PATHOLOGIC BASIS of DISEASE

Third Edition

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DISEASES OF WHITE CELLS, LYMPH NODES, AND SPLEEN* 15

White Cells and Lymph Nodes

*With gratitude to Dr. Jose Hernandez, Southwestern Medical School, Dallas, Texas, for a critical review of this chapter.

NORMAL

The origin and differentiation of white cells (granulocytes, monocytes, and lymphocytes) were briefly discussed in Chapter 14 along with the other formed elements of blood. Lymphocytes and monocytes not only circulate in the blood and lymph, but also accumulate in discrete and organized masses, the so-called lymphoreticular system. Components of this system include lymph nodes, thymus, spleen, tonsils, adenoids, and Peyer's patches. Less discrete collections of lymphoid cells also occur in the bone marrow, lungs, and gastrointestinal tract and other tissues. Lymph nodes are the most widely distributed and easily accessible component of the lymphoid tissue and are therefore frequently examined for the diagnosis of lymphoreticular disorders. It would therefore be advantageous to review the normal morphology of lymph nodes.

Lymph nodes, in general, are discrete structures, ovoid in shape, that vary from a few millimeters to 1 to 2 cm in length. Their consistency is soft and their cut surface is gray-white. They are surrounded by a capsule composed of connective tissue and a few elastic fibrils, perforated at various points by afferent lymphatics that empty into the peripheral sinus subjacent to the capsule. Branches of the sinus extend into the nodes and terminate at the hilus, where the efferent lymphatics emerge. All lymphatics are lined with reticuloendothelial cells. Situated in the cortex or peripheral portion of the node are spherical aggregates of lymphoid tissue, the so-called primary follicles, which represent the B-cell areas. Upon antigenic stimulation, the primary follicles enlarge and develop pale-staining germinal centers composed of follicular center cells (lymphocytes in varying stages of activation, described on p. 663). Surrounding these germinal centers are mantles of small unchallenged B cells. The T cells occupy the parafollicular regions (p. 158). The medullary cords, occupying the central portion of the node, contain predominantly plasma cells and some lymphocytes. A delicate reticulin that connects peripherally with the capsule is the predominant supporting structure within the lymph nodes.

The morphologic description of the lymph node just given is highly idealized and falsely static. The size and morphology of lymph nodes are modified by stress, thyroid and adrenal function, and immune responses. As secondary lines of defense, they are constantly responding to stimuli, even in the absence of clinical disease. Trivial injuries and infections effect subtle changes in lymph node histology. More significant bacterial infections inevitably produce enlargement of nodes and sometimes leave residual scarring. For this reason, lymph nodes in the adult are almost never "normal," since they usually bear the scars of previous events, rendering the inguinal nodes particularly inappropriate for evaluative biopsies. Except in the child, it is difficult to find a "normal" node, and in histologic evaluations it is often necessary to distinguish changes secondary to past experience from those related to present disease.

PATHOLOGY

Disorders of white cells may be classified into two broad categories, *proliferative* and those characterized by a deficiency of leukocytes, i.e., *leukopenias*. Proliferations of white cells and lymph nodes may be reactive or neoplastic. Since their major function is host defense, reactive proliferation in response to an underlying primary, often microbial disease is fairly common. Neo-

plastic disorders, although less frequent, are much more important. In the following discussion, we will describe first the leukopenic states and summarize the common reactive disorders, and then consider in some detail malignant proliferations of the white cells that in many instances arise in the nodes.

LEUKOPENIA

The number of circulating white cells may be markedly decreased in a variety of disorders. An abnormally low white cell count *(leukopenia)* may occur because of decreased numbers of any one of the specific types of leukocytes, but most often involves the neutrophils *(neutropenia, granulocytopenia)*. *Lymphopenias* are much less common, and in addition to the congenital immunodeficiency diseases (p. 205) they are associated with specific clinical syndromes (e.g., Hodgkin's disease, nonlymphocytic leukemias, following corticosteroid therapy, and occasionally in chronic diseases). Only the more common leukopenias involving granulocytes will be discussed here.

Neutropenia—Agranulocytosis

Reduction in the number of granulocytes in the peripheral blood—*neutropenia*—may be seen in a wide variety of circumstances. Frequently it is transient and of trivial significance. Sometimes the reduction in circulating neutrophils is marked and has serious consequences by predisposing to infections. When of this magnitude, it is referred to as *agranulocytosis*. The lymphocytes are not affected, so the percentage of lymphocytes is increased (relative lymphocytosis).

PATHOGENESIS. Considering first the broad topic of neutropenia, whatever its severity, a reduction in circulating granulocytes will occur if (1) granulopoiesis fails to keep pace with the normal turnover rate of neutrophils or (2) there is accelerated removal of neutrophils from the circulating blood. You recall that the neutrophil is a very short-lived cell having a half-life of only six to seven hours. Any impairment of granulopoiesis can therefore induce a neutropenia within hours to a few days.

Inadequate or ineffective granulopoiesis may be encountered with (1) suppression of pluripotent myeloid stem cells, as occurs in aplastic anemia (p. 638) and a variety of leukemias and lymphomas (p. 683)—in these conditions, granulocytopenia is accompanied by anemia and thrombocytopenia; (2) suppression of the committed granulocytic precursors, which occurs after exposure to certain drugs, as discussed below; (3) megaloblastic anemias, due to vitamin B_{12} or folate deficiency (p. 630), in which defective DNA synthesis produces abnormal granulocytic precursors, rendering them susceptible to intramedullary death (ineffective granulopoiesis). Marrow granulopoiesis is increased but the number of mature neutrophils entering the blood is decreased.

Accelerated removal or destruction of neutrophils is encountered with (1) immunologically mediated injury to the neutrophils, which may be idiopathic with no other abnormality, associated with a well-defined immunologic disorder (e.g., Felty's syndrome, p. 1355), or produced by exposure to drugs, (2) splenic sequestration in which excessive destruction occurs secondary to enlargement of the spleen (p. 699), associated also with excessive destruction of red cells and platelets.

Among the many associations mentioned, *the most significant neutropenias (agranulocytoses) are produced by drugs.*[1] Certain drugs, such as alkylating agents and antimetabolites used in cancer treatment, produce agranulocytosis in a predictable, dose-related fashion. They cause a generalized suppression of the bone marrow, and therefore other cells are also affected (aplastic anemia). Agranulocytosis may also be encountered as an idiosyncratic reaction to a large variety of agents. The roster of implicated drugs includes aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, thiouracil, and phenylbutazone. Although the mechanism of agranulocytosis here is obscure, both decreased production and increased destruction have been implicated. The neutropenia induced by chlorpromazine and related phenothiazines is of slow onset and is believed to result from the suppression of granulocytic precursors in the bone marrow. Chlorpromazine can inhibit DNA synthesis of marrow cells in vitro, and therefore it is postulated that certain individuals unusually sensitive to this effect develop agranulocytosis. Neutrophil production gradually becomes normal after the cessation of drug therapy. Agranulocytosis following administration of aminopyrine, thiouracils, and certain sulfonamides is believed to result from immunologically mediated destruction of mature neutrophils. Antibodies reactive against a complex between the drug or its metabolite (acting as the hapten) and leukocyte proteins may evoke a Type II hypersensitivity reaction. Alternatively, neutrophils may be damaged as innocent bystanders by the adsorption of drug-antibody complexes on the surface and the subsequent activation of complement. In many cases, no antecedent cause of neutropenia can be detected but autoimmunity is suspected, since serum antibodies directed against neutrophil-specific antigens can be detected.

MORPHOLOGY. The anatomic alterations in the bone marrow depend on the underlying basis of the neutropenia. When it is caused by excessive destruction of the mature neutrophils, the marrow may be hypercellular with increased numbers of immature granulocytic precursors. Hypercellularity is also seen with ineffective granulopoiesis, as occurs in megaloblastic anemias. Agranulocytosis caused by agents that affect the committed granulocytic precursors are understandably associated with hypocellular marrow, resulting from greatly decreased leukopoietic elements. Erythropoiesis and megakaryocytes usually remain at normal levels, but with certain myelotoxic drugs all marrow elements may be affected. Occasionally, increased numbers of plasma cells and lymphocytes are found in the marrow, particularly as the marrow becomes acellular.

Infections are a characteristic feature 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 of agranulocytosis (Fig. 15–1). These ulcers are typically deep, undermined, and covered by gray to green-black necrotic membranes from which numbers of bacteria or fungi can be isolated. Similar ulcerations may occur in the skin, vagina, anus, or gastrointestinal tract, but these sites are much less frequently involved. Severe necrotizing infections are also encountered, but less prominently, in the lungs, urinary tract, and kidneys. All these sites of infection are characterized by massive growth of bacteria (or other agents) with relatively poor leukocytic response. In many instances, the bacteria grow in colony formation (botryomycosis) as though they were cultured on nutrient media. The regional lymph nodes draining these infections are enlarged and inflamed. The spleen and liver are rarely enlarged.

CLINICAL COURSE. Agranulocytosis tends to follow a fairly characteristic clinical pattern. The initial symptoms are often malaise, chills, and fever, followed in sequence by marked weakness and fatigability, symptoms that stem from the severe infections characteristic of this disorder. In severe agranulocytosis with virtual absence of neutrophils, these infections may become so overwhelming as to cause death within a few days. Less extreme depression of the marrow may appear insidiously and come to light only during the investigation of frequent and persistent minor infections.

Characteristically, the total white cell count is reduced to 1000 cells per mm^3 of blood and, in certain instances, to levels as low as 200 to 300 cells. Usually there is no associated anemia, save that caused by the infections, nor is there thrombocytopenia.

The prognosis is very unpredictable. Before the advent of antibiotics, the mortality rate ranged between 70 and 90%. At present the antibiotics and supportive measures such as neutrophil transfusions allow better survival since, in many instances, the adverse effects of the toxic drug are discovered early and the depression of white cells eventually remits. The idiopathic form, too, may spontaneously remit or may progressively worsen, leading to death.

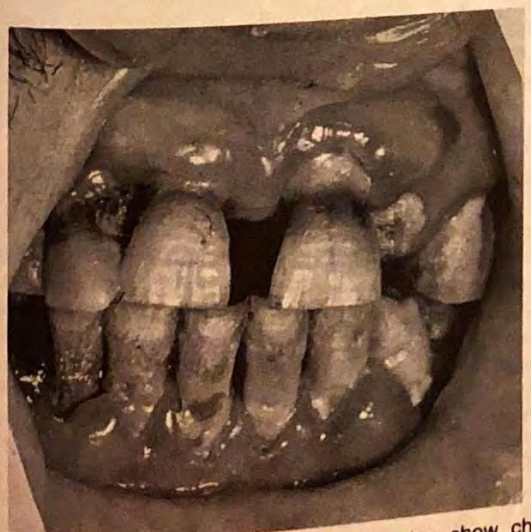

Figure 15–1. Granulocytopenia. Gingival margins show chronic suppurative necrotizing infection due to loss of protective white cells in circulation.

REACTIVE (INFLAMMATORY) PROLIFERATIONS OF WHITE CELLS

Leukocytosis

Leukocytosis is a common reaction in a variety of inflammatory states. The particular white cell series affected varies with the underlying cause. In Chapter 2 we discussed *polymorphonuclear leukocytosis* (granulocytosis), which accompanies acute inflammation. Pyogenic infections are common causes of neutrophilic leukocytosis, but it may also result from nonmicrobial stimuli such as tissue necrosis caused by burns or myocardial infarction. In patients with severe, life-threatening sepsis, in addition to leukocytosis there may be morphologic changes in the neutrophils such as toxic granulations, Döhle bodies, and cytoplasmic vacuoles. *Toxic granules* are coarse and darker than the normal neutrophilic granules. Although their precise origin is not entirely clear, they are believed to represent abnormal forms of azurophilic granules. *Döhle bodies* are pale blue, round or oval inclusions that represent aggregates of the rough endoplasmic reticulum.

Eosinophilic leukocytosis is characteristic of allergic disorders such as bronchial asthma, hay fever (p. 727), parasitic infections, and some diseases of the skin. The latter include pemphigus, eczema, and dermatitis herpetiformis, all of which are probably immunologic in origin. *Elevations in monocyte count* may be seen in several chronic infections including tuberculosis, bacterial endocarditis, brucellosis, rickettsiosis, and malaria. Certain collagen vascular diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis are also associated with monocytosis. *Lymphocytosis* may accompany monocytosis in chronic inflammatory states such as brucellosis and tuberculosis, representing in these instances a sustained activation of the immune response. The lymphocyte count may also be increased in acute viral infections such as viral hepatitis, in cytomegalovirus infections, and particularly in infectious mononucleosis (p. 288).

In most instances, reactive leukocytosis is easy to distinguish from neoplastic proliferation of the white cells (i.e., leukemias) by the rarity of immature cells in the blood. However, in some inflammatory states, many immature white cells may appear in the blood and a picture of leukemia may be simulated *(leukemoid reaction)*. The distinction from leukemias may then be difficult, as discussed on page 680.

Infections and other inflammatory stimuli may not only cause leukocytosis but also involve the lymph nodes, which act as defensive barriers. The infections that lead to lymphadenitis (described below) are so numerous and varied that it is impossible to detail each, since it would be a virtual catalog of all systemic

microbiologic diseases. Moreover, in most instances the lymphadenitis is of a banal variety and is entirely nonspecific, designated acute or chronic nonspecific lymphadenitis.

Acute Nonspecific Lymphadenitis

Lymph nodes undergo reactive changes whenever challenged by microbiologic agents or their toxic products, or by cell debris and foreign matter introduced into wounds or into the circulation, as in drug addiction.

Acutely inflamed nodes are most commonly caused by direct microbiologic drainage, and are seen most frequently in the cervical area in association with infections of the teeth or tonsil, or in the axillary or inguinal regions secondary to infections in the extremities. Similarly, acute lymphadenitis is found in those nodes draining acute appendicitis, acute enteritis, or any other acute infections. Generalized acute lymphadenopathy is characteristic of viral infections and bacteremia, particularly in children. The nodal reactions in the abdomen—mesenteric adenitis—may induce acute abdominal symptoms closely resembling acute appendicitis, a differential diagnosis that plagues the surgeon.

Macroscopically, the nodes become swollen, gray-red, and engorged. The capsules are generally intact, but permeation of infection may lead to inflammatory changes in the perinodal tissues. Histologically there is prominence of the lymphoid follicles and large germinal centers containing numerous mitotic figures. Histiocytes often contain particulate debris of bacterial origin or derived from necrotic cells (Fig. 15–2). When pyogenic organisms are the cause of the reaction, the centers of the follicles may undergo necrosis; indeed, the entire node may sometimes be converted into a suppurative mass. With less severe reactions, there is sometimes a neutrophilic infiltrate about the follicles, and numerous neutrophils can be found within the lymphoid sinuses. The cells lining the sinuses become hypertrophied and cuboidal and may undergo hyperplasia.

Clinically, nodes with acute lymphadenitis are enlarged because of the cellular infiltration and edema. As a consequence of the distention of the capsule, they are tender to touch. When abscess formation is extensive, they become fluctuant. The overlying skin is frequently red, and sometimes penetration of the infection to the skin surface produces draining sinuses, particularly when the nodes have undergone suppurative necrosis. With control of the infection, the lymph nodes may revert to their normal appearance or scarring may follow the more destructive disease.

Chronic Nonspecific Lymphadenitis

Chronic reactions assume one of three patterns, depending on their causation. Most chronic infections caused by organisms that represent B-cell antigens induce follicular hyperplasia. Microbiologic agents or antigens that stimulate T cells produce a second type of pattern, called paracortical lymphoid hyperplasia. Drugs such as the anticonvulsant Dilantin (phenytoin) serving as haptens may induce this pattern of parafollicular hyperplasia. A third nonspecific pattern, referred to as sinus histiocytosis, is encountered in regional nodes draining a site of cancer.

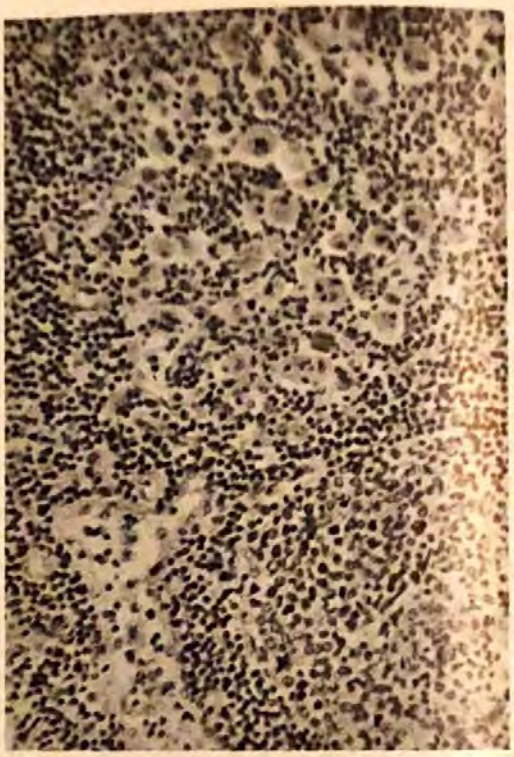

Figure 15–2. Acute lymphadenitis. High-power detail of germinal centers with large histiocytic cells showing phagocytic activity.

Follicular hyperplasia is distinguished by prominence of the large germinal centers, which appear to bulge against the surrounding collar of small B lymphocytes (Fig. 15–3). The follicular enlargement may be readily mistaken for nodular lymphoma (p. 658). Prominent within these germinal centers are lymphocytes in varying stages of "blast" transformation and large numbers of histiocytes containing phagocytized debris of bacterial or cellular origin. Plasma cells, histiocytes, and occasionally neutrophils or eosinophils may be found in the parafollicular regions, and there generally is striking hyperplasia of the reticuloendothelial cells lining the lymphatic sinuses.

Paracortical lymphoid hyperplasia is characterized by reactive changes within the T-cell regions of the lymph node, which encroach on, and sometimes appear to efface, the germinal follicles. In these regions the T cells undergo progressive transformation to immunoblasts. These large cells, when viewed within a sea of smaller lymphocytes, impart a mottled appearance to the T-cell zones. In addition, there is hypertrophy of the sinusoidal and vascular endothelial cells and a mixed cellular infiltrate, principally of macrophages and sometimes of eosinophils. The striking increase in the number of immunoblasts may produce a pseudolymphomatous pattern, sometimes referred to as pseudolymphomatous lymphadenitis. Such changes are encountered particularly often in immunologic reactions induced by drugs (especially Dilantin) or following smallpox vaccination. Similar reactions have been described after the use of other vaccines.

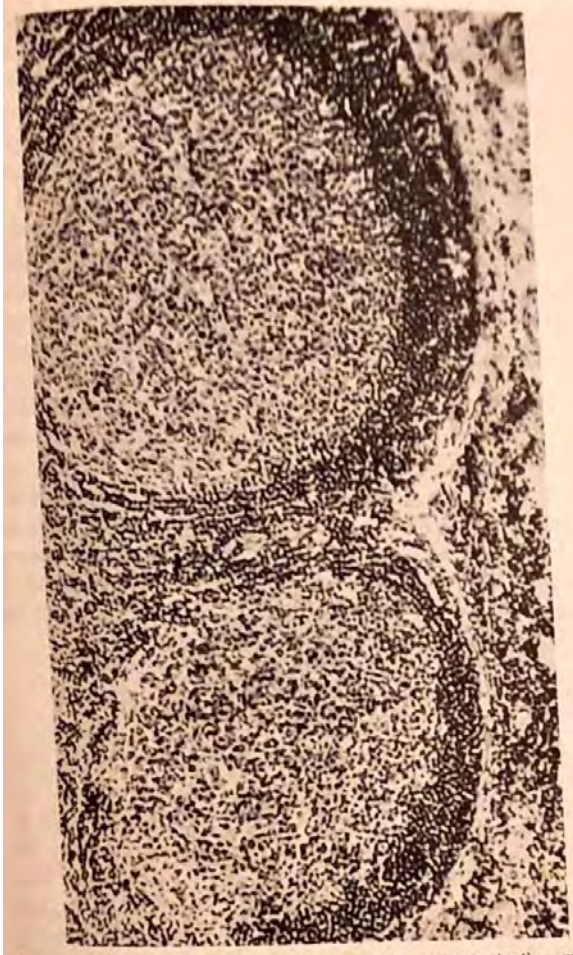

Figure 15–3. Chronic follicular hyperplasia, demonstrating marked enlargement and prominence of germinal follicles.

Sinus histiocytosis refers to distention and prominence of the lymphatic sinusoids, encountered in lymph nodes draining cancers, particularly carcinoma of the breast. The lining endothelial cells are markedly hypertrophied, and the sinuses may be virtually engorged with histiocytes (Fig. 15–4). This pattern of reaction has been thought to represent an immune response on the part of the host to the tumor or its products. According to some, the presence of sinus histiocytosis is a sign of a favorable prognosis, but this issue is debatable.

Although the three patterns of reaction have been described separately, frequent combinations and intergrades are encountered. Characteristically, lymph nodes in chronic reactions are not tender, because they are not under increased pressure. Chronic reactions are particularly characteristic of inguinal and axillary nodes. Both groups drain relatively large areas of the body and so are frequently challenged, for which reason these lymph nodes are inappropriate as biopsy specimens in the study of hematologic and lymphomatous disorders.

NEOPLASTIC PROLIFERATIONS OF WHITE CELLS

Malignant proliferative diseases constitute the most important of white cell disorders. The several categories of these diseases can be briefly defined as follows:

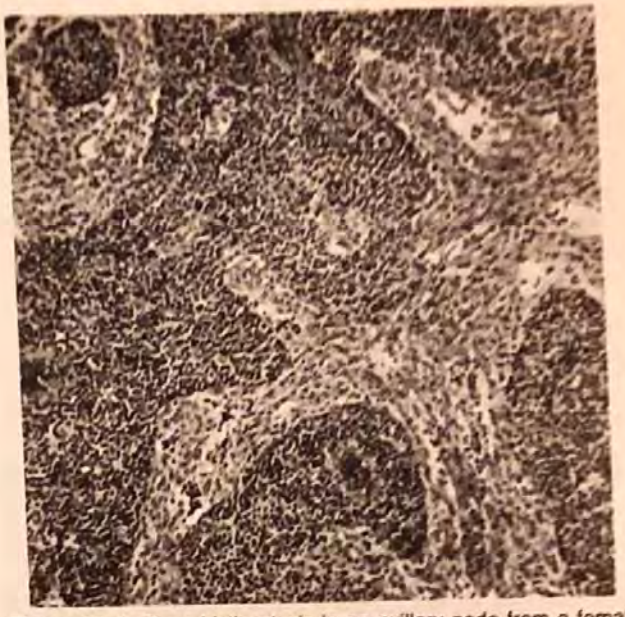

Figure 15–4. Sinus histiocytosis in an axillary node from a female patient with carcinoma of breast.

1. *Malignant lymphomas* take the form of cohesive tumorous lesions composed mainly of lymphocytes and rarely of histiocytes that arise in lymphoid tissue anywhere in the body, most commonly within lymph nodes.

2. *Leukemias* are systemic leukoproliferative disorders arising in the bone marrow that secondarily flood the circulating blood and other organs with leukemic cells.

3. *Plasma cell dyscrasias and related disorders* usually arising in the bones take the form of localized or disseminated proliferations of antibody-forming cells. Thus, this category is marked by the appearance in the peripheral blood of abnormal levels of immunoglobulins or the light or heavy chains of the immunoglobulins. Hence, these disorders are sometimes called gammopathies or dysproteinemias.

4. The *histiocytoses* represent proliferative lesions of tissue macrophages or histiocytes. There is unfortunately much confusion in the terminology of histiocytic disorders. First, as indicated above, the rare neoplastic proliferations of histiocytes originating within the lymphoid tissue are grouped with the malignant lymphomas. Second, there is no evidence that some of the tumor-like proliferations—the so-called histiocytoses X, which are traditionally listed under this category—are indeed neoplastic. Finally, there seem to be no clearly defined boundaries of histiocytoses since some investigators include clearly non-neoplastic, metabolic storage diseases in this category. These complexities will be discussed further on page 694.

As can be seen, the neoplastic disorders of the white cells are extremely varied. In the following sections, each of the categories is treated separately.

MALIGNANT LYMPHOMAS

Lymphomas are malignant neoplasms characterized by the proliferation of cells native to the lymphoid

tissues, i.e., lymphocytes, histiocytes, and their precursors and derivatives. Like other neoplasms, all lymphomas are of monoclonal origin, as can be documented by isoenzyme and cell markers. The term lymphoma is something of a misnomer, since these disorders are lethal unless controlled or eradicated through therapy. In the past, the term lymphosarcoma was applied to some of these disorders, but to so many that, although it revealed their ominous nature, it lost any specific meaning.

Within the broad group of malignant lymphomas, *Hodgkin's disease* (Hodgkin's lymphoma) is segregated from all other forms, which constitute the *non-Hodgkin's lymphomas*. Although both have their origin in the lymphoid tissues, Hodgkin's disease is set apart by the presence of a distinctive unifying morphologic feature, the Reed-Sternberg giant cells. In addition, there is a variable component of non-neoplastic inflammatory cells, which in the past raised questions about the neoplastic nature of Hodgkin's disease. Therefore, we will discuss non-Hodgkin's lymphomas and Hodgkin's disease separately.

Non-Hodgkin's Lymphomas (NHL)

The usual presentation of NHL is as a localized or generalized lymphadenopathy. However, in about one-third of cases it may be primary in other sites where lymphoid tissue is found, e.g., in the oropharyngeal region, gut, bone marrow, and skin. Lymph node enlargement due to lymphomatous disease must be differentiated from that caused by the more frequent infectious and inflammatory disorders. Lymphomatous involvement often produces marked nodal enlargement, which is almost always nontender. Although variable, all forms of lymphoma have the potential to spread from their origin in a single node or chain of nodes to other nodes, and eventually to disseminate to the spleen, liver, and bone marrow. Some, after becoming widespread, spill over into the blood, creating a leukemia-like picture in the peripheral blood. In such blood-borne dissemination, all lymph nodes throughout the body become flooded with lymphomatous cells. It may therefore be impossible to determine from microscopic examination of a lymph node alone whether it represents primary lymphomatous disease with involvement of the bone marrow and blood, or nodal changes incident to leukemia. This problem is encountered more often with certain cytologic forms of lymphoma than with others.

CLASSIFICATION OF NHL

Neoplastic proliferation of any one of the cell lines indigenous to lymphoid tissue can give rise to a lymphoma. Thus, theoretically it should be possible to classify them on the basis of cell types. Optimally, the classification should (1) provide categories that have clinical significance in terms of responsiveness to therapy and the outlook for the patient and (2) be based on morphologic criteria sufficiently distinctive to be generally applicable when interpreted by different observers. Regrettably, even among expert "lymphomaniacs" there are varying approaches to classification. Some use strictly morphologic criteria; others use morphologic criteria combined with functional features, e.g., immunologic markers and enzyme content of cells. Moreover, there are varying histogenetic interpretations of cell types. For example, when is a cell that looks like a histiocyte in reality a histiocyte and not a modified lymphocyte? What has emerged are more classifications than there are experts on the subject, or, to the "mere mortal," a veritable Augean stable in which the experts appear to have agreed to disagree. No attempt will be made to present all the current classifications.[2] Instead, two currently in favor in the United States—the Rappaport and Lukes-Collins classifications—will be discussed in some detail. Thereafter, brief comments will be made on the recent working formulation proposed by a panel of international experts.[3] Moreover, many of the potentially bewildering details of taxonomy to be found in the numerous references will be omitted, lest the forest get lost among the trees.

RAPPAPORT CLASSIFICATION

Proposed in 1966 and subsequently modified in 1978, this approach is based on two criteria: (1) the cytologic characteristics of the lymphomatous cells in routinely employed stains; and (2) separation of the lymphomas into two growth patterns—a nodular form in which the lymphomatous cells are clustered into identifiable nodules within the lymph nodes, and a diffuse form in which the cells diffusely infiltrate the entire lymph node, without any definite organized pattern.[4]

The *nodular* pattern is characterized by cohesive aggregates of neoplastic cells that somewhat resemble the germinal centers of the lymph node follicles; hence, this architecture is sometimes referred to as *follicular lymphoma*. The lymphomatous nodules are dispersed throughout the cortex and the medulla of the node and therefore efface the normal nodal architecture (Fig. 15–5). In many instances the capsular and pericapsular tissue is infiltrated by neoplastic cells, sometimes with the formation of nodules outside the capsule. This nodular or follicular pattern of lymphoma may be confused morphologically with the reactive follicular hyperplasia (lymphadenitis) of inflammatory states.[5] It is beyond our scope to go into all the subtle morphologic features in this differential, but several points may be noted. Favoring reactive follicular hyperplasia are (1) restriction of the follicles to the cortical region of the node, (2) *a mixed cell population of lymphocytes in different stages of differentiation and histiocytes within the germinal centers—lymphomatous nodules are monomorphic, reactive follicles pleomorphic;* and (3) evidence of cellular phagocytic activity in the germinal centers.

Approximately 50% of all NHLs in adults are of the nodular variety. On the basis of cytology, nodular lymphomas are divided into three subtypes (Table 15–

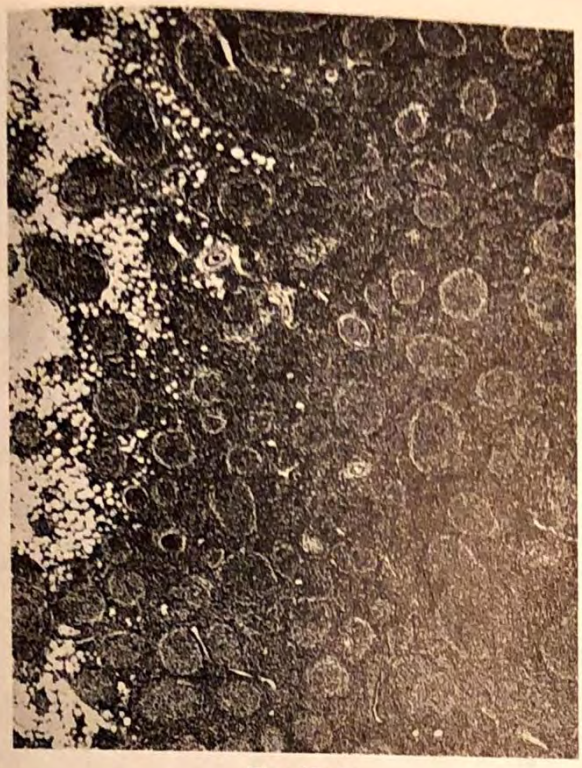

Fig. 15–5

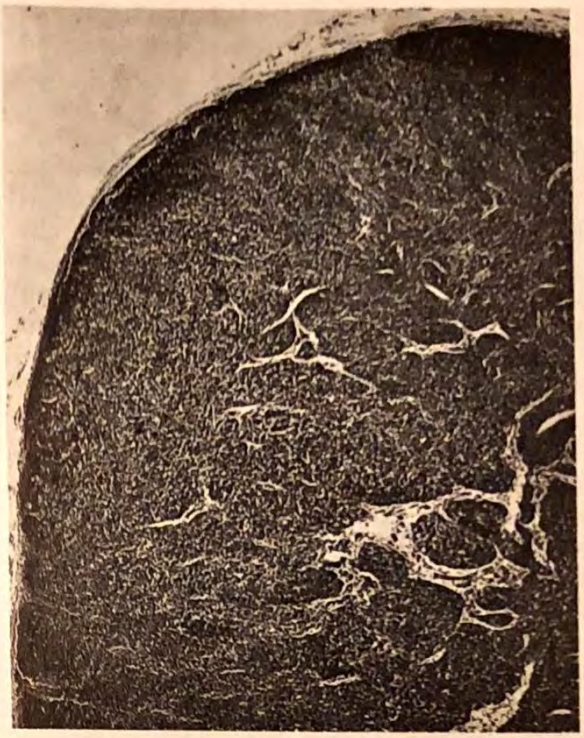

Fig. 15–6

Figure 15–5. Non-Hodgkin's lymphoma, nodular pattern. Nodular aggregates of lymphoma cells are present throughout lymph node and in perinodal fat. (From Jackson, H. J., Jr., and Parker, F. Jr. (eds.): Hodgkin's Disease and Allied Disorders. New York, Oxford University Press, 1947.)
Figure 15–6. Non-Hodgkin's lymphoma, diffuse. Nodal architecture is replaced by a diffuse sea of neoplastic lymphoid cells.

1). Since the cytologic features of nodular lymphomas overlap with those of the diffuse type, these will be described later. *The nodular lymphomas have distinctive clinical features: (1) they occur predominantly in older individuals (rarely persons under 20 years of age); (2) they affect males and females equally; and (3) despite the common finding of involvement of many or all nodes as well as possibly extranodal sites at the time of diagnosis, they have a much better prognosis than diffuse lymphomas.*[6]

The *diffuse lymphomas* are characterized by flooding of the nodal architecture by a monotonous sea of cells (Fig. 15–6). All underlying architecture, such as the distinction between cortex and medulla and the sinusoidal morphology, is totally obscured. The capsule of the node and the extracapsular tissue are often heavily infiltrated. The diffuse lymphomas are more heterogeneous with regard to cell type (Table 15–1) and clinical behavior. Since some diffuse lymphomas are cytologically identical to their nodular counterparts, they are considered to represent progression of the disease from a nodular to a diffuse pattern. Indeed, the coexistence of nodular and diffuse patterns and the documented transformation over time of nodular to diffuse pattern in a small number of cases does support this concept. However, it should be emphasized that *there is no critical evidence that all diffuse lymphomas are preceded by nodular lesions.* Indeed, as will be discussed, some variants such as the well-differentiated lymphocytic lymphoma are not encountered as nodular lesions. *More-*

Table 15–1. RAPPAPORT CLASSIFICATION

Diffuse Lymphomas	% All Cases*	Nodular Lymphomas	% All Cases*
Lymphocytic, well differentiated	5		
Lymphocytic, poorly differentiated	16	Lymphocytic, poorly differentiated	24
Lymphoblastic†			
Histiocytic	28	Histiocytic	3
Mixed, lymphocytic-histiocytic	6	Mixed, lymphocytic-histiocytic	12
Undifferentiated (Burkitt's and non-Burkitt's)	6		

over, nodular lymphomas may persist in the individual over the span of years and may disseminate throughout the body to cause death while retaining the distinctive nodular architecture.

In addition to the "nodular" and "diffuse" categorization, all NHLs are further subdivided into cytologic subsets. When Rappaport first presented the classification of NHLs, the immunologic typing of lymphoid cells was in its infancy, and so subdivision in the Rappaport scheme is based entirely on morphology. It takes into account first the apparent similarity of tumor cells to various normal cell types. Thus, terms such as lymphocytic and histiocytic lymphomas are used, to imply similarity and presumed derivation from normal lymphocytes or histiocytes. Second, within a cytologic category it further segregates tumors on the basis of degree of differentiation as judged by nuclear and cell size, nuclear configuration, chromatin pattern, and the presence or absence of nucleoli. The combined use of these two criteria permits differentiation of the following patterns.

WELL-DIFFERENTIATED LYMPHOCYTIC LYMPHOMA (WDLL). This pattern makes up approximately 5% of all NHLs and occurs only in the diffuse form; nodular variants have not been identified. The cell type consists of compact, small, apparently unstimulated lymphocytes with dark-staining round nuclei, scanty cytoplasm, and little variation in size (Fig. 15–7). Mitotic figures are very rare, and there is little or no cytologic atypia. *Diffuse WDLL may occur without involvement of the blood and bone marrow, but in about 40% of cases it may seed the blood, evoking a chronic lymphocytic leukemia–like blood picture.*[7] Conversely, in patients with the primary diagnosis of chronic lymphocytic leukemia (CLL), the nodes are invariably flooded with well-differentiated lymphocytes. Thus, it is impossible from a lymph node biopsy alone to differentiate CLL from WDLL. Their clinical features are also similar. Both occur primarily in the older age groups. Typically, these patients have generalized lymphadenopathy with mild-to-moderate enlargement of the liver and spleen; the associated symptoms are mild and prolonged survival is usual. Some patients with a histologic picture closely resembling WDLL also have monoclonal IgM immunoglobulin in the serum and a distinctive clinical syndrome called Waldenström's macroglobulinemia (p. 692). In these patients the lymph nodes often contain variable numbers of plasma cells or "plasmacytoid lymphocytes," in addition to the well-differentiated lymphocytes described above. As discussed later, WDLL, CLL, and Waldenström's macroglobulinemia represent different manifestations of the neoplastic proliferation of B lymphocytes, and as such are closely related to each other.

POORLY DIFFERENTIATED LYMPHOCYTIC LYMPHOMA (PDLL). The tumor cells in PDLL consist of atypical lymphocytes, which may appear in nodular or diffuse patterns. The cells are somewhat larger than those seen in WDLL (but smaller than the nuclei of benign endothelial cells or histiocytes, which are used as a reference

Figure 15–7. Non-Hodgkin's lymphoma, well-differentiated lymphocytic type. Cytology is that of mature, uniform, unstimulated lymphocyte. (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

when evaluating size). *Much more distinctive are the nuclei, which are irregular, with marked indentations and angularity* (Fig. 15–8). The chromatin is coarse and condensed, and mitoses are rare. The nodular and diffuse patterns of PDLL together account for approximately 30% of all NHLs. Some cases of PDLL may spill over into the blood and produce a leukemic picture, the so-called acute lymphosarcoma cell leukemia. The precise incidence of leukemia in PDLL is not known. However, leukemic spread is definitely less common than in WDLL. Patients with PDLL are usually middle-aged to elderly and present commonly with generalized disease involving multiple lymph nodes, liver, spleen, and bone marrow. Despite the presence of extensive disease, the prognosis is relatively favorable, especially in nodular PDLL. The prognosis in diffuse PDLL is poorer, as is the case with most diffuse lymphomas.

HISTIOCYTIC LYMPHOMA (HL). *Characteristic of this form of NHL is the large size of tumor cells.* They are two to three times larger than normal lymphocytes and their nuclei are larger than those of benign tissue histiocytes or endothelial cells. As compared with WDLL and PDLL, the nuclei in HL not only are larger but also are more vesicular and usually have more prominent nucleoli (Fig. 15–9). The nuclear shape, however, is quite variable: it may be round and smooth, or irregular with marked indentations and lobulations. *Several cytologic subtypes can be recognized, ranging from a monotonous proliferation of large cells to ex-*

Figure 15–8. Non-Hodgkin's lymphoma, poorly differentiated lymphocytic type. Nuclei are irregular with indentations *(arrows)* and marked angularity. (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

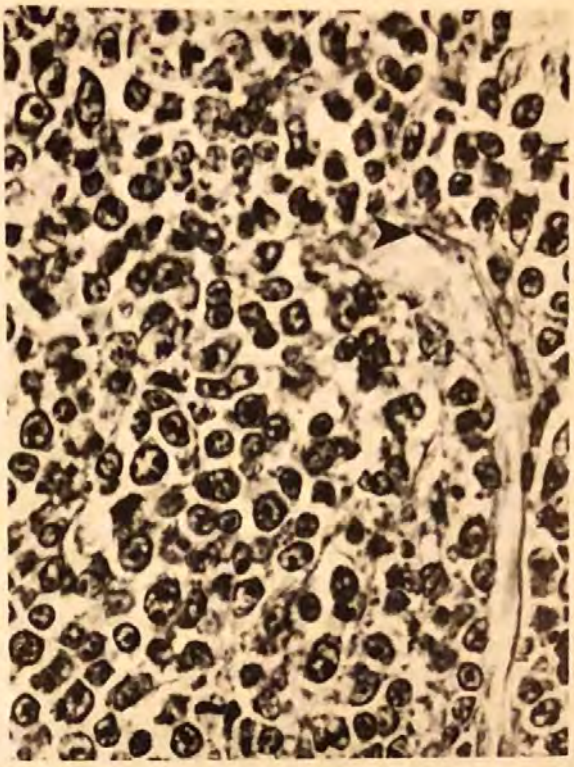

Figure 15–9. Non-Hodgkin's lymphoma, diffuse histiocytic type. Tumor cells in this example have large nuclei (compare with endothelial cell nucleus at tip of arrow) and prominent, centrally placed nucleoli. Nuclear pleomorphism is not marked. (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

tremely pleomorphic tumors with bizarre cells. Although HL can occur in both the nodular and diffuse forms, the latter is much more frequent and constitutes one of the most common forms of NHL (Table 15–1). The few cases of nodular HL tend to progress rapidly into the diffuse form and have the worst prognosis among nodular lymphomas. Diffuse histiocytic lymphomas are associated with somewhat distinctive clinical presentations. As compared with lymphocytic lymphomas, involvement of extranodal sites is more frequent; indeed, involvement of the gastrointestinal tract, skin, bone, or brain may be the presenting, and in some cases the only, feature, suggesting extranodal origin. When nodal involvement is the main presentation, it is usually restricted to one side of the diaphragm. Involvement of liver and spleen is not common at the time of presentation, but when it occurs the lymphoma cells form large, destructive tumorous masses. In contrast, for example, involvement of the liver and spleen in PDLL is associated with the formation of uniform discrete miliary nodules throughout these organs. Leukemic manifestations are distinctly uncommon, and when present indicate a very poor prognosis. HL is an aggressive disease, and the prognosis for the group as a whole is poor. However, several recent studies have indicated that up to 60% of patients with HL can achieve sustained clinical remission with combination chemotherapy, which may lead to long-term survival.[8]

Mixed Lymphocytic-Histiocytic Lymphoma. In this variant, cells of the PDLL type as well as large cells (histiocytic) are present. In general, a tumor is classified as mixed if the large cells constitute 30 to 50% of the total number of cells. This cytologic pattern is seen more commonly in the nodular form. As for most other nodular lymphomas, the prognosis is good.

Lymphoblastic Lymphoma. This is a relatively new addition to the Rappaport classification.[9] Previously, these cases were included under diffuse PDLL, but recent studies indicate that lymphoblastic lymphoma is a distinct clinicopathologic entity closely related to T-cell acute lymphoblastic leukemia (ALL) (p. 676). This variant is seen most commonly in adolescents or young adults, although any age group may be involved.[10] In affected males, there is a suggestion of bimodal age distribution, the two peaks being in the second and seventh decades. Overall, males are affected two to three times as often as females, but in the early peak encountered in the second decade, the male-to-female ratio is 6:1. *A very characteristic clinical feature, particularly in young males, is the presence of a mediastinal mass (50 to 70% of cases) at the time of diagnosis, suggesting a thymic origin.* This disease is rapidly progressive, and early dissemination to the bone marrow, blood, and central nervous system leads to the evolution of a picture resembling ALL.

The histologic pattern of the tumor is always diffuse

and the tumor cells resemble the lymphoblasts of ALL. They are fairly uniform in size, with scanty cytoplasm and nuclei that are somewhat larger than those of small lymphocytes. The nuclear chromatin is delicate and finely stippled, and nucleoli are either absent or inconspicuous. In many, but not all, cases the nuclear membrane shows deep subdivision, imparting a convoluted (lobulated) appearance. In keeping with its aggressive growth, the tumor shows a high rate of mitoses and, as with other tumors having a high mitotic rate (e.g., Burkitt's lymphoma), a "starry sky" pattern is produced by the interspersed benign macrophages. In the past, when this tumor was treated as diffuse PDLL, the survival was dismal, average life expectancy being less than one year. However, with the realization that lymphoblastic lymphoma is biologically more akin to ALL, treatment protocols employed for ALL have been utilized with much greater success, with a median survival in excess of 71 months in one series of adults.[11]

UNDIFFERENTIATED LYMPHOMA. This type is so termed because the cells do not have any morphologic evidence of "maturation" toward lymphocytes or histiocytes. Within this category, *two clinically distinct subgroups have been recognized: Burkitt's type and non-Burkitt's type.*

The *undifferentiated Burkitt's-type lymphoma* was described initially in Africa, where it is endemic in some parts, but it also occurs sporadically in nonendemic areas including the United States, where it has been called American Burkitt's lymphoma. Histologically, the African and the nonendemic American cases of Burkitt's lymphoma are identical, although there are some clinical and virologic differences. The relationship of these disorders to the Epstein-Barr virus (EBV) is discussed on pages 245 and 669. These tumors consist of a sea of strikingly monotonous cells, 10 to 25 μm in diameter, with round or oval nuclei containing two to five prominent nucleoli. The nuclear size approximates that of benign macrophages within the tumor. There is a moderate amount of faintly basophilic or amphophilic cytoplasm, which also is intensely pyroninophilic and often contains small, lipid-filled vacuoles (better appreciated on stained imprints of the tumor). A high mitotic index is very characteristic, as is cell death, accounting for the presence of numerous tissue macrophages with ingested nuclear debris. Since these benign macrophages, which are diffusely distributed among the tumor cells, are often surrounded by a clear space, they create a "starry sky" pattern (Fig. 15–10), which can also be seen in other lymphomas, such as the lymphoblastic type, with a high mitotic rate. Both the African and non-African cases are found largely in children or young adults. In both forms, the disease rarely arises in the lymph nodes. In African cases, involvement of the maxilla or mandible is the common mode of presentation (Fig. 15–11), whereas abdominal tumors (bowel, retroperitoneum, ovaries) are more common in cases seen in America. Leukemic transformation of Burkitt's lymphoma is uncommon, especially in African cases. These tumors respond well to aggressive chemotherapy, and long remissions have been reported. Although a relapse occurs in many cases, a 50% long-term survival rate can be expected with present methods of treatment.

Figure 15–10. Burkitt's lymphoma. Tumor cells have multiple small nucleoli and high mitotic index. Lack of significant variation in nuclear shape and size lends a monotonous appearance interrupted by pale-staining, benign tissue macrophages *(arrow)*, which impart a "starry sky" appearance better appreciated at a lower magnification. (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

The undifferentiated, non–Burkitt's-type lymphoma differs from the Burkitt's tumor both clinically and histologically.[12] This disease more commonly affects adults (median age 34 years) and is somewhat less responsive to treatment. There is no known clinical or virologic association with EBV. Histologically, the nuclei are approximately the same size as in Burkitt's tumor, but they show much greater variation both in shape and size, and occasional multinucleate cells are also seen. The nuclear chromatin is delicate and there is usually a single prominent eosinophilic nucleolus. Because of the nuclear appearance, this tumor has also been called undifferentiated, pleomorphic lymphoma. The cytoplasm is pale and scanty. The general view that this tumor is distinct from Burkitt's lymphoma has been challenged.[13] Since the frequency of these neoplasms is very low, more studies will be required to resolve this issue satisfactorily.

LUKES-COLLINS CLASSIFICATION

On the premise that the malignant lymphomas are neoplasms of the immune system, Lukes and Collins

Figure 15–11. Burkitt's lymphoma in a 9-year-old child. The maxillary tumor mass is a characteristic presentation of this disease.

have classified the non-Hodgkin's lymphomas on the basis of their origins from T or B lymphocytes or histiocytes.[14] This classification proposes that lymphomas develop through either a block or a "switch-on" (derepression) in transformation of either B cells or T cells. Correlations are drawn between the cytologic patterns in lymphomatous nodes and those evoked by antigenic challenge or mitogen stimulation of lymphocytes.

In the germinal centers of the follicles, four distinctive morphologic stages could be identified in the process of transformation of the unchallenged B lymphocyte into an immunoblast. *These stages include (1) small cleaved cells, (2) large cleaved cells, (3) small noncleaved cells, and (4) large noncleaved cells,* as depicted in Figure 15–12. First, the small, round B cell in and about the follicle changes into a slightly larger cell having an angulated, a folded, or (as Lukes and Collins refer to it) a cleaved nucleus. The term "cleaved" refers to sharp infoldings of the nuclear membrane. Further transformation produces larger cleaved cells. In both these cell forms, the cytoplasm is scanty and the nuclear chromatin is slightly more dispersed than in the resting lymphocyte, and the nucleoli are inconspicuous. Up to this point in the sequence there is little evidence of mitotic activity. In the next stage of transformation, nuclear cleavage disappears as the nucleus becomes round or oval, the nuclear chromatin is finely dispersed, and one to three nucleoli appear along with a readily visible peripheral rim of pyroninophilic cytoplasm. Pyroninophilia (increased affinity for the pyronin stain) results from increased amounts of cytoplasmic RNA as cells become active in protein (antibody) synthesis. Numerous mitotic figures now appear. The fourth stage in B-cell transformation involves the continued enlargement of the noncleaved cell up to four or more times the size of the original small lymphocyte. Simultaneously, one to two nucleoli become prominent in the large, round vesicular nucleus, along with an increase in the quantity of the cytoplasm. Mitotic figures are frequent in these cells. *All four of these cell types are referred to as follicular center cells (FCC) and all are of B-cell origin.* The noncleaved cells are the dividing FCC, whereas the cleaved cells are the nondividing but morphologically altered FCC. It is the large noncleaved cells that ultimately undergo further enlargement to become immunoblasts. The immunoblasts have more marked pyroninophilia, larger and more vesicular nuclei, and prominent centrally located nucleoli. They also tend to show plasmacytoid features. Further proliferation of immunoblasts provides daughter cells that eventually either become plasma cells or revert to the dormant state as small memory lymphocytes. The small T cells in the T-cell regions of the lymph node may

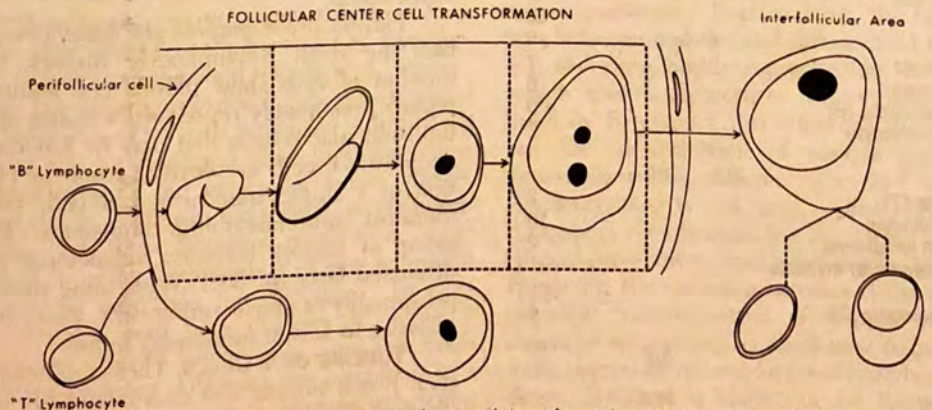

Figure 15–12. Schematic representation of normal transformation of follicular center B cells in comparison with transformation of T cells. (From Lukes, R. J., and Collins, R. D.: New approaches to the classification of the lymphomata. Br. J. Cancer *31*(Suppl. 2):7, 1975.)

undergo a parallel "blast" transformation without showing nuclear cleavage. From such studies, Lukes and Collins concluded that most cells interpreted as histiocytes in the Rappaport classification were actually neoplastic FCC. Lukes and Collins recognize true histiocytic lymphomas, but consider them rare, and cell marker techniques have supported this view.

Since *the Lukes-Collins classification is based on the concept that the various cytologic subtypes of malignant lymphomas arise by neoplastic transformation of the normal components of the immune system,* it divides NHL into three functional categories: B-cell tumors, T-cell tumors, and tumors of histiocytes (macrophages). A fourth undefined cell category includes tumors that cannot be assigned to the three functional categories by any of the presently available criteria. As seen in Table 15–2, B-cell tumors are the most common,, and true histiocytic tumors are rare. *Although this classification divides NHL into functional groups, Lukes and associates have repeatedly emphasized that "the classification of cases is based entirely on the morphologic features."*[14] Implicit in this view is the assertion that the cytologic features are distinctive enough to define immunologically homogeneous entities without requiring cytochemical and immunologic methods, except in those few cases in which morphology is not distinctive. We will examine the validity and practical implications of this view after a description of the morphologic features of NHL, according to the Lukes-Collins system.

TUMORS OF B LYMPHOCYTES. The great preponderance of NHLs are of B-cell origin (Table 15–2). Within this group, they are subclassified on the basis of the morphologic features characteristic of the different stages of normal B-cell differentiations, as depicted in Figure 15–12.

The *small B-cell lymphoma* apparently results from neoplastic transformation of the small B cells of the follicular mantle, which are blocked from further differentiation. The tumor cells have uniform round nuclei with compact chromatin and a narrow rim of pale cytoplasm, resembling normal lymphocytes. Mitoses are rare. Since the tumorous B cells are apparently arrested in this early stage, they fail to form follicles or plasma cells. This category conforms to the diffuse WDLL of the Rappaport classification and the closely related CLL.

Follicular center cell (FCC) lymphomas, like the normal follicles, are comprised of four cytologic subtypes, which are segregated on the basis of the similarity of cell size and nuclear characteristics to those of normal FCCs (Fig. 15–12 and Table 15–2). Since the neoplastic FCCs apparently retain their ability to form follicles, there is usually some degree of follicle formation (recall nodular architecture). The degree of follicle formation, however, varies with the state of B-cell transformation. Thus, FCC lymphomas of small cleaved cells and large cleaved cell types that are composed of less actively dividing cells are more frequently associated with follicle formation, whereas the rapidly proliferating small and large noncleaved cell tumors exhibit the follicular pattern in only 10% of cases. Most FCC lymphomas are of the small cleaved type, but in some cases a mixture of cell types is present. Such tumors are usually classified on the basis of the predominant cell type. (Fig. 15–8, representing PDLL according to the Rappaport classification, would be classified as small cleaved FCC lymphoma in the Lukes-Collins scheme.) Burkitt's tumor is believed to represent a form of small noncleaved FCC lymphoma; although these usually have a diffuse architectural pattern, in some cases there are follicles supporting their origin from the FCC.

Immunoblastic sarcoma of B cells is believed to arise from transformed interfollicular B cells; it therefore does not form follicles. The tumor cells resemble the large noncleaved FCCs, but have more abundant pyroninophilic cytoplasm and plasmacytoid features. In 30% of cases this aggressive tumor of transformed B lymphocytes is associated with a previous history of an immunologic disorder such as Sjögren's syndrome, SLE, or Hashimoto's thyroiditis or with states of immunosuppression.

Plasmacytoid lymphocytic lymphoma closely resembles the small B-lymphocyte tumors, but a variable number of cells show plasma cell features. This lymphoma presumably represents a tumor of differentiated interfollicular B cells that may be functional. Since the neoplastic B cells are derived from the clonal proliferation of a single transformed B cell, they all secrete identical immunoglobulin molecules. Therefore, this group of tumors includes monoclonal gammopathies, discussed later (p. 688). With some tumors, composed presumably of nonsecreting cells, there is no associated increase in serum immunoglobulins.

TUMORS OF T CELLS. These are much less frequent than B-cell tumors and understandably much less well defined. Four types have been recognized: small lymphocytic T-cell lymphoma, convoluted T-cell lymphoma,

Table 15–2. LUKES-COLLINS CLASSIFICATION*

	Percentage
B Cell	65
Small lymphocyte (B)	9
Follicular center cell	
Small cleaved	28
Large cleaved	5
Small noncleaved	7
Large noncleaved	6
Immunoblastic sarcoma (B)	3
Plasmacytoid lymphocyte	7
T Cell	20
Small lymphocyte (T)	2
Convoluted lymphocyte	10
Cutaneous T-cell lymphoma	2
(Sézary syndrome and mycosis fungoides)	
Immunoblastic sarcoma (T)	4
Histiocytes	0.2
U (Undefined) Cell	14.8

*Adapted from reference 12.

the cutaneous T-cell lymphomas (mycosis fungoides Sézary syndrome), and immunoblastic sarcoma of T cells.

Small lymphocytic T-cell lymphoma is extremely rare, making up only 10 out of 425 cases in one large series.[14] The cells resemble small B lymphocytes, from which they cannot be easily differentiated morphologically. They may be associated with the uncommon T-cell CLL (p. 676).

Convoluted T-cell lymphoma in the Lukes-Collins classification is essentially identical to the lymphoblastic lymphoma of the Rappaport classification (p. 661); therefore, only brief additional comments will be offered. As mentioned earlier, in most cases of lymphoblastic lymphoma the tumor cells have markedly convoluted nuclei, an appearance said to resemble "chicken footprint." Those few cases that do not have the typical nuclear convolutions are excluded from this group in the Lukes-Collins classification. Recent studies with monoclonal antibodies, however, indicate that most tumor cells (with or without nuclear convolutions) express OKT10, a marker of primitive intrathymic T cells, and that nuclear configuration does not affect the clinical course. This, then, is a tumor of *immature intrathymic T cells*, and understandably no morphologic counterpart of the convoluted T cells is found in normal lymph nodes.

Cutaneous T-cell lymphomas include a spectrum of disorders, of which mycosis fungoides and Sézary syndrome are the best characterized.[16] Involvement of skin is a hallmark of the tumors within this group. Clinically, the cutaneous lesions of *mycosis fungoides* show three somewhat distinct stages, discussed later (p. 1271). Briefly, mycosis fungoides presents with an inflammatory premycotic phase and progresses through a plaque phase to a tumor phase. *Histologically, there is infiltration of the epidermis and upper dermis by neoplastic T cells, which have an extremely unusual cerebriform nucleus.* This appearance results from marked and complex infolding of the nuclear membrane. In most patients with progressive disease, extracutaneous manifestations, characterized by nodal and visceral dissemination, appear. *Sézary syndrome* is a related condition in which skin involvement is manifested clinically as a generalized exfoliative erythroderma, but *in contrast with mycosis fungoides, the skin lesions rarely proceed to tumefaction.* Instead, there is an associated leukemia of "Sézary" cells that have the same cerebriform appearance noted in the tissue infiltrates of mycosis fungoides. Circulating Sézary cells can also be identified in up to 25% of cases of mycosis fungoides in the plaque or tumor phase, indicating that the two diseases have much in common. Fundamentally, both these disorders result from clonal proliferations of T cells, presumably in the lymphoid tissues, followed by migration into the skin.[17] In most cases, Sézary-mycosis cells bear markers of helper T cells ($OKT4^+$), but $OKT8^+$ tumor cells have also been detected in some patients. Although the prognosis in a given case depends on the extent of disease at the time of diagnosis, a median survival rate of eight to nine years is not unusual.[18]

Immunoblastic sarcoma of T cells is the most poorly characterized category in the Lukes-Collins classification. Intended to include lymphomas derived from the transformed T lymphocytes in the paracortical area, this group contains tumors that have a mixture of small lymphocytes and many large transformed cells. The latter have round or oval nuclei with fine chromatin, and one or more small but distinctly eosinophilic nucleoli. Absence of plasmacytoid features and pyroninophilia are considered helpful in distinguishing them from B immunoblasts. However, this definition of T-immunoblastic sarcomas is extremely hazy and at present no distinct clinical or morphologic entity has emerged.[15]

Tumors of Histiocytes. True histiocytic lymphomas, i.e., those that can be cytochemically and immunologically confirmed to have arisen from macrophages, are extremely rare. Most tumors classified as histiocytic lymphomas in the Rappaport classification are accommodated in the B-cell category of the Lukes-Collins classification.

U-Cell (Undefined) Group. This group includes lymphomas that cannot be classified into a definite category either by morphologic or currently available immunocytochemical markers. These may indeed be tumors of very primitive T cells, B cells, or macrophages, or the so-called "null" cells.

Rappaport and Lukes-Collins Classifications—Comments and Comparisons

The basic purpose of a classification is to provide guidance in the clinical management of patients; i.e., it should define groups that are relatively homogeneous with respect to response to therapy and prognosis. Ideally, such a classification should also be scientifically accurate, highly reproducible, and readily learned by the practicing pathologist. It is by these criteria that we should assess the classifications of NHL.

Separation of NHL into nodular and diffuse categories has been a major contribution of the Rappaport classification, since nodular architecture is associated with a prognosis significantly superior to that of the diffuse pattern.[3, 4] Furthermore, the histologic distinction between nodular and diffuse NHL is easily learned and therefore highly reproducible. In addition to the lymph node architecture, the cytologic categories defined by Rappaport also influence the clinical course,[19] but the identification of various cytologic subtypes (based on subtle differences in cell size and nuclear characteristics) is not very reproducible. Overall, the Rappaport classification has the virtue of long use, good clinical correlations, and a fair degree of reproducibility. However, the recent awareness of the remarkable morphologic transformation of lymphocytes in different stages of activation has shed new light on the histogenetic origins of various forms of lymphomas, particularly those classified as histiocytic by Rappaport. It is now evident from the studies of Lukes and Collins that approximately 76% of the so-called histiocytic or large-

cell lymphomas are tumors of "transformed" (activated) B lymphocytes—some immunoblastic sarcomas (e.g., Fig. 15–9), others large cleaved and noncleaved cell types.[14, 20] Of those remaining, 8% are T-cell lymphomas, 11% cannot be defined by presently available immunocytochemical techniques, and only 5% are true histiocytic tumors. It is obvious, therefore, that histiocytic lymphomas in the Rappaport classification are not homogeneous with respect to their origin. Grouping of histogenetically diverse tumors purely on morphologic grounds is considered scientifically inaccurate and a major weakness of the Rappaport classification.

Conceptually, the Lukes-Collins classification is much more acceptable, since it places various lymphoid tumors into well-defined functional categories based on their origin from specific normal cell types. However, are the immunologically homogeneous categories associated with uniform clinical behavior? At present there are no clear answers, and disagreement persists regarding the clinical utility of an immunologically based classification of NHL.[21, 22] Another important difference between the Lukes-Collins and Rappaport classifications relates to the significance of nodular versus diffuse pattern. Recall that, according to Rappaport, nodular growth pattern is associated with an indolent disease. According to Lukes and Collins, however, when patients are stratified into groups based on the cell of origin, differences between nodular and diffuse lymphomas become biologically minimal. It is claimed, for example, that the observed superior survival of patients with nodular lymphomas is related to the fact that the nodular pattern is seen most often with small cleaved cell tumors, which are the least aggressive of the FCC lymphomas. Although this issue is not completely resolved, most published studies continue to support the notion that the nodular growth pattern, independent of the cytologic subtype, is associated with a better prognosis.[3]

In addition to clinical utility, we must also ask whether the Lukes-Collins classification is practical and reproducible. Although its authors contend that the functional classification can be applied by using only morphologic criteria, others have failed to achieve more than 60% accuracy in classifying the cell of origin on the basis of histologic examination.[23] Therefore, it has been advocated that markers that characterize various immune cells (Table 15–3) be routinely utilized as an adjunct to morphology. With this refinement, it is claimed that meaningful correlations can be made between the immunologic type and the clinical behavior

Table 15–3. TECHNIQUES USED FOR IDENTIFICATION OF T CELLS, B CELLS, AND HISTIOCYTES

	T Cells	B Cells	Histiocytes Monocytes	Comments
Rosette methods*				Cytocentrifuge preparations of value in evaluating lymphomas
Spontaneous sheep erythrocyte (E) receptor	+	–	–	Present on all peripheral T cells
Complement (EAC) receptor	(+)	+	+	Convoluted T-cell lymphomas are observed with complement receptors; normal T cells negative
Fc (EA) receptor	(+)	+	+	Present only on some T-cell subsets
Surface immunoglobulin	–	+	(+)	By immunofluorescence; monocytes may mark because of Fc receptors
Cytoplasmic immunoglobulin	–	+	–	Immunoperoxidase more useful than immunofluorescence in lymphomas because it can be used on paraffin sections
Monoclonal antibodies OKT3, OKT11	+	–	–	Present on all peripheral T cells; OKT11 is antibody to sheep red blood cell (E) receptor
OKT10	+	–	–	Present only on intrathymic T cells and tumors of immature T cells
Anti–HLA-DR	(+)	+	+	Present only on activated T cells; seen also on Langerhans' cells and dendritic cells
Cytochemistry				
α-Naphthyl butyrase (NSE)†	(+)	–	+	Focal staining reported in T cells; specificity for T cells is not proved
Acid phosphatase	(+)	–	–	Reported in convoluted T-cell lymphomas and T-cell ALL
Tartrate-resistant acid phosphatase	–	(+)	–	Present in hairy cell leukemia
Muramidase (lysozyme)	–	–	+	Immunoperoxidase method on paraffin sections or imprints
TdT	(+)	(+)	–	Present only in primitive T and B cells

*A rosette is identified as a nucleated cell surrounded by a cluster of appropriately treated sheep erythrocytes. Spontaneous sheep erythrocyte (E) receptor is detected by use of unsensitized sheep red cells. For detection of complement receptors, sheep erythrocytes (E) are coated with IgM antierythrocyte antibody (A) and sublytic amounts of complement (C); Fc receptors are detected by rosetting with erythrocytes (E) coated with IgG antierythrocyte antibody (A).

†NSE = nonspecific esterase.

Parentheses indicate that the presence of the marker is not characteristic or specific for that cell type, as explained under comments.

Table 15–4. A WORKING FORMULATION OF NON-HODGKIN'S LYMPHOMAS FOR CLINICAL USAGE (EQUIVALENT OR RELATED TERMS OF RAPPAPORT AND LUKES-COLLINS CLASSIFICATIONS ARE SHOWN)

Working Formulation	Rappaport Classification	Lukes-Collins Classification
Low-Grade		
A. Small lymphocytic	Lymphocytic, well differentiated	Small lymphocyte and plasmacytoid lymphocytic
B. Follicular, predominantly small cleaved cell	Nodular, poorly differentiated lymphocytic	FCC, small cleaved
C. Follicular, mixed small cleaved and large cleaved cell	Nodular, mixed lymphocytic histiocytic	FCC, small cleaved and large cleaved
Intermediate-Grade		
D. Follicular, predominantly large cell	Nodular, histiocytic	FCC, large cleaved and/or non-cleaved
E. Diffuse, small cleaved cell	Diffuse, poorly differentiated lymphocytic	FCC, small cleaved diffuse
F. Diffuse, mixed large and small cell	Diffuse, mixed lymphocytic and histiocytic	FCC, small cleaved, large cleaved, or large noncleaved
G. Diffuse, large cell	Diffuse histiocytic	FCC, large cleaved or noncleaved
High-Grade		
H. Large cell, immunoblastic	Diffuse histiocytic	Immunoblastic B- or T-cell type
I. Lymphoblastic	Lymphoblastic lymphoma	Convoluted T-cell lymphoma
J. Small noncleaved cell	Undifferentiated, Burkitt's and non-Burkitt's	FCC, small noncleaved
Miscellaneous		

of various NHLs.[24] It must be admitted, however, that the complex immunocytochemical procedures presently available have not yet been widely applied to the routine diagnostic evaluation of lymph node biopsies.

In summary, it appears that, with respect to prognostication or patient management, the superiority of the Lukes-Collins approach to that of Rappaport has not yet been proved beyond reasonable doubt. The major contribution of the Lukes-Collins classification has been that it has significantly advanced our understanding of the histogenesis of NHL and has provided an impetus for improving the existing classifications.

A Working Formulation of NHL for Clinical Usage

In addition to the two discussed above, four other well-described classifications are currently used in different parts of the world.[3] Of these, the Kiel classification, used widely in Europe, is similar to the Lukes-Collins in being based partly on functional concepts. The others are purely morphologic. The existence of many classifications not only has resulted in much confusion and controversy, but also has made it impossible to compare effectively the results of clinical studies utilizing different systems. To resolve this, the National Cancer Institute of the U.S.A., in collaboration with several international experts, has suggested a new Working Formulation for Clinical Usage (Table 15–4).[3] As the name indicates, this classification has a strong clinical bias. NHLs are divided into three major prognostic groupings based on survival statistics, each group containing several morphologic categories. *The five-year survival rate for the tumors classified as low grade ranged from 50 to 70%, and for tumors of intermediate and high grade from 35 to 45% and 23 to 32%, respectively.* The descriptive terminology is somewhat similar to that of the Lukes-Collins classification, but there is no attempt to segregate lymphomas on the basis of the presumed cell of origin. The histologic appearance of the tumors within the working formulation may be surmised from the equivalent terms in the Rappaport and Lukes-Collins classification (Table 15–4). Detailed comparisons with the other classifications are available in the report.

Morphology. The precise categorization of lymphomas rests heavily on the cytologic details already presented, but without doubt immunocytochemical methods greatly increase diagnostic accuracy. Required for diagnosis are representative samples (usually excised nodes) of the lymphoma, which should be promptly transferred to the diagnostic laboratory unfixed, so that "touch imprints" of fresh cut surfaces and special immunologic and cytochemical procedures can be performed. Obviously the best possible histologic tissue sections are also necessary.

Most lymphomas are characterized by lymphadenopathy and, as the disease advances, splenomegaly, hepatomegaly, and eventually involvement of other viscera. At first only one or a single chain of nodes is involved. In an analysis of a large series of cases, the cervical chain (either side) was the primary site of involvement in approximately 30 to 40% of cases, and the axillary nodes in approximately 20%, followed in order by the inguinal, femoral, iliac, and mediastinal nodes.[25] In approximately one-third of cases, extranodal disease may be the presenting feature. This is seen most frequently with histiocytic (large-cell) lymphomas. In all forms of lymphoma, affected nodes are variably enlarged, sometimes up to massive size (10 cm in diameter). They are generally soft and fleshy and are usually discrete without adherence to surrounding structures. On cut surfaces, the nodular forms may present foci of nodularity barely apparent to the naked eye. Nodes with diffuse disease are homoge-

Figure 15–13. Cut surface of a lymph node with diffuse involvement with non-Hodgkin's lymphoma. The surface is homogeneous gray with total loss of nodal architecture.

neously gray and have the appearance of fish flesh (Fig. 15–13). Necrosis, hemorrhage, and foci of cystic softening are uncommon. With advance of the disease, progressively more nodes are affected, and the tumorous tissue may permeate the capsule of the node and extend into the pericapsular tissues to produce interadherence and matted, nodular tumorous masses (Fig. 15–14). Such a gross appearance is characteristic of the diffuse patterns of lymphoma. Lymphomatous spread to the spleen, liver, or other viscera may be inapparent macroscopically or may induce hepatosplenomegaly, sometimes without grossly visible lesions, but more often minute to moderate-sized tumorous nodules resembling metastases can be seen.

Etiology and Pathogenesis. The etiology and pathogenesis of NHLs is as mysterious as that of all cancers. However, since lymphomas are neoplasms of the immune system, certain special features that apply to these tumors will be discussed here. It is well-known that the proliferation of lymphocytes is a normal consequence of their exposure to antigens and that this physiologic response is kept in check by a variety of regulatory mechanisms. *It is postulated that malignant lymphomas develop when there is failure of immunoregulation in the face of a persistent stimulus for lymphocyte proliferation.* Several observations support such a hypothesis. Human recipients of organ transplants (e.g., kidney or heart), patients with congenital immune deficiency syndromes, and those with certain autoimmune diseases have an unusually high incidence of NHLs.

In the case of *allograft recipients*, the antigens of the graft provide persistent strong antigenic stimulus to the host lymphocytes, while feedback regulation of lymphoproliferation is impaired by simultaneous immunosuppressive therapy. In *autoimmune diseases*, chronic antigenic stimulation is provided by the constant exposure to self-antigens. In this clinical setting there is a genetically determined impairment of immunoregulation (p. 179), and immunosuppressive therapy with cytotoxic drugs further disturbs the regulatory networks. The greatly increased incidence of lymphomas with Sjögren's disease was mentioned earlier (p. 190); an increased risk is also noted with rheumatoid arthritis

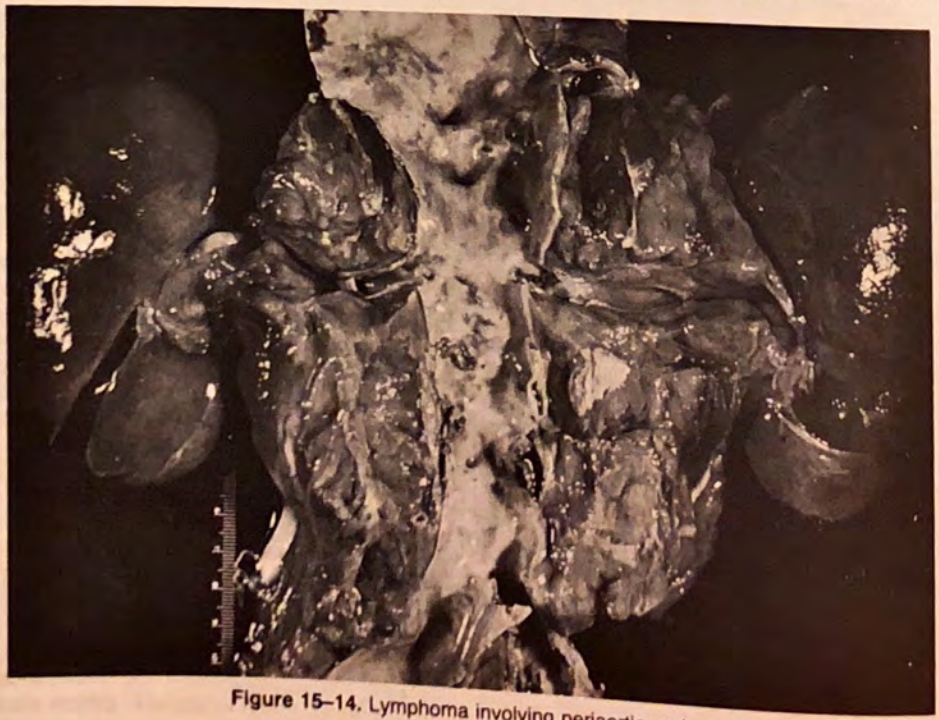

Figure 15–14. Lymphoma involving periaortic nodes.

and SLE. In *primary immunodeficiency syndromes*, recurrent infections are the obvious source for antigenic stimulation. Many of these disorders are also associated with abnormalities in T-suppressor cells (p. 205). One form of immunodeficiency, the X-linked lymphoproliferative syndrome (XLP), is of particular interest. Unlike patients with the generalized immunodeficiency states in whom there is predilection for a wide variety of bacterial and viral infections, those with XLP have specific defects in immune responsiveness to EBV.[26] As might be expected with any X-linked disorder, only males are affected, who develop a variety of progressive and rapidly fatal disorders following exposure to EBV in early childhood. You may recall that in infectious mononucleosis the EBV-induced B-cell proliferation is contained by the activation of immunoregulatory T cells, and the disease is therefore self-limited (p. 288). By contrast, in patients with the XLP syndrome, infection with EBV may lead to fatal infectious mononucleosis or a malignant B-cell lymphoma, because they are unable to mount T-cell surveillance against the virus.[27] Paradoxically, in some patients abnormal and excessive T-suppressor cell response to the EBV infection may shut down normal hematopoiesis or immunoglobulin synthesis, leading to aplastic anemia or hypogammaglobulinemia, respectively.

The studies cited above have provided an alternative explanation of the well-known association between EBV and Burkitt's lymphoma. According to this view, the pathogenesis of Burkitt's lymphoma is a three-step process. In the *first step*, the EBV acts as a B-cell mitogen and initiates a polyclonal B-cell proliferation. In most individuals the lymphoproliferation is arrested at this stage owing to the activation of immunoregulatory T cells, and there is either no clinical disease or a self-limited episode of infectious mononucleosis (p. 288). A congenital (e.g., XLP syndrome) or acquired (e.g., immunosuppression in allograft recipients) defect in the T-cell response to EBV leads to the *next step*, characterized by sustained polyclonal B-cell proliferation, which in some cases may present as acute severe infectious mononucleosis. Although usually fatal, this condition does not represent a true neoplasm since the proliferating B cells are not monoclonal. In other patients, the polyclonal B-cell proliferations may be chronic, setting the stage for the *third and final step*, lymphomagenesis—the emergence of a truly neoplastic clone of B cells. What brings about such a transition is not clear, but it seems reasonable to assume that the rapidly proliferating B cells are at a greatly enhanced risk of acquiring cytogenetic aberrations (such as translocations), some of which may offer growth advantage to the affected cell. In due course, the progeny of the cell with the translocated chromosome would replace all other B cells, resulting in a monoclonal B-cell neoplasm. Recall that the tumor cells in Burkitt's lymphoma frequently show a nonrandom t(8;14) chromosomal translocation (p. 245). This translocation may so derange cellular regulation that the cells become autonomous. *According to this view, then, EBV itself is not directly oncogenic but, by acting as a B-cell mitogen, it creates an environment for the oncogenic event involving some critical gene rearrangements.* Evidence for the stepwise transition from polyclonal to monoclonal B-cell proliferation has been observed, not only in cases with the XLP syndrome, but also in angioimmunoblastic lymphadenopathy, an unusual disorder described later in this chapter (p. 696). Although this scheme is derived largely from the study of Burkitt's lymphoma, it is not essential to invoke EBV in the causation of other malignant lymphomas. Sustained polyclonal proliferation of lymphocytes, an essential ingredient of this hypothesis, may derive from any one of the causes of chronic antigenic stimulation discussed earlier. It is interesting to note in this context that many distinctive nonrandom chromosomal abnormalities (mostly translocations) have been identified with a high frequency in several B-cell lymphomas other than Burkitt's tumor.[28] In most of these, chromosome 14 is involved in the translocation and the breakpoint is almost always at the same band, i.e., q32. There is no satisfactory explanation for this remarkable constancy of the breakpoint, but it has been suggested that genes close to band q32 on chromosome 14 are somehow capable of affecting the proliferative state of the affected cells, as discussed on pages 249 and 677.

In closing, it should be pointed out that in the great majority of patients with NHLs there is no overt immunologic abnormality. However, this does not preclude the possibility that subtle disturbances in immune regulation not easily detected by present-day techniques may underlie most cases of NHL.

STAGING. A staging system of Hodgkin's disease is described on page 674. Like NHL, Hodgkin's disease usually arises within lymph nodes and then disseminates more widely. A rigorous protocol has been devised to express the extent and distribution of Hodgkin's disease within the patient, employing meticulous physical examination, blood studies, lymphangiography, laparotomy, liver biopsy, and splenectomy. Unlike Hodgkin's disease, however, staging is of limited value in deciding therapy or offering prognosis for patients with NHL. This stems from the fact that in NHL the histologic type influences prognosis much more profoundly than does the extent of disease. For example, nodular lymphomas have the best prognosis despite disseminated (Stage IV) disease at the time of diagnosis. Staging is most valuable in the diffuse histiocytic lymphomas, since they often present with localized disease. However, staging is essential in order to compare different modalities of treatment within a given histologic category.

CLINICAL COURSE. Non-Hodgkin's lymphomas are most often diagnosed in adults, usually in the fifth to sixth decades of life, but may occur in children. *Childhood lymphomas* differ in many respects from those in adults. In general, extranodal (abdominal, mediastinal) disease is much more common and nodular lymphomas are rare. Lymphoblastic lymphoma and undifferentiated lymphomas constitute the two most common histologic types. Although these are aggressive lesions, they respond well to therapy and approximately 50% are curable.[29]

Typically, lymphomas present with the insidious

onset of peripheral, painless nodal enlargement. In some patients, these tumors come to attention as mediastinal masses, as gastrointestinal lesions, or as causes of splenomegaly or hepatomegaly. Rarely, they present as a bone tumor, tonsillar enlargement, or the cause of an anemia or leukemia. The range of clinical presentations is almost limitless, since they may be primary in any site bearing lymphoid tissue. Wherever they present, unless controlled by therapy, more and more nodes become involved over the span of months, along with the spleen and liver as well as other tissues and organs. Unlike Hodgkin's disease, the spread is not predictable. With more advanced disease, fever, sweats, and weight loss may appear. The hepatosplenomegaly may be quite massive. When the lymphomatous cells spill into the peripheral blood, a leukemia-like pattern of disease is created with lymphomatous seeding of all organs of the body.

As expected, the prognosis varies with the extent of the dissemination, the specific form of lymphoma, and the therapeutic modalities employed. Radiation alone may be used in the earlier stages of these diseases, but in the later stages, chemotherapy or combined radiation and chemotherapy are generally employed. The range of cytotoxic and cytostatic drugs used alone and in variable combinations is now quite large and beyond our scope. These diseases once cast a hopeless pall, but some have yielded remarkably to therapy, to the point at which it is now possible to speak of "long remissions" lasting for years of some of these once rapidly progressive disorders.

Hodgkin's Disease (Hodgkin's Lymphoma)

Hodgkin's disease has been segregated from NHL for many reasons. First, it is characterized histologically by the presence of neoplastic giant cells called Reed-Sternberg cells admixed with a variable inflammatory component. Second, its spread is almost always by contiguity—from one chain of nodes to the adjacent groups. Finally, it almost never has a leukemic component.

Several histologic variants of Hodgkin's disease have been recognized. The *one common denominator among all forms is the presence of a distinctive tumor giant cell known as the Reed-Sternberg (RS) cell.* It is considered to be the essential neoplastic element in all forms of Hodgkin's disease, and its identification is essential for the histologic diagnosis. *Classically, it is a large cell (15 to 45 μm in diameter), most often binucleate or bilobed with two halves often appearing as mirror images of each other (Fig. 15–15). At other times there are multiple nuclei, or the single nucleus is multilobate and polypoid. The nucleus is enclosed within an abundant amphophilic cytoplasm. Prominent within the nuclei are large, inclusion-like, "owl-eyed" nucleoli generally surrounded by a clear halo.* In typical RS cells the nucleoli are acidophilic or, at the least, amphophilic, and react strongly with RNA stains. Giant cells are sometimes found that have all the characteristics of the

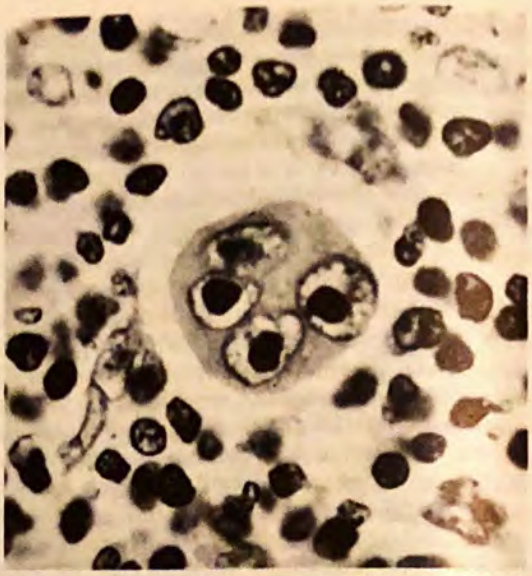

Figure 15–15. Reed-Sternberg cell. (From Neiman, R. S.: Current problems in histopathologic diagnosis and classification of Hodgkin's disease. Pathol. Annu. *13*:289, 1978.)

multinucleate cell just described and that contain only a single nucleus replete with large nucleolus. Although such cells may be biologic variants of the RS cell, they are not diagnostic of Hodgkin's disease. Other cells, uninucleate or multinucleate, may not have a nucleolus; these, too, are nondiagnostic. One additional variant, the so-called *lacunar cell*, is encountered primarily within one of the distinctive patterns of Hodgkin's disease called nodular sclerosis.

It is somewhat anticlimactic to report that cells closely simulating or identical with RS cells have been identified in conditions other than Hodgkin's disease. Lukes et al.[30] have reported RS-like cells in infectious mononucleosis, and Rappaport and colleagues[31] have observed cells that resemble the RS cell in solid tissue cancers, mycosis fungoides, lymphomas, and other conditions.[32] Thus, to quote Rappaport et al., "we believe that a definitive diagnosis of Hodgkin's disease cannot be rendered in the absence of Sternberg-Reed cells, but that the diagnosis depends upon the total histologic picture."[31] Stated another way, *the RS cell is necessary but not sufficient for the diagnosis.* Thus, we are faced with the dilemma that a histologic diagnosis of Hodgkin's disease cannot be made without identifying RS cells, but RS cells cannot be identified unless they are present in Hodgkin's disease. Recognizing this difficulty, we can turn to a characterization of the morphologic forms of Hodgkin's disease.

CLASSIFICATION. It is heartening that unlike the situation with NHLs, there is nearly universal acceptance of a single, well-characterized classification—the Rye.[33] Four distinctive patterns have been defined that vary in their gravity. The essential morphologic feature that separates three of the four subgroups (lymphocytic predominance, mixed cellularity, and lymphocytic depletion) is the frequency of the RS cells, relative to the number of lymphocytes, representing the host response. The frequency of lymphocytes seems to have a direct

bearing on the spread and prognosis of Hodgkin's disease. The fourth variant, nodular sclerosis, which has distinctive histologic as well as clinical features, is believed to represent a special expression of the disease. In most series, nodular sclerosis is the most common variant (40 to 75%) followed by mixed cellularity (20 to 40%). The two polar groups, i.e., lymphocyte predominance and lymphocytic depletion groups, are the least common (5 to 15% each).

Lymphocyte-predominance Hodgkin's disease is characterized by a diffuse or sometimes vaguely nodular infiltrate of mature lymphocytes admixed with variable numbers of benign histiocytes. Scattered among these cells are the distinctive RS cells, but these are almost always few in number (Fig. 15–16). Variants that lack the large "owl-eye" nucleoli are somewhat more common, but are not diagnostic. However, they serve as useful clues since their presence warrants a careful search for typical RS cells. Without the identification of RS cells, the lymphocyte-predominance pattern could be readily mistaken for one of the lymphocytic forms of NHL. There usually is little fibrosis and no evidence of areas of necrosis.

Mixed-cellularity Hodgkin's disease is marked by a diffuse infiltrate of lymphocytes, histiocytes, eosinophils, and plasma cells. Classic RS cells are usually plentiful and lymphocytes are much less numerous than in the lymphocyte-predominance form. Small areas of necrosis and fibrosis may be present, but are not as prominent as in the lymphocyte-depletion form. Mixed cellularity disease occupies an intermediate position in clinical gravity between the lymphocyte-predominant and lymphocyte-depletion patterns.

The *lymphocyte-depletion pattern shows a paucity of lymphocytes and a relative abundance of RS cells or their atypical pleomorphic variants.* Since the ratio of the neoplastic elements to the reactive lymphocytes is tilted in favor of tumor cells, this pattern constitutes the most ominous form of Hodgkin's disease. It presents a somewhat broad range of morphologic changes, sometimes subdivided into *diffuse fibrosis* and *reticular variants*. In the diffuse-fibrosis variant, the hypocellular node is largely replaced by a proteinaceous fibrillar material that represents a disorderly, nonbirefringent connective tissue. Scattered within this background are lymphocytes, pleomorphic (atypical) RS cells, and a few typical RS cells (Fig. 15–17). The reticular variant is much more cellular and is composed of a diffuse infiltrate of highly anaplastic, large, pleomorphic cells, which may simulate RS cells but which lack all their classic features. Only a few typical RS cells can be identified.

The *nodular-sclerosis* pattern of this disease is described last because in many respects it appears to represent a distinct entity having a different biologic significance and epidemiology from the other three variants. Clinically, it is the only form more common in women and it has a striking propensity to involve mediastinal, supraclavicular, and lower cervical nodes. It is characterized morphologically by two features: (1) *birefringent, well-defined bands of collagen that traverse the lymph node, enclosing nodules of normal or abnormal lymphoid tissue (Fig. 15–18);* (2) *a tendency for the RS cells to assume the lacunar morphology.* The lacunar cells have a single hyperlobated nucleus with multiple small nucleoli and an abundant, pale-staining cytoplasm with well-defined borders. In formalin-fixed tissue, the pale cytoplasm of these cells often retracts, giving rise to the appearance of the nuclei lying in a clear space or a "lacuna" (Fig. 15–19). Classic RS cells are infrequent. In some cases the fibrosis is abundant, leaving only suggestive islets of lymphoid tissue. Within the lymphoid nodules the pattern may take the form of lymphocyte predominance, may show mixed cellularity, or at times may be composed almost entirely of lacunar cells. In other instances the fibrosis is quite scant, and diagnosis rests on the numerous lacunar cells.

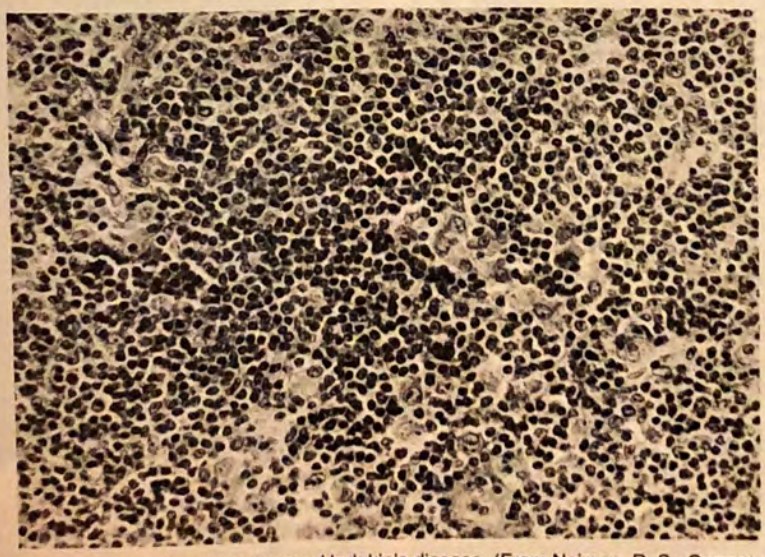

Figure 15–16. Lymphocyte-predominance Hodgkin's disease. (From Neiman, R. S.: Current problems in histopathologic diagnosis and classification of Hodgkin's disease. Pathol. Annu. *13*:289, 1978.)

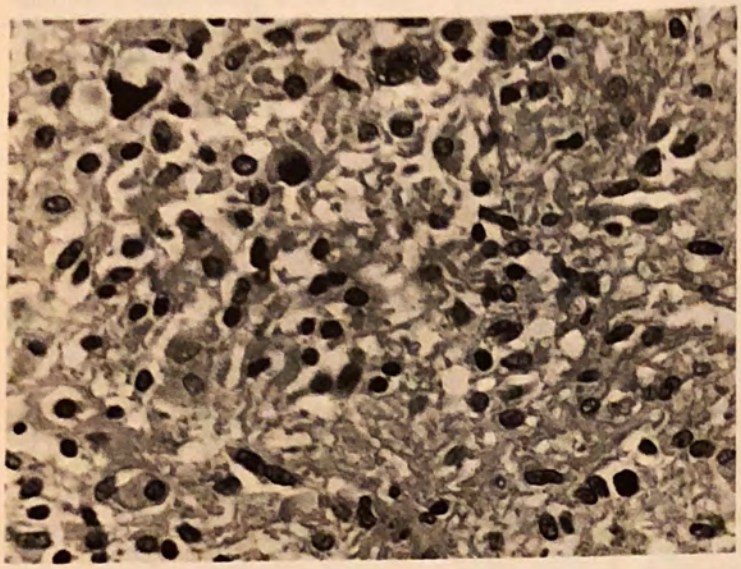

Figure 15–17. Lymph node in diffuse-fibrosis Hodgkin's disease. All cellular elements are greatly diminished, and granular, proteinaceous interstitial material is prominent. A few highly atypical polyploid cells that lack the cytologic features of Reed-Sternberg cells are present. (From Neiman, R. S.: Current problems in histopathologic diagnosis and classification of Hodgkin's disease. Pathol. Annu. *13*:289, 1978.)

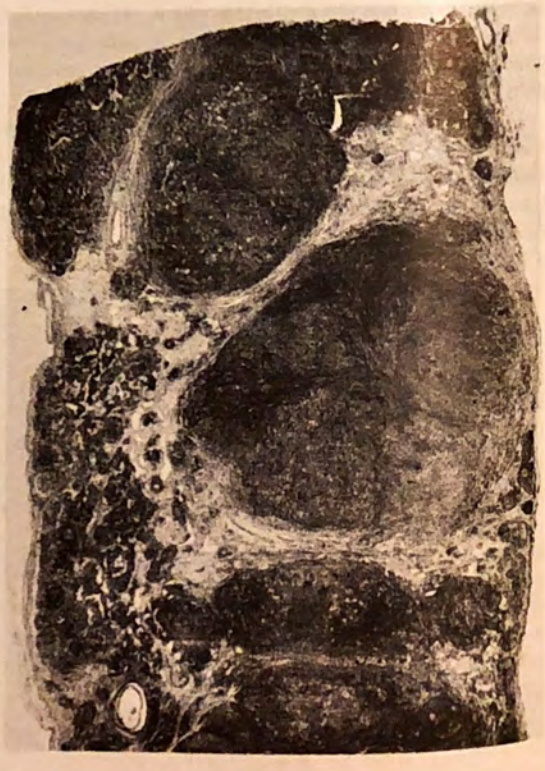

Figure 15–18. Hodgkin's disease—nodular sclerosis. This low-power view shows well-defined bands of collagen enclosing nodules of abnormal lymphoid tissue. On left, some compressed remnants of normal lymph node can be seen under capsule. (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

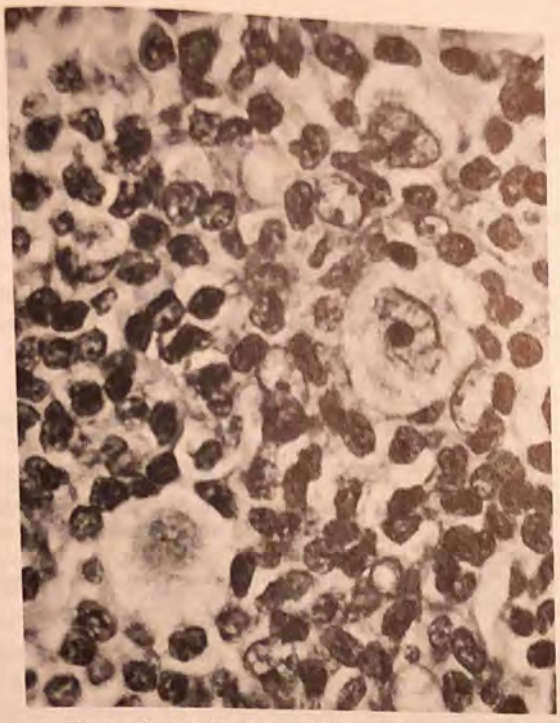

Figure 15–19. Hodgkin's disease—lacunar cells.

MORPHOLOGY. Hodgkin's disease almost always begins in a single node or chain of nodes, but occasionally it arises within the thymus or spleen. The nodular-sclerosis pattern most often arises in the mediastinum, suggesting a thymic origin, but it too may first appear in a node in the clavicular or neck region. Over the course of time the disease spreads to contiguous chains of nodes, a feature considered quite characteristic of Hodgkin's disease.

The gross appearance of involved nodes depends on the particular histologic pattern. With the lymphocyte predominance pattern, the nodes have a soft, uniform, fish-flesh appearance and are not distinguishable from nodes involved by the diffuse NHLs. With the mixed-cellularity pattern, foci of pale, opaque, yellow-white necrosis may be evident on the cut surface. With nodular sclerosis and the more fibrous lymphocyte-depletion patterns, the involved nodes may be tough and gray-white, as would be expected. In such instances, groups of nodes are often firmly matted together. As the disease extends, particularly in the more aggressive patterns, it may penetrate the nodal capsules to involve the perinodal tissue and to produce matted chains of nodes. Involvement of the spleen, liver, bone marrow, and other organs and tissues may appear in due course, taking the form of irregular, tumor-like nodules of tissue resembling that present in the nodes. At times, the spleen is greatly enlarged and the liver is moderately enlarged by these nodular masses. At other times, the involvement is more subtle and becomes evident only on microscopic examination.

The histologic details of the four variants of Hodgkin's disease have already been presented. **No morphologic variant can be diagnosed without identification of the distinctive, albeit not pathognomonic, RS cells.** This is particularly important to remember since some forms of Hodgkin's disease with an abundance of inflammatory cells (eosinophils, neutrophils, histiocytes, and plasma cells) come deceptively close to simulating a reactive inflammatory process, whereas others (such as the reticular form of lymphocyte-depletion Hodgkin's disease) can easily be mistaken for non-Hodgkin's, histiocytic lymphoma.

ETIOLOGY AND PATHOGENESIS. The origins of Hodgkin's disease are unknown. The question of etiology is especially complex since several fundamental issues have not been resolved. What is the derivation of the neoplastic RS cells? Do the various histologic variants of Hodgkin's disease represent a single disorder with a common etiology? Are some forms of Hodgkin's disease caused by an infectious agent? Central to many of these issues is a large body of epidemiologic data.[34] Hodgkin's disease has a bimodal age-incidence curve, with one early peak at 15 to 34 years and a second peak after the age of 45 years. In the younger age group there is an increased risk associated with smaller families, better housing, and higher education. These factors are known to be associated with late exposure to a variety of common childhood infections, including poliomyelitis. Therefore, it has been suggested that Hodgkin's disease, like paralytic poliomyelitis, may be a rare consequence of delayed infection with a common agent—possibly the EB virus. Some indirect evidence supports the viral hypothesis. In young adults with infectious mononucleosis, there is a two- to threefold higher incidence of Hodgkin's disease. Furthermore, relative to healthy controls, patients with Hodgkin's disease have a higher titer of antibody to EBV capsid antigen. However, none of this evidence can be considered conclusive. The role of EBV in the etiology of Hodgkin's disease is not supported by the reported absence of EBV nucleic acid sequences in cultured RS cells.[35] Thus, it could very well be that the epidemiologic association between EBV infection (or infectious mononucleosis) and Hodgkin's disease reflects a common population at risk for both the diseases. Several earlier reports suggested clustering of Hodgkin's disease in young adults, thus implicating a horizontal transmission of an infectious agent, but this hypothesis has not yet received wide support. In contrast with the younger age group, viral infection has not been implicated in the pathogenesis of Hodgkin's disease in older patients.

There are also clinical and histologic differences in the two age groups. In the younger patients, the male-to-female ratio is about equal, and most of the cases have the nodular-sclerosis pattern. In the older group, the male-to-female ratio is higher and there is greater frequency of the mixed-cellularity pattern. Whether these differences are truly indicative of two distinct etiologic forms of Hodgkin's disease remains to be proved. At present, the possibility cannot be excluded that the bimodal age incidence as well as other differences may reflect variation in host response to a single unknown causative agent.

A major hurdle to an understanding of the nature of Hodgkin's disease has been the mystery surrounding the genealogy of the "transformed" neoplastic cells. *It is now widely accepted that RS cells or their variant forms represent the tumorous element.*[36] However, there are disagreements over whether they are T cells, B

cells, or histiocytes. Since patients with Hodgkin's disease have a marked impairment of T cell–mediated immunity, manifested by cutaneous anergy and increased susceptibility to various fungal and opportunistic infections, it has been suggested that RS cells represent transformed T cells. However, no T-cell markers have been detected on the RS cells, and moreover the impairment of T-cell immunity seems to be caused by activation of suppressor cells rather than loss of function due to neoplastic transformation of T cells.[37] Several workers have observed immunoglobulins either within or on the surface of RS cells, implicating a possible B-cell origin. However, recent studies with monospecific light-chain antisera indicate that both kappa and lambda light chains are present within the cytoplasm of RS cells. Since an individual B cell can produce only one kind of light chain, the intracytoplasmic immunoglobulins in the RS cells must derive from passive internalization rather than endogenous synthesis. Attention, therefore, is now focused on macrophages as the candidates for neoplastic transformations. This possibility is supported by some recent histochemical and cell culture techniques. RS cells are positive for two macrophage-associated enzymes, acid phosphatase and nonspecific esterase, but the staining pattern is weaker than that observed in normal histiocytes. Yet another possibility exists. A monoclonal antibody reactive against permanent cell lines obtained from Hodgkin's tissue seems to cross-react with a very small population of cells in the parafollicular areas of normal lymph nodes, suggesting an origin from the so-called "interdigitating reticulum cells" found in this site.[38] These cells are believed to represent a special type of histiocyte.[39] Thus, the mist that surrounds the origins of Hodgkin's disease seems about to clear, but we still await the clear light.

STAGING. The staging of Hodgkin's disease is of great importance since its extent and distribution influence the clinical course, choice of therapy, and prognosis (Table 15–5).

A rigorous protocol has been established to determine the extent of spread of the lymphoma within the patient. It comprises (1) meticulous physical examination with particular attention to all lymph nodes, spleen, and liver; (2) a bipedal lymphangiogram (i.e., injection of a radiopaque dye into lymphatic channels of the feet) to visualize possible involvement of iliac and para-aortic nodes; (3) computed tomography (CT scan), especially to visualize involved upper abdominal and thoracic lymph nodes; (4) laparoscopy to assess possible splenic and hepatic involvement; and (5) in many clinics, a staging laparotomy, which includes biopsies of the liver and intra-abdominal lymph nodes, and removal of the spleen. With such an approach, it has been shown that in about one-third of the cases the staging laparotomy materially alters previous assessments about the extent of disease. However, splenectomy, although it allows accurate staging, predisposes to severe fatal septicemias, and therefore the utility of this procedure in the management of Hodgkin's disease is being reevaluated.

CLINICAL COURSE. At the outset there is painless enlargement of a single node or group of nodes. With spread, symptoms such as fever, night sweats, weight loss, pruritus, and anemia may appear. The extent of the dissemination and the presence or absence of systemic symptoms are expressed by the clinical staging system (Table 15–5). As might be expected, most patients with lymphocyte-predominance disease are first diagnosed in clinical Stage I-A or II-A, whereas those with the lymphocyte-depletion variant are more apt to be in Stage III-B or IV-B. The mixed-cellularity pattern falls intermediate between these extremes. With nodular sclerosis, the great majority of individuals are in clinical Stages I-A and II-A, but occasionally some fall into II-B or III-B and rarely into IV-B.

Table 15–5. CLINICAL STAGES OF HODGKIN'S AND NON-HODGKIN'S 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 (I_E).
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 (II_E).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S) and/or limited contiguous extralymphatic organ or site (III_E, III_{ES}).
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.

From Carbone, P. T., et al.: Symposium (Ann Arbor): Staging in Hodgkin's disease. Cancer Res. *31*:1707, 1971.

It is impossible at this time to express a prognosis for the various forms of Hodgkin's disease because of the rapidly changing and ever more effective modes of therapy. Before the introduction of current treatment protocols employing high voltage irradiation of lymph nodes and chemotherapy, there was a marked influence of the specific morphologic variant on the outlook. However, in the very recent past, much more aggressive modes of therapy have largely obliterated these differences. *Currently, the extent of disease appears to be the most important prognostic indicator.* Five-year survival of patients with Stages I and II-A is now close to 100%, and most can expect to be cured. With advanced (Stages III and IV) disease, approximately 50% can achieve long-term, relapse-free survival. It is evident that the outlook for this disease has dramatically improved. However, progress has created a new set of problems. Long-term survivors of combined chemotherapy and radiotherapy have an increased risk of developing acute leukemia or some form of NHL. The many therapeutic steps forward, in the light of this unhappy byproduct, may require a few steps backward.

LEUKEMIAS

The leukemias are best viewed as *malignant neoplasias of white blood cell precursors, characterized by*

(1) diffuse replacement of the bone marrow with proliferating leukemic cells; (2) abnormal numbers and forms of immature white cells in the circulating blood; and (3) widespread infiltrates in the liver, spleen, lymph nodes, and other sites throughout the body. The term leukemia ("white blood") was first used by Virchow to denote the tendency to reverse the usual ratio of red cells to white cells in the circulation. The white cell count in the peripheral blood may achieve staggering levels of over 500,000 cells/mm^3, but in some cases, the count is less than 10,000 cells/mm^3. Instances in which the white count is abnormally low have sometimes been referred to as *aleukemic* or *leukopenic leukemia*. However, it should be emphasized that the peripheral white count is merely the tip of the iceberg, having little to do with the ultimately fatal nature of leukemia. *It is the anemia, thrombocytopenia, and loss of normally functioning leukocytes incident to the suppression of normal marrow elements by leukemic cells as well as the infiltrates of the various tissues and organs in the body that give these disorders their ominous aspect.*

CLASSIFICATION. Inevitably, the classification of leukemias has become increasingly complex. They are first divided into acute and chronic forms. The acute forms are characterized by a rapidly fatal course when untreated (on the order of two to four months from the time of diagnosis) and by the appearance in the blood of poorly differentiated cells, called "blasts." The initial white count is subnormal in about one-third of the cases but is above 100,000 cells/mm^3 in 20% of cases. The chronic forms permit longer survival even when untreated (two to six years in many cases) and are associated with more mature circulating leukocytes. The peripheral white count may be subnormal but is more often markedly elevated into the hundreds of thousands (Fig. 15–20).

The leukemias are then subclassified according to the particular type of white cell involved into (1) lymphocytic and (2) myelocytic or myelogenous. A rudimentary classification therefore has four patterns of leukemia: acute lymphocytic (lymphoblastic) (ALL), chronic lymphocytic (CLL), acute myelocytic (myeloblastic) (AML), and chronic myelocytic (CML). Regrettably, difficulties arise with the acute leukemias, which are extremely heterogeneous both morphologically and with respect to cell surface markers. In the widely accepted French-American-British (FAB) classification,[40] the acute leukemias are subclassified on the basis of morphology, apparent differentiation, and histochemistry. In Table 15–6 a brief characterization of cell types is given along with each category, but more details are provided in the later section on morphology. It should be noted, however, that monocytic leukemia and acute erythroleukemia (Di Guglielmo's syndrome), which were previously classified separately, are now included in the AML category. This change reflects a greater understanding of the origins of these variants, discussed later (p. 676). In addition to the FAB morphologic subgrouping, ALLs are also classified immunologically on the basis of cell markers.[41] In 65% of ALL the

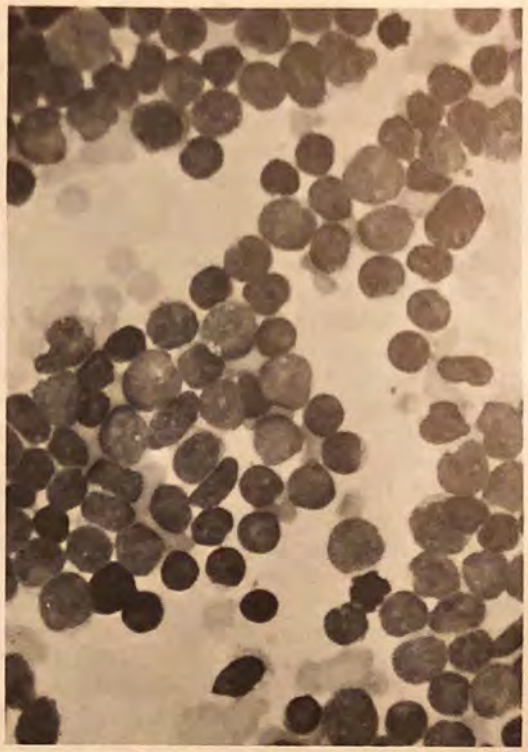

Figure 15–20. Peripheral blood smear from a patient with chronic lymphocytic leukemia who had a WBC count of 120,000.

Table 15–6. FRENCH-AMERICAN-BRITISH (FAB) CLASSIFICATION OF ACUTE LEUKEMIAS

Lymphocytic Acute (Lymphoblastic) (ALL)	
L1	Small cells predominate but may vary, with some cells up to twice diameter of small lymphocytes. Nuclei are generally round and regular with occasional clefts. Nucleoli often are not visible. Cytoplasm is scanty. Cell population is homogeneous.
L2	Cells are heterogeneous in size, and share in features of both L1 and L3. Nuclei often show clefts. Nucleoli are often present.
L3	There is a homogeneous population of large cells (3 to 4 times the diameter of small lymphocytes). Nuclei are round-to-oval with prominent nucleoli. Cytoplasm is abundant and deeply basophilic.
Acute Myelocytic (Myeloblastic) (AML)	
M1	Myeloblastic leukemia without maturation—cells are dominantly blasts without Auer rods or granules.
M2	Myeloblastic leukemia with maturation—many blasts but some maturation to promyelocytes or beyond.
M3	Hypergranular promyelocytic leukemia—mostly promyelocytes with cytoplasm packed with peroxidase-positive granules. Many Auer rods.
M4	Myelomonocytic leukemia—both myeloid and monocytic differentiation. Myeloid element resembles M2.
M5	Monocytic leukemia—both "monoblasts" and monocytes, the former having large round nuclei with lacy chromatin and prominent nucleoli. Diagnosis must be confirmed by fluoride-inhibited esterase reaction.
M6	Erythroleukemia—erythropoietic elements make up more than 50% of cells in marrow and have bizarre multilobate nuclei. May also be present in circulating blood, along with an admixture of myeloblasts and promyelocytes.

lymphoblasts *lack surface immunoglobulin, do not form E rosettes*, or react with monoclonal anti–T-cell antibodies (non-T, non-B group). The leukemic cells in the non-T, non-B group express the common ALL (CALLA) antigen, and therefore this group is referred to as common ALL (cALL). In approximately 20% of cases of cALL, the lymphoblasts have *cytoplasmic Ig*, suggesting that they represent immature (pre–B) cells. ALL, with the mature B-cell phenotype characterized by the presence of *surface Ig*, is quite uncommon (5%). T-cell ALL makes up 15 to 20% of all cases and is similar to the lymphoblastic lymphoma, already discussed (p. 661). The remaining cases (10 to 15%) do not bear any distinctive cell surface markers and hence cannot be classified at present. This immunologic subclassification has not only shed light on the origins of ALL, but is prognostically meaningful and hence widely accepted.

INCIDENCE. Leukemia is a common form of neoplasia. In 1983, it was expected to be the sixth leading cause of cancer death in the United States. It is particularly devastating in children under the age of 15, among whom it is the dominant cause of cancer death. ALL is the most frequent type in children under 15, and its peak incidence occurs at about age 4. AML dominates in the 15- to 39-year age range, and both AML and CML are encountered at ages 40 to 59. Thus, AML predominates in adults under 60. CLL predominates in adults over 60. Males are affected somewhat more often than females in all types of leukemia, the sex ratio reaching approximately 2:1 in CLL of the elderly. Overall 60% of leukemias are acute, of which 60% are classified as AML according to the FAB terminology and the remainder as ALL. Approximately 40% of cases are chronic, about two-thirds being CLL and one-third CML. Varying incidences have been reported from countries around the world, but there is some question whether these data reflect real differences or are the spurious results of differing levels of medical care and case-finding. There is, however, one example of a striking "racial" difference—the great rarity of CLL among the Japanese and other oriental populations.[42] Although the survivors of atomic bomb blasts in Japan later showed a marked increase in the other forms of leukemia, there was no observable increase in the incidence of CLL.

ETIOLOGY AND PATHOGENESIS. The origins of leukemia are shrouded in the mysteries of all forms of cancer. No single etiologic or pathogenetic factor is likely to be applicable to all forms. The complex issues relating to leukemogenesis include (1) the cell of origin in various leukemias, (2) the nature of proliferative defect in the transformed cells, (3) changes in the genome responsible for the expression of leukemic phenotype, and (4) etiologic factors responsible for initiating the genomic alterations.

All leukemias have their origin in neoplastic monoclonal proliferations of hematopoietic stem cells. The evidence that they are clonal disorders comes from the study of chromosomal markers such as the Philadelphia (Ph^1) chromosome (p. 232 and below) and analysis of the glucose-6-phosphate dehydrogenase (G6PD) isoenzymes (p. 221). The specific stem cells involved in different forms of leukemias have not been established with certainty, but progress has been made. In patients with the common form of acute lymphoblastic leukemia (cALL), the leukemic cells do not bear surface markers of T cells or B cells, but they contain the enzyme terminal deoxynucleotidyl transferase (TdT), which is presumed to be a marker of primitive lymphoid cells. Study of the immunoglobulin genes in the cALL leukemic cells suggests that in many cases they are genetically committed to B-cell differentiation.[43] Thus, it may be that in most cases cALL originates from very primitive B cells that have not yet acquired cytoplasmic or surface Ig. In the other major form of ALL, surface markers of intrathymic T cells are present, suggesting origin from cells committed to the T-cell differentiation pathway. These cells are also positive for TdT. *Thus, TdT, which is present in most cases of ALL, can be of help in differentiating ALL from other acute leukemias.*

The acute myelogenous leukemias are also of diverse origins. In some cases the leukemic transformation seems to occur at the level of pluripotent myeloid stem cells, whereas in others the committed granulocyte-macrophage stem cells are involved (Fig. 14–1). The transformation of myeloid stem cells is responsible for the presence of common cytogenetic abnormalities in the myeloid as well as the erythroid precursors, even though myeloblasts commonly dominate the blood and bone marrow. Less often, the dominant cells may be erythroblasts or monoblasts, giving rise to acute erythroleukemia (FAB, M6), or acute monocytic leukemia (FAB, M5). In *chronic myeloid leukemia*, the involvement of platelets, erythroid precursors, and granulocytic cells points to an origin from the pluripotent myeloid stem cells.[44] Some evidence, however, indicates that B cells and possibly T cells may also be a part of the neoplastic clone, suggesting that CML may result from transformation of the most primitive totipotential stem cells (p. 611).[45] With regard to CLL, most cases are of B-cell origin; in the individual patient all leukemic cells express identical immunoglobulins, confirming the monoclonality of the disease. This form of leukemia is closely associated with and sometimes indistinguishable from well-differentiated lymphocytic lymphoma (p. 660). CLL, arising from T cells, is extremely rare.

Relative to the nature of the proliferative defect in leukemia, all *acute* leukemias are characterized by a paucity of mature white cells and an excess of immature precursors. The accumulation of primitive cells could result from (1) defective maturation with a larger population of immature cells capable of self-replication, (2) a prolonged life span due to delayed senescence, or (3) a shortened generation time with an increased rate of cell production. In acute leukemia *the pool of actively proliferating cells is expanded but the cells have a prolonged rather than a shortened generation time.* When normal stem cells divide, one of the daughter cells becomes committed to a differentiation pathway, whereas the other remains an uncommitted stem cell

with ability to self-replicate; thus, the normal ratio of stem cells to committed cells is maintained close to 1:1. When leukemic stem cells divide, this ratio is altered owing to a block in maturation, yielding an increased proportion of stem cells. Thus, *in acute leukemia there is an accumulation of leukemic cells resulting from a failure of maturation into functional end cells rather than hyperproliferation of neoplastic stem cells.*[46] This concept has important therapeutic implications, since in principle it may be possible with therapy to induce differentiation of the leukemic stem cells. The situation is quite different with CML, in which *there is a 10- to 20-fold increase in myeloid stem cells, but the accumulation is not due to a block in maturation.* The leukemic stem cells continue to differentiate, as evidenced by the presence of vast numbers of mature cells in the peripheral blood and by the ability of the leukemic cells to form colonies of differentiated progeny in vitro. Moreover, cell kinetic studies reveal that the leukemic myeloid stem cells do not divide more rapidly than normal stem cells.[47] Instead, the evidence points to some failure of leukemic stem cells to respond to physiologic growth regulators such as colony-stimulating factor (p. 612) and/or prostaglandins. The pathogenesis of *CLL* seems to involve an accumulation of mature-looking but immunologically incompetent B lymphocytes (Fig. 15–21). The turnover of leukemic B cells in CLL is extremely slow, since most of the cells are fairly long-lived and recirculate for several months.

Although the precise derangements that affect growth and differentiation of leukemic cells have not yet been identified, much interest is centered on defining the genetic alterations responsible for expression of the leukemic phenotype. Most exciting are the recent observations implicating chromosomal rearrangements as critical events in leukemogenesis. It has been known for several years that CML is characterized by a unique chromosomal abnormality, the Ph^1 (Philadelphia) chromosome. *In approximately 95% of patients with CML, the Ph^1 chromosome, usually representing a reciprocal translocation from the long arm of chromosome 22 to another chromosome (usually the long arm of chromosome 9), can be identified in all the dividing progeny of pluripotent myeloid stem cells (p. 611).* More recently, high-resolution techniques have allowed the detection of several nonrandom chromosomal abnormalities in acute leukemias as well. Some of these were discussed earlier (p. 231), but several points are worth reiterating. *Two specific translocations are consistently associated with particular subtypes of AML:* a translocation involving the long arm of chromosome 8 and 21 t(8q−, 21q+), which is seen with AML-M2 in the FAB classification, and that between 15 and 17 t(15q+, 17q−), which characterizes acute promyelocytic leukemia (AML-M3 in the FAB classification).[48] A third group of patients with AML is associated with Ph^1 chromosome similar to that seen in CML. In addition, monosomy or partial deletion of chromosomes 5 or 7 and a trisomy of chromosome 8 are also seen in several cases. These and other chromosomal abnormalities can be readily demonstrated in 50% of cases, but reports suggest that, with improved methods, subtle deletions and rearrangements can be found in virtually every patient with AML.[49] *Specific karyotypic changes have also been seen in ALL, although less frequently.* These include t(4q−; 11q+) in cALL; t(8q−; 14q+), similar to the translocation seen in Burkitt's lymphoma, in B-cell ALL; and, surprisingly, t(9q+; 22q−), i.e., the Ph^1 chromosome, in approximately 25% of adults with ALL.[50]

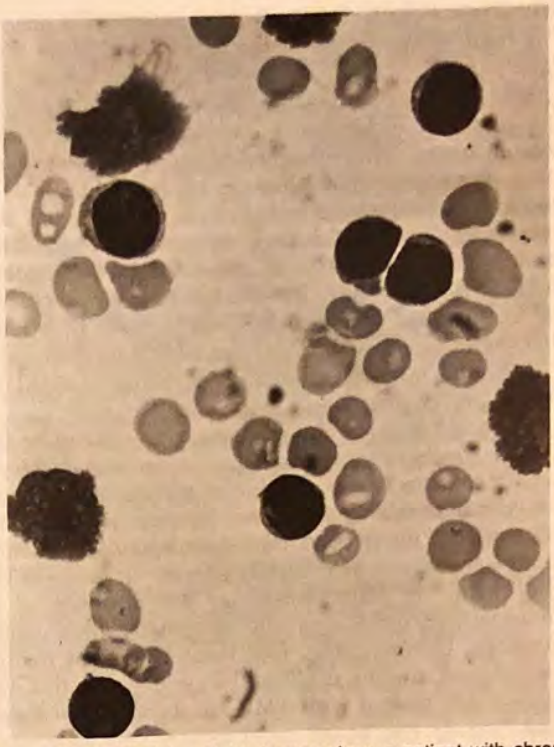

Figure 15–21. Peripheral blood smear from a patient with chronic lymphatic leukemia. Most leukemic cells have the appearance of unstimulated small or medium-size lymphocytes. Owing to excessive fragility, the neoplastic lymphocytes are often damaged, giving rise to several "smudge" cells. (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

Although the idea that specific chromosomal abnormalities may be associated with certain cancers is not new, the significance of the cytogenetic changes has been far from clear until recently. The current flurry of excitement in this area stems from convergence of the research on oncogenes and chromosomal abnormalities.[51] Recall that Burkitt's lymphoma is associated with t(8q−; 14q+), and a cellular oncogene has been mapped close to the breakpoint on chromosome 8. With translocation, the oncogene is shifted close to the gene coding for immunoglobulin heavy chain on chromosome 14 (p. 249). More recently, it has been discovered that the formation of Ph^1 chromosome is associated with the translocation of a cellular oncogene present on chromosome 9 to the proximity of immunoglobulin light chain gene on chromosome 22.[52] *It seems remarkable that in both instances the oncogenes are translocated*

close to genes that are actively transcribed in the process of normal immunoglobulin synthesis. It could be speculated, therefore, that oncogenes may be "turned on" at their new chromosomal locations owing to the influence of promoter sequences in the adjacent immunoglobulin genes. The enhanced transcription and translation of oncogenes may alter growth regulation so as to produce an autonomous cell. Shifting of genes may also contribute to the well-known association between the chromosomal instability syndromes (ataxia telangiectasia, Bloom's syndrome, and Fanconi's anemia, p. 241) and leukemias and other neoplasms (p. 264). In trisomy 21 (Down's syndrome), the 10- to 20-fold increased risk of leukemia may result from disturbances caused by changes in the gene dosage.

In addition to their significance in unraveling the possible mechanisms of leukemogenesis, certain karyotypic changes are also valuable in the clinical management of leukemia. It is known, for example, that Ph¹-negative patients with CML respond poorly to chemotherapy and have a significantly shorter survival. On the other hand, in acute leukemias the presence of an abnormal karyotype is usually associated with a poorer prognosis. However, this notion may have to be revised if additional studies confirm the observation that virtually every patient with AML has an abnormal karyotype.[49]

We come finally to the possible etiologic factors that initiate leukemogenesis. The increased incidence of leukemia following exposure to *ionizing radiation* (p. 242) and *chemicals* such as benzene (p. 237) is well-known. More recently, the combined use of irradiation and alkylating agents for the treatment of Hodgkin's disease has been found to increase severalfold the incidence of AML in survivors.[53] A *viral causation* of human leukemias has long been suspected, but it is only recently that solid evidence has begun to accumulate.[54] The candidate retrovirus has been designated human T-cell leukemia virus (HTLV) owing to its association with certain forms of T-cell leukemias and lymphomas.[55] Much of the evidence linking HTLV to leukemogenesis was presented on page 243. A few summarizing observations follow. HTLV has been isolated from cultured neoplastic cells of a variety of T-cell malignancies, including cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome), T-cell lymphomas arising in lymph nodes, and most consistently from the adult T-cell leukemia endemic in some parts of Japan and the Caribbean countries (p. 685). Hybridization and related studies reveal that HTLV is unique and is only distantly related to the other known mammalian retroviruses. HTLV proviral sequences are present in the DNA of neoplastic T cells but not in the DNA of non-neoplastic B cells of the same patient, indicating that HTLV is acquired by infection and not transmitted in the germ line. Over 90% of patients with adult T-cell leukemia in the endemic areas have HTLV antibodies in their serum. In Japan, 48% of the patients' relatives and some normal individuals also possess anti-HTLV antibodies. Although these serologic data are strongly suggestive of horizontal spread, the precise mechanism of HTLV transmission is still unknown, as are many other aspects of the HTLV puzzle. Nonetheless, the evidence obtained so far has electrified this area of research.

MORPHOLOGY. The morphologic features of leukemia fall into two categories: (1) the specific cytologic features of the particular type of leukemia, and (2) the gross alterations common to all forms of leukemia. Turning first to the specific cytologic details, identification of the specific form of leukemia requires an accurate assessment of the cell types found in the peripheral blood and bone marrow. Identification of individual cell types is best performed on Romanowsky-stained (Wright's, Giemsa) preparations (Fig. 15–22). Cytochemical stains are of particular value in the subcategories of acute myelogenous leukemia. Granulocytes possess two types of granules—azurophil and specific. During differentiation of neutrophils the azurophil granules are produced early, at the promyelocyte level of differentiation. These granules are primary lysosomes and contain various enzymes such as acid phosphatase and β-glucuronidase, common to all lysosomal granules (including those in lymphocytes) as well as myeloperoxidase specific to the granulocytic series. The specific granules that develop later (at the myelocyte stage) contain alkaline phosphatase, lactoferrin, and lysozyme. Esterases are found in granulocytic and monocytic cells. Thus, it is possible to differentiate the various myeloid cells by the battery of cytochemical techniques presented in Table 15–7. In addition, myeloblasts or promyelocytes contain rod-

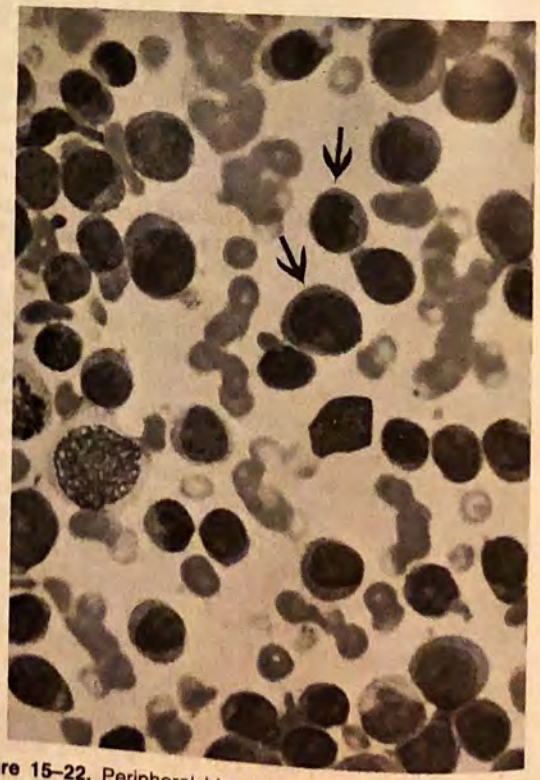

Figure 15–22. Peripheral blood smear from a patient with acute myelomonocytic leukemia (FAB, M4). Many of the leukocytes are monocytes and earlier blast forms, and several classic monocytic reniform indented nuclei are visible in upper center *(arrows)*. (WBC 46,000—42% monocytes and monoblasts.)

Table 15–7. CYTOCHEMICAL STAINING IN THE ACUTE MYELOID LEUKEMIAS

Cytochemical Stain	Acute Leukemia		
	Myelogenous (FAB, M1–3)	*Myelogenous-Monocytic (M4)*	*Monocytic (M5)*
Peroxidase	+	+	–
α-Naphthyl acetate esterase (ANE)	–	+	+
Naphthyl AS-D chloroacetate esterase (NCE)	+	+	–
Naphthyl AS-D acetate esterase (NAE) + fluoride inhibition	–	+	+
Sudan Black B	+	+	±

shaped, reddish structures called **Auer bodies or rods.** These are abnormal lysosomal structures found principally in myelocytic, but occasionally in monocytic, cells, which aid in their identification. Immature blasts lack these distinctive features and are therefore extremely difficult to identify unless there are also some more differentiated cell forms. Another cytochemical feature to be noted is that the **leukemic cells in CML usually have greatly reduced or no alkaline phosphatase.** This feature is helpful in distinguishing CML from nonleukemic elevations of the white cell count (p. 655). In acute erythroleukemia (FAB, M6), primitive erythroid cells, particularly proerythroblasts, dominate the bone marrow. Often these immature erythroid forms are extremely atypical and have distorted nuclear shapes, megaloblastic features, multiple nuclei, and all forms of bizarre conformations (Fig. 15–23). In keeping with the stem-cell origin of AML, variable numbers of myeloblasts (with Auer rods) and promyelocytes are also to be found in the bone marrow.

Identification of the cell types in lymphocytic leukemias may be aided by the use of rosetting and immunocytochemical techniques, as detailed in the consideration of NHL (p. 666). Also, as stated earlier, the enzyme terminal deoxynucleotidyl transferase is present in the leukemic cells of most cases of ALL. This enzyme is also found in some cases of CML in "blast crisis" (p. 685).

The shared gross alterations found in the various types of leukemia can be conveniently divided into **primary changes that are directly related to the abnormal numbers of white cells, and secondary changes that stem from the destructive effects of the cellular infiltrates and overgrowths as they seed various organs and tissues.** Macroscopic changes are much more prominent in the chronic leukemias. All, however, are characterized by abnormal flooding or infiltration of the bone marrow, lymph nodes, spleen, liver, and kidney. Any other tissue of the body may be involved, but with less frequency and usually less severely than the organs just cited. Leukemic cells more or less resemble their normal counterparts in the marrow or lymph nodes, save perhaps for a greater tendency to immaturity and the possible development of some anaplastic atypicality in individual scattered cells.

Primary Changes. The **bone marrow** in the full-blown case has a muddy red-brown to gray-white color as normal hematopoiesis is overrun by masses of white cells. The marrow replacement begins focally but, as the disease progresses, becomes generalized to affect all the normally active red marrow. It sometimes extends into areas of previously fatty marrow (Figs. 15–24 and 15–25). As the disease advances, the native marrow cells are progressively replaced. These neoplastic cells encroach upon and erode the cancellous and cortical bone. All the bones of the skeletal system are affected, but the process usually is first evident and most florid in the vertebral bodies, sternum, ribs, and pelvis. Sometimes the bony or soft tissue infiltrates in AML become tumorous masses called **chloromas** or granulocytic sarcomas. These may arise within the bone or subperios-

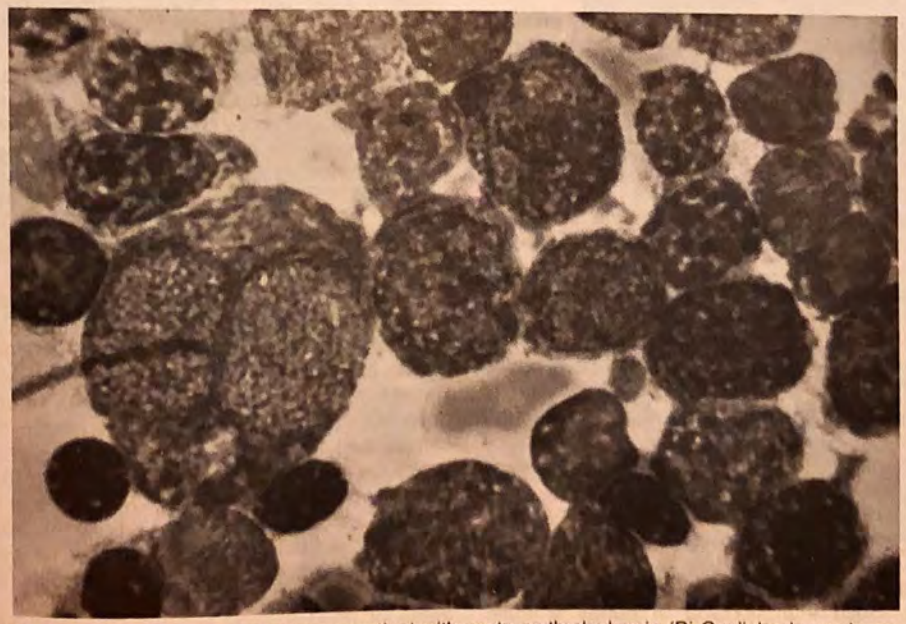

Figure 15–23. Marrow smear from a patient with acute erythroleukemia (Di Guglielmo's syndrome, FAB, M6) crowded with proerythroblasts.

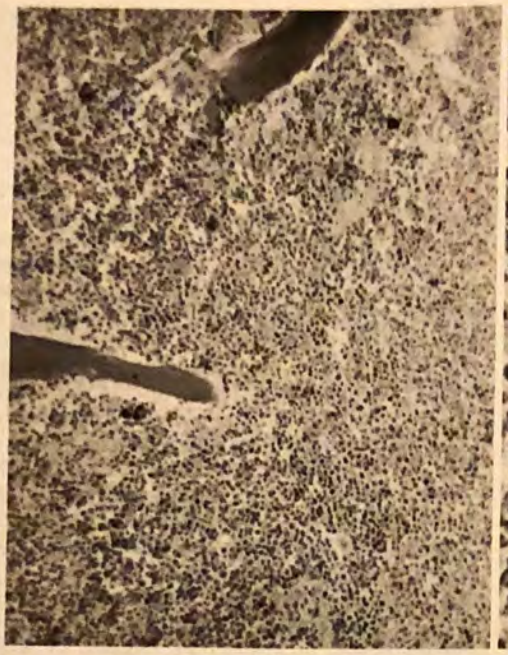

Fig. 15–24

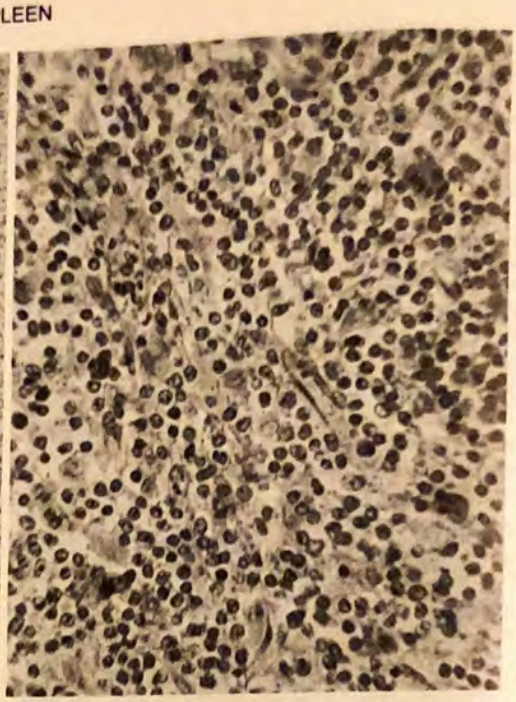

Fig. 15–25

Figure 15–24. Chronic lymphocytic leukemia. Low-power view of marrow flooded by uniform leukemic cells.

Figure 15–25. Chronic lymphocytic leukemia. Medium-power view of same marrow as in Figure 15–24, to illustrate monotony of lymphocytes.

teally in any portion of the skeleton, but more often they affect the skull. Owing to the presence of myeloperoxidase the tumors are a distinctive evanescent green when first examined, but rapidly fade as the pigment oxidizes. The color can be restored by the use of such reducing agents as hydrogen peroxide and hyposulfite. As variants of the myelogenous infiltrates, these tumors are interesting but have no specific clinical significance.

The lymph nodes throughout the body may be enlarged in all forms of leukemia. There is, however, a marked difference in the degree of enlargement in various forms. Since lymphocytic leukemias arise within lymphoid tissue, they are associated with the most striking degrees of lymphadenopathy (4 to 5 cm in diameter), particularly in CLL (Fig. 15–26). The nodal enlargement of myelogenous leukemia is usually less prominent except in the monocytic variant (M5). In all the leukemias, involved lymph nodes characteristically remain discrete, rubbery, and homogeneous, features that distinguish these enlargements from the matted, sometimes soft fluctuance of inflammatory involvement. The cut section is soft and gray-white and tends to bulge above the level of the capsule. When the enlargement is extreme, areas of hemorrhage or infarction may appear. Not all nodes in the body are uniformly affected, and the distribution of lymphadenopathy is quite variable from one case to another.

On histologic examination, the nodes are partially or completely flooded by the neoplastic cell type to an extent that is roughly proportional to the enlargement of the node and the stage of advancement of the leukemia. Eventually, the sinuses are flooded and all structures, including the germinal follicles, are obliterated. The leukemic cells may invade the capsule of the node and infiltrate into the surrounding tissues. Such total flooding of nodes is quite characteristic of lymphocytic leukemia but less so of myelogenous leukemia.

The **spleen** is enlarged to a variable degree in almost all instances. CML produces the most striking splenomegaly; splenic weights of 5000 gm or more are not unusual. Such spleens may virtually fill the whole abdominal cavity and extend into the pelvis (Fig. 15–27). Infarcts due to leukemic infiltration and obstruction of vessels are frequent in CML (Fig. 15–28). In lymphocytic leukemias, the spleen rarely exceeds 2500 gm in weight. In monocytic leukemia, it is uncommon for the spleen to exceed 1000 gm. In all instances, the capsule becomes somewhat thickened. Frequently, fibrous adhesions to surrounding structures develop.

On section, the splenic substance is usually more firm than normal and has a muddy gray appearance. In extreme splenomegaly, the normal splenic follicles become indistinct and the tissue assumes a homogeneous appearance. Histologically, the leukemic infiltrations of the spleen follow the patterns described in the lymph nodes. They vary from focal to diffuse involvement to progressive obliteration of the underlying architecture in the areas affected.

The **liver** is commonly enlarged in all forms of leukemia but not to the same degree as the spleen. Hepatomegaly tends to be somewhat more striking in CLL than in the other forms, but rarely does the liver weight exceed 2500 gm. Hepatic involvement is usually diffuse in nature and therefore does not cause any striking alterations in the cut surface. Occasionally, however, patchy aggregates about portal areas may cause a diffuse, fine mottling that is visible on gross inspection (Fig. 15–29). Massive foci of infiltration of gray-white tissue sometimes appear that closely resemble metastatic patterns of other forms of cancer. The hepatic infiltrates tend to follow certain microscopic patterns that are somewhat distinctive for each form of leukemia. The infiltrates of myelogenous leukemia are not well defined and are present throughout the lobule (Fig. 15–30). Some aggregates of cells may be found in the portal triads but, in

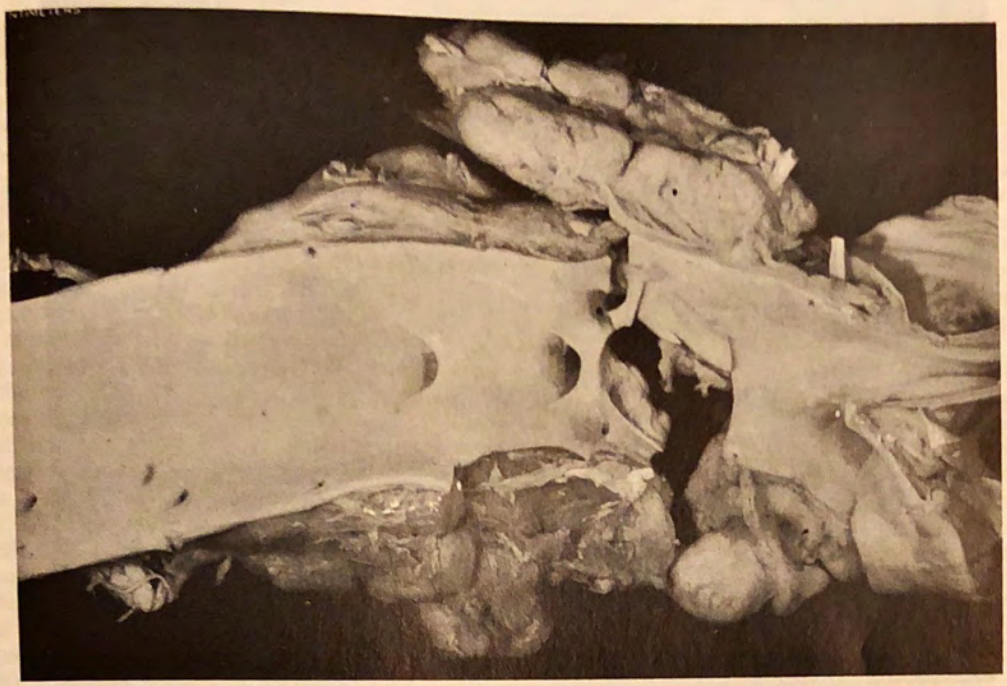

Figure 15–26. Periaortic lymph node enlargement in chronic lymphocytic leukemia.

Figure 15–27. Viscera in a patient with chronic myelogenous leukemia. Note massive hepatosplenomegaly, pale leukemic infiltrates in liver, and hemorrhages in subepicardial fat as manifestations of depression of platelet formation. This case of CML was unusual in that it occurred in an 8-year-old child.

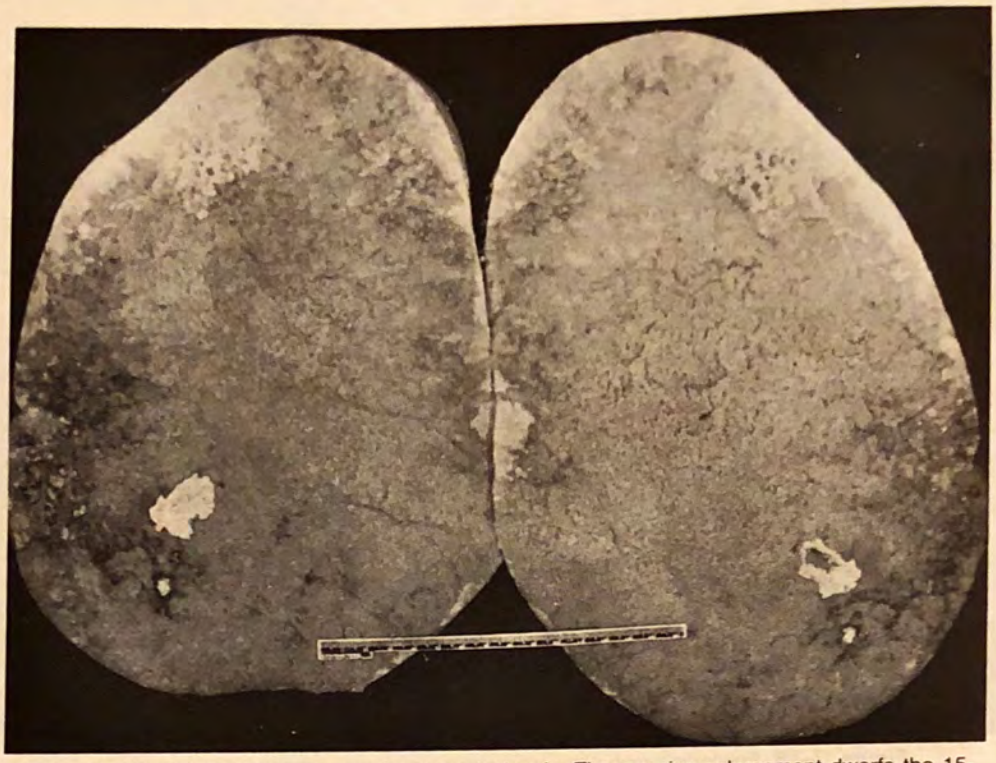

Figure 15–28. Spleen in chronic myelogenous leukemia. The massive enlargement dwarfs the 15-cm rule. Numerous small infarcts are dispersed through the cut surface.

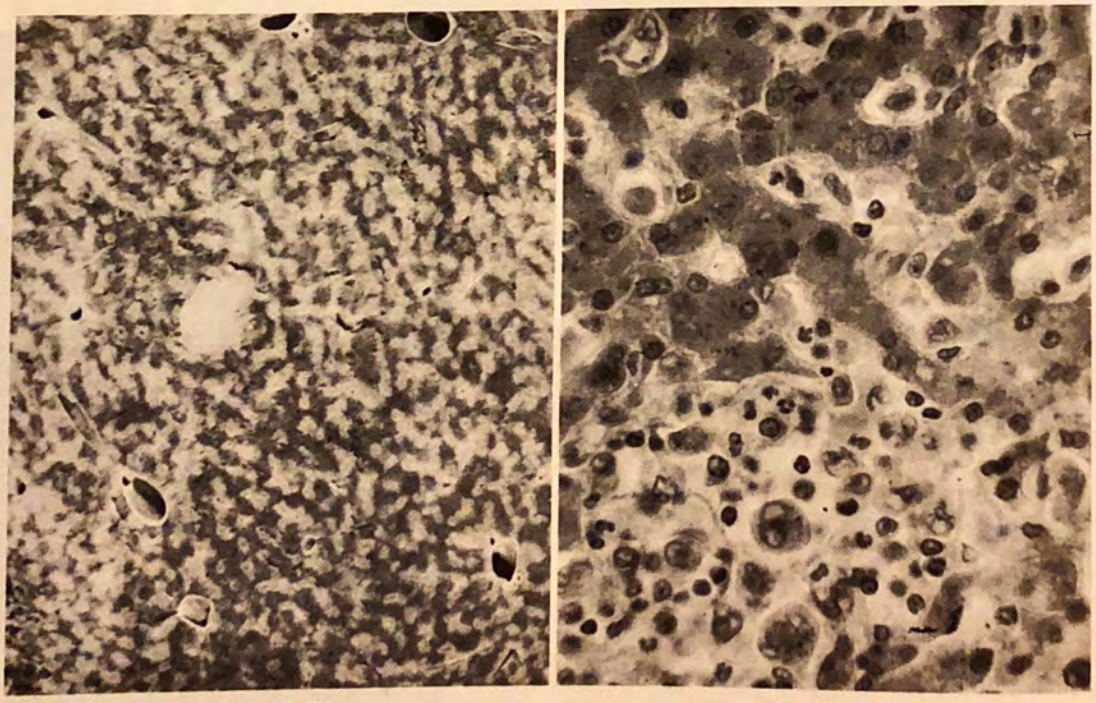

Fig. 15–29 Fig. 15–30

Figure 15–29. Chronic lymphocytic leukemia in liver. Close-up of cut surface of liver to illustrate unusually prominent leukemic infiltration producing a fine regular mottling.

Figure 15–30. Acute myelogenous leukemia in liver. Microscopic detail to illustrate scattered "polys" and immature myeloid cells through sinusoids.

addition, cells are dispersed along the liver cords subjacent to the vascular sinusoidal walls. The infiltrates are characteristically localized to the portal areas in lymphocytic leukemia (Fig. 15–31). The central regions of the liver lobule are relatively spared in this dyscrasia. The hepatic infiltrates of the monocytic variant are least prominent and are very often absent. When present, they tend to follow the pattern described in myelogenous leukemia.

In addition to these organ involvements, leukemic infiltrates are frequently found in the kidneys, adrenals, thyroid, and myocardium and in many other body tissues. Of particular importance is the infiltration of the central nervous system by the leukemic cells; this occurs most commonly in ALL. Protected by the blood-brain barrier, cells infiltrating the meninges may escape the effects of systemically administered drugs and eventually initiate a relapse. In all affected tissues, the infiltrates begin as small perivascular aggregates that progressively diffuse through the stroma of the affected organ. As the cells accumulate in sufficient number, they may compress and destroy adjacent parenchymal structures. When the infiltrates become large enough, they may produce macroscopically visible, pale-gray areas of infiltration. However, these infiltrates are usually different from ordinary metastases. They tend to be less sharply circumscribed and are more diffusely infiltrated, so that they do not wipe out the underlying architecture as completely as do the metastases of other types of cancer (Fig. 15–32).

Special mention should be made of the leukemic infiltrates of the skin and mucous membranes of the gingiva. On occasion, abnormal cells accumulate in the dermal and subcutaneous connective tissue **(leukemia cutis).** These cause variable forms of elevated-to-flat, pale-to-red skin macules or papules and are common in leukemias of T cells. Infiltrates in the gingiva are particularly characteristic of the monocytic variant of AML. Swelling and hypertrophy of the gingival margins occur, and frequently the soft tissues involved freely ooze blood, or secondary bacterial infection develops, forming superficial necrotic ulcerations.

Secondary Changes. By secondary changes are meant those lesions that stem from the destructive, erosive effects of the aggressive leukemic infiltrates and from the functional incompetence of leukemic cells. **Anemia and thrombocytopenia are characteristic secondary consequences of leukemic involvement of the bone marrow.** The marrow failure results not only from replacement of the hemopoietic cells but also from the inhibition of normal stem-cell function by leukemic cells or their products. The anemia may become quite profound and lead to systemic and local tissue hypoxia. A hemorrhagic diathesis results from the thrombocytopenia, and abnormal bleeding is one of the most characteristic manifestations of acute leukemias. Purpura and ecchymoses may occur in the skin, with or without leukemic infiltrates. Hemorrhages into the gingivae as well as hemorrhagic foci in the urinary bladder, the mucosa of the renal pelves and calyces, the serosal membranes lining the body cavities, and the serosal coverings of the viscera (particularly of the heart and lungs) are standard features in advanced leukemia. Not uncommonly, intraparenchymal hematomas develop, most frequently in the brain. Many times, this widespread hemorrhagic tendency is the most obvious anatomic postmortem finding in these cases. In acute promyelocytic leukemia (FAB, M3), the release of procoagulant substances from the granules often leads to DIC and the attendant hemorrhagic diathesis (p. 649).

Although the total white cell count is usually elevated in leukemia, the circulating abnormal white cells have little

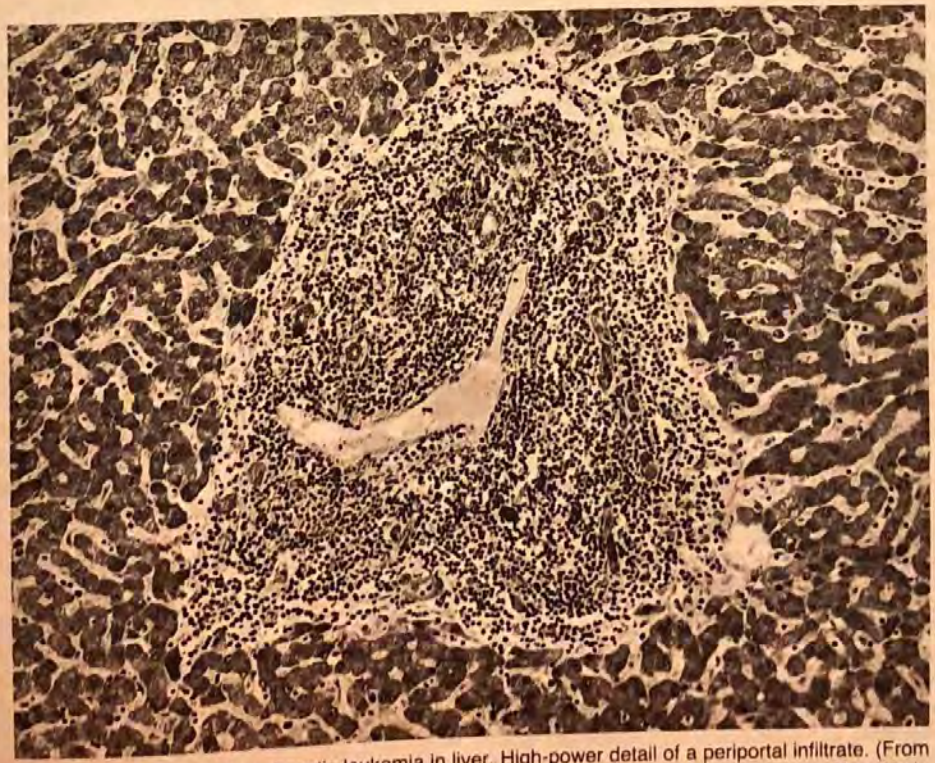

Figure 15–31. Chronic lymphocytic leukemia in liver. High-power detail of a periportal infiltrate. (From Jackson, H. J., Jr., and Parker, F., Jr. (eds.): Hodgkin's Disease and Allied Disorders. New York, Oxford University Press, 1947.)

Figure 15–32. Chronic lymphocytic leukemia infiltrates in heart muscle. (From Jackson, H. J., Jr., and Parker, F., Jr. (eds.): Hodgkin's Disease and Allied Disorders. New York, Oxford University Press, 1947.)

defensive capacity, resulting in an enhanced susceptibility to bacterial infection. The morphologic changes of these infections may be found in any organ or site in the body but are particularly common in the oral cavity, skin, lungs, kidneys, urinary bladder, and colon. The bacterial infections of leukemia resemble, to a great extent, those found in granulocytopenia, since both have in common a deficiency of functioning leukocytes.

The leukemic proliferation in the bone marrow causes expansion of the marrow spaces, encroachment upon the cancellous and cortical bone, and resultant osteoporosis with increased radiolucency. The infiltrates within other tissues and organs remain confined for the most part to the interstitial connective tissue. The parenchymal elements are thus spread apart but usually are not severely damaged. For this reason, hepatic, renal, or cardiac failure is extremely uncommon in these cases. Only rarely does enlargement of the portahepatic nodes encroach sufficiently upon the extrahepatic biliary ducts to cause obstructive jaundice.

Therapy may significantly modify the anatomic changes. The use of cytotoxic drugs before death may virtually destroy all viable cells. It is not uncommon to find, post mortem, a striking paucity of preserved leukemic cells and indeed of all forms of marrow cells in patients who received intensive radiation therapy and chemotherapy in the terminal stages of their disease. Thus, the pathologist is sometimes confronted with the paradox of a patient having a clinically well-documented leukemia without anatomic changes to permit confirmation of the diagnosis.

CLINICAL COURSE. Acute leukemias have an almost totally different clinical presentation from chronic leukemias. *Chronic leukemias appear insidiously, but the acute disorders have a sudden, often stormy onset.* You recall that ALL is a disease of childhood, whereas AML usually appears in adult life. Symptoms, when they appear, are related to depression of normal marrow function and include (1) fatigue due mainly to anemia; (2) fever, usually reflecting an infection; and (3) bleeding (petechiae, ecchymoses, epistaxis, and gingival bleeding) secondary to thrombocytopenia. Generalized lymphadenopathy, splenomegaly, and hepatomegaly, the results of organ infiltration by leukemic cells, are characteristic of ALL but usually are not prominent with AML. The marrow involvement in both disorders leads to subperiosteal bone infiltration, marrow expansion, and bone resorption, often resulting in bone pain and tenderness on palpation. CNS manifestations may appear with leukemic infiltration of the meninges, producing headache, nausea, vomiting, papilledema, cranial nerve palsies, and sometimes seizures and coma. More acute CNS complications may arise, such as intracerebral or subarachnoid hemorrhages. Occasionally, DIC punctuates the course of the promyelocytic form of AML (p. 649), especially when cell lysis caused by therapy result in the release of thromboplastic substances from the granules.

Both forms of acute leukemia are characterized by distinctive laboratory findings. Anemia is almost always present. The white count in about half the patients is less than 10,000 cells/mm^3 of blood, whereas in about 20% it is elevated above 100,000 cells/mm^3. Much more important is the finding of immature white cells, including "blast" forms, in the circulating blood and the bone marrow, where they make up 60 to 100% of all the cells. The platelet count is almost always depressed and in a great majority of cases is less than 100,000/mm^3. Although not linearly related, the danger of bleeding manifestations progressively increases as the platelet count falls. Without treatment, the course of the acute leukemias is usually progressively downhill, ending in death in two to four months.

The onset of the chronic leukemias is so insidious that they are sometimes discovered only during a routine physical examination. Symptoms, when they appear, are related to the hypermetabolism of the leukemic cells and include low-grade fever, night sweats, weight loss, weakness, and easy fatigability. The profound anemia causes considerable exertional dyspnea. In some cases the patient first becomes aware of a heavy dragging sensation in the abdomen produced by the splenomegaly. In other instances, lymphadenopathy calls attention to the underlying condition. Frequently, generalized lymphadenopathy, splenomegaly, and hepatomegaly are already present at the time of diagnosis. *Generalized lymphadenopathy is most typical of CLL, whereas marked splenomegaly is most characteristic of CML.* Bleeding manifestations may dominate the clinical presentation, particularly as marrow failure develops. *CLL, characterized by accumulation of immunoincompetent*

B cells, is often associated with hypogammaglobulinemia and increased susceptibility to infections. Paradoxically, some patients develop anti–red cell antibodies and hemolytic anemia.

As with acute leukemias, anemia is usually present in chronic leukemias, but the critical laboratory finding is the presence of abnormal immature leukocytes in the peripheral blood, accompanied by an elevated white cell count. In chronic leukemias the white cell count ranges from 50,000 to 500,000 cells/mm^3 of blood. In CML the circulating white cells are predominantly neutrophils and metamyelocytes, but more immature forms are also present. An increased number of basophils is quite typical of CML, helping to distinguish it from *leukemoid reactions*, which may produce a peripheral blood picture deceptively similar to that of leukemia (p. 655). *Other features that help to differentiate leukemoid reactions from CML are the absence of the Ph^1 chromosome and the increased level of leukocyte alkaline phosphatase.* In CLL the peripheral white cells are largely mature lymphocytes, but some immature forms are also found. In both forms of chronic leukemia, platelets are depressed with advanced disease, but in the early course of CML the platelet count may be above normal.

The prognoses for each of the various forms of acute and chronic leukemia are best considered individually, since they differ so much. Remarkable advances in therapy bring fresh gains yearly, rendering data out of date by the time they are set to paper. In particular, the outlook for children with ALL is spectacularly improved. Intensive chemotherapy and the use of corticosteroids now induce a remission in almost all children. With prophylactic irradiation and intrathecal chemotherapy for CNS involvement, over 50% are living after five years, many apparently free of disease. In these fortunate young ones, a much more prolonged remission or even a cure is not beyond hope. The adult with ALL fares less well and, although remissions can be achieved, the average survival is for two to three years.

The outlook for patients with AML is more grim. Remissions can be achieved with chemotherapy in over half the patients, but these are generally transient and only 15 to 20% are alive after three years. In view of such a grim prognosis, bone marrow transplantation has been attempted in some centers. Early results are promising, with 50% long-term remissions, but this form of treatment is not yet widely available.

The course of the chronic leukemias is one of slow progression, and even without treatment permits survivals of two to three years. In CML, therapy may induce remissions, but there is little improvement in overall survival. Death in most cases is heralded by an acute phase known as a blast crisis during which a picture resembling acute leukemia develops. In about 25% of cases, blasts contain the enzyme TdT and thus represent lymphoblasts; the remaining cases have a myeloblastic crisis. Recent studies indicate that the blast cells found in the lymphoblastic crises belong to the B-cell lineage;[55A] this observation supports the thesis that CML represents a disease of totipotential stem cells (p. 611). CLL is the most indolent of the leukemias, and with therapy the median survival is four to six years. Unlike CML, blast crisis is rare and most patients die of infections, progressive leukemic infiltration, or causes unrelated to leukemia.

Unusual Types of Leukemias and Lymphomas

Hairy Cell Leukemia. This is an uncommon but distinctive form of chronic leukemia involving an unusual cell, which shows several features of B lymphocytes. The disorder derives its picturesque name from the appearance of the leukemic cells, which have fine "hairlike" cytoplasmic projections best recognized under the phase-contrast microscope or scanning electron microscope, but also visible in routine blood smears. The genealogy of the transformed cells has proved extremely baffling. In most cases the pathognomonic hairy cells synthesize surface immunoglobulins of restricted light-chain type, a feature characteristic of monoclonal B-cell proliferations. On the other hand, some relationships to the monocyte-macrophage lineage and T cells have also been described.[56] Confusingly, the markers may fluctuate from those of B cells to those of T cells during the course of the disease or in culture.[57] Without delving into further complexities, *hairy cell leukemia may be said to result from the neoplastic transformation of a poorly characterized cell with features most strongly suggestive of B cells; however, origin from a totipotent stem cell (p. 611) with some differentiation along the T-cell or monocyte pathway cannot be ruled out at present.* Mercifully, there is one cytochemical feature that is quite characteristic of hairy cell leukemia, i.e., the presence of tartrate-resistant acid phosphatase (TRAP). The exceptions to this observation are so few that positive TRAP staining in leukemic cells endowed with "hair" is considered virtually diagnostic of hairy cell leukemia in the appropriate clinical setting.

Hairy cell leukemia occurs mainly in older males and *its manifestations result largely from infiltration of bone marrow liver and spleen. Splenomegaly*, often massive, is the most common and sometimes the only abnormal physical finding. *Hepatomegaly* is less common and not as marked, and lymphadenopathy is distinctly rare. *Pancytopenia*, resulting from marrow failure and splenic sequestration, is seen in over half the cases. *Leukocytosis* is not a common feature, being present in only 25% of patients. Hairy cells can be identified in the peripheral blood smear in most cases. The course of this disease is chronic with no satisfactory treatment; the median survival is four years.

Adult T-cell Leukemia-Lymphoma. This uncommon T-cell neoplasm has gained much prominence owing to its association with human T-cell leukemia virus (p. 243). Most of the initial cases were described from the southern part of Japan, where it is endemic,[58] but similar cases have now been found in the West Indies and sporadically in several other countries, in-

cluding the U.S. *Characteristic clinical features of adult T-cell leukemia include generalized lymphadenopathy, hepatosplenomegaly, frequent skin involvement, severe hypercalcemia, and a poor prognosis.*[59] The tumor cells are usually OKT4-positive, a feature shared with the closely related cutaneous T-cell lymphomas. These disorders, along with T-cell chronic lymphocytic leukemia and the T-cell lymphomas involving lymph nodes (p. 665), represent the spectrum of differentiated *T-cell neoplasms*. In contrast, T-cell ALL and lymphoblastic lymphoma (convoluted T-cell lymphoma) represent tumors of *immature T cells*.

HISTIOCYTIC MEDULLARY RETICULOSIS (MALIGNANT HISTIOCYTOSIS). This disease is widely believed to represent a malignant tumor of mature and immature histiocytes with diffuse invasion of the viscera and bone marrow. For mysterious reasons, however, it usually is not included among histiocytic lymphomas. Earlier it was classified into a poorly defined category called histiocytoses, which also included the "histiocytoses X," discussed later (p. 694). It derives its name from the infiltration of the medullary zone of lymph nodes by the histiocytes, which by no means is a diagnostic feature.

Masses of histiocytes and their precursors may be seen in the skin, bone marrow, lymph nodes, spleen, and liver. The levels of cellular maturation differ, but in most instances the cells are immature and variable in size and shape, with large round nuclei and an abundant amphophilic or slightly basophilic cytoplasm. The nuclear chromatin is lacy and the nucleoli are prominent. In other cases, the cells may closely resemble mature histiocytes, with oval-to-reniform nuclei, small nucleoli, and abundant amphophilic cytoplasm. It is impossible to differentiate these cell types from those encountered in histiocytic lymphoma. Sometimes these cells appear to fill the sinuses of lymph nodes. In the various organ involvements the infiltrates may be difficult to differentiate from histiocytic lymphoma with systemic dissemination. However, **characteristic of histiocytic medullary reticulosis is prominent erythrophagocytosis,** not seen in histiocytic lymphoma. The neoplastic histiocytes may also contain other phagocytized material, including leukocytes and platelets, all of which contribute to the pancytopenia associated with this disease.

The major clinical features of histiocytic medullary reticulosis include (1) lymphadenopathy, (2) hepatosplenomegaly, (3) anemia or pancytopenia, (4) fever, and sometimes (5) skin infiltrates. Leukemic spread to the blood has been reported, but is rare. It is a rapidly progressive and fatal disease. Survival for more than 15 months is unusual, the average being six months.

Agnogenic Myeloid Metaplasia (Myeloid Metaplasia with Myelofibrosis)

Agnogenic myeloid metaplasia, along with polycythemia vera, chronic granulocytic leukemia, and idiopathic thrombocythemia, belongs to the group of *myeloproliferative syndromes*. As discussed earlier, these disorders arise from the clonal, neoplastic proliferation of the pluripotent myeloid stem cells (p. 641). Although the dominant differentiated cell line differs in the various myeloproliferative diseases, all the myeloid cell types (i.e., granulocytes/macrophages, erythroid cells, and platelets) can be demonstrated to be monoclonal. Some cases of polycythemia vera and CML may ultimately evolve into a stage characterized by marrow fibrosis and extramedullary hematopoiesis in the spleen *(myeloid metaplasia)*. In many patients, however, splenic myeloid metaplasia and the accompanying marrow fibrosis arise insidiously without an identifiable preceding syndrome; hence, the term agnogenic (idiopathic) myeloid metaplasia.

The cause of marrow fibrosis in agnogenic myeloid metaplasia is not clear. In the initial formulation of the concept of myeloproliferative diseases, it was assumed that marrow fibroblasts were derived from the hematopoietic stem cells, and therefore proliferation of fibroblasts was considered but one manifestation of the stem-cell disorder. Several subsequent studies do not support this view. First, it is established that fibroblasts within the marrow do not arise from the hematopoietic stem cells, and second, studies with G6PD isoenzymes clearly indicate that the marrow fibroblasts in myelofibrosis do not belong to the neoplastic hematopoietic clone.[60] Thus, *fibrosis of the bone marrow appears to be a reactive phenomenon*. However, no cause for marrow destruction or scarring can be demonstrated, a feature that distinguishes myeloid metaplasia with myelofibrosis from myelophthisic anemia (p. 640). It has been suggested that the proliferation of marrow fibroblasts is triggered by the release of a platelet-derived growth factor (PDGF), which is a normal component of platelet alpha granules.[60] PDGF is known to be mitogenic for fibroblasts and a variety of other mesenchymal cells, but it is not clear why or how it is released in the marrow of patients with myelofibrosis. In one study, circulating immune complexes were detected in most patients, and it was suggested that interaction of the IgG in the complexes with the Fc IgG receptors on the platelets may lead to the release of PDGF.[61] It is also conceivable that the inappropriate release of PDGF is due to an intrinsic defect of the platelets, which are a part of the abnormal clone of myeloid cells. Attractive as these theories may be, they are entirely hypothetical.

MORPHOLOGY. The principal anatomic change is striking extramedullary hematopoiesis. The principal site of this is the spleen, which is usually moderately to markedly enlarged, sometimes up to 4000 gm (Fig. 15–33). The capsule is unaffected but occasionally shows underlying small infarcts. On section the spleen is firm, red to gray, and not dissimilar from that seen in CML. However, the lymphoid follicles are usually preserved, implying that there has been no neoplastic obliteration of the native architecture. Occasionally, small red masses of hematopoietic tissue can be discerned grossly. Histologically, the extramedullary hematopoiesis seems to be largely confined to the red pulp. Intrasinusoidal proliferation of normoblasts and immature granulocytic cells is present, sometimes in small aggregates. Megakaryocytes are also prominent in the sinuses. These myeloid elements may diffuse into the splenic cords. Usually

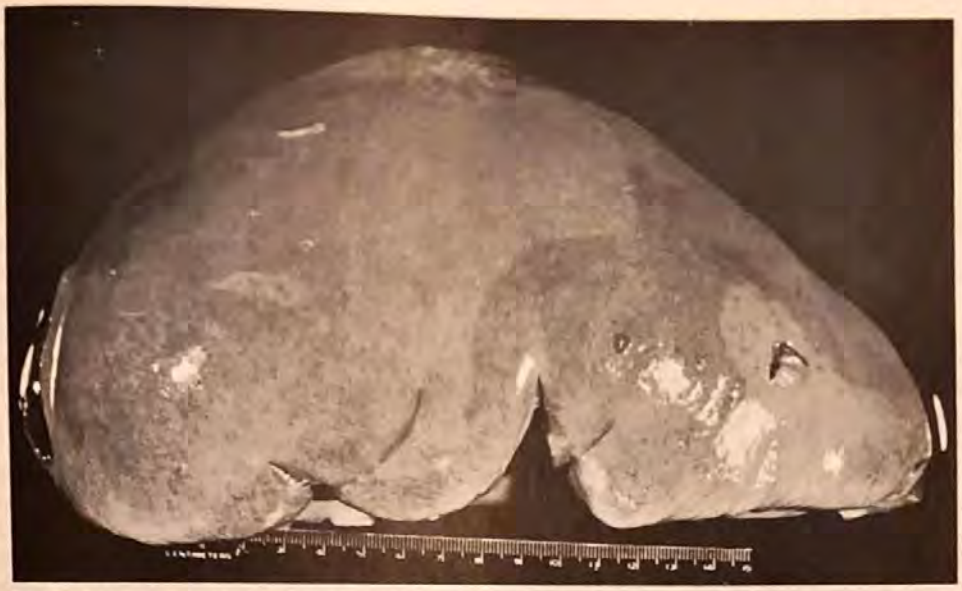

Figure 15–33. Myeloid metaplasia with myelofibrosis. Spleen is markedly enlarged and dwarfs the 15-cm rule. Irregular shading of capsule is an artifact.

the hematopoiesis is orderly, with relatively normal proportions of maturing red cells, white cells, and platelets, but certain cases show a disproportional activity in any one of these three major lines. Most readily visualized are the nests of normoblasts and megakaryocytes.

The liver is often moderately enlarged, with foci of extramedullary hematopoiesis. The lymph nodes are only rarely the site of blood formation and usually are not enlarged.

The classic bone marrow finding is diffuse fibrosis with obliteration of the normal myeloid elements (Fig. 15–34). On occasion, however, marrow biopsy discloses hypercellularity with proliferation of all the myeloid elements and sometimes prominent abnormal-looking megakaryocytes. Even in the early cellular phase, a tell-tale finding of the more extensive fibrosis to come is a delicate deposition of reticulin, only evident on special stains. Moreover, sequential studies have shown that the fibrosis appears first in centrally located bones, whereas the large bones of the extremities contain hyperplastic marrow.

Clinical Course. Myeloid metaplasia is uncommon in individuals under 50 years of age. Except when preceded by polycythemia vera or CML, it usually comes to clinical attention because of either progressive anemia or marked splenic enlargement, producing a dragging sensation in the left upper quadrant. Some patients are asymptomatic. Most striking are the laboratory findings. There is usually a moderate-to-severe normochromic normocytic anemia. Red cells show all manner of variation in size and shape, but *particularly characteristic are teardrop-shaped erythrocytes (poikilocytes)*. In addition, numerous normoblasts and basophilic stippled red cells appear in the peripheral blood. The white cell count may be normal, leukopenic, or markedly elevated (80,000 to 100,000/mm^3), with a shift to the left. Typically, myeloblasts, myelocytes, and metamyelocytes constitute a small fraction of the white cell population on peripheral smear. The platelet count is usually elevated at the time of diagnosis, but thrombocytopenia supervenes as the disease progresses. Morphologic abnormalities of the platelets (giant forms) are frequent, and sometimes fragments of megakaryocytes may be detected in the peripheral blood. Biopsy of the marrow to detect the early deposition of reticulin or the more advanced fibrosis is essential for diagnosis. The differential diagnosis of CML frequently arises in these

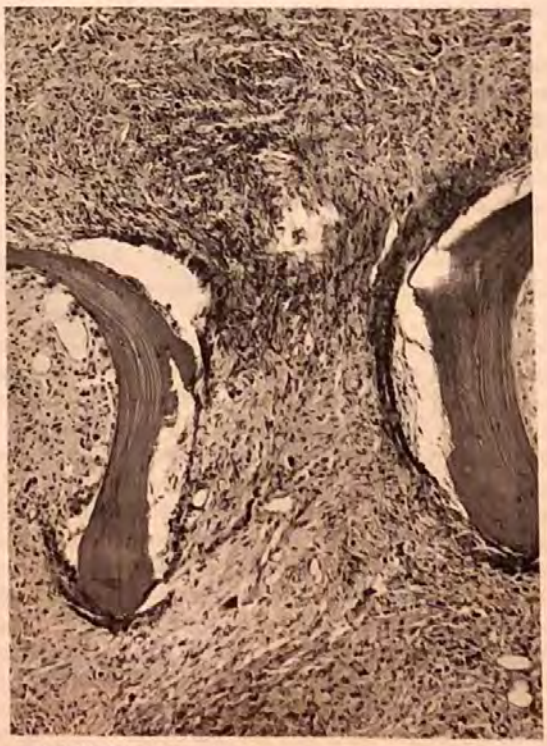

Figure 15–34. Myelofibrosis. Marrow cavity is virtually replaced by fibrous tissue, totally obliterating normal hematopoietic elements.

patients. In myeloid metaplasia, leukocyte alkaline phosphatase levels are often elevated, or at least normal, whereas in CML these levels are low or absent. Moreover, most patients with CML disclose the Ph^1 chromosome, which is absent in agnogenic myeloid metaplasia. An equally difficult differential diagnosis is myelophthisic anemia secondary to an identifiable cause of marrow injury. In such cases the diagnosis of agnogenic myeloid metaplasia can be established only by careful history-taking to elicit the cause of marrow injury, or by morphologic detection of the underlying cause (e.g., cancer) in the marrow biopsy.

The course of this disease is difficult to predict. Despite weight loss attributed to the increased metabolism of the hyperproliferating cells, most patients can survive for years with transfusions. Sometimes the course is punctuated by episodes of acute left upper quadrant pain arising from splenic infarctions. Secondary gout may appear as a manifestation of the rapid turnover of blood cells. Threats to life are intercurrent infections, thrombotic or hemorrhagic crises related to the thrombocytosis, and in some cases (10%) conversion to acute leukemia.

PLASMA CELL DYSCRASIAS AND RELATED DISORDERS

This rather vague title refers to a diverse group of conditions having in common: *(1) uncontrolled proliferation of plasma cells or closely related cell types, and (2) abnormally high levels in the blood and/or urine of a monoclonal homogeneous immunoglobulin or one of its constituent polypeptide chains.* In essence these conditions are neoplasms of B cells. They differ, however, from the B-cell lymphomas discussed earlier by virtue of the fact that in plasma cell dyscrasias the neoplastic B cells are differentiated enough to secrete immunoglobulins or their components. In the individual patient the immunoglobulin belongs to a single class, subclass, and type and is indistinguishable in structure from a normal immunoglobulin. Thus, there are IgG, IgM, IgA, IgD, and rarely IgE dyscrasias. It would appear, then, that the plasma cell proliferation in the individual patient is monoclonal in origin. The immunoglobulin as identified in the blood is referred to as a complete M component in reference to *M*yeloma. Since complete M components have molecular weights of 160,000 or higher, they are largely restricted to circulating plasma and extracellular fluid. However, they may appear in the urine when there is some form of glomerular damage with heavy proteinuria. In some of these dyscrasias, excess light (L) or heavy (H) chains are also synthesized along with complete immunoglobulins, but the polypeptide chains are always identical to those found in the complete immunoglobulin, and thus the L chains are either kappa or lambda (never both) or the H chains of a single class (e.g., either alpha, gamma, or mu, etc.), depending on the particular class of Ig. Occasionally only L chains or H chains are produced but no complete Ig. The *free L chains, known as Bence Jones proteins,* are sufficiently small in size to be rapidly excreted in the urine, and so may be totally cleared from the blood or persist only at very low levels. However, with renal failure or massive synthesis, they may appear in the blood in significant concentrations. Thus, *the common thread throughout this diverse group of entities is the appearance of excessive levels of complete or incomplete immunoglobulins in the plasma and/or urine. Hence, a variety of alternative designations have been applied to these dyscrasias, such as gammopathies, monoclonal gammopathies, dysproteinemias, and paraproteinemias.* It is of interest that, of the innumerable M components studied to date, no two have been structurally identical.

A variety of clinicoanatomic patterns, listed below, can be differentiated among these gammopathies.

1. *Multiple myeloma (plasma cell myeloma)* is the most important and most common syndrome. It is characterized by multiple neoplastic tumorous masses of more or less mature plasma cells, haphazardly scattered throughout the skeletal system and sometimes in soft tissues (Fig. 15–35). *Solitary myeloma or solitary plasmacytoma* is an infrequent variant consisting of a solitary neoplastic mass of plasma cells found in bone or some soft tissue site. Some, but not all, patients with solitary lesions eventually develop multiple myeloma, suggesting that the solitary lesions represent an early stage of the disseminated disease.

2. *Waldenström's macroglobulinemia* has been separated from the other gammopathies by virtue of the fact that it is characterized by the synthesis, usually of IgM and rarely IgG or IgA, and a diffuse infiltrate throughout the bone marrow, as well as extramedullary lymphoid tissues of plasma cells, plasmacytoid lymphocytes, and lymphocytes. The lytic bone lesions typical of myeloma are not present in this condition.

3. *Heavy-chain disease* is a rare gammopathy distinguished by neoplastic medullary and extramedullary infiltrates of plasma cells, and precursors that synthesize only heavy chains.

4. *Primary or immunocyte-associated amyloidosis* is also an expression of plasma cell dyscrasia. It may be recalled that this form of amyloidosis results from a monoclonal proliferation of plasma cells, with excessive production of free light chains that are deposited as amyloid (p. 197).

5. *Lymphoproliferative disease with dysproteinemia* refers to those uncommon cases of CLL and NHL in which the neoplastic B cells are differentiated enough to produce monoclonal immunoglobulins.

6. *Monoclonal gammopathy of undetermined significance (MGUS)* refers to instances in which M components are identified in the blood in patients having no symptoms or signs of any of the better characterized monoclonal gammopathies. At one time this condition was termed benign monoclonal gammopathy, but this designation is misleading because some of these patients develop symptomatic multiple myeloma or other plasma cell dyscrasias after a variable interval.[62]

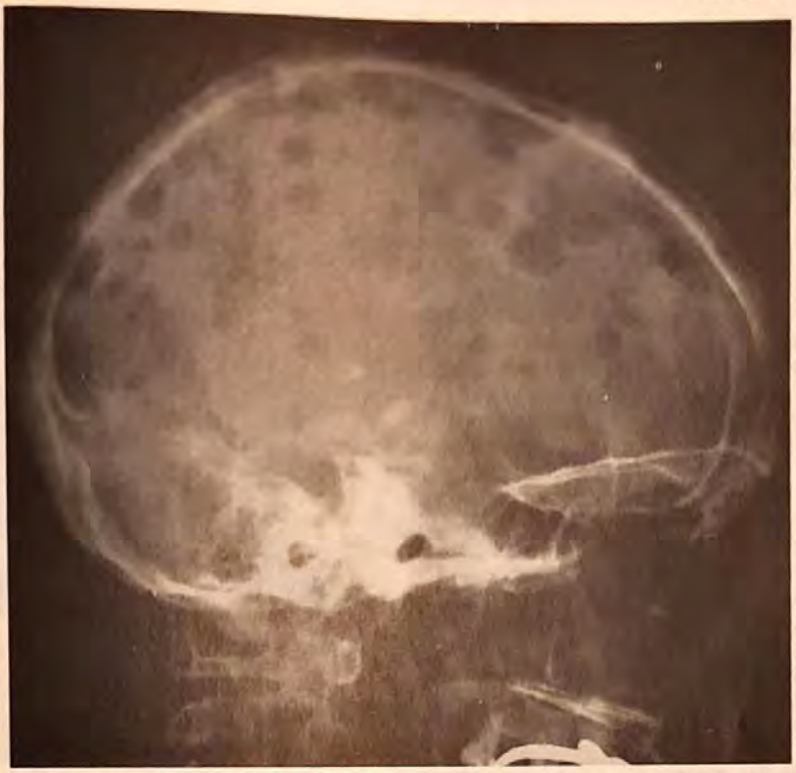

Figure 15–35. Radiograph of skull extensively involved by focal, sharply punched-out lesions of plasma cell myeloma.

Against this background we can turn to some of the specific clinicoanatomic entities not discussed elsewhere in this text.

Multiple Myeloma (Plasma Cell Myeloma)

Multiple myeloma is basically a multifocal plasma cell cancer of the osseous system that in the course of its dissemination may involve many extraosseous sites. As pointed out, the neoplastic plasma cells synthesize complete and/or incomplete immunoglobulins. It is the most common of the gammopathies and represents approximately 60%. Most patients are symptomatic when diagnosed. Clinical manifestations stem from the effects of (1) infiltration of organs, particularly the bones, by tumorous masses of plasma cells; and (2) the abnormal immunoglobulins secreted by the tumor cells.

In 99% of patients with multiple myeloma, electrophoretic analysis will disclose increased levels of one of the immunoglobulin classes in the blood and/or light chains in the urine (Bence Jones protein). In approximately 60% of patients, the M component is IgG, in 15 to 20% IgA, and rarely IgM, IgD, or IgE. In the remaining 15 to 20% of cases, Bence Jones proteinuria alone without serum M components is present. However, Bence Jones proteins are present in the urine along with plasma M components in 60 to 80% of all myeloma patients.[63] *Identification of these proteins in the blood and urine constitutes one of the most important diagnostic features of this disease.* Electrophoresis of the serum or urine (paper, agar, cellulose, acetate) is the most readily available and reliable procedure. When the serum electrophoretic pattern is analyzed, the homogeneous M component yields a high spike, referred to as an M protein or M-component "spike." Immunoelectrophoresis, using appropriate monospecific antisera directed against the various heavy and light chains, is essential to establish the monoclonal nature of the M component. Bence Jones proteins in the urine are similarly detected by immunoelectrophoretic techniques.

Pathogenesis. Some workers believe that long-persisting antigenic stimulation of B cells may in time provide the opportunity for spontaneous mutation or the activation of a latent oncogenic virus, leading eventually to neoplastic transformation.[64, 65] This proposition is supported by the increased frequency of plasma cell neoplasms in patients with long-standing chronic infections such as osteomyelitis, tuberculosis, cholecystitis, and pneumonitis.[66] Experimentally, plasma cell tumors have been induced in mice by the intraperitoneal injection of a variety of irritant substances, including Freund's adjuvant, mineral oil, and plastic. In recent years, these tumors have been widely utilized to produce monoclonal antibodies by the hybridoma technology (p. 159). Despite the association between persistent antigenic stimulation of B cells and plasma cell neoplasms, the cause-and-effect relationship is still uncertain.

MORPHOLOGY. Despite the abundance of abnormal biochemical findings, the ultimate diagnosis of plasma cell dyscrasias rests on the morphologic identification of the abnormal aggregates of plasma cells (Fig. 15–36). In most cases these cells make up more than 15%, and sometimes up to 90%, of all marrow cells. In many instances the neoplastic cells appear as mature plasma cells, but all ranges of immaturity may be encountered, including undifferentiated cells resembling lymphoid precursors as well as lymphocyte–plasma cell intermediates. It may be difficult to identify the neoplastic nature of the well-differentiated plasma cell lesions from the cytology of the individual cells; more important is their abnormal aggregation or evidence of their destructive potential in the form of infiltration, invasion, and erosion. Sometimes bi- or even trinucleate cells are seen in these lesions, essentially reproducing cancerous giant cells (Fig. 15–37). Electron microscopy has disclosed, in the myeloma cell, a highly developed endoplasmic reticulum, often stuffed with amorphous material compatible with immunoglobulin aggregates.[67] Under the light microscope, the protein aggregates may appear as acidophilic inclusions known as **Russell bodies.** These, however, are not pathognomonic of myeloma, since they can also be seen in reactive plasma cells that are actively synthesizing immunoglobulins.

Multiple myeloma presents as multifocal destructive bone lesions throughout the skeletal system. The bone resorption results from the activation of osteoclasts by an osteoclast-activating factor secreted by the myeloma cells. Although any bone may be affected, the following distribution obtains in large series of cases—vertebral column, 66%; ribs, 44%; skull, 41%; pelvis, 28%; femur, 24%; clavicle, 10%; and scapula, 10%. These focal lesions generally begin in the medullary cavity, erode the cancellous bone, and progressively destroy the cortical bone. On section, the bony defects are filled with red, soft, gelatinous tissue. **Radiographically, the lesions appear as punched-out defects,** usually ranging between 1 and 4 cm in diameter. In the late stages of multiple myeloma, plasma cell infiltrations of soft tissues may be encountered in spleen, liver, kidneys, lungs, and lymph nodes or more widely.

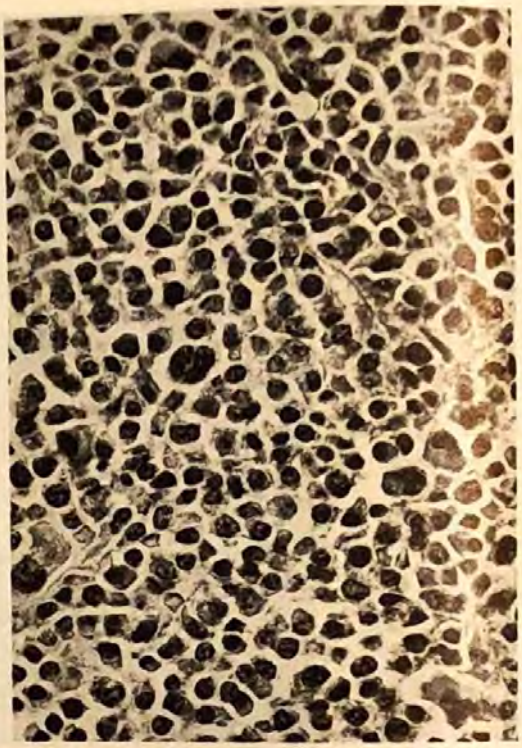

Figure 15–37. Multiple myeloma to show masses of plasma cells, mostly mature, but some with anaplasia and forming tumor giant cells.

Figure 15–36. Multiple myeloma. High-power detail of tumor composed of mature characteristic plasma cells.

Renal involvement, generally called **myeloma nephrosis,** appears in 60 to 80% of cases. Grossly, the kidneys may be normal in size and color, slightly enlarged and pale, or shrunken and pale because of interstitial scarring. The most distinctive features are microscopic.[68] Interstitial infiltrates of abnormal plasma cells or chronic inflammatory cell infiltrates may be encountered. However, the most prominent lesions are found in the distal convoluted and collecting tubules, which contain protein casts (Fig. 15–38). The casts are homogeneous and eosinophilic or polychromatic. Sometimes they are lamellar or granular. On immunofluorescent microscopy the casts reveal albumin, all classes of immunoglobulins, kappa and lambda light chains, as well as Tamm-Horsfall protein.[69] In some cases the casts have the tinctorial and birefringent characteristics of amyloid (p. 201). The fact that amyloid fibrils can be produced in vitro by the proteolytic digestion of human Bence Jones protein makes this morphologic finding not so surprising.[70] The casts are usually surrounded by multinucleated giant cells, which were previously thought to be formed by the fusion of tubular epithelial cells. More recent studies suggest that the giant cells are derived from macrophages that migrate into the area through discontinuities in the tubular basement membrane. The tubular atrophy associated with these lesions is accompanied by an increase of interstitial fibrous tissue. A number of other intercurrent changes may be present, in-

cluding metastatic calcifications as a reflection of bone destruction and secondary hypercalcemia, pyelonephritis incident to the predisposition to infection in these patients, and systemic amyloidosis. All of these contribute to renal insufficiency.

A myeloma neuropathy may develop owing to tumorous infiltrations of nerve trunk roots. Vertebra fractures and compression of roots may add to these neurologic complications. Occasionally, a form of neuropathy occurs in the absence of obvious causes and may represent the nonspecific carcinomatous polyneuropathy discussed on page 1432. Pathologic fractures are sometimes produced by the plasma cell lesions; they are most common in the vertebral column but may affect any of the numerous bones suffering erosion and destruction of their cortical substance.

Systemic amyloidosis occurs in about 10% of patients. When this complication supervenes, it may introduce all the morphologic changes associated with the widespread deposits of amyloid described in an earlier chapter (p. 195).

In most cases, infiltrates of neoplastic plasma cells may be found in the spleen, liver, lymph nodes, and other locations.

Clinical Course. The peak age incidence of multiple myeloma is between 50 and 60 years. Both sexes are affected equally. As previously stated, the *clinical features of myeloma stem from the effects of (1) infiltration of organs, particularly bones, by the neoplastic plasma cells; and (2) the production of excessive immunoglobulins, which lack antibody activity and often have abnormal physicochemical properties.* Infiltration of bones is manifested by pain and pathologic fractures.

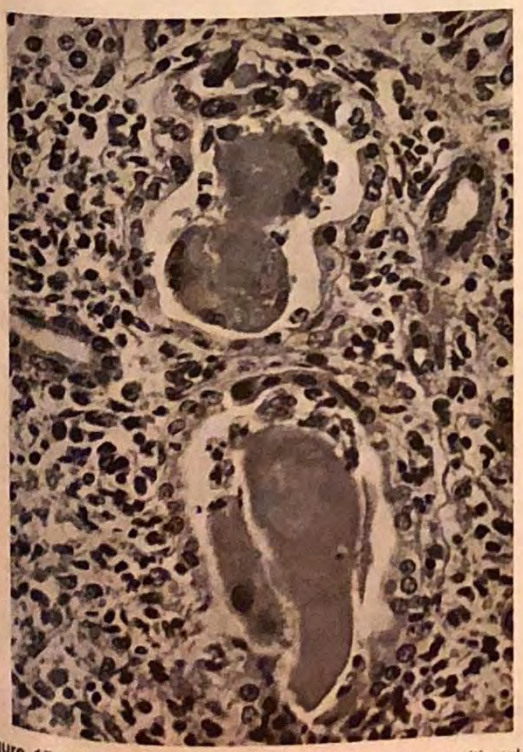

Figure 15–38. Proteinaceous casts surrounded by multinucleate giant cells in collecting tubules of kidney in myeloma nephrosis.

Hypercalcemia resulting from bone resorption may give rise to neurologic manifestations such as confusion, weakness, lethargy, constipation, and polyuria. It also contributes to renal disease. Recurrent infections with encapsulated bacteria (e.g., pneumococci) resulting from severe suppression of normal immunoglobulins pose a major clinical problem. Cellular immunity is relatively unaffected. To explain the loss of normal immunoglobulins it is postulated that the myeloma cells secrete a factor capable of activating suppressor macrophages, which in turn inhibit normal B cells.[71] Excessive production and aggregation of myeloma proteins may lead to the hyperviscosity syndrome in approximately 7% of patients. Those with the IgA myeloma are particularly prone to this complication because of the tendency of IgA molecules to form polymers. Manifestations of the hyperviscosity syndrome including retinal hemorrhages, prolonged bleeding, and neurologic changes are much more common with Waldenström's macroglobulinemia and are therefore discussed later (p. 693). Amyloidosis of the AL type results from excessive imbalanced production of immunoglobulin light chains (p. 197). Of great significance is *renal insufficiency*, which is second only to infections as a cause of death. Renal failure develops in two different settings. In the more common form it develops insidiously and usually progresses slowly over a period of months or years. Another form occurs suddenly in the absence of obvious previous renal impairment and is manifested by acute renal failure. The pathogenesis of renal failure, which may occur in up to 50% of patients, is multifactorial and is discussed in Chapter 21 (p. 1040). The most important factor appears to be Bence Jones proteinuria, since the excreted light chains are believed to be directly toxic to the tubular epithelial cells.[72] In addition to these specific symptoms, some patients may present with unexplained anemia or weakness.

The clinical diagnosis of multiple myeloma rests on radiographic and laboratory findings and ultimately on biopsy of a lesion to reveal the tumorous aggregates of plasma cells. The radiographic changes are so distinctive that a reasonably certain diagnosis can usually be made. Classically, the individual lesions appear as sharply punched-out defects, having a rounded soap-bubble appearance on x-ray film, but generalized osteoporosis may also be seen. Almost all patients have a normochromic normocytic anemia, sometimes accompanied by moderate leukopenia and thrombocytopenia due to marrow failure. Rarely, neoplastic plasma cells flood the peripheral blood, giving rise to *plasma cell leukemia*. The hyperglobulinemia leads to rouleaux formation on blood smear and an increased erythrocyte sedimentation rate. Hypercalcemia is frequently present. Most confirmatory of the diagnosis are M-protein spikes on blood or urine analysis. Quantitative analyses usually disclose more than 3 gm of Ig per 100 ml of serum and more than 6 mg of Bence Jones proteins per 100 ml of urine. The presence of the latter generally implies a graver prognosis.[73] As the disease progresses and the total mass of plasma cells expands, the level of M proteins in-

creases. It should be remembered, however, that rarely elevated serum immunoglobulins are absent in this disease (nonsecretory myeloma). Perhaps one-third of the patients lack Bence Jones light chains. On the other hand, sometimes only Bence Jones proteins are present without increased serum gamma globulins (in so-called "light-chain disease").

The prognosis for this condition depends on the stage of advancement at the time of diagnosis. Patients with multiple bony lesions, if untreated, rarely survive for more than six to 12 months. Chemotherapy in the form of alkylating agents induces remission in 50 to 70% of patients, but the median survival is still a dismal two to three years. For reasons not entirely clear, these patients have an increased incidence of nonplasmacytic cancers, particularly acute myelogenous leukemias. It is unknown whether these are induced by alkylating agents used in therapy, or whether disordered immune surveillance underlies this predisposition to superimposed malignant neoplasia.

Solitary Myeloma (Plasmacytoma)

About 3 to 5% of monoclonal gammopathies consist of a solitary plasmacytic lesion, in either bone or soft tissue. The bony lesions tend to occur in the same location as in multiple myeloma. Extraosseous lesions are often located in the lungs, oronasopharynx, or nasal sinuses. Wherever they arise, they have the fleshy, red-brown appearance characteristic of the lesions in multiple myeloma. The cytologic detail is also similar. Elevated levels of M proteins in the blood or urine are found in approximately 25% of cases, but when present they are not as extreme as with multiple myeloma.[74] When patients with such localized disease are followed, *progression to classic multiple myeloma becomes manifest in most patients with osseous plasmacytoma, whereas extraosseous primaries rarely disseminate.* It appears that the solitary plasmacytoma involving the bones is an early stage of multiple myeloma, but in some individuals it may be present for many years without progression.[75] Extraosseous plasmacytomas, particularly those involving upper respiratory tracts, represent limited disease that can usually be cured by local resection.

Waldenström's Macroglobulinemia

This dyscrasia, constituting about 5% of monoclonal gammopathies, *is marked by a diffuse, leukemia-like infiltrate of the bone marrow by lymphocytes, plasma cells, and hybrid forms that synthesize a structurally and antigenically homogeneous IgM immunoglobulin, leading to macroglobulinemia.* When first described, it was thought that the immunoglobulin was always of the IgM class, but it is now known that in some patients it may be IgG or IgA.[76] Approximately half the patients have lymphadenopathy, hepatomegaly, or splenomegaly, alone or in combination. This disease may best be viewed as a cross between multiple myeloma and well-differentiated lymphocytic lymphoma. As in myeloma, the neoplastic B cells secrete a monoclonal immunoglobulin. However, unlike myeloma but resembling lymphoma, the tumor cells diffusely infiltrate the lymphoid tissues including bone marrow, spleen, and lymph nodes.

Morphology. Typically there is a diffuse, sparse-to-heavy infiltrate of the bone marrow by lymphocytes, plasma cells, lymphocytoid plasma cells, and other variants on this theme (Fig. 15–39). The infiltrate is rarely as heavy as that encountered in leukemia and does not occur in tumorous masses that are characteristic of plasma cell myeloma. Thus, there is no bone erosion or characteristic radiographic finding. Abnormal plasma cells are sometimes found. For example, "flame" cells have diffuse, intensely eosinophilic-staining cytoplasm. Thesaurocytes (storage cells) contain both cytoplasmic and intranuclear inclusions, which stain intensely with PAS (Fig. 15–40). The inclusions represent IgM or IgA, having the highest content of carbohydrate among the immunoglobulins. These cells are not diagnostic of Waldenström's macroglobulinemia and are sometimes encountered in other gammopathies, such as IgA myeloma. An increased number of mast cells may also be present.

A similar infiltrate may be present in the lymph nodes, spleen, or liver in patients having disseminated disease. Infiltration of the nerve roots, meninges, and cerebral substance by proliferating cells has also been reported.[77]

Clinical Course. Waldenström's macroglobulinemia is a disease of old age, rarely presenting before

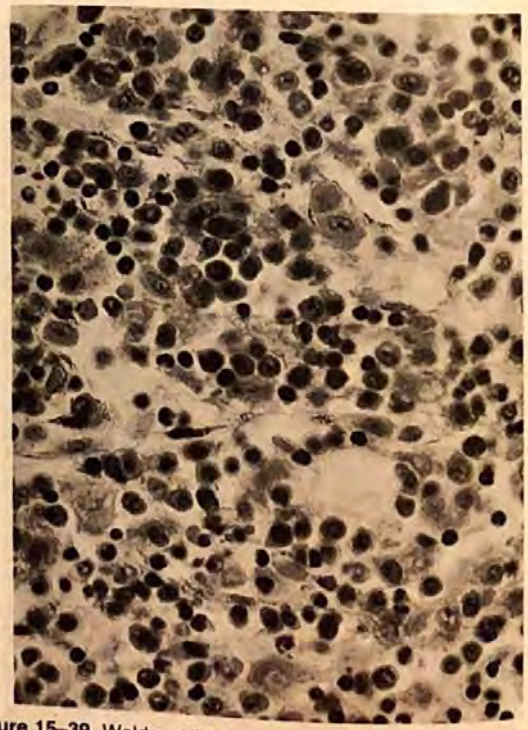

Figure 15–39. Waldenström's macroglobulinemia. Detail of marrow with pleomorphic cellularity containing recognizable lymphocytes, and plasma cells admixed with many hybrid forms. (From Cabot Case Record 26–1964. N Engl. J. Med. 270:1190, 1964. Reprinted by permission from The New England Journal of Medicine.)

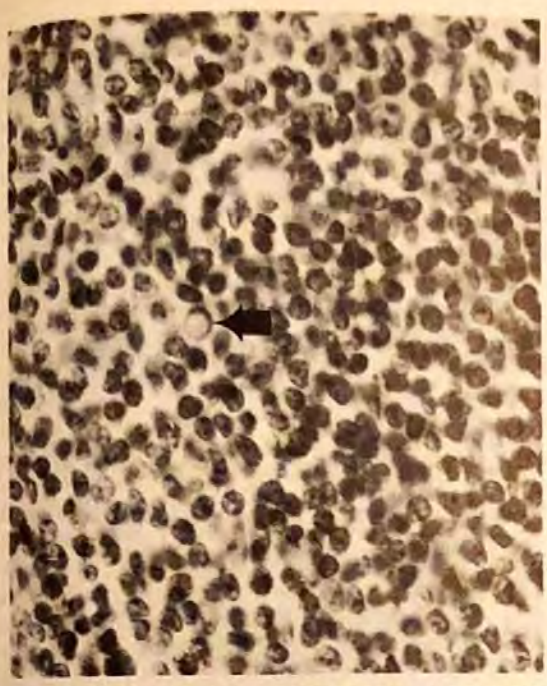

Figure 15–40. Waldenström's macroglobulinemia. High-power detail of infiltrate disclosing an intracellular inclusion *(arrow)* made up of macroglobulins. (H and E stain.) (Courtesy of Dr. Jose Hernandez, Department of Pathology, Southwestern Medical School, Dallas, Texas.)

the seventh decade. The dominant presenting complaints are weakness, fatigability, and weight loss—all nonspecific symptoms.[78] As pointed out, lymphadenopathy, hepatomegaly, and splenomegaly may be present. The specific complaints stem largely from the abnormal physicochemical properties of the macroglobulins. Because of their large size and increased concentration in blood, these paraproteins tend to form large aggregates that greatly increase the viscosity of blood. The resulting *hyperviscosity syndrome is characterized by visual impairment, neurologic signs, and excessive oozing from wounds.* The visual disturbances are related to the striking tortuosity and distention of retinal veins, with narrowing at arteriovenous crossings, producing what has been likened to a "sausage-link" pattern. Sometimes, retinal hemorrhages and exudates result from venous distention. The neurologic symptoms stemming from sluggish blood flow and sludging are protean; they include headache, dizziness, deafness, and even stupor in some cases. Excessive bleeding is related not only to hyperviscosity but also to interference in platelet function, as well as inhibition of clotting factors by macroglobulins. In some cases the abnormal globulins precipitate at low temperatures, giving rise to symptoms of *cryoglobulinemia* such as Raynaud's phenomenon and cold urticaria.

Despite the numerous clinical findings, diagnosis rests heavily on laboratory data. Unlike myeloma, there are no distinctive radiologic findings. Classically, the electrophoretic analysis of the serum discloses an M-protein spike, which is identified as IgM by immunoelectrophoresis. Associated Bence Jones proteinuria occurs in 20 to 30% of cases; for unknown reasons, however, renal damage is much less common than in multiple myeloma. A variety of other laboratory findings are present but are of less value diagnostically. These include anemia, an increased sedimentation rate, rouleaux formation, hyperviscosity, and cryoglobulinemia. Ultimately, *diagnosis rests on the typical bone marrow findings along with an M-protein spike, usually due to IgM, in the serum.* Differentiation of Waldenström's macroglobulinemia from malignant lymphoma is sometimes difficult. Since most lymphomas also have a B-cell origin, clinical forms intermediate between them and Waldenström's are not entirely unexpected. Differentiation, then, becomes largely a matter of semantics and is usually based on the predominant clinical symptoms.

The average survival in this disease is two to five years with appropriate chemotherapy.

Heavy-chain Disease

These extremely rare monoclonal gammopathies will be discussed only briefly. Three variants have been described, each characterized by elevated levels in the blood or urine of a specific heavy chain of immunoglobulins.[79] *Gamma-chain disease*, encountered most often in the elderly, resembles a malignant lymphoma more than a multiple myeloma. The manifestations consist of lymphadenopathy, anemia, and fever often accompanied by malaise, weakness, and hepatomegaly or splenomegaly. Immunoelectrophoresis with monospecific antisera discloses gamma chains in the serum or urine. Histologic study reveals an infiltrate of plasma cells and lymphocytes admixed with eosinophils and histiocytes. Lytic bone lesions are not present. Because levels of normal immunoglobulins are low, patients with this condition are susceptible to infection. In some instances the disease appears in association with tuberculosis, rheumatoid arthritis, and various autoimmune diseases, but no causal relationship has been established. The course can be rapidly downhill to death within a few months, or may be protracted for years.

Alpha-chain disease, the most common in this group, may be viewed as a disorder of IgA-producing cells involving mainly the sites of normal IgA synthesis. It occurs mainly in young adults in two clinical patterns. One, seen most commonly in the Mediterranean area, is characterized by massive infiltration of the lamina propria of the intestine and abdominal lymph nodes by lymphocytes, plasma cells, and histiocytes. Villous atrophy and severe malabsorption with diarrhea, steatorrhea, and hypocalcemia are consequences of the infiltrate. With progression, the infiltrate may be replaced by large neoplastic cells and transform into an immunoblastic sarcoma of B cells (p. 664). This abdominal form of alpha-chain disease is now designated "immunoproliferative small intestinal disease."[79A] The other clinical variant marked by a similar infiltrate limited to the respiratory tract is much less common.[80] Required

for the diagnosis of both conditions is the demonstration of alpha-chain protein in the serum. Occasionally, small amounts of alpha-chains appear in the urine.

Mu-chain disease is the rarest of these entities, most often encountered in patients having chronic lymphocytic leukemia.[81] Characteristic are vacuolated plasma cells in the marrow. Immunoelectrophoresis reveals an excess of mu chains in the blood, and sometimes also kappa-type light chains in the urine. Hepatomegaly and splenomegaly are usually present, but in contrast to the usual case with CLL, peripheral lymphadenopathy is inconspicuous.

Monoclonal Gammopathy of Undetermined Significance

When large numbers of individuals above the age of 50 are screened by electrophoresis for M-protein serum spikes, about 1 to 3% are found to have elevated levels of IgG, IgA, or IgM, despite the fact that they are completely asymptomatic and clinical investigation does not disclose any of the well-defined immunoglobulin-producing diseases. *To this dysproteinemia without associated disease, the term "monoclonal gammopathy of undetermined significance" (MGUS) is applied.* MGUS is much more common than previously appreciated; in one large study, over two-thirds of the cases with a monoclonal serum protein belonged to this category.[62] Contrary to previous beliefs, the course of MGUS is not entirely benign. In a ten-year follow-up of 241 patients with MGUS, 18% developed a well-defined plasma cell dyscrasia (myeloma, macroglobulinemia, amyloidosis, or lymphoma). In another 9%, no overt disease appeared but a significant increase in the serum monoclonal protein suggested expansion of the abnormal plasma cell mass.[62] In general, patients with MGUS have less than 2.0 gm per dl of monoclonal protein, no Bence Jones proteinuria, and fewer than 5% plasma cells in the bone marrow. However, none of these criteria is absolutely reliable, and therefore the *diagnosis of MGUS requires careful exclusion of all the other specific forms of monoclonal gammopathies.* Whether a given patient with MGUS will follow a benign course, as most do, or develop a well-defined plasma cell neoplasm cannot be predicted, and hence periodic assessment of serum M component levels and Bence Jones proteinuria is warranted.

HISTIOCYTOSES

Several classifications of these disorders have been proposed. Some are based on segregation into reactive and neoplastic categories, others on the level of maturation of the histiocyte-macrophages involved. Still others include the histiocytic proliferations encountered in storage diseases such as Gaucher's and Niemann-Pick disease. Regardless of the nosologic scheme employed, it is relatively easy to segregate the clearly neoplastic proliferations such as the monocytic leukemias, the rare histiocytic lymphomas (p. 665), and histiocytic medullary reticuloses from the clearly reactive proliferations exemplified by tuberculosis and other infectious granulomas. Problems occur in trying to find a niche for certain rare proliferative disorders often described as *histiocytosis X. This term includes generalized histiocytosis (Letterer-Siwe syndrome), multifocal eosinophilic granuloma (Hand-Schüller-Christian disease), and unifocal or solitary eosinophilic granuloma.* These three conditions are believed to represent different clinicoanatomic patterns of the same basic disorder. Generalized histiocytosis, which behaves like a disseminated malignant tumor, lies at one end of the spectrum, whereas unifocal eosinophilic granuloma with its benign course represents the other end. In between lies multifocal eosinophilic granuloma, with intermediate prognosis. Although these disorders differ from each other with respect to the extent of organ involvement and the prognosis, they are unified by the presence in the lesions of large, histiocyte-like cells that bear several similarities to Langerhans' cells. These cells, you may recall (p. 160), are normally present within the epidermis and are believed to be related to the mononuclear phagocyte system. They have Fc receptors, bear HLA-D/DR antigens, and react with anti-OKT6 antibody, which also binds to thymocytes but not to peripheral T cells. These immunologic markers are also present on the so-called histiocytosis X cells (HXC) that infiltrate the organs involved by these disorders.[82] The similarity between Langerhans' cells and HXC extends also to the ultrastructural level. The cytoplasm of HXC contains characteristic inclusions called histiocytosis X (HX) bodies, which resemble Birbeck granules found in Langerhans' cells (Fig. 15–41).[83] *The HX body is seen as a pentalaminar, rodlike tubular structure with characteristic periodicity and sometimes a dilated terminal end (tennis-racquet appearance).* Thus, histiocytosis X is viewed currently as a proliferative disorder of Langerhans' cells or their marrow precursors, and hence the term "Langerhans' cell granulomatosis" has also been applied to them.[84] Although the cell of origin seems to be reasonably well established, the pathogenesis of histiocytosis X is still mysterious. Diffuse histiocytosis behaves like a malignant tumor, whereas eosinophilic granulomas, whether solitary or multifocal, appear to be non-neoplastic, rarely causing death. It is conceivable that they are all reactive disorders of variable severity, responding to unknown inciting agents.

Generalized Histiocytosis (Letterer-Siwe Syndrome)

This condition constitutes essentially an acute or subacute progressive systemic proliferation of mature and immature histiocytes. Classically, infants and young children under 3 years of age are affected. Sometimes the disease is present from birth. Occasional reports suggest that a closely similar disorder may also occur in adults.[85] In the very young the onset is marked by fever, sometimes related to a localized infection such as otitis

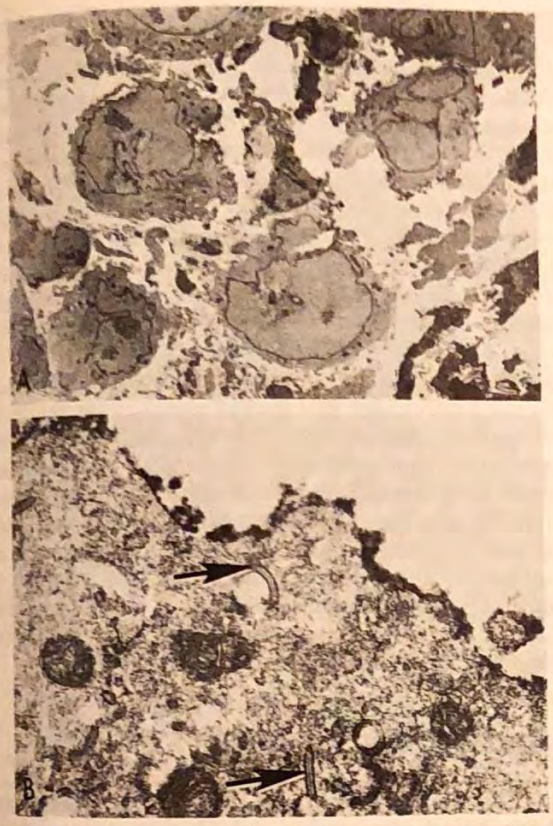

Figure 15–41. Histiocytosis X. Infiltrate is composed of large, rounded cells containing reniform and infolded nuclei (A). At higher power (B), characteristic Birbeck granules *(arrows)* and membrane reactivity for thymocyte differentiation antigen T6 (dense deposits along cell membrane) are observed. These features are also present in normal Langerhans' cells. (Courtesy of Dr. George Murphy, Harvard Medical School, Boston, MA.)

media or mastoiditis, followed soon by a diffuse maculopapular eczematous or purpuric skin rash and subsequent enlargement of the spleen, liver, and lymph nodes throughout the body. Cystic, rarefied lesions may become apparent radiographically in the skull, pelvis, and long bones. Anemia, thrombocytopenia, and leukopenia are frequently present as manifestations of flooding of the bone marrow by proliferating histiocytes. The clinical picture of diffuse histiocytosis shows several similarities to acute leukemia, histiocytic medullary reticulosis, and a variety of infectious processes. These must be clearly excluded by morphologic and other appropriate criteria before diagnosis is made.

Morphology. The characteristic microscopic feature of this disorder is an apparent neoplastic proliferation of histiocytes throughout virtually all the organs and tissues of the body. The cells have abundant, often vacuolated cytoplasm, which is amphophilic-to-acidophilic, and vesicular oval, reniform, or indented nuclei. Nucleoli, when present, are small. Occasionally, multinucleated giant histiocytes are present, and in some cases, especially those involving adults, there may be some atypia and variation in histiocyte size and shape. With electron microscopy, occasional histiocytes can be seen to contain HX bodies (Fig. 15–41), described earlier. The proliferating histiocytes sometimes disclose evidence of phagocytic activity in the form of inclusions of nuclear debris or occasional red cells, but striking erythrophagocytosis, such as is seen in histiocytic medullary reticulosis, is not present. The histiocytic infiltrates can be seen in the skin lesions, lymph nodes, spleen, and liver and particularly within the bone marrow, where they may cause erosive defects visible on x-ray film. In fatal cases, many other organs and tissues are affected, including the lungs, kidneys, gastrointestinal tract, and meninges.

The course of this condition is somewhat variable and appears to be related to age of onset. Up to the recent past, infants under 6 months of age generally pursued a rapid course to death within six months, and older children rarely survived more than one to two years. Intensive chemotherapy has remarkably improved this gloomy outlook. Lahey, in an analysis of a varied group of children with histiocytic disorders, cited "complete to good" remission in about two-thirds of infants under the age of 2 years with the use of several chemotherapy programs.[86] Several immunologic abnormalities, including a deficiency of T-suppressor cells, have been described in some patients. Administration of calf thymic extract has reversed some abnormal responses and also induced clinical remission, suggesting that deranged immunity may be an integral component of this disorder.[87] Thus, there is new hope in this previously grim situation. Death is usually related to intercurrent infections and progressive anemia and debility.

Eosinophilic Granuloma—Unifocal and Multifocal

The distinctive morphologic lesions of both the unifocal and multifocal variants consist of expanding, erosive accumulations of histiocytes usually within the medullary cavities of bones. Frequently, a few to many of the histiocytes are foamy and vacuolated. These are variably admixed with eosinophils, lymphocytes, plasma cells, and neutrophils (Fig. 15–42). Occasionally, there are areas of necrosis within these infiltrates, rimmed by a more intense infiltration of neutrophils and sometimes multinucleated histiocytes, resembling foreign body–type or Langhans' giant cells. The eosinophilic component ranges from scattered mature cells to sheetlike masses of cells. The foam cells, too, may be massed in some lesions, but since they merely reflect phagocytosis of lipid debris, they have no particular significance. Rod-shaped HX bodies may sometimes be present in the histiocytes within these lesions, similar to those described in the generalized histiocytoses. Although virtually any bone in the skeletal system may be involved, favored localities are the calvarium, ribs, and femurs. Thus, in a series of 50 cases of unifocal eosinophilic granuloma, approximately 60% of the lesions occurred in one of these three skeletal sites.[88] Similar lesions are sometimes found in the skin, lungs, or stomach, either as unifocal lesions or as components of the multifocal disease.

Unifocal eosinophilic granuloma is a benign disorder that occurs in children and young adults, especially males. The solitary lesions may be asymptomatic, or

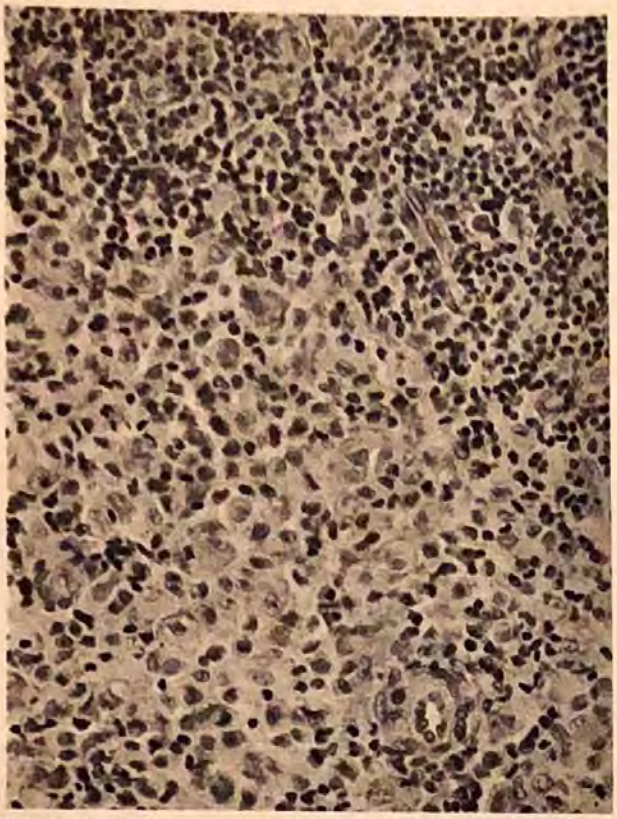

Figure 15–42. Eosinophilic granuloma. The typical round and oval macrophages are most numerous below and are interspersed with scattered lymphocytes, plasma cells, and eosinophils.

may cause pain and tenderness as the lesion erodes the bone and in some instances leads to pathologic fractures. There are usually no systemic manifestations, such as fever, nor involvement of the blood or viscera. Diagnosis is based on roentgenologic demonstration of a focal destructive bone lesion arising within the marrow cavity and on the characteristic morphologic findings. In some cases, spontaneous fibrosis and healing occur, usually in the span of a year or two. In other instances, curettage, excision, or local irradiation leads to a cure. Occasionally, individuals with an apparent unifocal lesion are encountered in whom, over the course of time, multiple lesions in bones or soft tissues develop. Whether such a sequence implies conversion of unifocal eosinophilic granuloma to the multifocal disease, or instead represents a single overt lesion presenting first in a patient with disseminated disease, is unknown. In any event, it is clear that patients with unifocal eosinophilic granuloma must be carefully followed for years.

Multifocal eosinophilic granuloma is a more disabling disease, with onset usually before the age of 5 years. *This syndrome was formerly called Hand-Schüller-Christian disease.* (p. 694). Typically, patients have fever; a diffuse, scaly, seborrhea-like eruption, particularly on the scalp and in the ear canals; and frequent bouts of otitis media, mastoiditis, and upper respiratory infections as well as gingival inflammations. Mild lymphadenopathy, hepatomegaly, and splenomegaly due to infiltrates may be present. Pneumonitis with diffuse radiographic pulmonary opacities are sometimes present, perhaps related to granulomatous involvement of the lungs or to intercurrent microbiologic infections. About half the patients have granulomatous involvement of the posterior pituitary stalk or hypothalamus leading to diabetes insipidus. Orbital granulomas induce exophthalmos in about one-third of patients. *The combination of calvarial bone defects, diabetes insipidus, and exophthalmos are referred to as the Hand-Schüller-Christian triad.* However, only a minority of patients with multifocal eosinophilic granuloma have the complete triad. It may be evident that the presentation of multifocal eosinophilic granuloma with fever, skin rash, and multiple histiocytic lesions in bones and viscera bears considerable resemblance to generalized histiocytosis, accounting for the belief that the two syndromes are variable expressions of a single disorder. However, in contrast to generalized histiocytosis, the prognosis in multifocal eosinophilic granuloma is good. In half the patients the lesions spontaneously resolve, and in the other half chemotherapy induces ultimate recovery.

ANGIOIMMUNOBLASTIC LYMPHADENOPATHY

This entity, sometimes also called "angioimmunoblastic lymphadenopathy with dysproteinemia," is an uncommon systemic disorder marked principally by generalized lymphadenopathy.[89] Seen principally in elderly individuals, it is characterized by fever, weight loss, generalized lymphadenopathy (present in all cases), hepatosplenomegaly, maculopapular rash, polyclonal hypergammaglobulinemia, and Coombs'-positive hemolytic anemia. A history of drug ingestion—penicillin, sulfonamides, aspirin, halothane, phenytoin sodium, griseofulvin, allopurinol, and methyldopa—is sometimes present and may precipitate the disease.

In addition to the involvement of the lymph nodes, less characteristic anatomic changes are encountered in the spleen, liver, bone marrow, skin, and lung.[90] The lymph nodes are generally 2 to 3 cm in diameter, soft, movable, nonmatted, and sometimes tender. *The histopathologic diagnosis rests on the following triad: (1) a pleomorphic cellular infiltrate of small and large lymphocytes, immunoblasts, and plasma cells that infiltrates the capsule and effaces the nodal architecture; (2) an arborizing vascular proliferation accompanied by endothelial cell hyperplasia; and (3) interstitial deposits of an amorphous, eosinophilic, PAS-positive material thought to be cellular debris (Fig. 15–43).* Immunofluorescent and immunoperoxidase techniques reveal cytoplasmic inclusions of immunoglobulins in many of the lymphoid cells.[91] Less characteristic pleomorphic infiltrates may be found in the other organs mentioned, sometimes with marked erythrophagocytosis in the spleen (accounting for the hemolytic anemia).

The nature of this entity is obscure, but the clinical

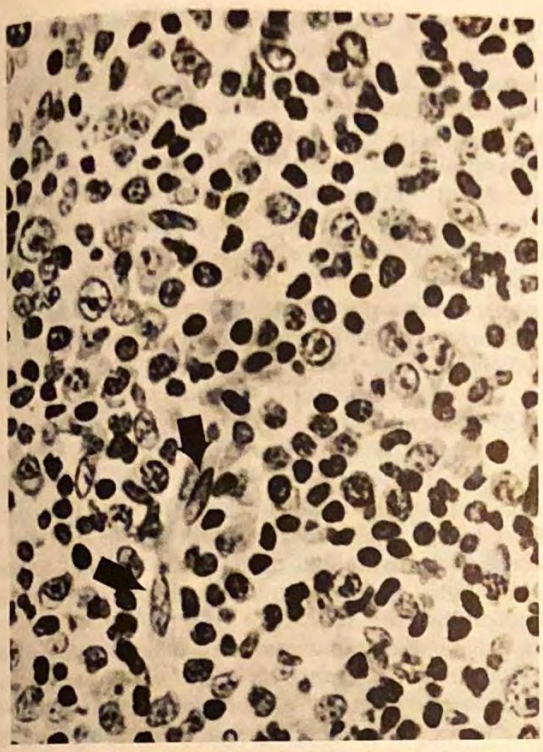

Figure 15–43. Angioimmunoblastic lymphadenopathy. Note pleomorphic infiltrate consisting of small dark cells (lymphocytes), plasma cells, and large cells with vesicular nuclei (immunoblasts). The elongated nuclei *(arrows)* represent endothelial cells, which are usually quite prominent owing to vascular proliferation. (Courtesy of Dr. Jose Hernandez Department of Pathology, Southwestern Medical School, Dallas, Texas.)

and anatomic findings are most consistent with chronic antigenic stimulation inducing non-neoplastic proliferation of B lymphocytes. The frequent, but not invariable, history of drug ingestion raises the possibility that these agents precipitate the immune response. Indeed, the anatomic changes in angioimmunoblastic lymphadenopathy are very similar to those encountered in lymph nodes in so-called "drug reactions," except that vasculitic lesions are often present in the latter. In patients without a history of drug ingestion, an autoimmune reaction is postulated, but no definite triggering agents have been identified. A variety of immunologic derangements including a deficiency of T-suppressor cells, cutaneous anergy, or the presence of suppressor monocytes have been described in patients with this disorder. However, there is no characteristic or constant immunologic abnormality, which suggests that angioimmunoblastic lymphadenopathy may evolve by several distinct mechanisms.

The course of this disorder is extremely variable. About one-half of the patients survive two to four years, some (25%) without any treatment, others (25%) with treatment (steroids, combination chemotherapy). In the remainder, the disease progresses rapidly, regardless of the treatment given. Most deaths are caused by severe infection, possibly related to immunologic incompetence, but some patients have developed immunoblastic sarcomas. In such cases, it is postulated that one of the several hyperactive B cells becomes autonomous and neoplastic. Thus, a monoclonal B-cell neoplasm, associated with a change from polyclonal to monoclonal hypergammaglobulinemia, may emerge (see also the discussion on p. 668).[92]

In this condition, confusion stems from two sources: (1) it is frequently misdiagnosed histologically as a lymphoma, particularly Hodgkin's disease, because of the pleomorphic cellular infiltrate; and (2) the presence in about 40% of patients of a pruritic, generalized, maculopapular rash, interpreted as a dermal drug reaction, may direct attention away from the potentially serious underlying systemic disorder.

Spleen

NORMAL

The spleen is to the circulatory system as the lymph nodes are to the lymphatic system. Among its functions are filtration from the bloodstream of all "foreign" matter including obsolescent and damaged blood cells, and participation in the immune response to all blood-borne antigens. Designed ingeniously for these functions, the spleen is a major repository of mononuclear phagocytic cells in the red pulp and of lymphoid cells in the white pulp. Normally in the adult it weighs about 150 gm and measures some 12 cm in length, 7 cm in width, and 3 cm in thickness. It is enclosed within a thin, glistening connective tissue capsule that appears slate gray and through which the dusky-red, friable parenchyma of the splenic substance can be seen. In man, unlike some animals, there is little if any smooth muscle in the capsule and therefore virtually no contractile function. The cut surface of the spleen is dotted with gray specks, the splenic or malpighian follicles that constitute the white pulp. In three dimensions this white pulp forms periarterial sheaths of lymphoid cells around the arteries, most abundant about the larger branches and pro-

gressively more attenuated as the arterial supply penetrates the splenic substance. A cross section of such an arrangement reveals a central artery surrounded eccentrically by a collar of T lymphocytes, the so-called periarteriolar lymphatic sheath. At intervals the lymphatic sheaths become expanded, usually on one side of the artery to form lymphoid nodules composed principally of B lymphocytes. Upon antigenic stimulation, typical germinal centers form within these B-cell areas (p. 656). Eventually the arterial system terminates in fine penicilliary arterioles, which at first are enclosed within a thin mantle of lymphocytes but which then enter the red pulp, leaving behind their "fellow-travelers."

The red pulp of the spleen is traversed by numerous thin-walled vascular sinusoids, separated by the splenic cords or "cords of Billroth." The endothelial lining of the sinusoid is of the open or discontinuous type, providing passage of blood cells between the sinusoids and cords. The splenic cords are spongelike and consist of a labyrinth of macrophages loosely connected through long dendritic processes to create both a physical and a functional filter through which the blood can slowly seep.

It is widely believed that the blood, as it traverses the red pulp, takes two routes to reach the splenic veins. Some of the capillary flow is into the splenic cords and is then gradually filtered out into the surrounding splenic sinusoids to reach the veins; this is the so-called "open circulation," which is functionally the slow compartment. The other pathway involves direct passage from the capillaries to the splenic veins without the intervening stage of passage through the cords. This, the "closed circuit," is understandably the more rapid compartment. According to current views, only a small fraction of the blood entering the spleen at any given time pursues the "open" route. Nevertheless, during the course of a day the total volume of blood passes through the filtration beds of the splenic cords, where it is exposed to the remarkably sensitive and effective phagocytic macrophages, which are able to screen the blood.

Most anatomic disorders of the spleen are secondary to some systemic disorder and thus are the consequence of normal splenic function. These can be segregated into four categories.

1. *Filtration of unwanted elements from the blood* by phagocytosis in the splenic cords is a major function of the spleen. As you know, 1/120th of all red cells are destroyed daily by phagocytosis in the reticuloendothelial system. Engulfment by splenic macrophages accounts for approximately half this removal of obsolescent red cells from the circulation. The splenic phagocytes are also remarkably efficient in "culling" damaged red cells and leukocytes, red cells rendered foreign by antibody coating, as well as the abnormal red cells encountered in several of the anemias (e.g., hereditary spherocytosis, sickle cell anemia). As discussed earlier (p. 615), the red cells have to undergo extreme degrees of deformation during passage from the cords into the sinusoids. In several hemolytic anemias, the reduced plasticity of the red cell membrane leads to trapping of the abnormal red cells within the cords and subsequent phagocytosis by the cordal macrophages. In addition to removal of the red cells, splenic macrophages are also involved in "pitting" of red cells by which inclusions such as siderotic granules, Heinz bodies, and Howell-Jolly bodies are neatly excised without destruction of the erythrocytes. The phagocytes are also active in removal of other particulate matter from the blood, such as bacteria, cell debris, or abnormal macromolecules produced in some of the inborn errors of metabolism (e.g., Gaucher's disease, Niemann-Pick disease).

2. A second function of the spleen relates to its role as a *major secondary organ in the immune system.* The reticular network in the periarterial lymphatic sheaths traps antigen, permitting it to come into contact with effector lymphocytes. Both T and B cells are present in the lymphoid tissue of the spleen, and thus it contributes to both humoral and cell-mediated immune responses.

3. The spleen is a *source of lymphoreticular cells and sometimes hematopoietic cells.* As you recall, splenic hematopoiesis normally ceases before birth, but in severe anemia, extramedullary splenic hematopoiesis may be reactivated. Lymphocyte and macrophage production normally occurs in the spleen throughout life, becoming progressively attenuated with increasing age.

4. Because of its rich vascularization and phagocytic function, the spleen also *constitutes a reserve pool and storage site.* In humans, the normal spleen harbors only about 30 to 40 ml of erythrocytes, but with splenomegaly this reservoir is greatly increased. The normal spleen also stores approximately 30 to 40% of the total platelet mass in the body. With splenomegaly this platelet storage may markedly increase, sometimes to up to 80 to 90% of the total platelet mass. Similarly, the enlarged spleen may trap a sufficient number of white cells to induce leukopenia. In addition to the blood elements, as mentioned, the spleen is a major storage site of red cell iron and macromolecular products of abnormal metabolism.

In view of all these functions it is no wonder that the spleen becomes secondarily involved in a wide variety of systemic disorders.

PATHOLOGY

As the largest unit of the reticuloendothelial system, the spleen is involved in all systemic inflammations and generalized hematopoietic disorders, and many metabolic disturbances. It is rarely the primary site of disease. When the spleen is involved in systemic disease, splenic enlargement usually develops, and therefore splenomegaly is a major manifestation of disorders of this organ.

SPLENOMEGALY

Splenic enlargement may be an important diagnostic clue to the existence of an underlying disorder, but the condition itself may cause problems. When sufficiently enlarged, the spleen may cause a dragging sensation in the left upper quadrant and, through pressure on the stomach, cause discomfort after eating. In addition, its storage function may lead to the sequestration of significant numbers of blood elements, giving rise to a syndrome known as *hypersplenism* (described below). A listing, by no means exhaustive, of the disorders associated with splenomegaly is provided in Table 15–8.

HYPERSPLENISM

Hypersplenism is encountered in only a minority of patients with splenic enlargement. In essence, this syndrome is characterized by the triad of (1) splenomegaly usually caused by one of the disorders listed in Table 15–8 (secondary hypersplenism), but sometimes of unknown etiology (primary hypersplenism); (2) a reduction of one or more of the cellular elements of the blood, leading to anemia, leukopenia, thrombocytopenia, or any combination of these, associated with hyperplasia of the marrow precursors of the deficient cell type; and (3) correction of the blood cytopenia(s) by splenectomy. The precise cause of this syndrome is still uncertain, but increased sequestration of the cells and the consequent enhanced lysis by the splenic macrophages seem to be the likely explanation for the cytopenias. In most cases there is a reasonable basis (underlying disease) for the splenomegaly, represented by the term secondary hypersplenism. In a minority of cases, however, the splenomegaly is of unknown origin and the syndrome is designated primary hypersplenism. In such cases, what caused the splenomegaly? Moreover, primary hypersplenism has also been diagnosed in patients having *no* apparent splenomegaly, in which case it must be assumed that sequestration was not operative. It is apparent that there are still many gray areas requiring explication. For now, it seems best to consider the diagnosis of hypersplenism to be appropriate only when there is splenic enlargement, however mild, and to view primary hypersplenism as covering those instances in which the systemic disease causing the splenomegaly has remained undiscovered.

The splenomegaly in virtually all the conditions previously mentioned has been discussed elsewhere. There remain only a few causes that require consideration.

Table 15–8. 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 liver
	Portal or splenic vein thrombosis
	Cardiac failure (right-sided)
III.	**Lymphohematogenous Disorders**
	Hodgkin's disease
	Non-Hodgkin's lymphomas
	Histiocytoses
	Multiple myeloma
	Myeloproliferative syndromes (chronic myelogenous leukemia, polycythemia vera, agnogenic myeloid metaplasia)
	Chronic lymphocytic leukemia
	Acute leukemias (inconstant)
	Hemolytic anemias (autoimmune hemolytic anemia, hereditary spherocytosis, hemoglobinopathies)
	Splenic neutropenia
	Thrombocytopenic purpura
IV.	**Immunologic-Inflammatory Conditions**
	Rheumatoid arthritis
	Felty's syndrome
	Systemic lupus erythematosus
V.	**Storage Diseases**
	Gaucher's disease
	Niemann-Pick disease
	Mucopolysaccharidoses
VI.	**Miscellaneous**
	Infarctions
	Amyloidosis
	Primary neoplasms and cysts
	Secondary neoplasms

CONGENITAL ANOMALIES

Complete absence of the spleen is rare and is usually associated with other congenital abnormalities. *Hypoplasia* is a more common finding.

Abnormal lobulations, either shallow or deep, are another form of anomaly. These must be distinguished from depressed healed infarcts.

Accessory spleens (spleniculi) are common and have been encountered singly or multiply in one-fifth to one-third of all postmortem examinations. They are usually small spherical structures that are histologically and functionally identical with the normal spleen, reacting to various stimuli in the same manner. They are generally situated in the gastrosplenic ligament or the tail of the pancreas, but are sometimes located in the omentum or mesenteries of the small or large intestine. Accessory spleens may have great clinical importance. In some hematologic disorders such as hereditary

spherocytosis, thrombocytopenic purpura, and hypersplenism, splenectomy is a standard method of treatment. If a large accessory spleen is overlooked, the benefit from the removal of the definitive spleen may be lost.

NONSPECIFIC ACUTE SPLENITIS

Enlargement of the spleen, sometimes also called "acute splenic tumor," occurs in any blood-borne infection. The nonspecific splenic reaction in these infections may be caused not only by the microbiologic agents themselves but also by the products of the inflammatory disease. Obviously, acute splenitis is also encountered in many specific infections, but these histologic changes usually provide some clue to the nature of the infection, as for example the striking reticuloendothelial hyperplasia and erythrophagocytosis in typhoid fever or the characteristic "mononucleosis cells" in infectious mononucleosis. In nonspecific acute splenitis it is impossible to identify the causative agent from the splenic changes.

Morphologically the spleen is enlarged (up to 200 to 400 gm) and soft. The color of the cut surface varies from grayish-red to deep red; the white pulp is usually obscured. The splenic substance is often diffluent and may be sufficiently soft literally to flow out from the cut surface. Microscopically, the major change is acute congestion of the red pulp, which may encroach on and sometimes virtually efface the lymphoid follicles. Reticuloendothelial hyperplasia and numerous free macrophages are prominent within the sinusoids, and these phagocytic cells are often filled with viable and disintegrating bacteria as well as amorphous debris. An infiltrate of neutrophils, plasma cells, and occasionally eosinophils is sometimes 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. Infarcts, either bland or septic, may be present in those cases associated with infective endocarditis.

REACTIVE HYPERPLASIA OF SPLEEN

This rather vague designation refers to the splenic changes encountered in chronic inflammatory states, systemic antigenemia, immunologic-inflammatory conditions (rheumatoid arthritis, Felty's syndrome, bacterial endocarditis, SLE), systemic viremias (infectious mononucleosis, herpes simplex), and chronic graft rejections. In all these situations, the spleen along with the lymph nodes reacts as a component of the immune system, and so the spleen in these settings has been referred to by Enriquez and Neiman as an "activated spleen."[93]

The spleen is enlarged, sometimes up to 1000 gm, and generally is moderately firm. The splenic capsule is unaffected. The red pulp may be unusually congested, and on cut surface the splenic follicles are often prominent. Microscopically, the dominant changes are hyperplasia of the splenic follicles and marked reticuloendothelial hyperplasia, sometimes filling the sinusoids with phagocytic cells showing phagocytosis of debris (Fig. 15–44). Large germinal centers may be seen in the follicles, with prominent mitotic activity and transformation of many of the follicular center cells into "blasts." Macrophages, eosinophils, and numerous plasma cells are often present in both white and red pulp.

Figure 15–44. Chronic reactive hyperplasia of spleen. View of spleen substance. Sinuses are filled with macrophages and other white cells so that the low-power architecture is suffused with cells.

Should the underlying condition causing the splenic changes be amenable to control, the spleen in time generally reverts to normal or near-normal size.

CONGESTIVE SPLENOMEGALY

Persistent or chronic venous congestion may cause enlargement of the spleen referred to as *congestive splenomegaly*. The venous congestion may be systemic in origin, may be caused by intrahepatic derangement of portal venous drainage, or may be due to obstructive venous disorders in 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, and therefore is found in any type of long-standing cardiac decompensation. It is particularly severe in tricuspid or pulmonic valvular

disease and in chronic cor pulmonale. In systemic venous stasis there are accompanying congestive changes in the liver and intestines, and frequently associated ascites and peripheral edema. Such systemic passive congestion produces only moderate enlargement of the spleen, so that it rarely exceeds 500 gm in weight.

The most common causes of striking congestive splenomegaly are the various forms of cirrhosis of the liver. The diffuse fibrous scarring of alcoholic cirrhosis and pigment cirrhosis evokes the most extreme enlargements. Less commonly, other forms of cirrhosis are implicated. In these conditions, there is sufficient impingement on the venous drainage through the liver to cause marked stasis within the portal system. At the same time, portohepatic artery shunts develop in the hepatic scars to raise the portal and splenic venous pressures even further. Only infrequently does tumorous obstruction of the vasculature of the liver give rise to congestive changes in the spleen. It is therefore uncommon for diffuse metastatic seeding of the liver to produce significant portal hypertension. Primary hepatic carcinoma may be an exception when it invades the major hepatic vessels.

Congestive splenomegaly is also caused by obstruction to the extrahepatic portal vein or splenic vein. The venous obstruction may be due to *spontaneous portal vein thrombosis*. Such thrombosis is usually associated with some intrahepatic obstructive disease, or may be initiated by inflammatory involvement of the portal vein *(pylephlebitis)* such as follows intraperitoneal infections. Thrombosis of the splenic vein itself may be initiated by the pressure of tumors in neighboring organs, e.g., carcinoma of the stomach or pancreas. Less often, it occurs as a splenic thrombophlebitis resulting from suppurative peritonitis, or as a bland thrombosis secondary to upper abdominal surgery or some disorder that predisposes to systemic venous thromboses.

Long-standing congestive splenomegaly 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 may reach 5000 gm. The capsule may be thickened and fibrous but is otherwise uninvolved. The cut surface has a meaty appearance and varies from gray-red to deep red, depending on the amount of fibrosis. Often the malpighian corpuscles are indistinct. Small gray-to-brown firm nodules scattered throughout the red pulp constitute the so-called **Gandy-Gamna** nodules described below. Microscopically, the pulp is suffused with red cells during the early phases but becomes increasingly more fibrous and cellular with time. The increased portal pressure causes deposition of collagen in the basement membrane of the sinusoids, which appear dilated owing to the rigidity of their walls (Fig. 15–45). The resulting impairment 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).[94] Foci of recent or old hemorrhage may be present with deposition of hemosiderin in histiocytes. It is the organization of these focal hemorrhages that gives rise to the Gandy-Gamna nodules—foci of fibrosis containing deposits of iron and calcium salts encrusted on connective tissue and elastic fibers. The trabeculae are thickened and fibrous. In long-standing splenic congestion, foci of hematopoiesis appear, presumably as a response to the local vascular stasis and hypoxia.

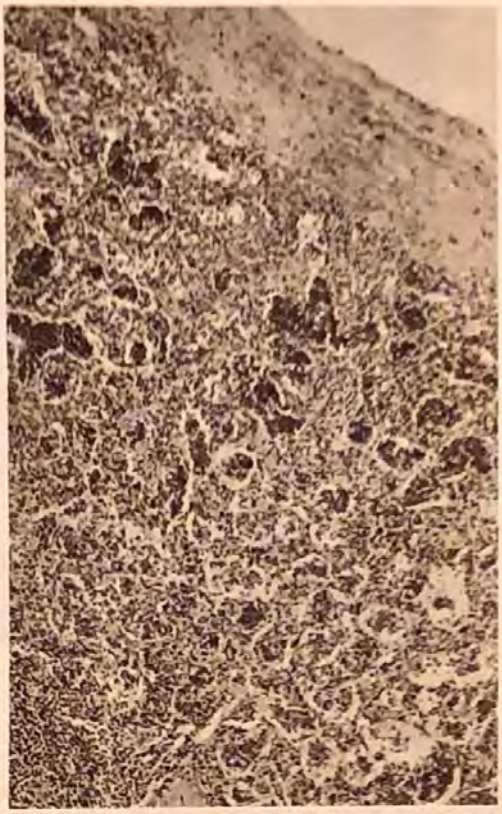

Figure 15–45. Congestive splenomegaly. Congestion of sinuses, fibrosis and widening of walls of sinuses, and fibrosis of capsule are the dominant features shown.

SPLENIC INFARCTS

During the acute stages, infarcts of the spleen may cause enlargement, depending on the size and number of the lesions. The splenomegaly, however, is at most slight, and as the infarcts undergo fibrosis the spleen returns to normal size. Indeed, in the late stages, multiple splenic infarcts may cause loss of splenic substance. Splenic infarcts are comparatively common lesions. Caused by occlusion of the major splenic artery or any of its branches, they are almost always due to emboli that arise in the heart. The spleen, along with kidneys and brain, ranks as one of the most frequent sites of localization of systemic emboli. The infarcts may be small or large, multiple or single, or sometimes may involve the entire organ. They are usually of the bland, anemic type. Septic infarcts are found in infective endocarditis of the valves of the left side of the heart. Much less often, infarcts in the spleen are caused by local thromboses, especially in the myeloproliferative syndromes, sickle cell anemia, polyarteritis nodosa, Hodgkin's disease, and bacteremic diseases.

Figure 15–46. Splenic infarcts. Multiple wedge-shaped lesions are present, the largest having developed cystic softening.

Infarcts are characteristically pale and wedge-shaped, with their bases at the periphery where the capsule is often covered with fibrin (Fig. 15–46). Septic infarction modifies this appearance as frank suppurative necrosis develops. In the course of healing of these splenic infarcts, large, depressed scars may occur. The uncommon pattern of scattered in situ thromboses is characterized as the "spotted spleen" or "fleckmilz." It is usually produced by acute infectious diseases that initiate acute vasculitis and thromboses of splenic vessels. In this condition, the splenic substance is dotted by minute infarctions that vary from 1 to 5 mm in diameter.

Splenic infarcts are an important clinical consideration in older cardiac patients who suddenly complain of left upper quadrant pain. This clinical accident is not an unusual accompaniment of bacterial infective endocarditis. Occasionally in these cases, the fibrinous perisplenitis leads to friction rubs that can be heard in the left upper quadrant. The destruction of splenic substance is not critically significant, and the major importance of these infarcts is their differentiation from other more serious intra-abdominal diseases that cause left upper quadrant pain: e.g., rupture of the spleen, perforation of the stomach or intestines, or rupture of an intra-abdominal aneurysm.

NEOPLASMS

Neoplastic involvement of the spleen, whether primary or secondary, may induce splenomegaly.

PRIMARY LESIONS

In general, primary tumors, either benign or malignant, are rare.

BENIGN. The following types of benign tumors may arise in the spleen: fibromas, osteomas, chondromas, lymphangiomas, and hemangiomas. The last-named two are the most common and are often cavernous in type. Undoubtedly, some of the hemangiomas are better classified as hamartomas than as neoplasms.

MALIGNANT. Any of the types of non-Hodgkin's lymphomas or Hodgkin's disease primary in the lymph nodes (p. 657) may be primary in the spleen, and in this organ they have the same characteristics as in the lymph nodes. In addition to these lesions, hemangiosarcomas with metastases, especially to the liver, do occur (p. 542).

SECONDARY LESIONS

Whether to call involvement of the spleen in systemic Hodgkin's disease or disseminated non-Hodgkin's lymphomas a secondary lesion is largely a semantic issue; however, as you recall, splenic involvement in these conditions is by no means uncommon. Metastases of other types of tumors to the spleen have been reported to be rare, or present in 50% of cases when assiduously sought. In either event, metastases appear in the spleen only when the primary lesion has disseminated widely, and are of little clinical consequence since the patients are almost always in a terminal stage.

Figure 15–47. Large spontaneous hemorrhage into spleen of a 27-year-old patient with infectious mononucleosis. Hematoma ruptured through capsule and caused massive intraperitoneal hemorrhage.

RUPTURE

Rupture of the spleen is usually caused by a crushing injury or severe blow. Much less often, it is encountered in the apparent absence of trauma: this event is designated as spontaneous rupture. It is a clinical maxim that the normal spleen never ruptures spontaneously. In all instances of apparent nontraumatic rupture, some underlying condition should be suspected as the basis for the enlargement or weakening of this organ. Spontaneous rupture is encountered most often in infectious mononucleosis, malaria, typhoid fever, leukemia, and the other types of acute splenitis (Fig. 15–47). Rupture is usually followed by extensive, sometimes massive, intraperitoneal hemorrhage. The condition usually must be treated by prompt surgical removal of the spleen to prevent death from loss of blood and shock. In rare instances, clotting staunches the flow of blood. In some cases, following rupture, spleniculi may be found either localized or scattered throughout the peritoneal cavity, apparently transplants of splenic substance.

1. Young, G.A.R., and Vincent, P.C.: Drug-induced agranulocytosis. Clin. Hematol. *9*:483, 1980.
2. Nathwani, B.N.: A critical analysis of the classification of non-Hodgkin's lymphoma. Cancer *44*:347, 1979.
3. National Cancer Institute: Sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a Working Formulation for Clinical Usage. Cancer *49*:2112, 1982.
4. Nathwani, B.N., et al.: Non-Hodgkin's lymphomas. A clinicopathologic study comparing two classifications. Cancer *41*:303, 1978.
5. Rappaport, H.: Follicular lymphoma, a reevaluation of its position in the scheme of malignant lymphoma based on a survey of 253 cases. Cancer *9*:792, 1956.
6. Mann, R.B., et al.: Malignant lymphomas—a conceptual understanding of morphologic diversity. A review. Am. J. Pathol. *94*:105, 1979.
7. Pangalis, G.A., et al.: Malignant lymphoma, well-differentiated lymphocytic: Its relationship with chronic lymphocytic leukemia and macroglobulinemia of Waldenström. Cancer *39*:999, 1977.
8. Fisher, R.I., et al.: Diffuse aggressive lymphomas: Increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann. Intern. Med. *98*:304, 1983.
9. Nathwani, B.N., et al.: Malignant lymphoblastic lymphoma. Cancer *38*:964, 1976.
10. Nathwani, B.N., et al.: Lymphoblastic lymphoma. A clinicopathologic study of 95 patients. Cancer *48*:2347, 1981.
11. Levine, A.M., et al.: Successful therapy of convoluted T-lymphoblastic lymphoma in the adult. Blood *61*:92, 1983.
12. Miliauskas, J.R., et al.: Undifferentiated non-Hodgkin's lymphoma (Burkitt's and non-Burkitt's types). The relevance of making this histologic distinction. Cancer *50*:2115, 1982.
13. Grogan, T.M., et al.: A comparative study of Burkitt's and non-Burkitt's "undifferentiated" malignant lymphoma: Immunologic, cytochemical, ultrastructural, cytologic, histopathologic, clinical and cell culture features. Cancer *49*:1817, 1982.
14. Lukes, R.J., et al.: Immunologic approach to non-Hodgkin's lymphomas and related leukemias. Analysis of the results of multiparameter study of 425 cases. Semin. Hematol. *15*:322, 1978.
15. Collins, R.D.: T-cell neoplasms. Am. J. Surg. Pathol. *6*:745, 1982.
16. Edelson, R.L.: Cutaneous T cell lymphoma. J. Dermatol. Surg. Oncol. *6*:358, 1980.
17. Miller, R.A., et al.: Sézary syndrome: A model for migration of T lymphocytes to skin. N. Engl. J. Med. *303*:89, 1980.
18. Broder, S., and Bunn, P.A., Jr.: Cutaneous T cell lymphomas. Semin. Oncol. *7*:310, 1980.
19. Byrne, G.E.: Rappaport classification of non-Hodgkin's lymphomas. Histologic significance. Cancer Treat. Rep. *61*:935, 1977.
20. Stein, R.S., et al.: Correlations between immunologic markers and histopathologic classifications—clinical implications. Semin. Oncol. *7*:244, 1980.
21. Whitcomb, C.C., et al.: Subcategories of histiocytic lymphoma: Association with survival and reproducibility of classification. The Southeastern Cancer Study Group. Cancer *48*:2464, 1981.
22. Nathwani, B.N., et al.: The clinical significance of the morphologic subdivision of diffuse "histiocytic" lymphoma. A study of 162 patients treated by Southwest Oncology Group. Blood *60*:5, 1982.
23. Jaffe, E.S., et al.: Predictability of immunologic phenotype by morphologic criteria in diffuse aggressive non-Hodgkin's lymphomas. Am. J. Clin. Pathol. *77*:46, 1982.
24. Rudders, R.A.: Surface markers in non-Hodgkin's lymphomas. Hosp. Pract. *18*:161, 1983.
25. Banfi, A., et al.: Preferential sites of involvement and spread in malignant lymphomas. Eur. J. Cancer *4*:319, 1968.
26. Purtillo, D.T., et al.: Epstein-Barr virus induced disease in boys with the X-linked lymphoproliferative syndrome (XLP). Update on studies of the registry. Am. J. Med. *73*:49, 1982.
27. Bird, A.G., and Britton, S.: The relationship between Epstein-Barr virus and lymphoma. Semin. Hematol. *19*:285, 1982.
28. Yunis, J.J., et al.: Distinctive chromosomal abnormalities in histologic subtypes of non-Hodgkin's lymphomas. N. Engl. J. Med. *307*:1231, 1982.
29. Murphy, S.B.: Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: Dissimilarities from lymphomas in adults. Semin. Oncol. *7*:332, 1980.
30. Lukes, R.J., et al.: Reed-Sternberg–like cells in infectious mononucleosis. Lancet *2*:1003, 1969.
31. Rappaport, H., et al.: Report of the committee on histopathological criteria contributing to staging of Hodgkin's disease. Cancer Res. *31*:1864, 1971.
32. Strum, S.B., et al.: Observation of cells resembling Sternberg-Reed cells in conditions other than Hodgkin's disease. Cancer *26*:176, 1970.
33. Lukes, R.J., et al.: Report of the nomenclature committee. Cancer Res. *26*:1311, 1966.
34. Gutensohn, N.M.: Social class and age at diagnosis of Hodgkin's disease: New epidemiologic evidence for the "two disease hypothesis." Cancer Treat Rep. *66*:689, 1982.
35. Gallo, R.C., and Gelmann, E.P.: In search of a Hodgkin's disease virus. N. Engl. J. Med. *304*:169, 1981.
36. Kaplan, H.S.: Hodgkin's disease: Biology, treatment, prognosis. Blood *57*:813, 1981.
37. Fisher, R.I.: Implications of persistent T cell abnormalities for the etiology of Hodgkin's disease. Cancer Treat. Rep. *66*:681, 1982.
38. Schwab, U., et al.: Production of a monoclonal antibody specific for Hodgkin's and Sternberg-Reed cells of Hodgkin's disease and a subset of normal cells. Nature *299*:65, 1982.
39. Kadin, M.E.: Possible origin of the Reed-Sternberg cell from an interdigitating reticulum cell. Cancer Treat. Rep. *66*:601, 1982.
40. Bennett, J.M., et al.: Proposals for the classification of the acute leukaemias. French-American-British (FAB) Cooperative Group. Br. J. Haematol. *33*:45, 1976.
41. Foon, K.A., et al.: Surface markers on leukemia and lymphoma cells: Recent advances. Blood *60*:1, 1982.
42. Tomonaga, M.: Statistical investigation of leukaemia in Japan. N.Z. Med. J. *65*:863, 1966.
43. Cossman, J., et al.: Induction of differentiation in a case of common acute lymphoblastic leukemia. N. Engl. J. Med. *307*:1251, 1982.
44. Goldman, J.M., and Lu, D.: New approaches in chronic granulocytic leukemia—origin, prognosis and treatment. Semin. Hematol. *19*:241, 1982.
45. Greaves, M.M.: "Target cells," cellular phenotypes, and lineage fidelity in human leukemia. J. Cell Physiol. (Suppl. 1):113, 1982.

46. Editorial: Leukaemogenesis and differentiation. Lancet *1*:33, 1983.
47. Koeffler, H.P., and Golde, D.W.: Chronic myelogenous leukemia—new concepts. N. Engl. J. Med. *304*:1201, 1981.
48. Lawler, S.D.: Significance of chromosomal abnormalities in leukemia. Semin. Hematol. *19*:257, 1982.
49. Yunis, J.J., et al.: All patients with acute non-lymphocytic leukemia may have chromosomal defect. N.Engl. J. Med. *305*:135, 1981.
50. Yunis, J.J.: Specific fine chromosomal defects in cancer: An overview. Hum. Pathol. *12*:503, 1981.
51. Marx, J.L.: The case of the misplaced gene. Science *218*:983, 1982.
52. Rowley, J.D.: Human oncogene locations and chromosomal aberrations. Nature *301*:290, 1983.
53. Bjergaard, J.P.: Incidence of acute non-lymphocytic leukemia, preleukemia and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. N. Engl. J. Med. *307*:965, 1982.
54. Editorial: Gallo on T-cell leukaemia-lymphoma virus. Lancet *2*:1083, 1982.
55. Blayney, D.W., et al.: The human T-cell leukemia/lymphoma virus, lymphoma, lytic bone lesions, and hypercalcemia. Ann. Intern. Med. *98*:144, 1983.

55A. Bakhshi, A., et al.: Lymphoid blast crises of chronic myelogenous leukemia represent stages in the development of B-cell precursors. N. Engl. J. Med. *309*:826, 1983.

56. Cawley, J.C., et al.: Hairy cell leukemia. Recent Results Cancer Res. *72*:58, 1980.
57. Worman, C.P., et al.: Alterations in the phenotype of hairy cells during culture in the presence of PHA: Requirement for T cells. Blood *59*:895, 1982.
58. Uchiyama, T., et al.: Adult T cell leukemia: Clinical and hematologic features of 16 cases. Blood *50*:481, 1977.
59. Shimoyama, M., et al.: Comparison of clinical, morphologic and immunologic characteristics of adult T-cell leukemia-lymphoma and cutaneous T-cell lymphoma. Jpn. J. Clin. Oncol. *9*(Suppl.):357, 1979.
60. Groopman, J.E.: Editorial—Pathogenesis of myelofibrosis in myeloproliferative disorders. Ann. Intern. Med. *92*:857, 1980.
61. Cappio, F.C., et al.: Idiopathic myelofibrosis: A possible role for immune complexes in the pathogenesis of bone marrow fibrosis. Br. J. Haematol. *49*:17, 1981.
62. Kyle, R.A.: Monoclonal gammopathy of undetermined significance (MGUS): A review. Clin. Hematol. *11*:125, 1982.
63. Solomon, A.: Bence Jones Proteins: Malignant or benign. N. Engl. J. Med. *306*:605, 1981.
64. Salmon, S.E., and Seligmann, M.: B-cell neoplasia in man. Lancet *2*:1230, 1974.
65. Isobe, T., and Osserman, E.F.: Pathologic conditions associated with plasma cell dyscrasias. A study of 806 cases. Ann. N.Y. Acad. Sci. *190*:507, 1972.
66. Baitz, T., and Kyle, R.A.: Solitary myeloma in chronic osteomyelitis. Arch. Intern. Med. *113*:872, 1964.
67. DePetris, S., et al.: Localization of antibodies in plasma cells by electron microscopy. J. Exp. Med. *117*:849, 1963.
68. Zlotnick, A., and Rosenmann, E.: Renal pathologic findings associated with monoclonal gammopathies. Arch. Intern. Med. *135*:40, 1975.
69. Cohen, A.H., and Border, M.D.: Myeloma kidney. An immunomorphogenetic study of renal biopsies. Lab Invest. *42*:248, 1980.
70. Glenner, G.G., et al.: Amyloidosis. Its nature and pathogenesis. Semin. Hematol. *10*:65, 1973.
71. Ullrich, S., and Zolla-Pazner, S.: Immunoregulatory circuits in myeloma. Clin. Hematol. *11*:87, 1982.
72. Defronzo, R., et al.: Renal function in patients with multiple myeloma. Medicine (Balt.) *57*:151, 1978.
73. Ritzmann, S.E.: Idiopathic (asymptomatic) monoclonal gammopathies. Arch. Intern. Med. *135*:95, 1975.
74. Bataille, R.: Localized plasmacytomas. Clin. Hematol. *11*:113, 1982.
75. Conklin, R., and Alexanian, R.: Clinical classification of plasma cell myeloma. Arch. Intern. Med. *135*:139, 1975.
76. Tursz, T.: Clinical and pathologic features of Waldenström's macroglobulinemia in 7 patients with serum monoclonal IgG or IgA. Am. J. Med. *63*:499, 1977.
77. Dutcher, T.F., and Fahey, J.L.: The histopathology of the macroglobulinemia of Waldenström. J. Natl. Cancer Inst. *22*:887, 1959.
78. Krajny, M., et al.: Waldenström's macroglobulinemia: Review of 45 cases. Can. Med. Assoc. J. *114*:899, 1976.
79. Seligmann, M., et al.: Heavy-chain diseases: Current findings and concepts. Immunol. Rev. *48*:145, 1979.

79A. Khojasteh, A., et al.: Immunoproliferative small intestinal disease. A "third world lesion." N. Engl. J. Med. *308*:1401, 1983.

80. Stoop, J.W., et al.: Alpha-chain disease with involvement of the respiratory tract in a Dutch child. Clin. Exp. Immunol. *9*:625, 1971.
81. Franklin, E.C.: Mu-chain disease. Arch. Intern. Med. *135*:71, 1975.
82. Murphy, G.F., et al.: Distribution of cell surface antigens in histiocytosis X cells. Quantitative immune electron microscopy using monoclonal antibodies. Lab Invest. *48*:90, 1983.
83. Corrin, B., and Basset, F.: A review of histiocytosis X with particular reference to eosinophilic granuloma of the lung. Invest. Cell Pathol. *2*:137, 1979.
84. Nezelof, C.: Histiocytosis X: A histologic and histogenetic study. Perspect. Pediatr. Pathol. *5*:153, 1979.
85. Wolfson, W.L., et al.: Systemic giant cell histiocytosis; report of a case and review of the adult form of Letterer-Siwe disease. Cancer *38*:2529, 1976.
86. Lahey, M.E.: Histiocytosis X—comparison of three treatment regimens. J. Pediatr. *87*:179, 1975.
87. Osband, M., et al.: Histiocytosis X. Demonstration of abnormal immunity, T cell histamine H-2 receptor deficiency, and successful treatment with thymic extract. N. Engl. J. Med. *304*:146, 1981.
88. Lieberman, P.H., et al.: A reappraisal of eosinophilic granuloma of bone, Hand-Schüller-Christian syndrome and Letterer-Siwe syndrome. Medicine *48*:375, 1969.
89. Berris, B., et al.: Immunoblastic lymphadenopathy: Report of four new cases and review of the disease. Can. Med. Assoc. J. *127*:389, 1982.
90. Pruzanski, W.: Lymphadenopathy associated with dysgammaglobulinemia. Semin. Hematol. *17*:44, 1980.
91. Neiman, R.S., et al.: Angioimmunoblastic lymphadenopathy. An ultrastructural and immunologic study with review of the literature. Cancer *41*:507, 1978.
92. Boros, L., et al.: Monoclonal evolution of angioimmunoblastic lymphadenopathy. Am. J. Clin. Pathol. *75*:856, 1981.
93. Enriquez, P., and Neiman, R.S.: The Pathology of the Spleen, A Functional Approach. Chicago, American Society of Clinical Pathologists, 1976, p. 11.
94. Bishop, M.B., and Lansing, L.S.: The spleen: A correlative overview of normal and pathologic anatomy. Hum. Pathol. *13*:334, 1982.