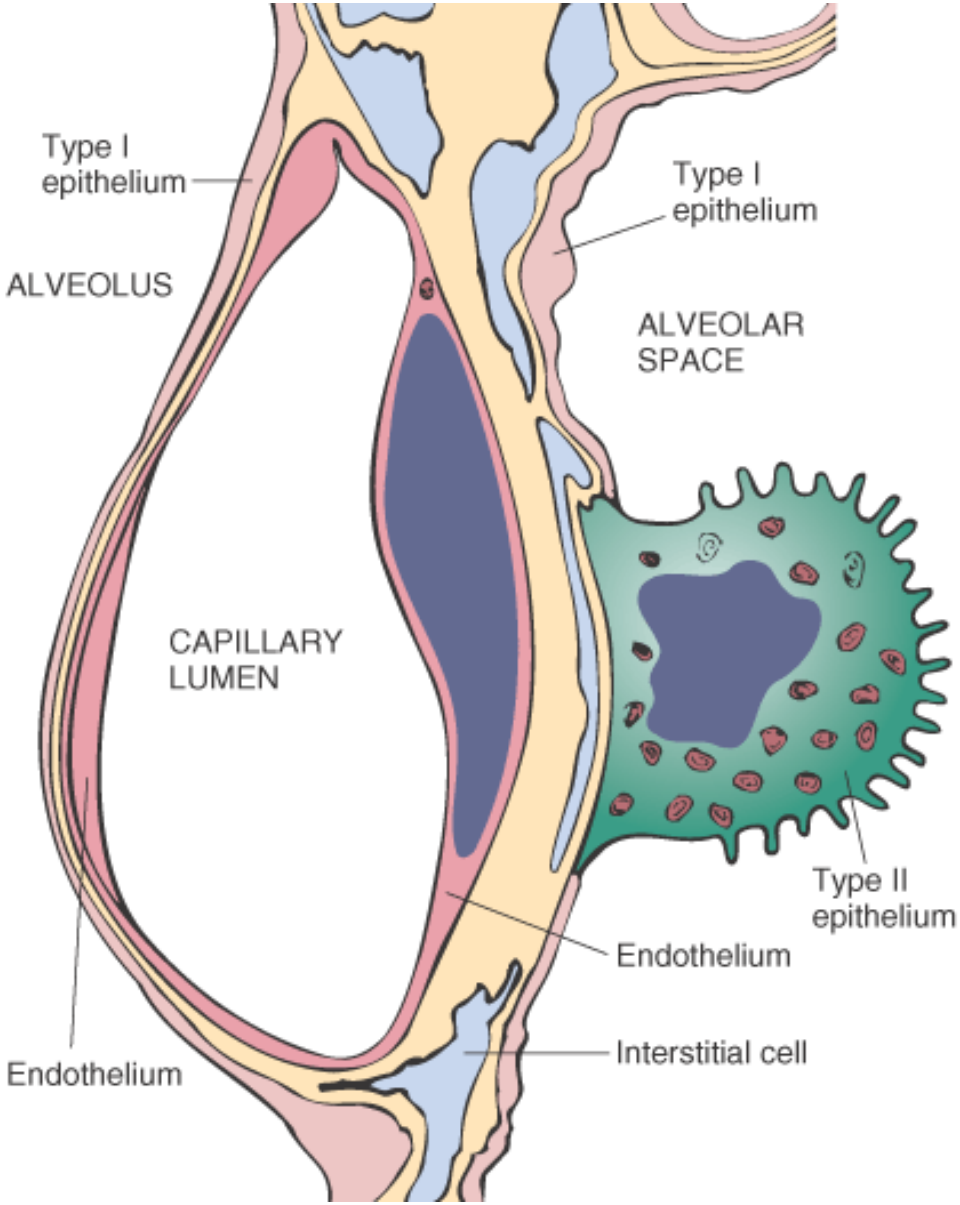
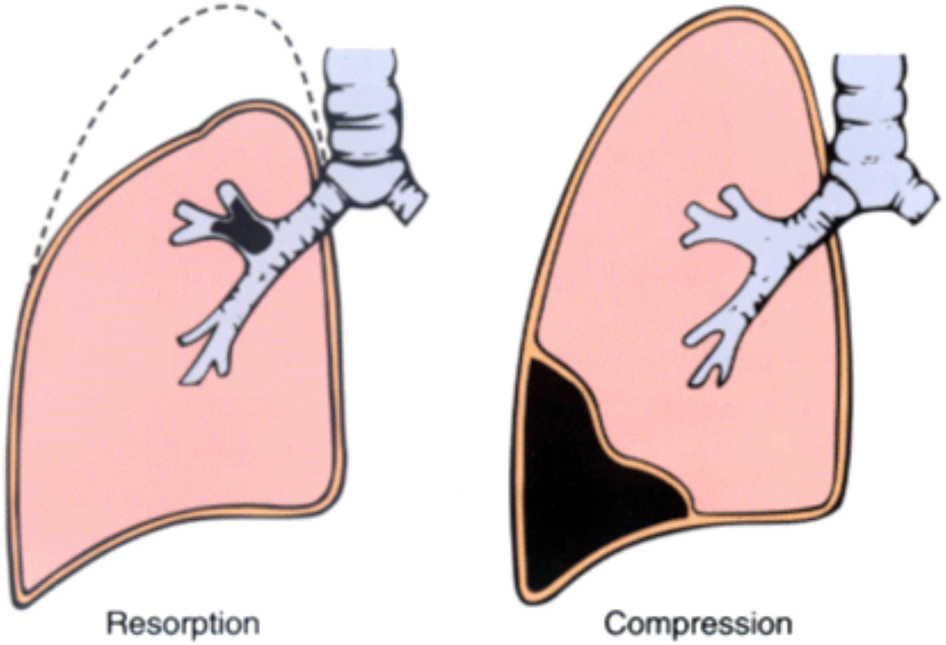


Figure 15-2 Various forms of atelectasis in adults.



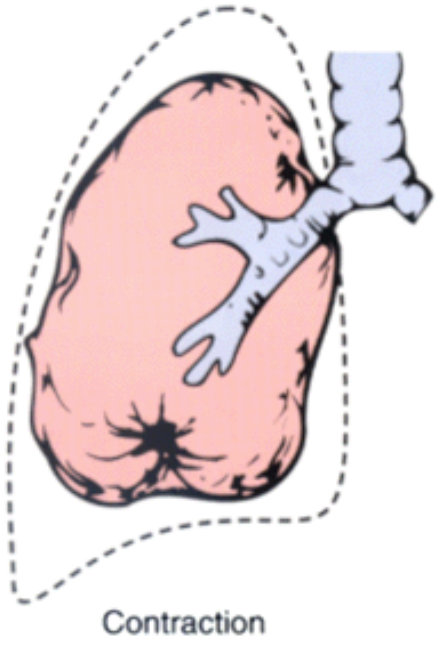


TABLE 15-1 -- Classification and Causes of Pulmonary Edema

Hemodynamic Edema

Increased hydrostatic pressure (increased pulmonary venous pressure)
••Left-sided heart failure (common)
••Volume overload
••Pulmonary vein obstruction
Decreased oncotic pressure (less common)
••Hypoalbuminemia
••Nephrotic syndrome
••Liver disease
••Protein-losing enteropathies
Lymphatic obstruction (rare)
Edema Due to Microvascular Injury (Alveolar Injury)
Infections: pneumonia, septicemia
Inhaled gases: oxygen, smoke
Liquid aspiration: gastric contents, near-drowning
Drugs and chemicals: chemotherapeutic agents (bleomycin), other medications (amphotericin B), heroin, kerosene, paraquat
Shock, trauma
Radiation
Transfusion related
Edema of Undetermined Origin
High altitude
Neurogenic (central nervous system trauma)

the clinical setting, pulmonary congestion and edema are characterized by heavy, wet lungs. Fluid accumulates initially in the basal regions of the lower lobes because hydrostatic pressure is greater in these sites (dependent edema). Histologically, the alveolar capillaries are engorged, and an intra-alveolar granular pink precipitate is seen. Alveolar microhemorrhages and hemosiderin-laden macrophages ("heart failure" cells) may be present. In long-standing cases of pulmonary congestion, such as those seen in mitral stenosis, hemosiderin-laden macrophages are abundant, and fibrosis and thickening of the alveolar walls cause the soggy lungs to become firm and brown (*brown induration*). These changes not only impair normal respiratory function, but also predispose to infection.

Edema Caused by Microvascular Injury

The second mechanism leading to pulmonary edema is *injury to the capillaries of the alveolar septa*. Here the pulmonary capillary hydrostatic pressure is usually not elevated, and hemodynamic factors play a secondary role. The edema results from primary injury to the vascular endothelium or damage to alveolar epithelial cells (with secondary microvascular injury). This results in leakage of fluids and proteins first into the interstitial space and, in more severe cases, into the alveoli. When the edema remains localized, as it does in most forms of pneumonia, it is overshadowed by the manifestations of infection. When diffuse, however, alveolar edema is an important contributor to a serious and often fatal condition, *acute respiratory distress syndrome*, discussed in the following section.

ACUTE RESPIRATORY DISTRESS SYNDROME (DIFFUSE ALVEOLAR DAMAGE)

Acute respiratory distress syndrome (ARDS) (synonyms include "shock lung," "diffuse alveolar damage," "acute alveolar injury," and "acute lung injury") is a clinical syndrome caused by diffuse alveolar capillary damage. It is characterized clinically by the rapid onset of severe life-threatening respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy and that may progress to extra-pulmonary multisystem organ failure. Chest radiographs show diffuse alveolar infiltration. Diffuse alveolar damage (DAD) is the histologic manifestation.

ARDS is a well-recognized complication of numerous and diverse conditions, including both direct injuries to the lungs and systemic disorders (Table 15-2). In many cases, a combination of predisposing conditions is present (e.g., shock, oxygen therapy, and sepsis).

Morphology.

In the acute stage, the lungs are heavy, firm, red, and boggy. They exhibit congestion, interstitial and intra-alveolar edema, inflammation, and fibrin deposition. The alveolar walls become lined with waxy **hyaline membranes** (Fig. 15-3) that are morphologically similar to those seen in hyaline membrane disease of neonates (Chapter 10). Alveolar hyaline membranes consist of fibrin-rich edema fluid mixed with the cytoplasmic and lipid remnants of necrotic epithelial cells. In the organizing stage, type

TABLE 15-2 -- Conditions Associated with Development of Acute Respiratory Distress Syndrome

Infection
Sepsis *
Diffuse pulmonary infections *
••Viral, *Mycoplasma*, and *Pneumocystis* pneumonia; miliary tuberculosis
Gastric aspiration *
Physical/Injury
Mechanical trauma, including head injuries *
Pulmonary contusions
Near-drowning
Fractures with fat embolism
Burns
Ionizing radiation
Inhaled Irritants

Oxygen toxicity
Smoke
Irritant gases and chemicals
Chemical Injury
Heroin or methadone overdose
Acetylsalicylic acid
Barbiturate overdose
Paraquat
Hematologic Conditions
Multiple transfusions
Disseminated intravascular coagulation
Pancreatitis
Uremia
Cardiopulmonary Bypass
Hypersensitivity Reactions
Organic solvents
Drugs

*More than 50% of cases of acute respiratory distress syndrome are associated with these four conditions.

Il epithelial cells undergo proliferation in an attempt to regenerate the alveolar lining. Resolution is unusual; more commonly, there is organization of the fibrin exudate, with resultant intra-alveolar fibrosis. Marked thickening of the alveolar septa ensues, caused by proliferation of interstitial cells and deposition of collagen. Fatal cases often have superimposed bronchopneumonia.

Pathogenesis.

ARDS and DAD are best viewed as the clinical and pathologic end results, respectively, of acute alveolar injury caused by a variety of insults and initiated by different mechanisms.[3] Central to the causation of ARDS is *diffuse damage to the alveolar capillary walls*; this is followed by a relatively nonspecific, often predictable series of morphologic

Figure 15-3 Diffuse alveolar damage (acute respiratory distress syndrome) shown in a photomicrograph. Some of the alveoli are collapsed; others are distended. Many contain dense proteinaceous debris, desquamated cells, and hyaline membranes (*arrows*).

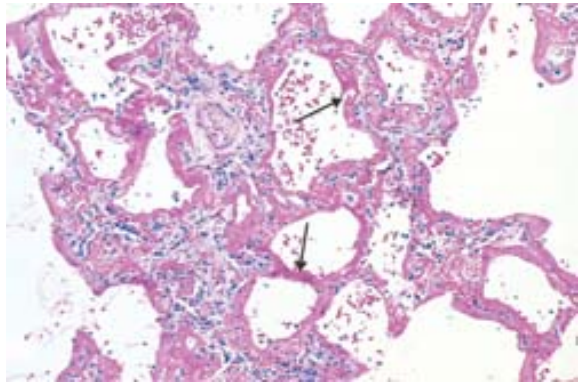


Figure 15-4 The normal alveolus (*left side*) compared with the injured alveolus in the early phase of acute lung injury and acute respiratory distress syndrome. Under the influence of proinflammatory cytokines such as interleukin 8 (IL-8), interleukin 1 (IL-1), and tumor necrosis factor (TNF) (released by macrophages), neutrophils initially undergo sequestration in the pulmonary microvasculature, followed by margination and egress into the alveolar space, where they undergo activation. Activated neutrophils release a variety of factors, such as leukotrienes, oxidants, proteases, and platelet-activating factor (PAF), which contribute to local tissue damage, accumulation of edema fluid in the airspaces, surfactant inactivation, and hyaline membrane formation. Macrophage inhibitory factor (MIF) released into the local milieu sustains the ongoing pro-inflammatory response. Subsequently, the release of macrophage-derived fibrogenic cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) stimulate fibroblast growth and collagen deposition associated with the healing phase of injury. *(Modified with permission from Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 342:1334, 2000.)*

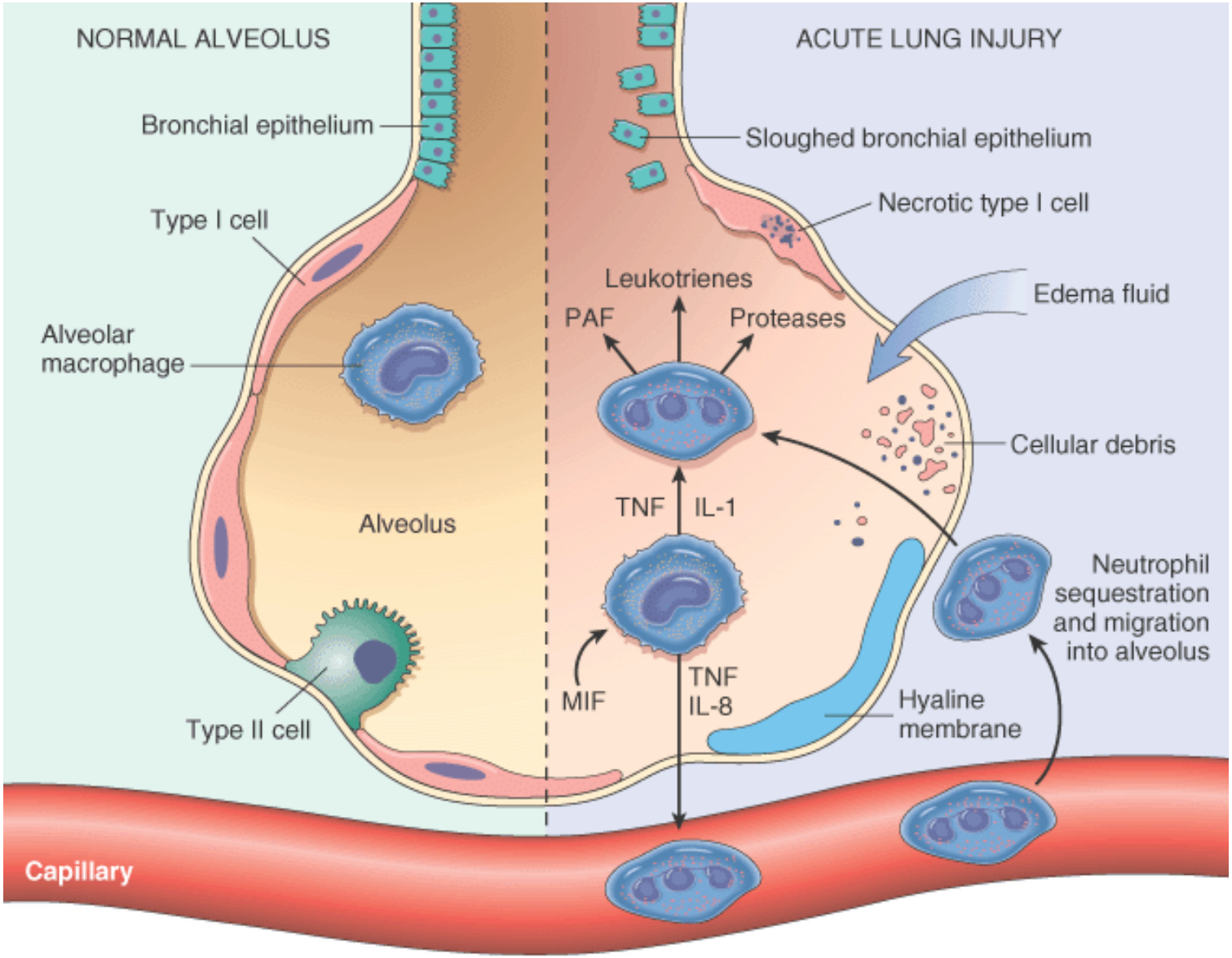


TABLE 15-3 -- Disorders Associated with Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Term	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever

Asthma	Bronchus	Smooth muscle hyperplasia, excess mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Airspace enlargement; wall destruction	Tobacco smoke	Dyspnea
Small airway disease, * bronchiolitis	Bronchiole	Inflammatory scarring/obliteration	Tobacco smoke, air pollutants, miscellaneous	Cough, dyspnea

*A feature of chronic bronchitis (see text).

Of these, only the first two cause clinically significant airflow obstruction (Fig. 15-5). Centriacinar emphysema is far more common than the panacinar form, constituting more than 95% of cases. Clinical management does not rely on precise anatomic diagnosis and classification, which, however, do provide important clues to pathogenesis.

Centriacinar (Centrilobular) Emphysema.

The distinctive feature of this type of emphysema is the pattern of involvement of the lobules; *the central or proximal parts of the acini, formed by respiratory bronchioles, are affected, whereas distal alveoli are spared* (Fig. 15-6*B*). Thus, both emphysematous and normal airspaces exist within the same acinus and lobule. The lesions are more common and usually more severe in the

Figure 15-5 *A,* Diagram of normal structures within the acinus, the fundamental unit of the lung. A terminal bronchiole (*not shown*) is immediately proximal to the respiratory bronchiole. *B,* Centriacinar emphysema with dilation that initially affects the respiratory bronchioles. *C,* Panacinar emphysema with initial distention of the peripheral structures (i.e., the alveolus and alveolar duct); the disease later extends to affect the respiratory bronchioles.

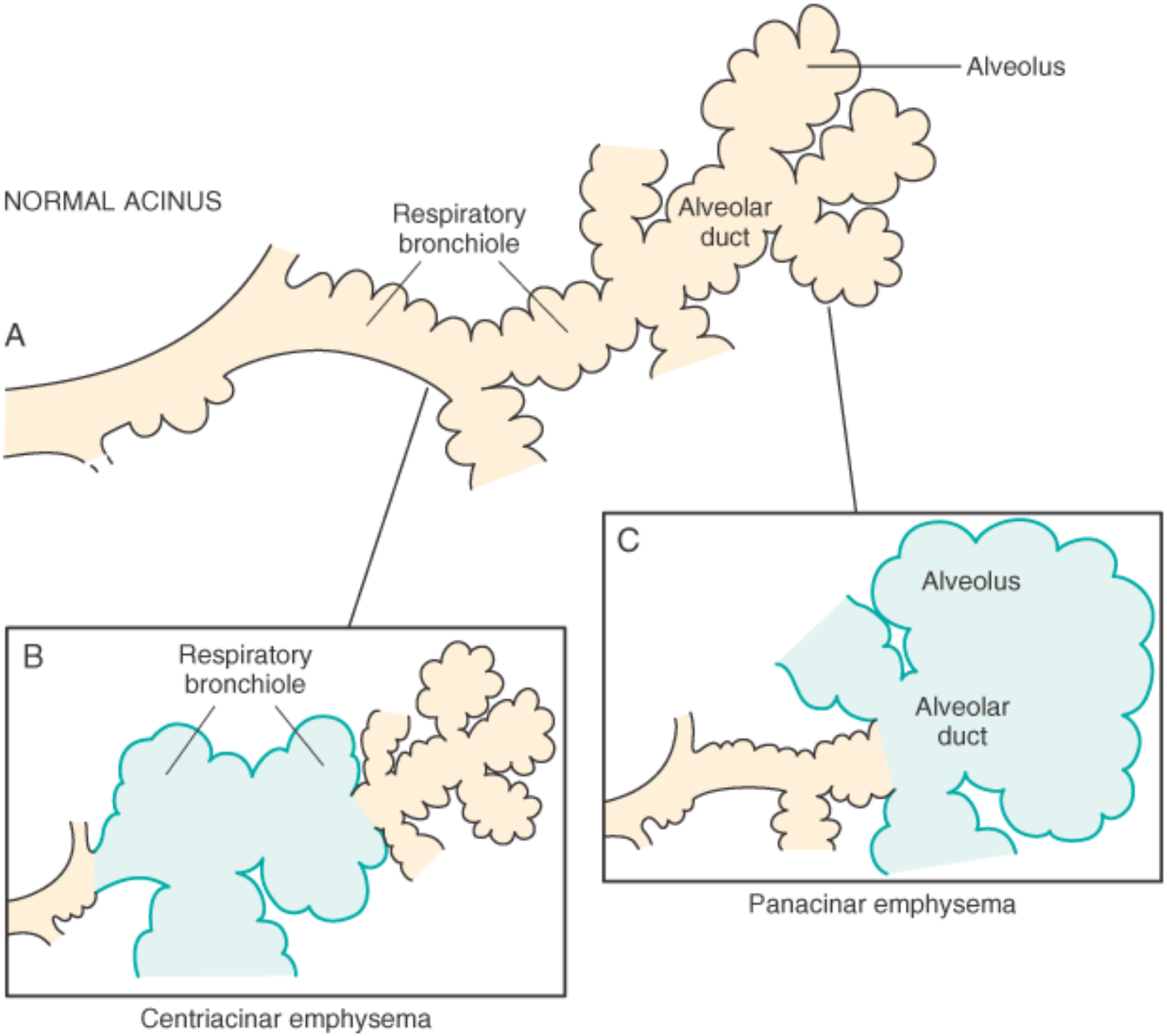


Figure 15-6 *A*, Centriacinar emphysema. Central areas show marked emphysematous damage (E), surrounded by relatively spared alveolar spaces. *B*, Panacinar emphysema involving the entire pulmonary architecture.

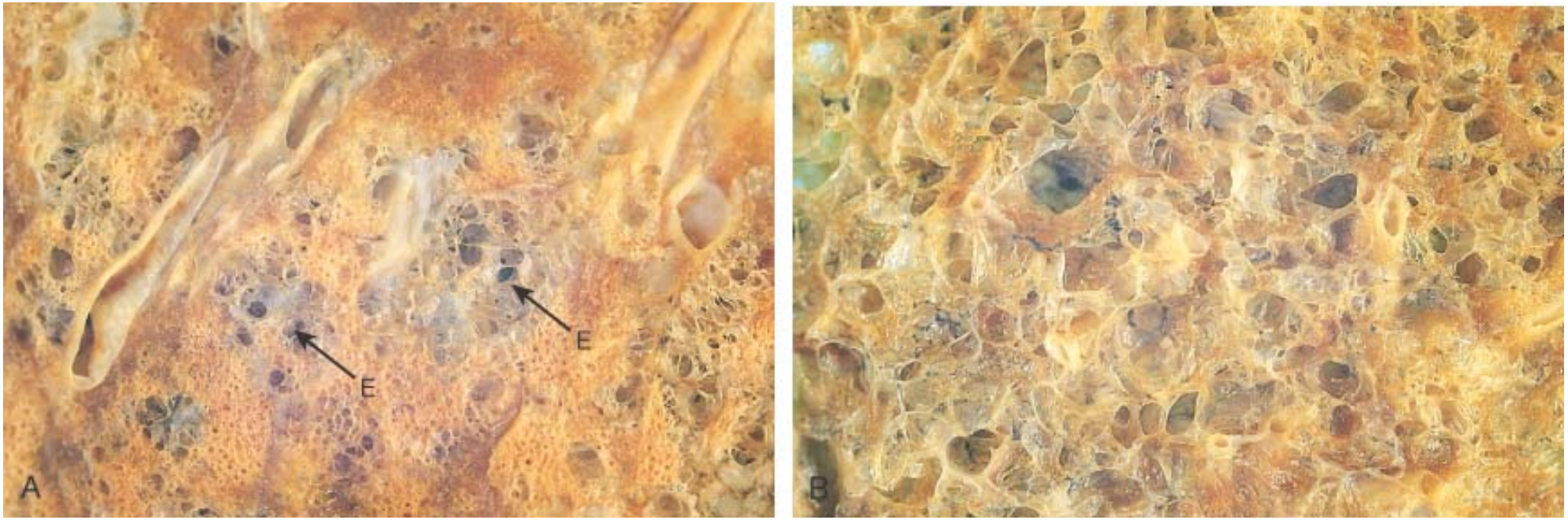


Figure 15-7 Pathogenesis of emphysema. The protease-antiprotease imbalance and oxidant-antioxidant imbalance are additive in their effects and contribute to tissue damage. α_1 -antitrypsin (α_1 -AT) deficiency can be either congenital or "functional" as a result of oxidative inactivation. See text for details. IL-8, interleukin 8; LTB_4 , leukotriene B_4 ; TNF, tumor necrosis factor.

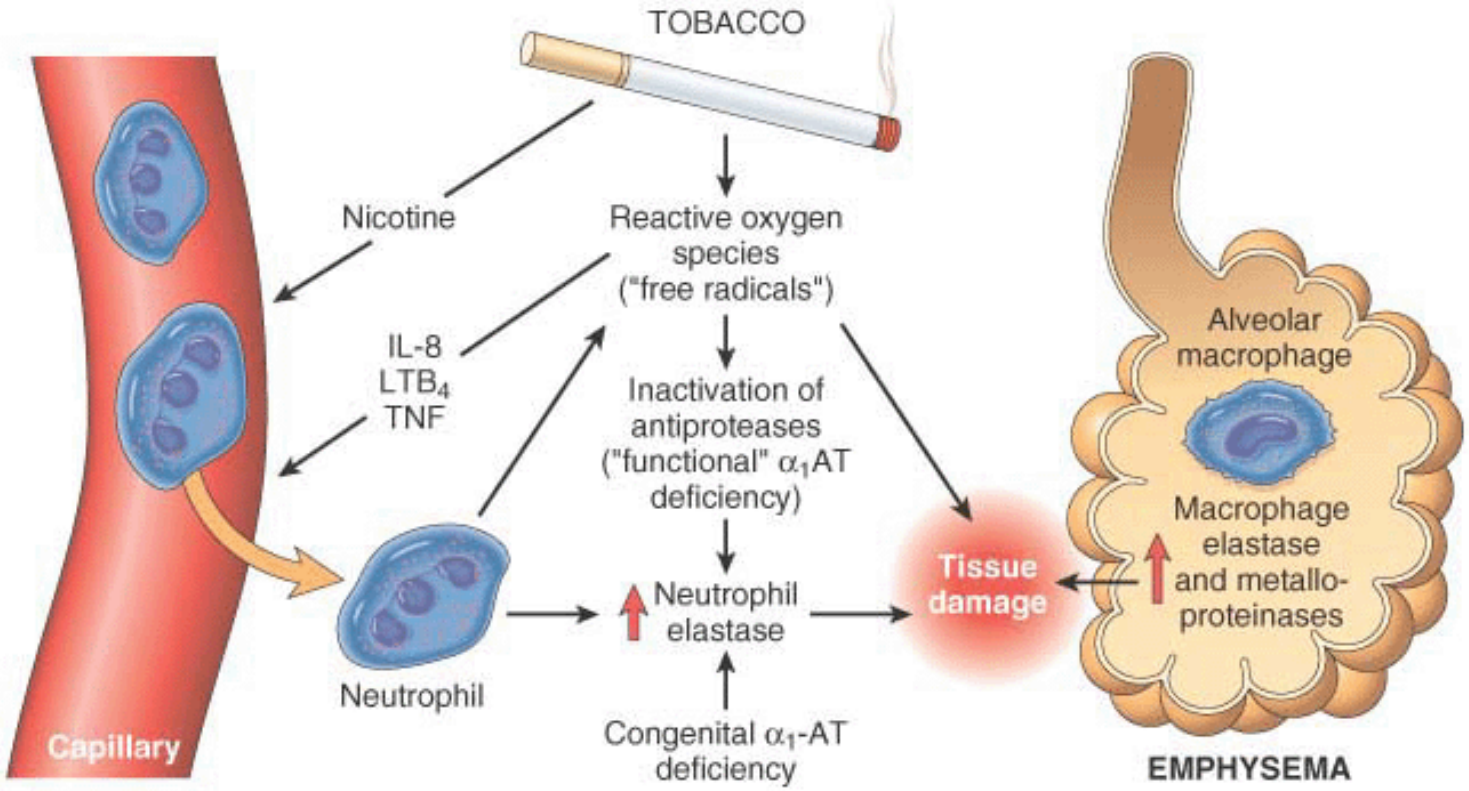


TABLE 15-4 -- Emphysema and Chronic Bronchitis

	Predominant Bronchitis	Predominant Emphysema
Age (yr)	40–45	50–75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Repeated	Terminal
Cor pulmonale	Common	Rare; terminal
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels; large heart	Hyperinflation; small heart
Appearance	*Blue bloater*	*Pink puffer*

Compensatory Hyperinflation (Emphysema).

The term *compensatory hyperinflation (emphysema)* is sometimes used to designate dilation of alveoli but not destruction of septal walls in response to loss of lung substance elsewhere. It is best exemplified by the hyperexpansion of the residual lung parenchyma that follows surgical removal of a diseased lung or lobe.

Obstructive Overinflation.

Obstructive overinflation refers to the condition in which the lung expands because air is trapped within it. A common cause is subtotal obstruction by a tumor or foreign object. A classic example is *congenital labor overinflation* in infants, probably resulting from hypoplasia of bronchial cartilage and sometimes associated with other congenital cardiac and lung abnormalities. Overinflation in obstructive lesions occurs either (1) because of a ball-valve action of the obstructive agent, so that air enters on inspiration but cannot leave on expiration, or (2) because the bronchus may be totally obstructed but ventilation through *collaterals* may bring in air from behind the obstruction. These collaterals are the *pores of Kohn* and other direct accessory *bronchioloalveolar connections* (the canals of Lambert). Obstructive overinflation can be a life-threatening emergency because the affected portion distends sufficiently to compress the remaining normal lung.

Bullous Emphysema.

Bullous emphysema refers merely to any form of emphysema that produces large subpleural blebs or bullae (spaces more than 1 cm in diameter in the distended state) (Fig. 15-8). They represent localized accentuations of one of the four forms of emphysema, are most often subpleural, and occur near the apex, sometimes in relation to old tuberculous scarring. On occasion, rupture of the bullae may give rise to pneumothorax.

Interstitial Emphysema

The entrance of air into the connective tissue stroma of the lung, mediastinum, or subcutaneous tissue is designated interstitial emphysema. In most instances, alveolar tears in pulmonary emphysema provide the avenue of entrance of air into the stroma of the lung, but rarely, a wound of the chest that allows air to be sucked in or a fractured rib that punctures the lung substance may underlie this disorder. Alveolar tears usually occur when there is a combination

Figure 15-8 Bullous emphysema with large subpleural bullae (*upper left*).

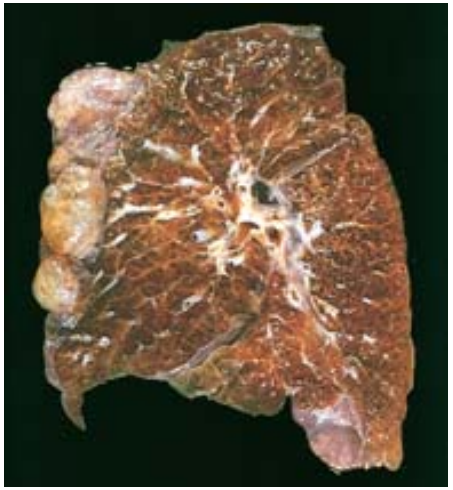


Figure 15-9 Schematic representation of evolution of chronic bronchitis (*left*) and emphysema (*right*). Although both can culminate in chronic bronchitis and emphysema, the pathways are different, and either one may predominate. The dashed arrows on the left indicate that in the natural history of chronic bronchitis, it is not known whether there is a predictable progression

from obstruction in small airways to chronic (obstructive) bronchitis. *(Redrawn from Fishman AP: The spectrum of chronic obstructive disease of the airways. In Fishman AP (ed): Pulmonary Diseases and Disorders, 2nd ed. New York, McGraw-Hill, 1988, p. 1164.)*

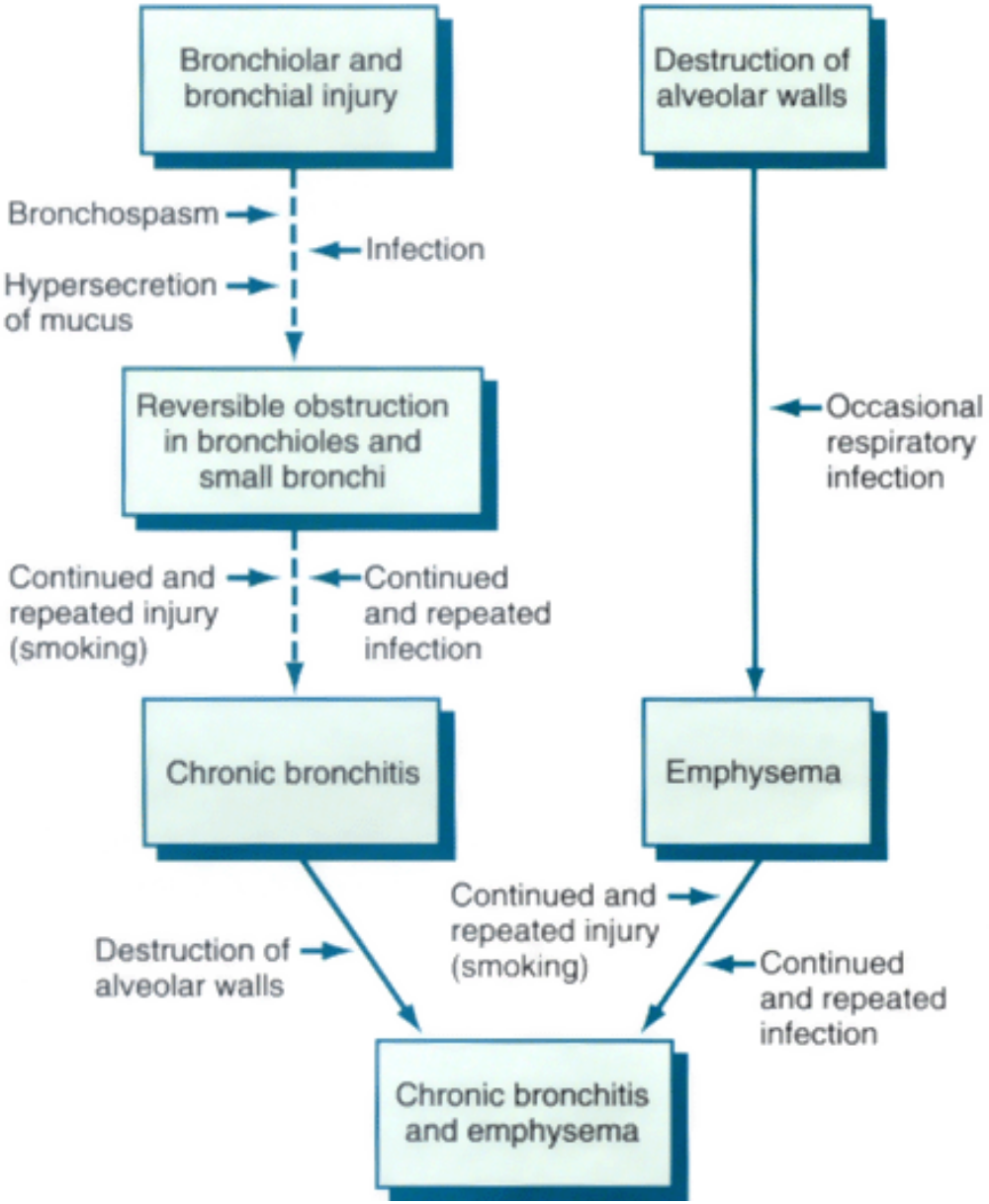


Figure 15-10 A simplified scheme of the system of type 1 helper T (T_H 1) and type 2 helper (T_H 2) cells. The differentiation of T_H 1 and T_H 2 cells depends on interleukin-12 and interleukin-4, cytokines produced by antigen-stimulated precursor CD4 T cells. In a regulatory loop, interferon-γ from T_H 1 cells inhibits T_H 2 cells and interleukin-4 from T_H 2 cells inhibits T_H 1 cells. An imbalance that favors T_H 2 cells may be important in asthma. Bronchial lymphocytes from patients with asthma have been found to lack T-bet, a transcription factor required for the production of interferon-γ (IFN-γ) by T_H 1 cells. *(From Schwartz RS: A new element in the mechanism of asthma. N Engl J Med 346(11):857, 2002. Permission requested.)*

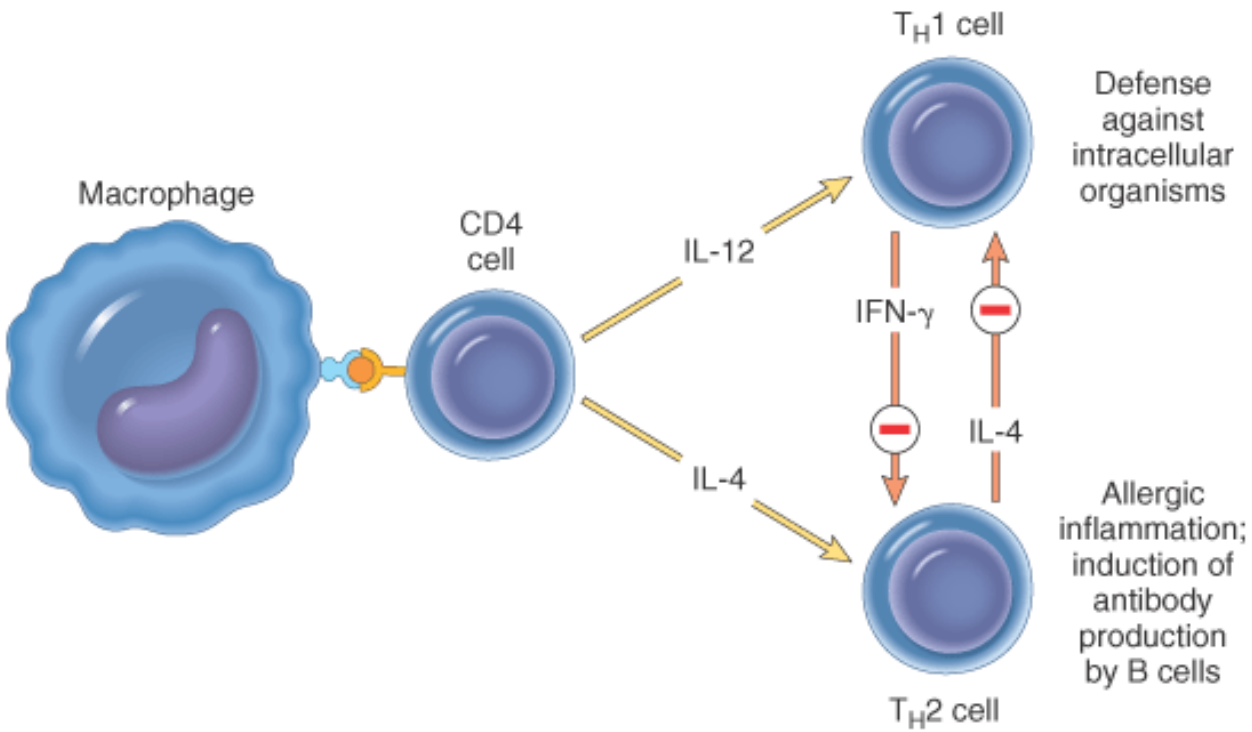
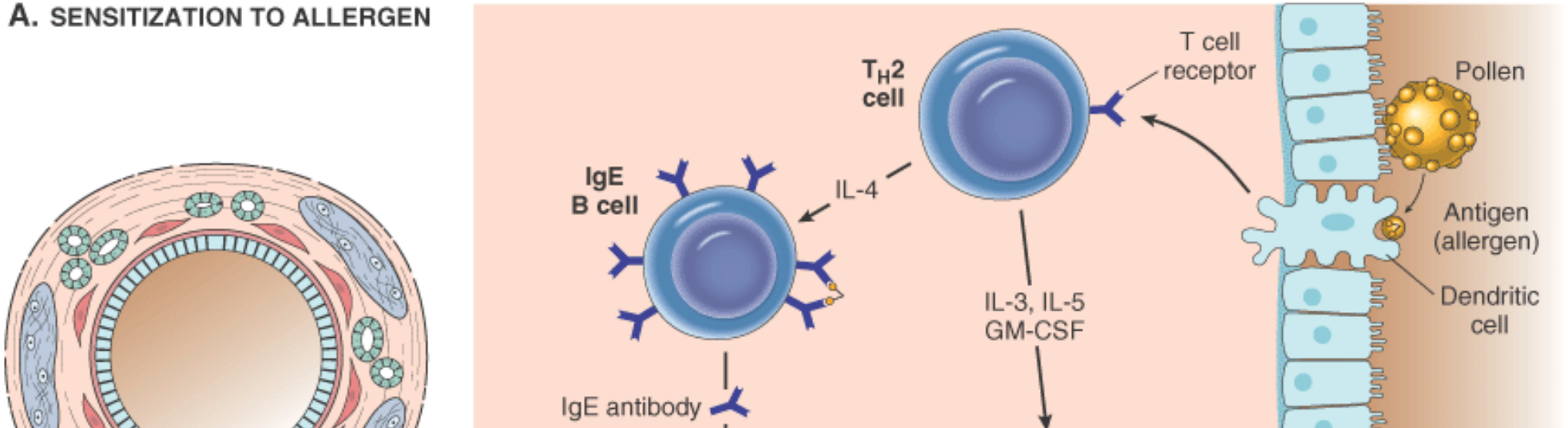
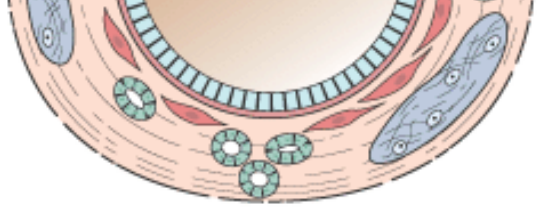
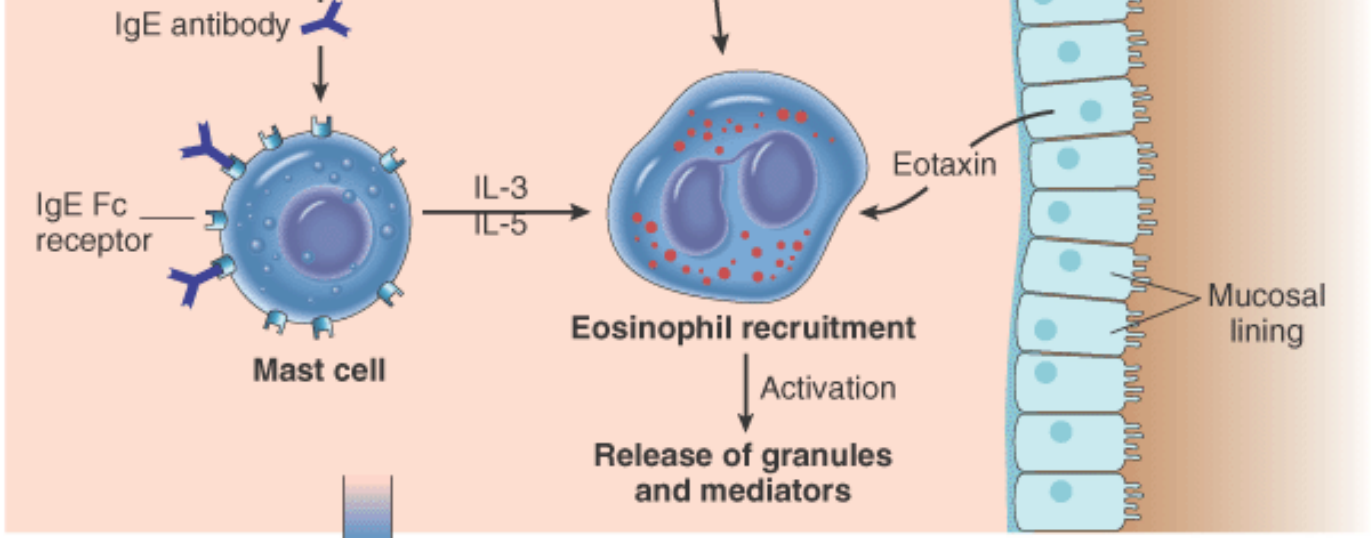


Figure 15-11 A model for allergic asthma. *A*, Inhaled allergens (antigen) elicit a T_H 2-dominated response favoring IgE production and eosinophil recruitment (priming or sensitization). *B*, On re-exposure to antigen (Ag), the immediate reaction is triggered by Ag-induced cross-linking of IgE bound to IgE receptors on mast cells in the airways. These cells release preformed mediators that open tight junctions between epithelial cells. Antigen can then enter the mucosa to activate mucosal mast cells and eosinophils, which in turn release additional mediators. Collectively, either directly or via neuronal reflexes, the mediators induce bronchospasm, increased vascular permeability, and mucus production and recruit additional mediator-releasing cells from the blood. *C*, The arrival of recruited leukocytes (neutrophils, eosinophils, and basophils; also lymphocytes and monocytes [*not shown*]) signals the initiation of the late phase of asthma and a fresh round of mediator release from leukocytes, endothelium, and epithelial cells. Factors, particularly from eosinophils (e.g., major basic protein, eosinophil cationic protein), also cause damage to the epithelium.

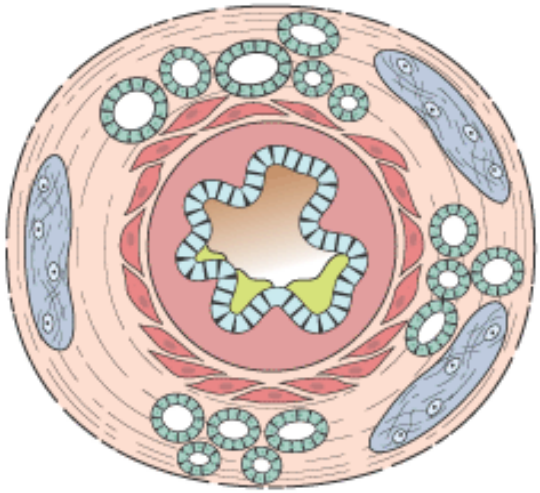




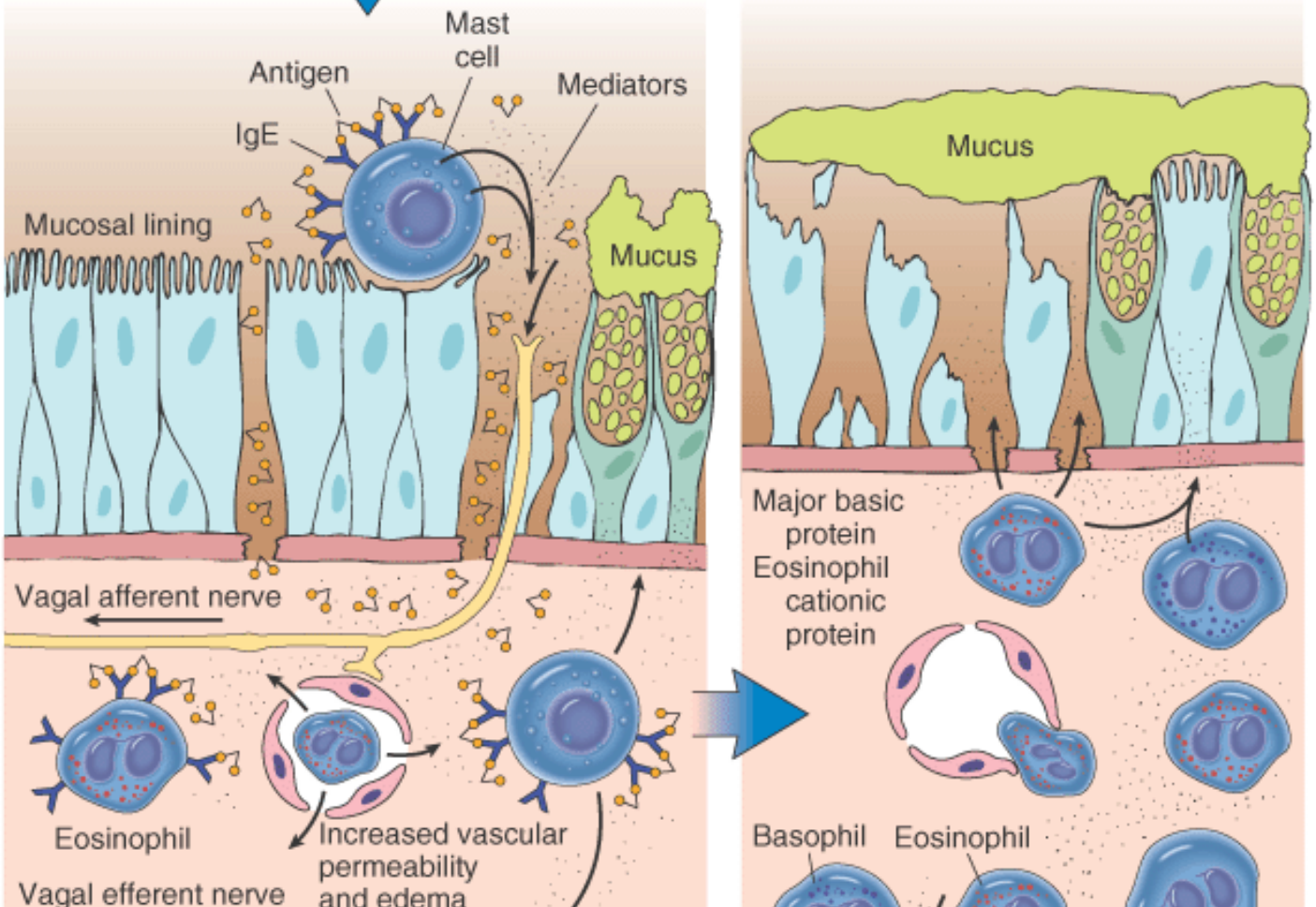
NORMAL AIRWAY



B. ALLERGEN-TRIGGERED ASTHMA



CONSTRICTED AIRWAY IN ASTHMA



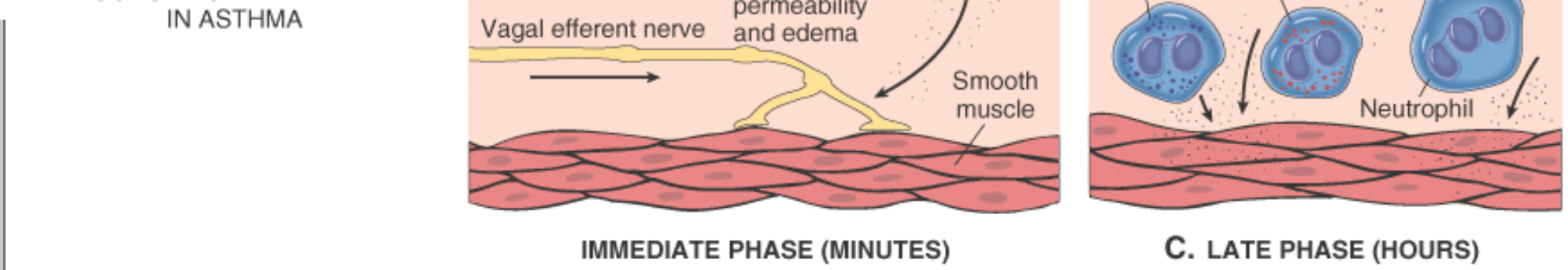


Figure 15-12 Comparison of a normal bronchiole with that in a patient with asthma. Note the accumulation of mucus in the bronchial lumen resulting from an increase in the number of mucus-secreting goblet cells in the mucosa and hypertrophy of submucosal mucus glands. In addition, there is intense chronic inflammation due to recruitment of eosinophils, macrophages, and other inflammatory cells. Basement membrane underlying the mucosal epithelium is thickened, and there is hypertrophy and hyperplasia of smooth muscle cells.

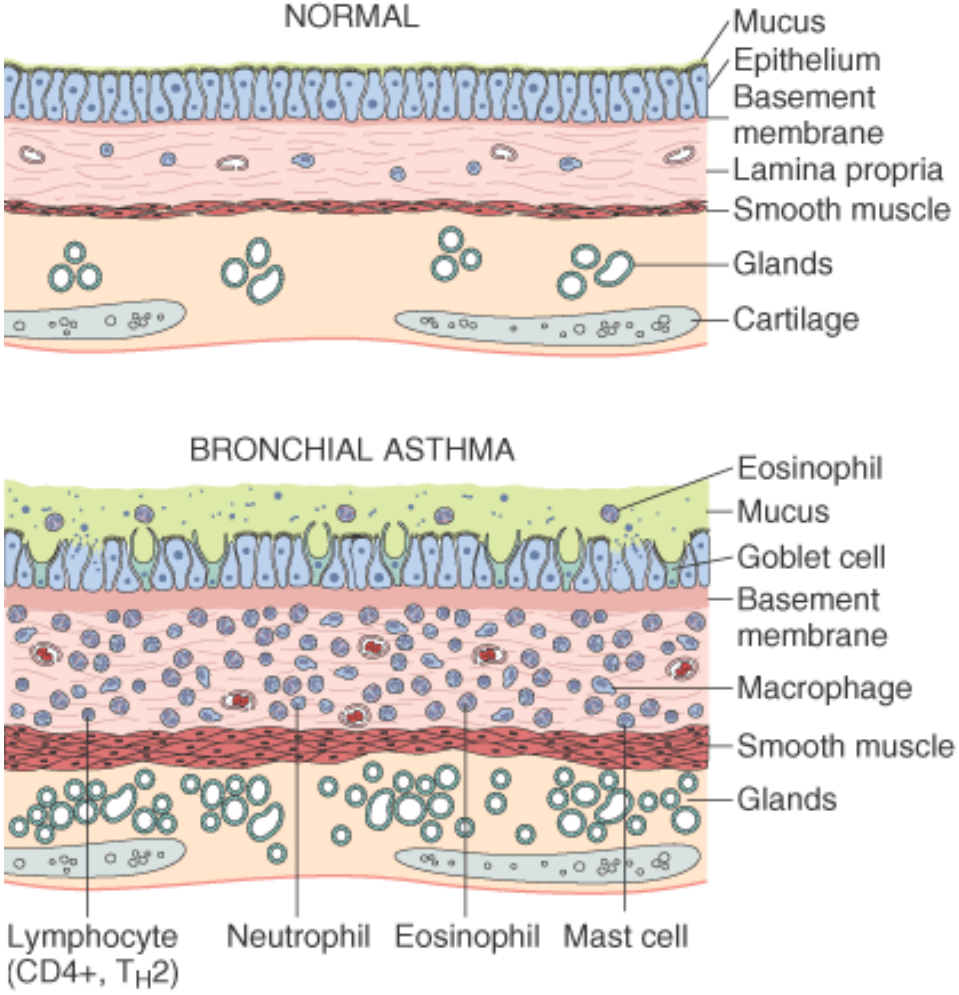


Figure 15-13 Bronchiectasis in a patient with cystic fibrosis, who underwent lung transplantation. Cut surface of lung shows markedly distended peripheral bronchi filled with mucopurulent secretions.

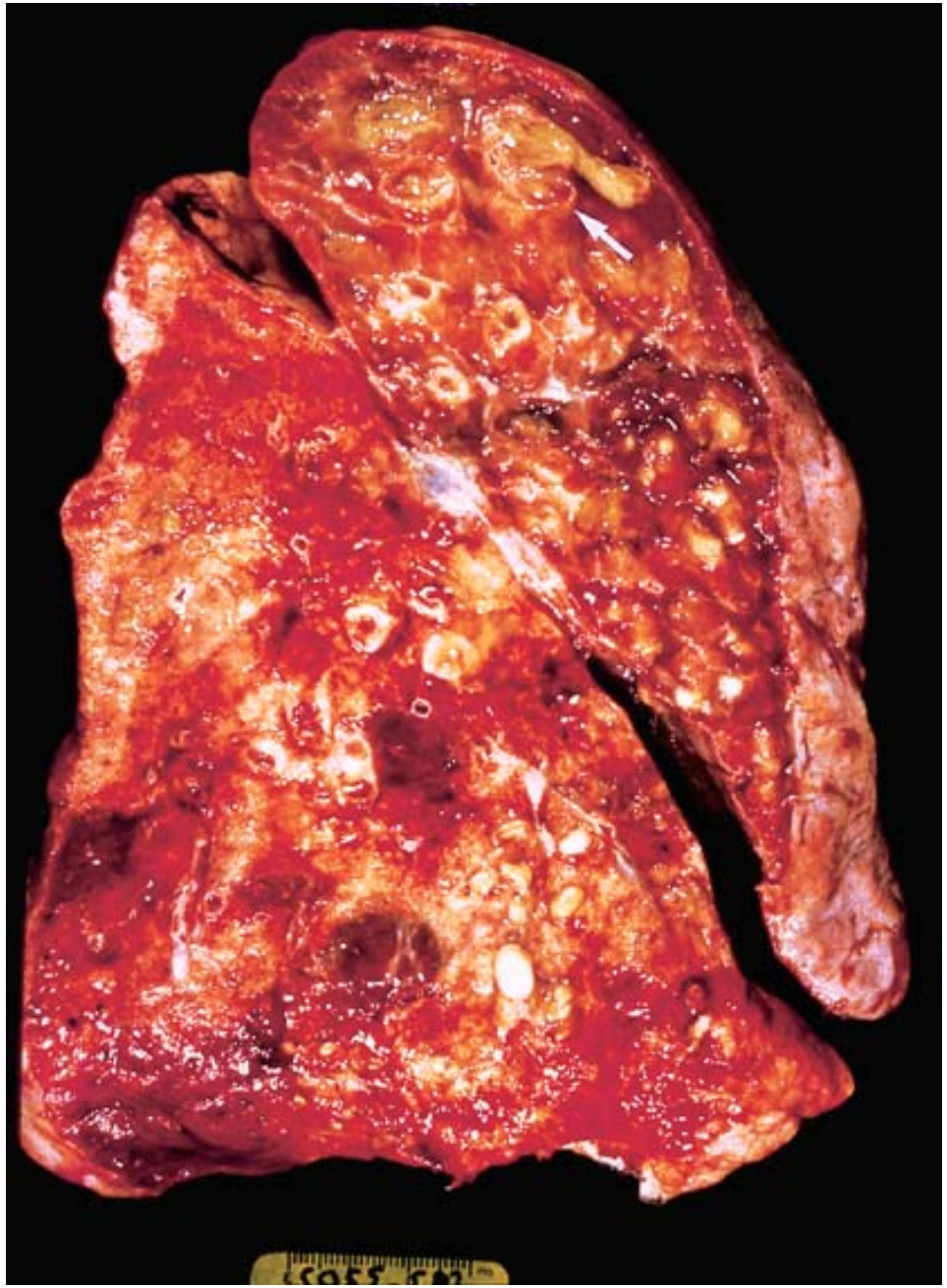


TABLE 15-5 -- Major Categories of Chronic Interstitial Lung Disease

Fibrosing

Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Associated with collagen vascular diseases
Pneumoconiosis
Drug reactions
Radiation pneumonitis
Granulomatous
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis-associated interstitial lung disease
Other
Pulmonary alveolar proteinosis

toxic to endothelial cells, epithelial cells, or both. Beyond direct toxicity, a critical event is the *recruitment and activation of inflammatory and immune effector cells*. Neutrophil recruitment can be caused by complement activation in some disorders,[45] but in addition, the alveolar macrophages, which increase in number in all interstitial diseases, release *chemotactic factors* for neutrophils (e.g., IL-8,[46] leukotriene B_4 [47]). In diseases such as sarcoidosis, *cell-mediated immune reactions* result in the accumulation of monocytes and T lymphocytes and in the formation of granulomas (Chapter 6). It is thought that interactions among lymphocytes and macrophages and the release of lymphokines and monokines are responsible for the slowly progressive pulmonary fibrosis that ensues. The alveolar macrophage, in particular, plays a central role in the development of fibrosis, as reviewed in the discussion of chronic inflammation (Chapter 2).

FIBROSING DISEASES

Idiopathic Pulmonary Fibrosis

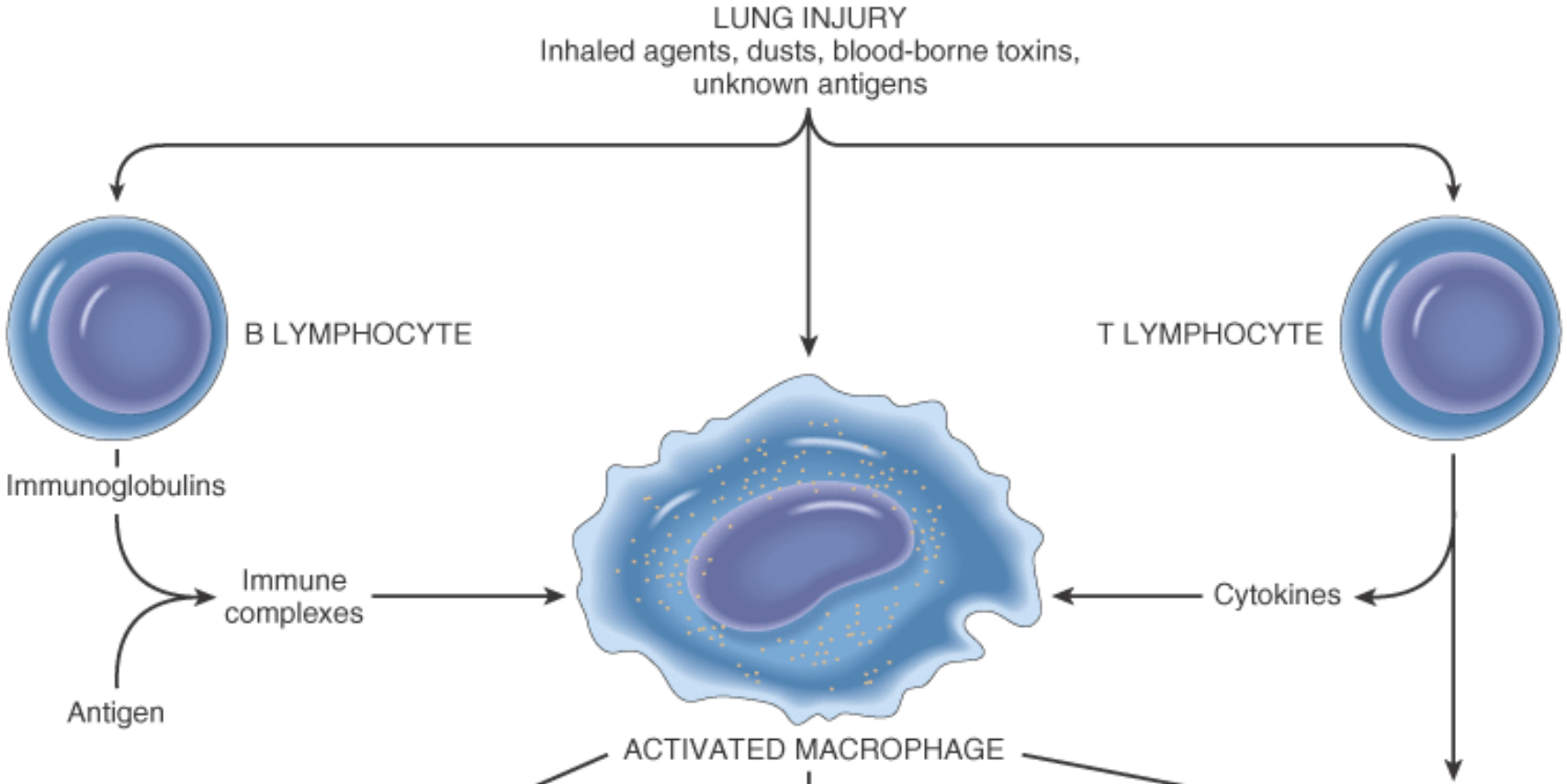
The term "idiopathic pulmonary fibrosis" (IPF) refers to a clinicopathologic syndrome with characteristic radiologic, pathologic, and clinical features. In Europe, the term "cryptogenic fibrosing alveolitis" is more popular. The histologic pattern of fibrosis is referred to as usual interstitial pneumonia (UIP), which is required for the diagnosis of IPF but can also be seen in other diseases, notably collagen vascular disorders and asbestosis. Desquamative interstitial pneumonia (DIP), previously considered an early form of IPF, has now been shown to be a smoking-related disorder. "Hamman-Rich syndrome" is a term that was used to describe a rapidly progressive type of IPF but is now considered a form of acute lung injury and is synonymous with acute interstitial pneumonia. The International Multidisciplinary Consensus Classification is an excellent reference for definitions and understanding of idiopathic interstitial pneumonias.[48] [49]

Pathogenesis.

While the causative agent(s) of IPF remain unknown, our concepts of pathogenesis have evolved over the past several years. The earlier view that IPF was initiated by an unidentified insult that gives rise to chronic inflammation resulting in fibrosis is probably not correct. According to this hypothesis, if the inflammatory response could be controlled before irreversible tissue injury occurs, fibrosis may be prevented. In clinical practice, however, anti-inflammatory therapy has failed to provide much benefit.[50] The current concept, therefore, is that IPF is caused by "repeated cycles" of acute lung injury (alveolitis) by some unidentified agent. "Wound healing" at these sites gives rise to exuberant fibroblastic proliferation, giving rise to the "fibroblastic foci" that are so characteristic of IPF. Mediators of wound healing such as TGF-β are expressed at these sites.

The inflammatory response in IPF may be modified by genetic or environmental factors and is thought to be of the T_H 2 type. Thus, eosinophils, mast cells, and IL-4 and IL-13 are found in the lesions. Repeated cycles of injury and wound healing ultimately lead to widespread fibrosis and loss of lung function. Hence, one effective therapeutic strategy might be to reduce or prevent fibroblast replication. It is interesting to note in this connection that there is an abnormal activation of the Wnt-β-catenin signaling pathways (Chapter 7) within the mesenchymal cells of the fibroproliferative lesions of IPF. [51]

Figure 15-14 A possible schema of the pathogenesis of idiopathic pulmonary fibrosis.



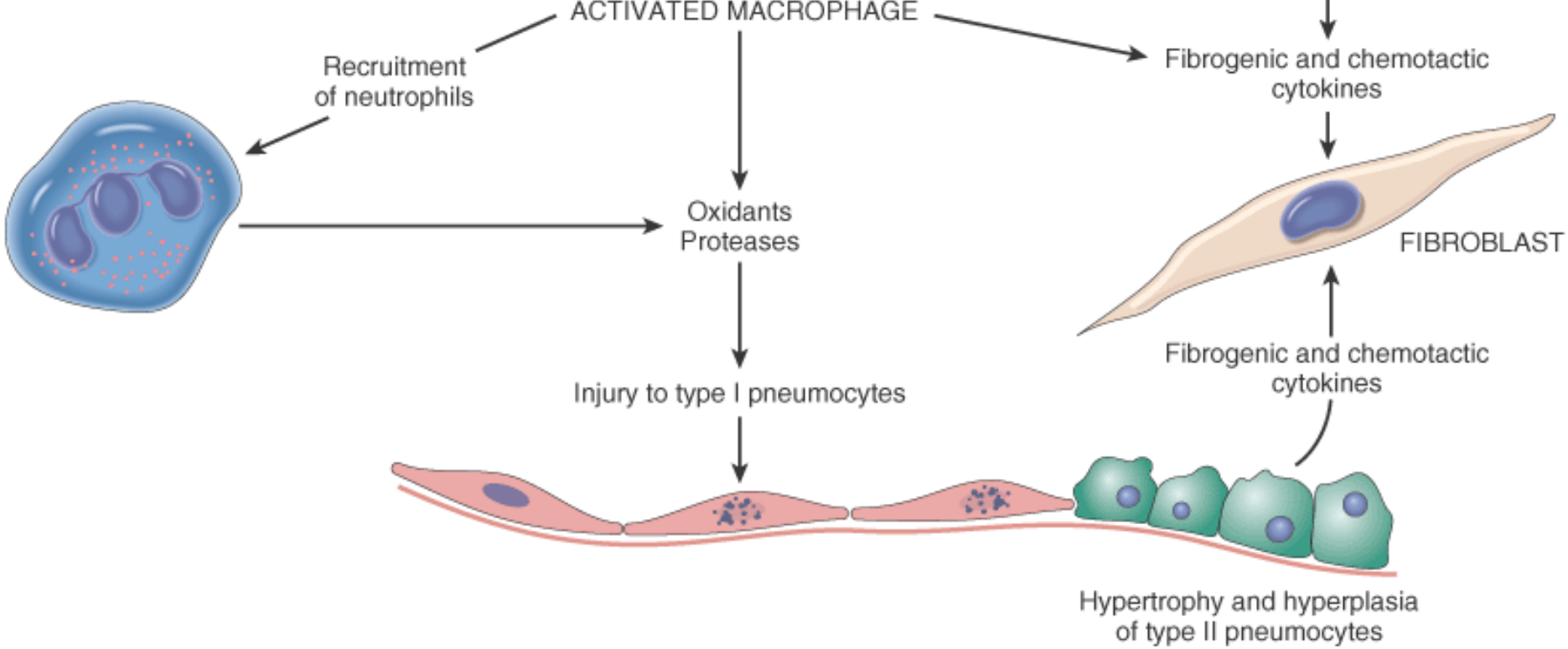


Figure 15-15 Usual interstitial pneumonia. The fibrosis, which varies in intensity, is more pronounced in the subpleural region.

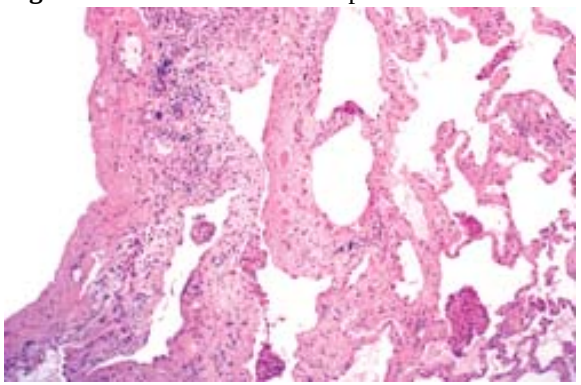


Figure 15-16 Usual interstitial pneumonia. Fibroblastic focus with fibers running parallel to surface and bluish myxoid extracellular matrix.

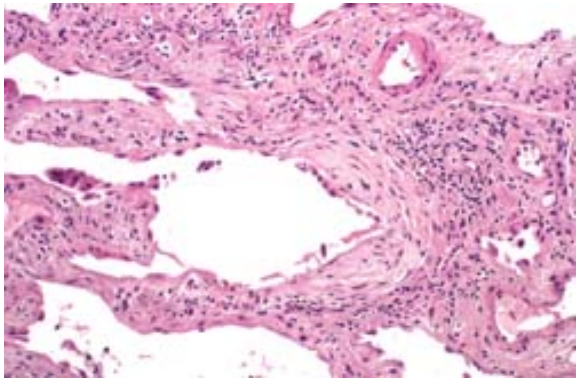


Figure 15-17 Cryptogenic organizing pneumonia (COP). Alveolar spaces are filled with balls of fibroblasts (Masson bodies), while the alveolar walls are relatively normal.

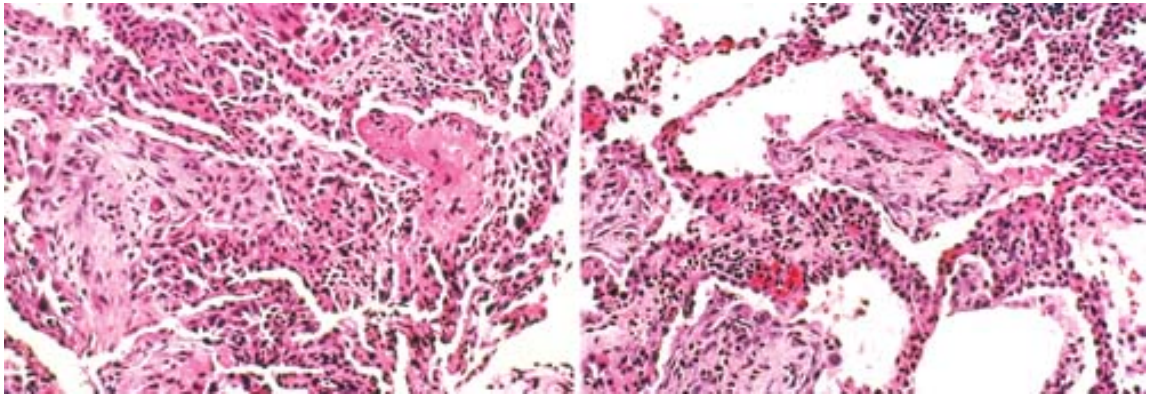


TABLE 15-6 -- Lung Diseases Caused by Air Pollutants

Agent	Disease	Exposure
Mineral Dusts		
Coal dust	Anthracosis	Coal mining (particularly hard coal)
	Macules	
	Progressive massive fibrosis	
	Caplan syndrome	
Silica	Silicosis	Foundry work, sandblasting, hardrock mining, stone cutting, others
	Caplan syndrome	
Asbestos	Asbestosis	Mining, milling, and fabrication; installation and removal of insulation
	Pleural plaques	

	Caplan syndrome	
	Mesothelioma	
	Carcinoma of the lung, larynx, stomach, colon	
Beryllium	Acute berylliosis	Mining, fabrication
	Beryllium granulomatosis	
	Bronchogenic carcinoma (?)	
Iron oxide	Siderosis	Welding
Barium sulfate	Baritosis	Mining
Tin oxide	Stannosis	Mining
Organic Dusts That Induce Hypersensitivity Pneumonitis		
Moldy hay	Farmer's lung	Farming
Bagasse	Bagassosis	Manufacturing wallboard, paper
Bird droppings	Bird-breeder's lung	Bird handling
Organic Dusts That Induce Asthma		
Cotton, flax, hemp	Byssinosis	Textile manufacturing
Red cedar dust	Asthma	Lumbering, carpentry
Chemical Fumes and Vapors		
Nitrous oxide, sulfur dioxide, ammonia, benzene, insecticides	Bronchitis, asthma	Occupational and accidental exposure
	Pulmonary edema	
	ARDS *	
	Mucosal injury	
	Fulminant poisoning	

*Acute respiratory distress syndrome.

In general, only a small percentage of exposed people develop occupational respiratory diseases. In one study, genetic variation of serum and erythrocytic proteins was shown to correlate with susceptibility to developing silicosis, chronic bronchitis, and occupational asthma. Such studies could be useful for assessment and forecast of individual risk of occupational diseases. [60] Many of the diseases listed in Table 15-6 are quite uncommon. Hence only a selected few that cause fibrosis of the lung are presented next.

COAL WORKERS' PNEUMOCONIOSIS (CWP).

Dust reduction measures in coal mines around the globe have drastically reduced the incidence of coal dust-induced disease. The spectrum of lung findings in coal workers is wide, varying from (1) asymptomatic anthracosis to (2) simple coal workers' pneumoconiosis (CWP) with little to no pulmonary dysfunction to (3) complicated CWP, or progressive massive fibrosis (PMF), in which lung function is compromised.[61] It should be noted that PMF is a generic term that applies to a confluent, fibrosing reaction in the lung that can be a complication of any pneumoconiosis, although it is more common in CWP and silicosis.

The pathogenesis of complicated CWP, particularly what causes the lesions of simple CWP to progress to PMF, is incompletely understood. Contaminating silica in the coal dust can favor progressive disease. In most cases, carbon dust itself is the major culprit, and studies have shown that complicated lesions contain considerably more dust than simple lesions do.

Morphology.

Anthracosis is the most innocuous coal-induced pulmonary lesion in coal miners and is commonly seen in all urban dwellers and tobacco smokers. Inhaled carbon pigment is engulfed by alveolar or interstitial macrophages, which then accumulate in the connective tissue along the lymphatics, including the pleural lymphatics, or in organized lymphoid tissue along the bronchi or in the lung hilus. At autopsy, linear streaks and aggregates of anthracotic pigment readily identify pulmonary lymphatics and mark the pulmonary lymph nodes.

Simple CWP is characterized by **coal macules** (1 to 2 mm in diameter) and the somewhat larger **coal nodules**. The coal macule consists of carbon-laden macrophages; the nodule also contains small amounts of a delicate network of collagen fibers. Although these lesions are scattered throughout the lung, the upper lobes and upper zones of the lower lobes are more heavily involved. They are located primarily adjacent to respiratory bronchioles, the site of initial dust accumulation. In due course, dilation

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of adjacent alveoli occurs, a condition sometimes referred to as **centrilobular emphysema**.

Complicated CWP (PMF) occurs on a background of simple CWP and generally requires many years to develop. It is characterized by intensely blackened scars larger than 2 cm, sometimes up to 10 cm in greatest diameter. They are usually multiple (Fig. 15-18). Microscopically, the lesions consist of dense collagen and pigment. The center of the lesion is often necrotic, resulting most likely from local ischemia.

Clinical Course.

CWP is usually a benign disease that causes little decrement in lung function. Even mild forms of complicated CWP fail to demonstrate abnormalities of lung function. In a minority of cases (fewer than 10%), PMF develops, leading to increasing pulmonary dysfunction, pulmonary hypertension, and cor pulmonale. Once PMF develops, it may become progressive even if further exposure to dust is prevented. Unlike silicosis (discussed later), there is no convincing evidence that coal dust increases susceptibility to tuberculosis. There is some evidence that exposure to coal dust increases the incidence of chronic bronchitis and emphysema,

Figure 15-18 Progressive massive fibrosis superimposed on coal workers' pneumoconiosis. The large, blackened scars are located principally in the upper lobe. Note the extensions of scars into surrounding parenchyma and retraction of adjacent pleura. *(Courtesy of Dr. Werner Laquer, Dr. Jerome Kleinerman, and the National Institute of Occupational Safety and Health, Morgantown, WV.)*