Review Article

EXPERIMENTAL MODELS OF LYMPHOPROLIFERATIVE DISEASE: THE MOUSE AS A MODEL FOR HUMAN NON-HODGKIN'S LYMPHOMAS AND RELATED LEUKEMIAS

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Experimental Models of Lymphoproliferative Disease

The Mouse as a Model for Human Non-Hodgkin's Lymphomas and Related Leukemias

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The present review focuses on the mouse as an experimental immunopathologic model for human non-Hodgkin's lymphomas and related leukemias. Immunomorphologic evidence is presented that clearly demonstrates that B- and T-cell subtypes of mouse (murine) lymphoma/leukemia closely resemble and are analogous to B- and T-cell subtypes of human lymphoma/leukemia as defined by recently proposed immunomorphologic classifications. Further evidence is presented that favors the hypothesis that certain types of murine and human B-cell lymphoma develop out of prodromal, prelymphomatous states, which exhibit antecedent morphologic and immunologic abnormalities. The many experimental advantages of the murine systems are stressed, as well as the concept that the presently defined immunomorphologic approach should be effectively combined with molecular and cytogenetic parameters. (Am J Pathol 1983, 113: 237–265)

WHAT IS the rationale for studying animal models of lymphoma and related leukemias? If one is able to demonstrate that lymphomas and related leukemias in animals possess clinical and immunopathologic similarities to analogous diseases in man, one can then utilize these models experimentally to ask relevant questions that are not readily addressed from the study of human disease. In particular, the study of mouse (murine) models provides direct access to large genetically uniform populations and, furthermore, allows for the performance of carefully controlled, *prospective* studies that relate to etiology, pathogenesis, and therapeutic modalities. The purposes of this review are, first, to provide a focused rationale for murine lymphoma/leukemia as a model for human non-Hodgkin's lymphoma/leukemia and, second, to describe certain prelymphomatous states in the mouse, the study of which may provide further insight into the analogous prelymphomatous conditions of man.

Murine Models of Lymphomas and Related Leukemias

Classification of Lymphoma/Leukemia

Our understanding of the so-called lymphoreticular neoplasms of man has increased dramatically during the past decade. This has resulted in a radical reevaluation of concepts and a revised nomenclature and classification more in keeping with current knowledge of the form, function, and potentialities of the lymphocyte. Thus, the older designations of lymphosarcoma, giant follicular lymphoma, and reticulum cell sarcoma, together with the terms *lymphocytic, mixed*, and *histiocytic lymphoma* have been replaced by a new nomenclature that recognizes the lymphocytic origin of the great majority of primary lymphoreticular neoplasms. Several classifications were formulated in an attempt to incorporate these newer immunomorphologic concepts, but only two, the Lukes-Collins[1] and the Kiel (Lennert)[2] classifications, have achieved widespread recognition. The more recently devised National Institutes of Health (NIH) Formulation[3] represents an attempt to develop a generally acceptable "universal" classification. The essence of these proposals is summarized in Table 1 and is published in more detail elsewhere.[4]

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Table 1—Immunomorphologic Classification of Human Lymphoid Cell Neoplasms

Morphologic division* (lymphoid cell type)	Immunologic division†	
	B-cell	T-cell
Small lymphocyte	Lymphocytic lymphoma/leukemia (including B-CLL)	Lymphocytic lymphoma/leukemia (including T-CLL)
Follicular center cell (FCC)	FCC lymphoma/leukemia‡	0
Lymphoblast§	Lymphoblastic lymphoma/leukemia (Burkitt or Burkitt-like)	Lymphoblastic lymphoma/leukemia, convoluted lymphocytic lymphoma/leukemia
Immunoblast	Immunoblastic lymphoma (sarcoma)	Immunoblastic lymphoma (sarcoma)
Plasma cell	Plasmacytoma/plasma cell lymphoma/myeloma	0
Plasmacytoid lymphocyte	Plasmacytoid lymphocytic lymphoma	0
Hairy cell	Hairy cell leukemia	0
Small lymphocyte with epithelioid cells	0	Lymphoepithelioid cell lymphoma
Cerebriform lymphocyte	0	Sezary/mycosis fungoides

CLL, chronic lymphocytic leukemia; 0, not observed or expected.

* Modified from Lukes-Collins[1] and Lennert.[2]

† The only generally accepted non-B, non-T process in man is acute lymphoblastic leukemia (ALL), particularly occurring in childhood. The tumor cells do not bear the usual T- or B-cell markers, although recently a pre-B cell category has been distinguished within this group on the basis of cytoplasmic μ chain (no detectable surface Ig). Sporadic cases of nonmarking (ie, non-B, non-T) human lymphomas involving small lymphocytes or immunoblasts have been observed. The concept that morphologically defined small lymphocytes or immunoblasts may represent nonmarking stem or progenitor cells is alluded to in Table 2 and discussed in more detail in the "Mouse Non-B, Non-T Lymphoma/Leukemia" section of this review.

‡ Certain subtypes of FCC lymphoma frequently show early peripheral blood and marrow involvement (ie, leukemic phase of lymphoma).

§ This category is frequently difficult to define. B-cell lymphoblastic lymphoma/leukemia (Burkitt's or Burkitt-like) is considered by Lukes and Collins[1] to be a small noncleaved FCC lymphoma. T-cell lymphoblastic lymphoma/leukemia is also difficult to define because of the continuing controversy over whether or not convoluted T cells are always recognizable in this process; in the absence of convolutions or marker techniques, these processes are not cytologically distinguishable from ALL.

In parallel with the recognition that lymphomas in man are neoplasms of lymphoid cells, it became evident that the corresponding designations of lymphocytic neoplasm (lymphosarcoma) and reticulum cell sarcoma (RCS), as originally defined in the mouse by Dunn,[5-8] also required reevaluation and revision.[9]

Because the immune system in mice, as in men, is divided into T- and B-cell compartments and because lymphomas represent neoplastic conversions of these normal cell counterparts, it is logical to classify lymphomas and related leukemias in mice as either B or T cells, with regard to their morphologic

Table 2—Immunomorphologic Classification of Murine Lymphoid Cell Neoplasms as Proposed by Pattengale and Taylor (1981)*

Morphologic type† (lymphoid cell morphology)	Immunologic type‡		
	B-cell	T-cell	Non-B, Non-T-cell
Follicle center cell (FCC)§			
Small cell type	+	0	0
Large cell type	+	0	0
Large and small (mixed) type	+	0	0
Plasma cell	+	0	0
Immunoblast	+	(+)	(+)
Small lymphocyte	+	(+)	(+)
Lymphoblast	+‖	+	+

+, already observed and documented; (+), not yet observed, but expected; 0, not observed or expected.

* The proposed classification refers only to lymphoid cell, lymphocyte-derived neoplasms and therefore *excludes* those derived from the monocyte/macrophage/histiocyte series (ie, true histiocytic lymphoma). It is also stressed that the diagnosis of lymphoma/leukemia is based *primarily* on morphologic criteria and is then *subsequently* combined with immunologically based parameters.

† The morphologic cell types listed are those that have been observed and documented to date. If analogous to man, one would expect to observe additional cell types such as the cerebriform lymphocyte (ie, Sézary-mycosis fungoides T-cell) and the plasmacytoid B-lymphocyte (ie, Waldenström's macroglobulinemia), as well as others (see Table 1).

‡ A B cell is defined as having *easily* detectable surface and/or cytoplasmic immunoglobulin; a T-cell is defined as having *easily* detectable surface Thy 1 (ie, theta antigen); a non-B non-T cell is defined as lacking *both* easily detectable Thy-1 and surface and/or cytoplasmic immunoglobulin.

§ Follicular center cell (FCC) lymphomas with a marked lymph node follicular pattern analogous to those appearing in man have not yet been well documented. FCC lymphomas may also contain equally prominent mixtures of both large and small FCC types (FCC lymphoma [mixed] large and small cell types).

‖ Lymphoblastic lymphoma of B cells is considered by some[1] to be a FCC lymphoma and by others[2] to be a separate category. In either event, it closely resembles the Burkitt's lymphoma spectrum.

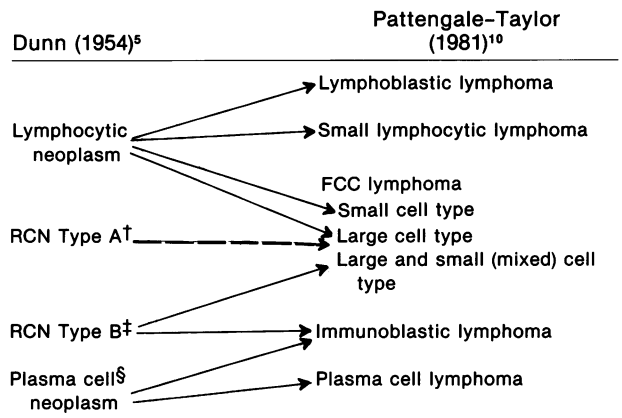
features, location, and functional characteristics. We therefore attempted to correlate the morphologic features of the neoplastic lymphoid cells in the mouse with their B-, T-, or non-B, non-T nature, in a manner somewhat analogous to that proposed for the corresponding lymphomas in man.[1-4] This proposed immunomorphologic classification[10] (Table 2) presently lists five major morphologic cell types and is intended to be scientifically accurate, easily taught, easily learned, reproducible, and ultimately clinically useful. It should be stressed that the diagnosis of lymphoma/leukemia is based *first* on morphologic criteria and is then *subsequently* combined with immunologic parameters. A B cell is defined as having *easily* detectable surface and/or cytoplasmic immunoglobulin (Ig); a T-cell is defined as having *easily* detectable surface Thy-1; a non-B, non-T cell is defined as *lacking* both easily detectable surface Thy-1 as well as easily detectable surface and/or cytoplasmic Ig.

In Table 3 the morphologic classification of Dunn (1954)[5] is compared with the neoplastic lymphoid cell types defined by the present authors (1981),[10] and it is demonstrated that there is considerable heterogeneity within the "lymphocytic" and "reticulum cell neoplasm" (RCN) categories of Dunn. It should also be noted that RCN, Type B, includes *both* lymphomatous and prelymphomatous conditions of the non-Hodgkin's type, and that these conditions can occasionally bear a superficial resemblance to Hodgkin's disease.[9] It should be further stressed that, to the best of our knowledge, there is no available mouse model for Hodgkin's lymphoma at the present time.

Like human lymphoid cell neoplasms, the neoplastic lymphocytic proliferation may be seen as a lymphoma (involving primarily lymph nodes and splenic white pulp) and/or a leukemia (involving primarily bone marrow, peripheral blood, and the splenic red pulp). As with man, this distinction can be, at times, rather difficult and somewhat arbitrary.

The cytologic and histologic features of the various murine lymphoid cell types are given in more detail in Table 4. Using cell size, cytoplasmic as well as nuclear characteristics, mitotic activity, and pattern of tissue involvement, one can usually discriminate between the various cell types, provided that the tissue is adequately fixed and appropriately processed. In this context, Mercury-containing fixatives (B-5) and thin (1-3 μ) sections are essential to the proper evaluation of lymphoid cell proliferations.[11] It should be further stressed that formalin fixation is *less* than optimal, since it induces both nuclear and cytoplasmic shrinkage artifacts. It may therefore be difficult in formalin-fixed tissues to distinguish a lymphoma of small lymphocytes from a lymphoma of lymphoblasts, both of which are noncohesive in tissue section and have scant cytoplasm and a high nuclear/cytoplasmic (N/C) ratio. With proper fixation, however, one can distinguish the primitive, rapidly dividing lymphoblast by its immature, finely dispersed nuclear chromatin, as compared with the slowly dividing small lymphocyte with its mature clumped and condensed nuclear chromatin. Other pertinent examples include the distinction of large follicular center cells (FCCs) from immunoblasts on cytoplasmic and N/C ratio criteria, as well as the distinction of small lymphocytes from small FCCs on the basis of nuclear cleavage planes.

Table 3—Comparison of the Proposed Classifications for Murine Lymphoma and Related Leukemias*



* As proposed by Dunn, lymphocytic neoplasms can be localized (ie, lymphoma) or generalized (ie, leukemia) involving the peripheral blood and bone marrow compartments. By comparison and direct analogy, lymphomas of lymphoblasts, small lymphocytes, and follicle center cells can manifest with leukemic phases (ie, lymphoma/leukemias). RCN, Type C is considered by Dunn to be nonneoplastic and nonlymphoid in origin.

† Most RCNs (reticulum cell neoplasms), Type A, as proposed by Dunn, are considered to be derived from true histiocytic cells (ie, true *nonlymphoid*, phagocytic histiocytes) and rarely can present as a monocytic leukemia. The dotted line stresses the fact that a few tumors morphologically classified as RCN, Type A, may represent large FCC (follicular center cell) lymphomas.

‡ Although RCN, Type B, is now considered *not* to be representative of Hodgkin's disease, it can include *both* prelymphomatous, nonneoplastic lymphoproliferations and true lymphoid cell lymphomas (mixed FCC and immunoblastic cell types). A lymphoma is defined as a lymphoid cell neoplasm (ie, an autonomous monoclonal new growth, presumably derived from one cell). In contrast, a prelymphoma is defined as a conditioned, atypical lymphoid cell hyperplasia derived from more than one cell (*non*monoclonal, oligoclonal, or polyclonal derivation), with a propensity to progress to a true lymphoid cell neoplasm with time.

§ As stated by Dunn, a proportion of plasma cell neoplasms were formed by typical well-differentiated plasma cells, while others were formed of a cell type resembling a reticulum cell (ie, a B-immunoblast with plasmacytoid features). This concept was in agreement with Rask-Nielsen classification of plasma cell neoplasms. It should be noted that the term *plasma cell leukemia* was used to denote a localized growth (lymphoma). True plasma cell leukemia with peripheral blood and bone marrow involvement is rare.

Table 4—Cytologic* and Anatomic Features of Lymphoid Cell Types Observed in Murine Lymphoid Cell Neoplasms

Morphologic cell type	Cytologic features				Anatomic features
	Size†	Cytoplasmic (C) features	Nuclear (Nu) features	Other‡	
Small lymphocyte (Figure 1)	Small (4–8 μ)	Scant; high Nu/C ratio	Mature condensed chromatin, round to slightly irregular	Uniform, noncohesive; absent to low mitotic rate (<2/hpf)	Diffuse involvement of spleen and lymph nodes; frequently leukemic
Follicular center cell (FCC)§					
Small (Figure 2)	Small to intermediate (6–10 μ)	Scant; high Nu/C ratio	Mature condensed chromatin, cleaved, nucleoli inconspicuous	Cohesive; absent to low mitotic rate (<2/hpf)	Early lesions are confined to the white pulp of the spleen; leukemic phase may be difficult to recognize
Large (Figures 3 and 4)	Intermediate to large (8–16 μ)	Scant to moderate; moderate to high Nu/C ratio	Round (noncleaved) and cleaved types; nucleoli often juxtaposed to nuclear membrane	Cohesive, intermediate to high mitotic rate (4–8/hpf); often admixed with small FCC cells (Figure 5)	Early lesions are confined to the white pulp of the spleen and progress to confluence first in the spleen and later in the lymph nodes, liver, lungs, and kidney
Immunoblast (Figure 6)	Large (10–18 μ)	Moderate to abundant (often indented); low to intermediate Nu/C ratio; B-cell type is amphophilic	Vesicular, round to oval; nucleoli usually conspicuous and large; B-cell nucleus often eccentric (plasmacytoid)	Usually noncohesive; intermediate to high mitotic rate (4–8/hpf)	Same as for large FCC type (as above) but usually more invasive; sarcomatous involvement of extralymphoid sites (eg, exocrine pancreas)
Plasma cell (Figure 7)	Small to large (7–16 μ)	Abundant, amphophilic; low to intermediate Nu/C ratio	Eccentric, marginated condensed chromatin; round to oval	Noncohesive; mitotic activity and nucleoli are variable	Spontaneous plasma cell lymphomas are uncommon (see text); mineral-oil–induced tumors involve the peritoneum
Lymphoblast‖ (Figures 8 and 10)	Small to large (7–12 μ)	Barely distinguishable to scant; high Nu/C ratio	Immature, finely dispersed and stipled chromatin; round to irregular; nucleoli often inconspicuous but occasionally central and prominent	Uniform, noncohesive; intermediate to very high mitotic rate (6–10/hpf)	Distinct diffuse involvement of spleen, lymph nodes,thymus, marrow, liver, lungs, and kidneys; frequent involvement of central nervous system and genitourinary and gastrointestinal tracts; often secondary leukemia involvement (ie, spillover)

* Discrimination of cell type with the use of the above features is highly dependent on adequately fixed and processed tissue. Ideally, lymphoid tissue should be fixed in mercury fixative (B-5) and then cut at 1–3 μm and stained with hematoxylin and eosin (H and E) as well as methyl green pyronin (MGP).

† A good and reliable tissue yardstick for comparison is the mouse red blood cell, which averages 6 μm in diameter.

‡ hpf, high-power field.

§ Murine large FCC lymphomas are composed of either noncleaved (ie, round nucleus) (Figure 4) or cleaved (ie, irregularly shaped, elongated, indented, notched nucleus) (Figure 3) B-cell types. Either type can predominate, but frequently one observes equal mixtures of both large cell types. Frequently FCC lymphomas have an equally prominent and distinct population of small follicular center cells admixed with the large follicular center cells (ie, large and small [mixed] FCC type) (Figure 5). A useful guideline for the designation of an FCC lymphoma as mixed (large and small) is a ratio of large to small follicular center cells in the range of 30:70 to 70:30 (ie, large/small follicular center cells). Furthermore, lymphoid cell neoplasms with >70% large or small follicular center cells would be designated either large or small FCC lymphomas.

‖ Although it is sometimes difficult to morphologically distinguish lymphoblastic lymphomas (Figures 8 and 10) from an FCC lymphoma of large, noncleaved (ie, rounded nuclei) type (Figure 4), the following comparative features are often helpful. In general, cells from large noncleaved FCC lymphomas are considerably larger than lymphoblastic lymphomas. In addition, large, noncleaved FCCs usually have prominent vesicular nuclei (white areas), often with one or more nucleoli marginated toward the nuclear membrane (Figure 4). In contrast, lymphoblastic lymphoma cells usually have finely dispersed nuclear chromatin with (Figure 8) or without (Figure 10) a prominent central nucleolus.

Table 5—Correlation of the Normal Murine Lymphoid Cell Types With the Known Corresponding Lymphoma/Leukemias in Various Mouse Model Systems

Normal lymphoid cell counterpart	Corresponding lymphoid cell neoplasm in the mouse	Mouse strain	Comments
B-cell			
Small lymphocyte	Small lymphocytic lymphoma, B-cell type (ie, CLL-like)	2a4b (double congeneic)[12] BALB/c (BCL_1)[13-15]	Model for human B-CLL (ie, chronic lymphocytic leukemia); BCL_1 is spontaneous, both are monoclonal
Small follicular center cell (FCC)	FCC lymphoma, small cell type	NFS/N congeneic* BALB/c[16]	NFS/N congeneic are inbred NIH Swiss mice that are congeneic for AKR ecotropic MuLV (Akv-1 or 2)[17]
Large FCC	FCC lymphoma, mixed and large cell types	SJL/J†[8,9,18,19] NZB[8,9,18] C57BL[8] C57L[8] (C57BLxC3H)F_1[20,21] BALB/c[8,16,22-24]	All strains listed show a spontaneous incidence of RCN, Type B (Dunn), in older mice. Decreased latencies and increased incidences are observed‡ with various inducing agents[25,26]
Immunoblast	Immunoblastic lymphoma, B-cell type	C3H[8] DBA/2[8]	
Plasma cell	Plasma cell lymphoma	BALB/c[27-29] NZB[30] (BALB/cxNZB)F_1[31-33] C3H[6] (CBAxDBA/2)F_1[34]	Occur spontaneously in (CBAxDBA/2)F_1 and C3H (particularly in the ileocecal area); BALB/c, NZB and their F_1 hybrids are inducible with mineral oil
Lymphoblast	Lymphoblastic lymphoma, B-cell type	BALB/c[16]	Occur spontaneously and resemble the Burkitt's lymphoma spectrum
T-cell			
Lymphoblast	Lymphoblastic lymphoma, T-cell type	AKR[35] C58[35] HRS/J[36] C57BL[37,38] BALB/c[39]	AKR, C58, and HRS/J (hr/hr) lymphomas are spontaneous; C57BL and BALB/c[16] have a low spontaneous incidence that is greatly increased with irradiation or chemicals
Non-B, Non-T cell			
Lymphoblast§	Lymphoblastic lymphoma, Non-B, Non-T-cell type	Wild (feral)[40] NIH (Swiss)[40] BALB/c[41-45]	Wild mouse lymphoma is spontaneous; NIH(S) and BALB/c are retrovirus-induced

* Fredrickson T, Rowe WP, Hartley JW, Morse HC, Pattengale PK: Spontaneous development of B cell lymphomas in NFS/N mice congeneic for AKR ecotropic MuLV (manuscript in preparation).

† Although considerable controversy exists, it appears that at least a portion of the spontaneous SJL/J lesions are lymphoid neoplasms of B cells. A larger percentage are probably preneoplastic (ie, prelymphomatous) B cell conditions, while a smaller group probably represent a neoplasm of true histiocytes (ie, muramidase, esterase positive, nonlymphoid histiocytes).

‡ Various inducing agents have included chronic antigenic stimulation (with or without immunosuppression) as well as chemical treatments. Not listed in the table is the observation that certain F_1 hybrids undergoing chronic graft-versus-host disease, after injection of parental cells, develop RCN, Type B, lesions which are likely to be B cell-derived lymphomas.[9,46,47]

§ It should be pointed out that Abelson-MuLV most commonly induces a lymphoblastic lymphoma of non-B, non-T cells. A pre-B cell lymphoma is not rigidly considered a B cell lymphoma by our definition, because its cytoplasmic heavy chain (Ig) is not *easily* demonstrable using conventional techniques (see Tables 1 and 2).

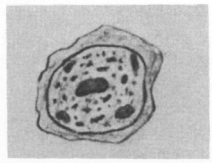
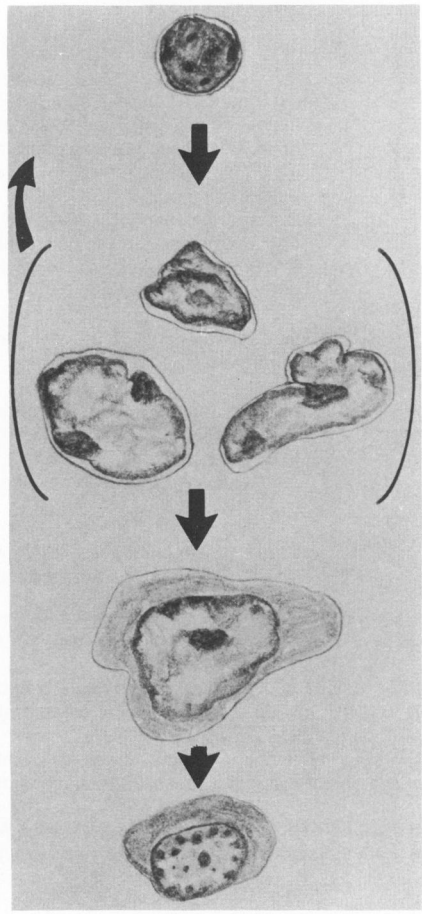
Table 5 lists the various types of murine lymphoid cell neoplasms (lymphomas) with the particular strains in which they occur.[12-47]

Mouse B-Cell Lymphoma/Leukemia

Lymphoid cell neoplasms involving the B-cell arm of the immune system are depicted in Table 6 and are illustrated in Figures 1–8. The corresponding normal cell types include the small B-lymphocyte (Figure 1), the various FCC types (Figures 2–5), the B-immunoblast (Figure 6), the plasma cell (Figure 7), and the B-lymphoblast (Figure 8). Lymphomas within these different B-cell categories vary in frequency, according to strain, age, and whether or not the lymphoid cell neoplasm occurred spontaneously or was induced by exposure to various agents (eg, mineral oil, irradiation) (see Table 5). Although the comparative features of mouse B-cell lymphomas versus human B-cell lymphomas will be discussed in greater length in a subsequent section, it should be noted that in Figures 1–8 the murine lymphomas are morphologically compared with the analogous human counterparts (eg, Figure 1A [murine] versus Figure 1B [human]). With minor exceptions, the comparative features are remarkably similar.

In the context of this discussion, a malignant B-cell lymphoma is defined as a lymphoid cell neoplasm that originates from a single B-lymphocyte or one of its derivatives. Furthermore, it is autonomous with regard to its growth characteristics and possesses a monoclonal distribution of cytoplasmic and/or sur-

Table 6—Immunomorphologic Classification of Murine B-Cell Lymphoma/Leukemia*

	Morphologic B-cell type	Relationship to follicle
	Lymphoblast†	Prefollicular (intrafollicular?)
	Small lymphocyte‡	Prefollicular and postfollicular
	Follicular center cell Small cell type Large cell type Large and small (mixed) cell type	Intrafollicular
	Immunoblast§	Postfollicular
	Plasma cell§	Postfollicular

* A B cell is defined as having *easily* detectable surface and/or cytoplasmic immunoglobulin. The morphologic lymphoid cell types listed are those which have been observed and documented to date.

† Lymphoblastic lymphoma of B-cell type is considered by Lukes and Collins[1] to be a follicular center cell (FCC) lymphoma (ie, small noncleaved FCC type), and by Lennert[2] as a category separate from FCC lymphomas. It appears reasonably certain, however, that the B-lymphoblast is fetal in origin and, during ontogeny, is found in both the bone marrow and gut-associated lymphoid tissue. Whether or not the B-lymphoblast is able to seed FCC areas is unclear at the present time.

‡ Small B-lymphocytes (ie, primarily memory cells) are able to enter the follicle (ie, prefollicular) or leave the follicle (ie, postfollicular).

§ B-immunoblasts and plasma cells are conceptualized as representing major components of postfollicular lymphoid cells. Although plasmacytoid lymphocytes can be easily found in some postfollicular lymphoproliferations, a lymphomatous proliferation of predominantly plasmacytoid lymphocytes has not yet been described, to our knowledge, in the mouse; the plasma cell neoplasms of the mouse may simply reflect a more complete differentiation process of the neoplastic cells than occurs in the plasmacytoid lymphocytic lymphomas of man, which appear to arrest at the IgM stage, prior to the "switch" to IgG- and IgA-producing plasma cells. It should also be stressed that bone-marrow-based plasma cells can arise without an apparent requirement to go through follicular centers. This hypothesis is further substantiated in man by the primary occurrence of malignant plasma cells in multiple bone marrow sites (ie, multiple myeloma).

face Ig consistent with its origin from a single B cell. Because most (ie, approximately 95%) murine light chains are of the kappa type, a cautious approach to the interpretation of monoclonality should be exercised when using conventional anti-isotype and anti-light chain reagents. It should be stressed that the ultimate proof of monoclonality is idiotypic homogeneity.[14,48]

In keeping with the concept that malignant lymphomas may develop from blockages in the differen-

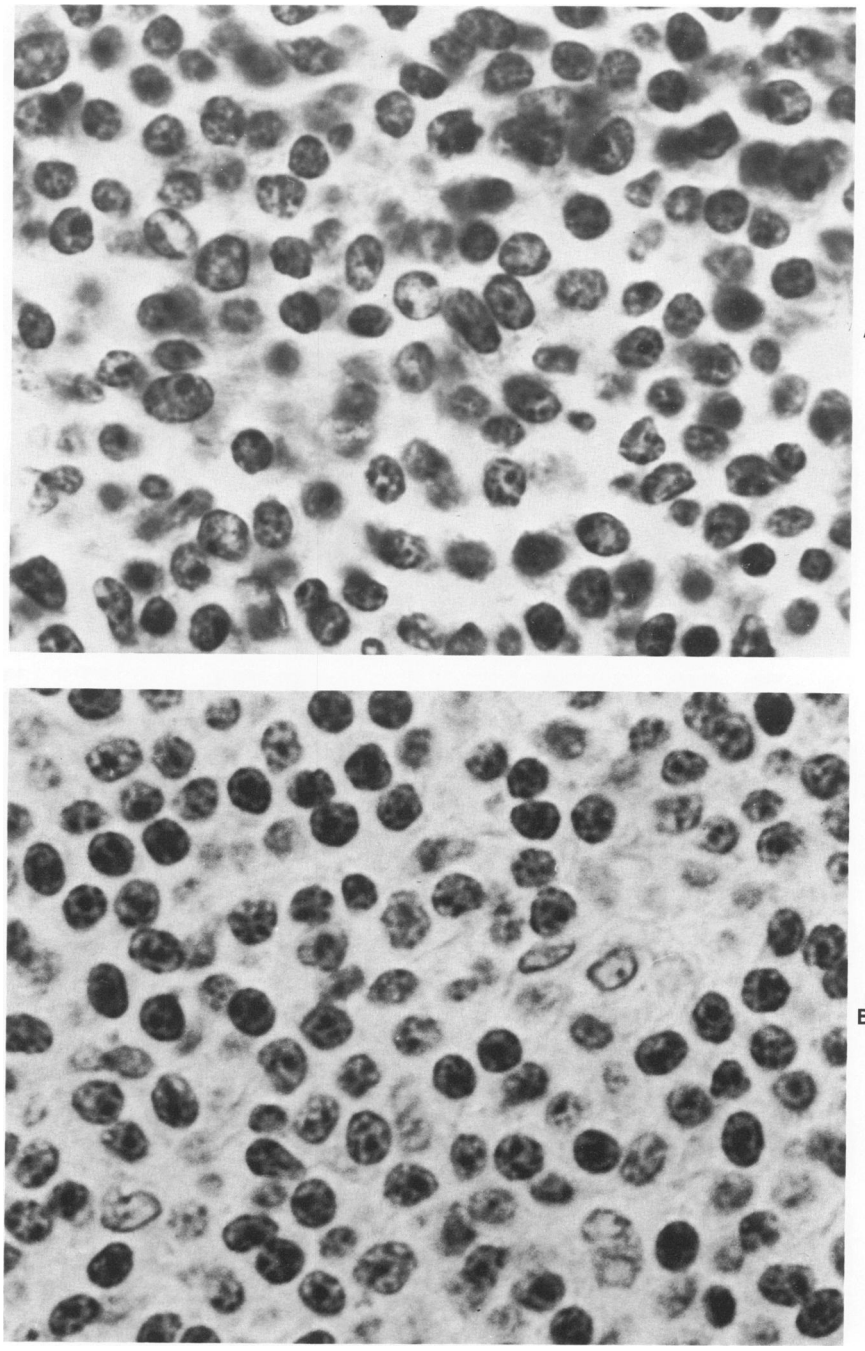


Figure 1A—Murine lymphoma of small B lymphocytes (small lymphocytic lymphoma, B-cell type). Note the small, noncohesive, and round to slightly irregular lymphoid cells with scant cytoplasm and mature, condensed chromatin. This process was surface Ig (SIg)-positive for the IgM-D-κ isotype. (H&E, lymph node nu/nu NIH(S) mouse, ×1100) **B**—Human small lymphocytic lymphoma, B-cell type. Note the close similarities to the murine analogue (**A**). This process was SIg-positive for the IgM-D-λ isotype. (H&E, human lymph node, ×1000)

tiation process, which ultimately lead to abnormal accumulations of lymphoid cells, the *monoclonal* neoplastic B-cell population may appear relatively *monomorphous* on morphologic examination. However, it is clear that for these neoplastic populations to proliferate, some fraction of the overall B-cell population must be in active cell cycle, and such cells may be morphologically different from the predominating cell type (see diagram, Figure 9).[49,50] For example, the B-lymphocyte–derived FCC lymphomas are *monoclonal* with respect to Ig phenotype and may appear relatively *monomorphic*, consisting of a rather monotonous population of small cleaved follicular center cells. However, upon closer examination, a minor component of larger FCCs, representing the actively proliferating fraction of the cell population, will always be discerned. If the proliferating fraction amounts to one-third or more of the overall population, then the morphologic appearance of the tumor as a whole will change, either to a mixed FCC

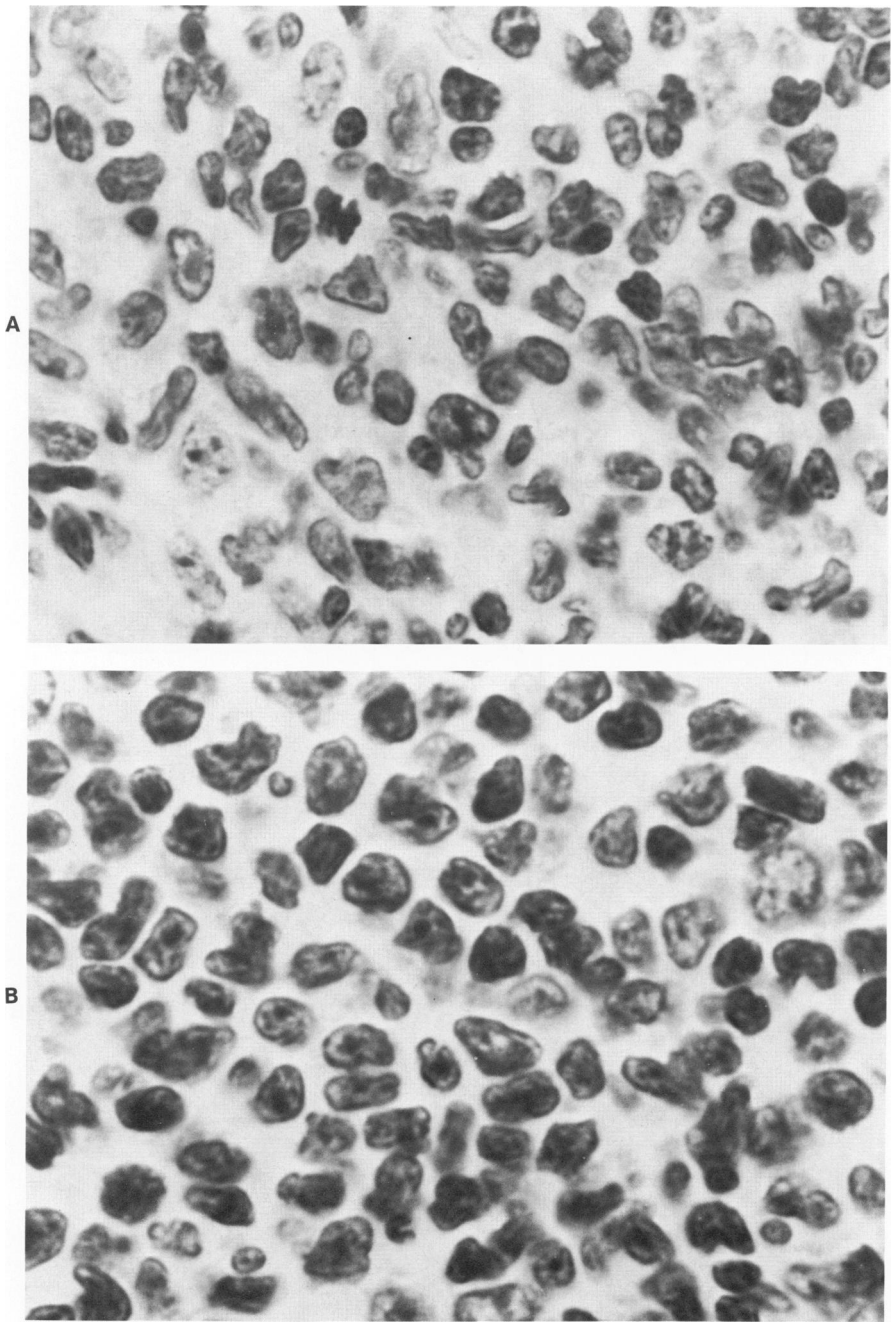


Figure 2A — Murine lymphoma of small cleaved follicular center cells (FCC lymphoma, small cell type). Note the small-to-intermediate-sized and markedly irregular lymphoid cells with scant cytoplasm (cleaved cells [Lukes and Collins] or centrocytes [Lennert]). The mature, condensed chromatin of the predominant small FCC population is often marginated and juxtaposed to the nuclear membrane. Nucleoli are usually not prominent. This process was surface Ig (SIg-positive for the IgM-κ isotype. (H&E, spleen NFS/N congeneic mouse, ×1000) **B** — Human FCC lymphoma, small cleaved type. The human process is similar to the murine analogue (**A**) and was also positive for surface IgM-κ. (H&E, human lymph node, ×1100)

lymphoma or a large cell FCC lymphoma (cleaved or noncleaved), depending upon the proportion of larger cells (see Table 4, footnote). However, even in such circumstances, where a lymphoma consists of a mixture of small and large FCCs, the complete spectrum of differentiating lymphocytes, from small lymphocytes through follicular center cells, immunoblasts, plasma cells, and intermediate forms, is usually lacking. This apparent accumulation or arrest of disproportionate numbers of cells at one phase of this hypothetic differentiation pathway helps distinguish neoplastic populations from the reactive hyperplasias and can therefore be a valuable diagnostic feature. It should also be noted that a proportion of small B-lymphocytes may be considered postfollicular B cells (small memory B cells). It should be

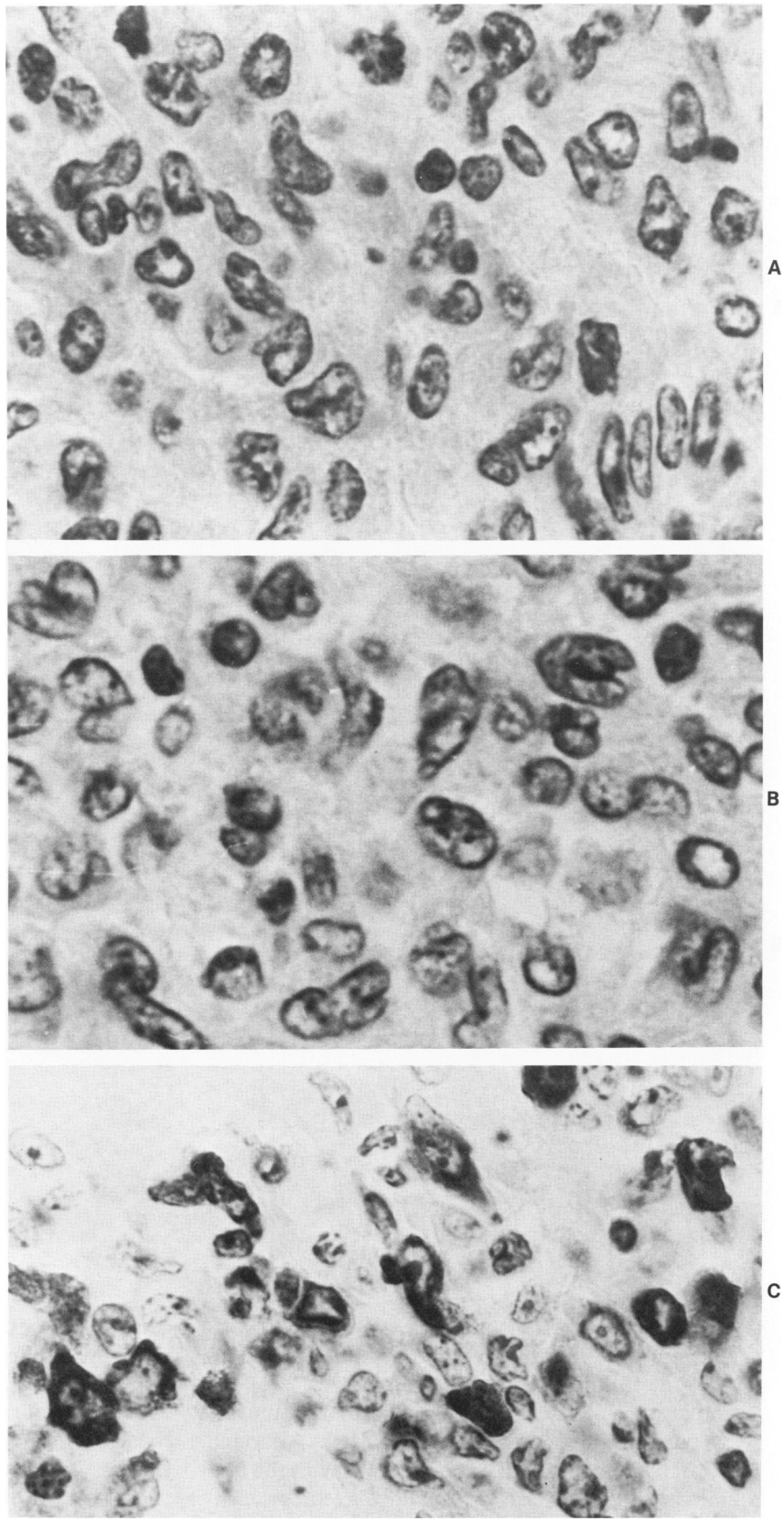


Figure 3A — Murine lymphoma of large cleaved follicular center cells (FCC lymphoma, large cell type). Note the predominance of intermediate to large, cohesive lymphoid cells with irregularly shaped, notched (cleaved) nuclei and moderate amounts of cytoplasm. Similar to that of small FCC populations (see Figure 2), the chromatin is often condensed and marginated on the nuclear membrane. Staining was positive for intracytoplasmic IgA-κ (see C below). (H&E, spleen, NFS/N congeneic mouse, ×1000) **B** — Human FCC lymphoma, large cleaved type. Note the close similarities to the murine analog (**A**). (H&E, human lymph node, ×1100) **C** — Murine lymphoma of large cleaved FCCs. The same process as depicted in **A** stains positively for cytoplasmic IgA-κ. Note the positive staining (black) for κ light chain in the cytoplasm of the large cleaved follicular center cells. (Immunoperoxidase stain counterstained with hematoxylin, spleen, NFS/N congeneic mouse, ×900)

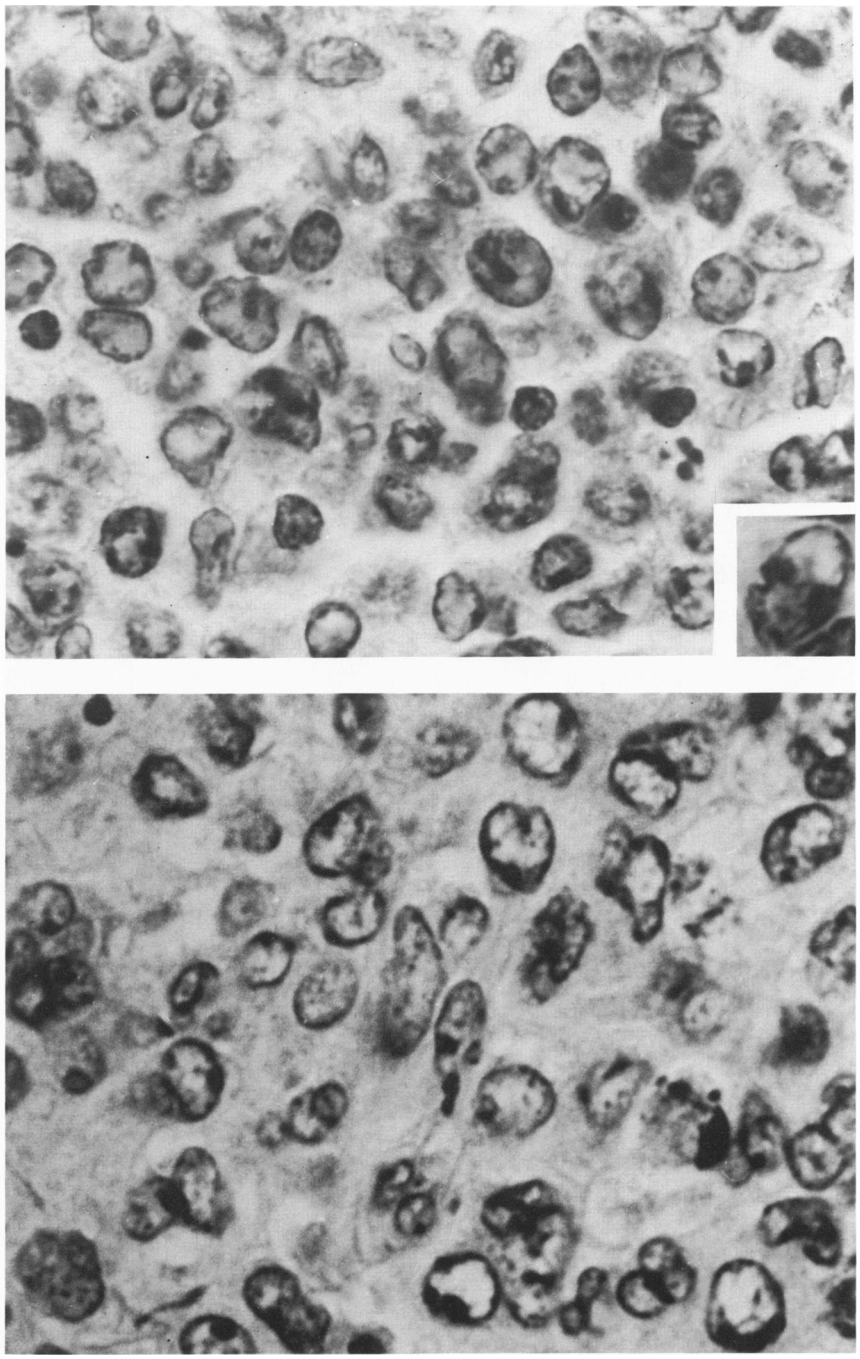


Figure 4A — Murine lymphoma of large noncleaved follicular center cells (FCC lymphoma, large cell type). Note the predominance of intermediate to large, cohesive lymphoid cells with rounded (noncleaved), vesicular nuclei. This process stained positively for cytoplasmic IgM-κ with immunoperoxidase staining. **Inset** — A large, noncleaved cell with characteristic double nucleoli juxtaposed to the nuclear membrane. (H&E, lymph node, BALB/c mouse, ×1000; **Inset**, ×1200) **B** — Human FCC lymphoma, large noncleaved type. Note the close similarities to the murine analog (**A**). (H&E, human lymph node, ×1000)

stressed, however, that such cells are difficult to distinguish morphologically from nonstimulated (uneducated), prefollicular, small B-lymphocytes.

Some additional comparative features of murine FCC lymphomas should be emphasized. Although one observes small cell FCC lymphomas with the predominant cell being that of "small cleaved" or "centrocytic" type, the pattern in lymph nodes is usually diffuse. This is in marked contrast to the majority of human small cleaved (centrocytic) FCC lymphomas, which have a prominent follicular pattern.[1,2] Similarly, the murine large cell FCC type, which corresponds with the large cleaved (ie, centrocytic) and/or large noncleaved (ie, centroblastic) FCC types in man, is also diffuse in nature. An additional note is that the lymphoblastic lymphoma of B cells in hu-

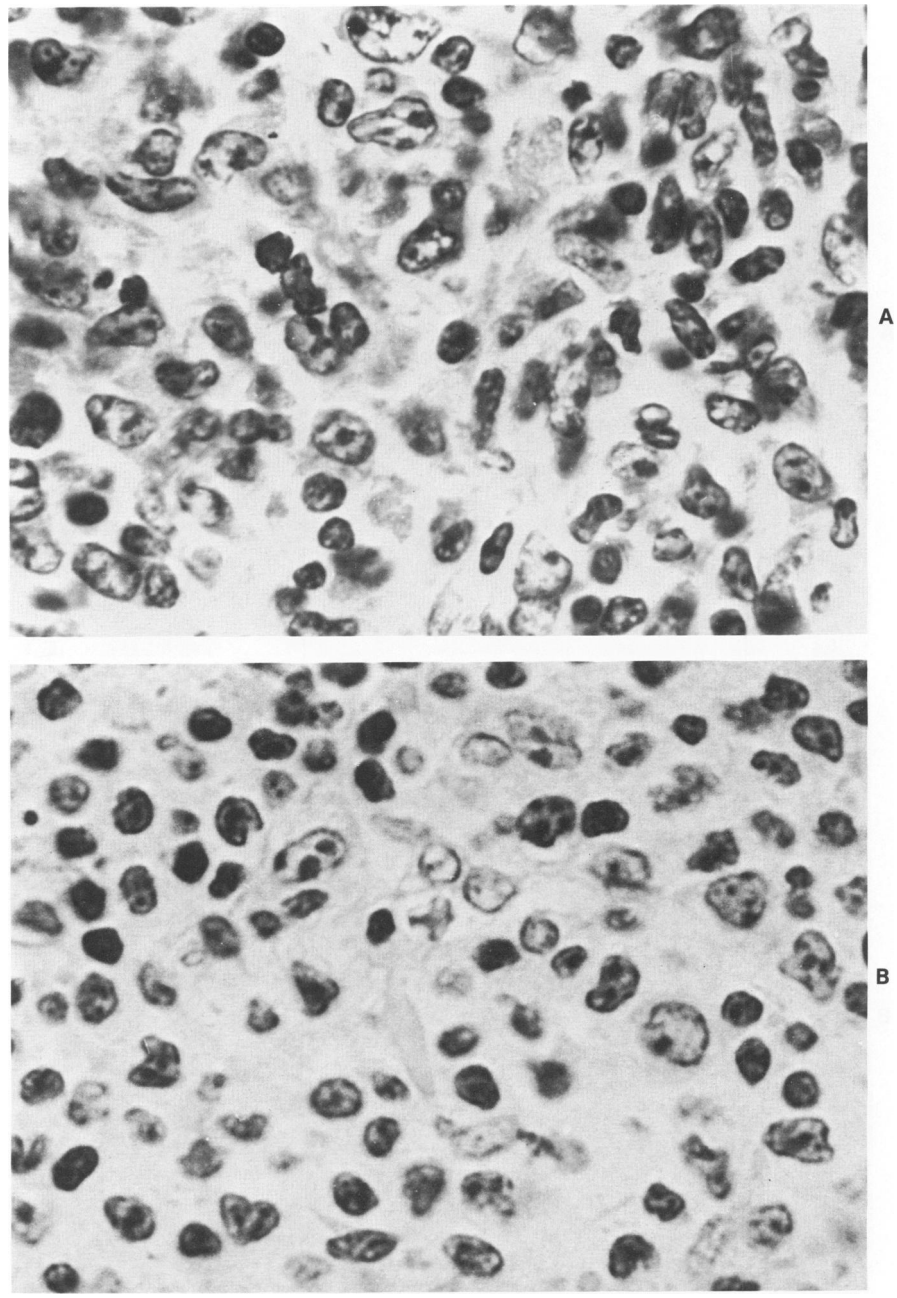


Figure 5A — Murine lymphoma of large and small (mixed) follicular center cells (FCC lymphoma, large and small [mixed] cell type). Note the almost equal proportions of small and large (cleaved and noncleaved) follicular center cells. This process stained positively for cytoplasmic IgA-κ with specific immunoperoxidase staining. (H&E, spleen, BALB/c mouse, ×1000) **B** — Human FCC lymphoma, small cleaved type, with a prominent large cell component. Note the similarities to the murine analog (**A**). (H&E, human lymph node, ×900)

mans is considered by Lukes and Collins to be an FCC lymphoma[1] (small noncleaved FCCs) and by Lennert to be a separate entity.[2]

In a recent study[16] the proposed immunomorphologic classification of murine lymphoma/leukemia[10] (see Table 2) was applied retrospectively to 70 lymphoid cell neoplasms occurring spontaneously in female BALB/c mice. As is seen in Table 7, FCC lymphomas of varying histologic subtypes, occurring at approximately 2 years of age, were the most common cell type (42/70, or 60% total incidence). Immunoblastic lymphoma of B-cell type also occurred in aged female BALB/c mice, but at a considerably lower incidence (5/70, or 7% total incidence). Of these 47 morphologically defined B-cell lymphomas (42 FCC and 5 immunoblastic), 37 (or approximately 80%) contained distinct cytoplasmic immunoglobulin (CIg), as determined by the use of well-established immunoperoxidase techniques. In contrast to these morphologically well-defined B-cell–derived FCC

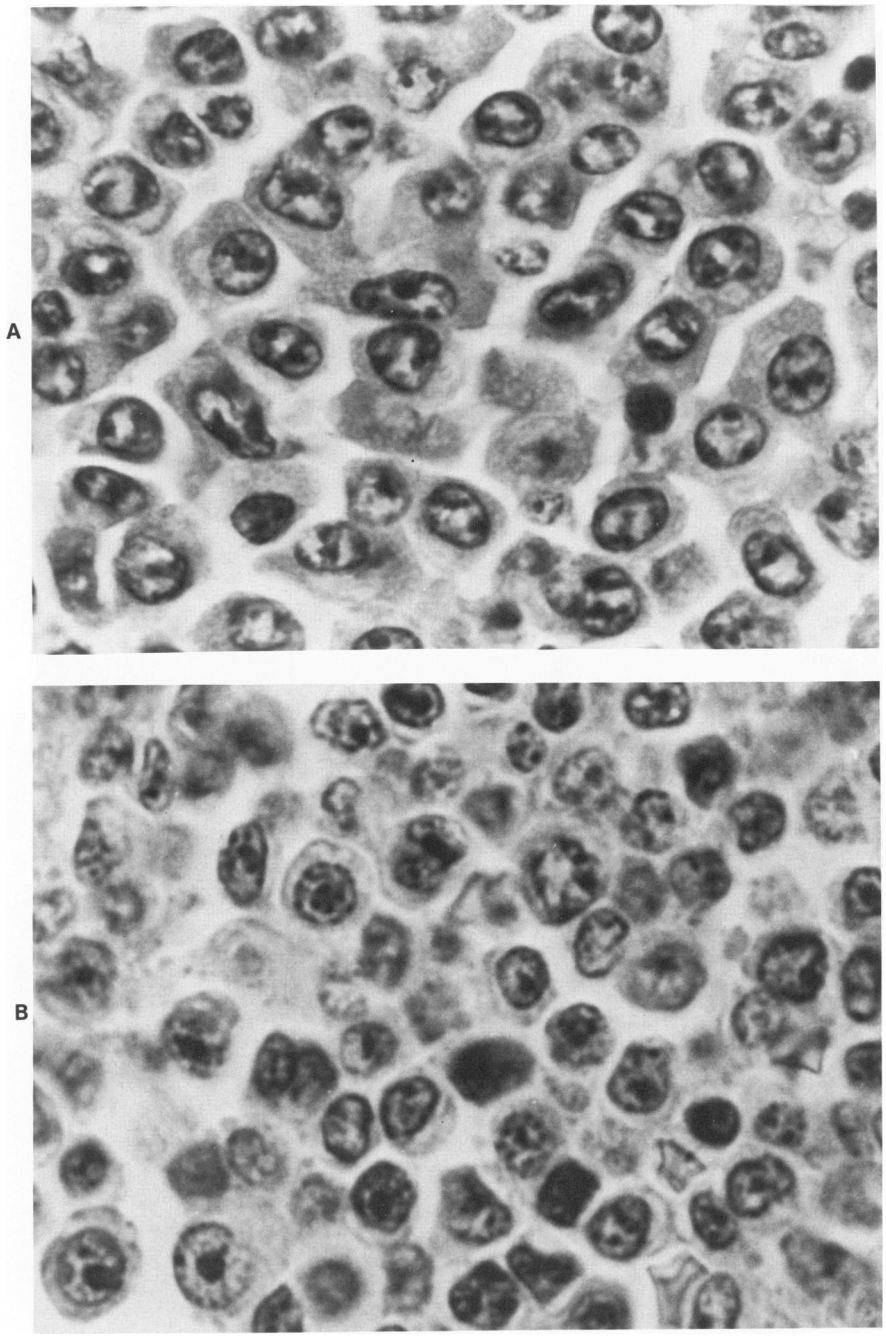


Figure 6A – Murine lymphoma of B immunoblasts (immunoblastic lymphoma [sarcoma], B-cell type). Note the monomorphous population of noncohesive, large lymphoid cells with round to oval vesicular nuclei with prominent and distinct nucleoli and abundant conspicuous cytoplasm. In addition, the nuclei are eccentric and occasionally have clumped, peripherally marginated, clockface-like chromatin (ie, plasmacytoid features). Also note the moderately (amphophilic) dense cytoplasm. This process stained positively for intracytoplasmic IgG_3-x. (H&E, spleen, BALB/c mouse, ×900) **B** – Human immunoblastic sarcoma (lymphoma), B-cell type. Although the lymphoid cell population is not as monomorphic and the cytoplasm not as amphophilic, these processes are similar (see **A**). (H&E, human lymph node, ×850)

and immunoblastic lymphomas were 23 cases of morphologically diagnosed lymphoblastic lymphoma, which occurred at an average mean age of 442 days. On closer examination, with the use of combined morphologic, clinicopathologic and immunologic parameters, this group of 23 lymphoblastic lymphomas was proven to be quite heterogeneous (Table 8). Seven of the 23 cases occurred at a mean age of 607 days and were composed of neoplastic lymphoblasts, which were characterized by a prominent central nucleolus and a visible rim of methyl green–pyronin (MGP)-positive cytoplasm (Figure 8A). In addition, 6 of these 7 cases demonstrated easily detectable CIg and were therefore immunologically confirmed as B-cell lymphomas. The remaining 16 cases of lymphoblastic lymphoma, although occurring in a bimodal incidence pattern (young and old BALB/c), were uniformly CIg-negative and consistently showed massive involvement of the anterior mediastinum (thymus, pericardium, lung, and lymph nodes). These 16 cases

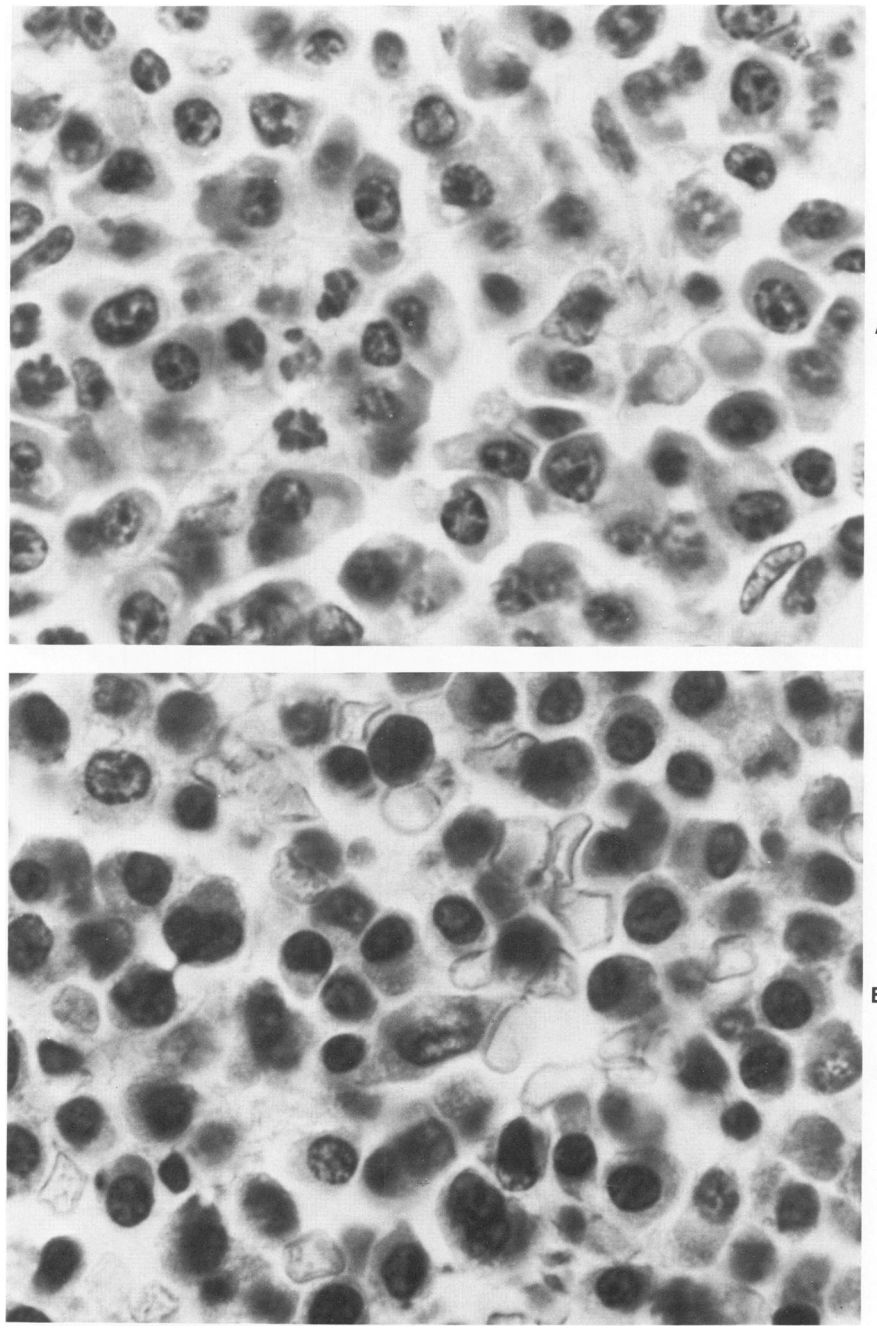


Figure 7A – Murine lymphoma of plasma cells (plasma cell lymphoma; plasmacytoma). Notice the population of plasma cells with dense, amphophilic cytoplasm and eccentric nuclei with clockface-like chromatin. Also note the presence of occasional prominent nucleoli. This process stained positively for cytoplasmic, monoclonal IgG_1-x with specific immunoperoxidase staining. (H&E, lymph node, BALB/c mouse, ×1000) **B** – Human lymphoma of plasma cells (plasmacytoma). Extramedullary plasmacytoma is uncommon in man; it is not listed in the Lukes-Collins classification, but is recognized in the Lennert and NIH classifications. (H&E, human lymph node, ×1000)

of (presumptive) T-lymphoblastic lymphoma demonstrated distinct, but sometimes subtle, morphologic differences, when compared with the 7 cases of B-lymphoblastic lymphoma (compare Figure 10A [lymphoblastic lymphoma of T cells] with Figure 8A [lymphoblastic lymphoma of B cells]). It should also be stressed that the morphologic characteristics of the neoplastic (presumptive) T-lymphoblasts encountered in this BALB/c retrospective study are virtually identical to immunologically confirmed, Thy-1-positive, neoplastic T-lymphoblasts observed in AKR or radiation-induced C57BL/6 thymic lymphomas[51] (see Figure 10A and below).

Mouse T-Cell Lymphoma/Leukemia

In marked contrast to the rarely encountered lymphoblastic lymphoma of B cells in the mouse is the well-described lymphoblastic lymphoma of T cells (Table 9 and Figure 10A). This lesion has been exten-

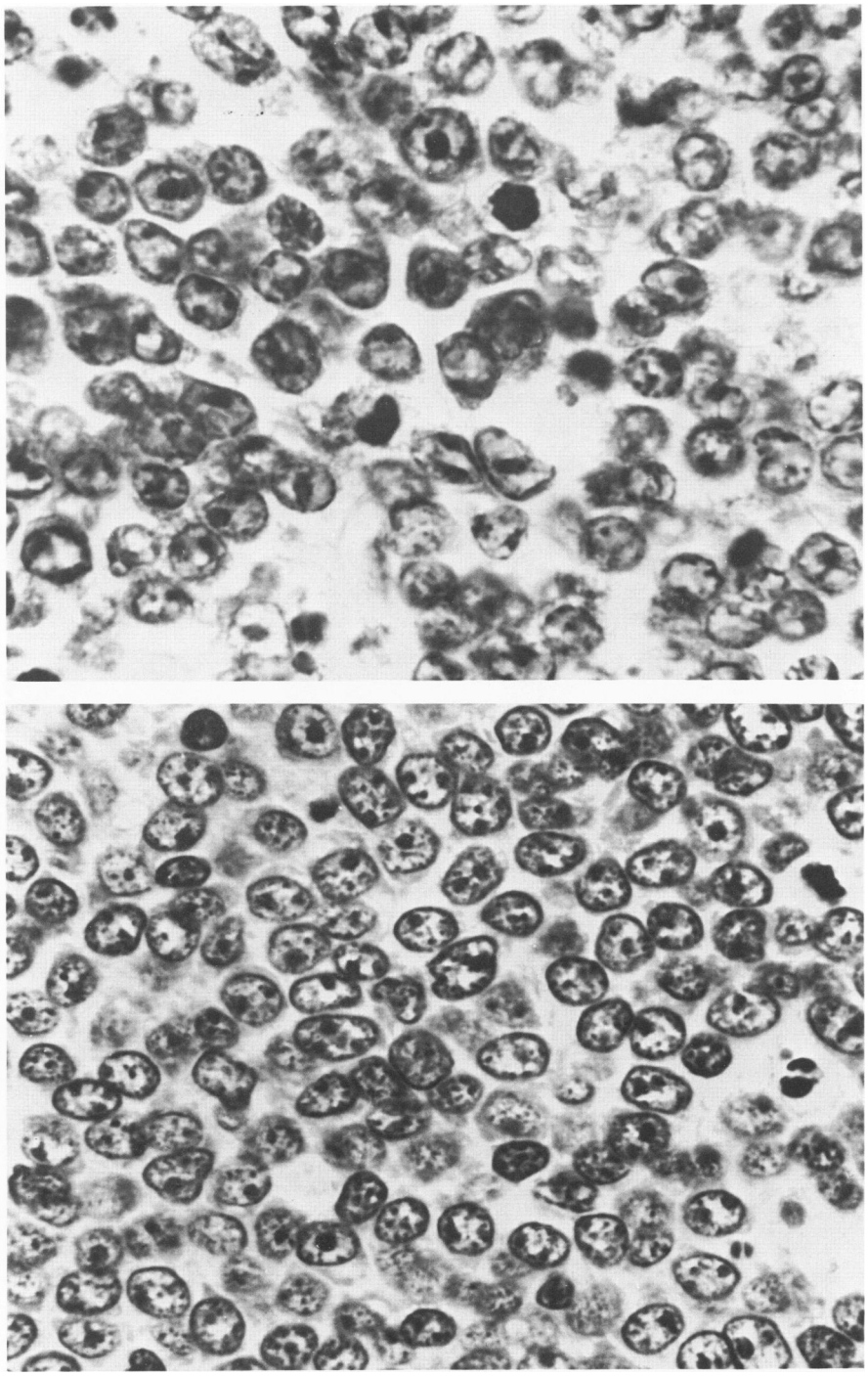


Figure 8A — Murine lymphoma of B-lymphoblasts (lymphoblastic lymphoma, B-cell type). Notice the monomorphic, mitotically active, population of intermediate-sized lymphoblasts with round to oval nuclei, immature chromatin, and conspicuous, multiple, and often central nucleoli. Also notice the presence of a visible rim of scant cytoplasm. In addition to being methyl green-pyronin positive, the cytoplasm stained positively for intracytoplasmic IgA-κ with immunoperoxidase techniques. (H&E, spleen, BALB/c mouse, ×1000) **B** — Human lymphoma of B-lymphoblasts (Lennert) or small noncleaved follicular center cells (FCCs) (Lukes-Collins) (lymphoblastic lymphoma, B-cell type; FCC lymphoma, small noncleaved type). Although the fixation in this human case is superior (B-5 fixation in **B** versus formalin fixation in **A**), the processes are quite similar (see **A**). (H&E, human lymph node, ×1000)

sively studied in the AKR[35] and C57BL/6[37,38] mouse strains and appears to be analogous to the lymphoblastic (convoluted or nonconvoluted) T-cell lymphoma/leukemia of man[52] (Figure 10B).

AKR lymphoblastic lymphoma/leukemia occurs spontaneously at 6–12 months of age and is closely associated with indigenous murine leukemia retroviruses (MuLV-Gross virus system).[35] In contrast, the C57BL/6 lymphoblastic lymphoma/leukemia is not spontaneous, but is inducible with another class of indigenous murine leukemia viruses (ie, MuLV), which were first isolated from C57BL/6 mice after split-body irradiation (ie, 170 R × 4).[37,38] Both are Thy-1-positive, arise in the thymus, and subsequently involve other lymphoid organs (spleen and lymph nodes) as well as peripheral blood, bone

marrow, the central nervous system, and other extranodal sites.[35,37,38] These models, therefore, have some clinical and pathologic similarities to the lymphoblastic T-cell lymphoma/leukemia observed in children and young adults.[52] It should be stressed that the marked nuclear convolutions often seen in the human condition[53] have, to the best of our knowledge, *not* been consistently observed in the murine analog. The remaining T-cell lymphoma types identified in man (small T-lymphocyte, T-immunoblast, Sézary-MF T cell, and the lymphoepithelioid T cell) have not yet, to our knowledge, been described in the mouse.

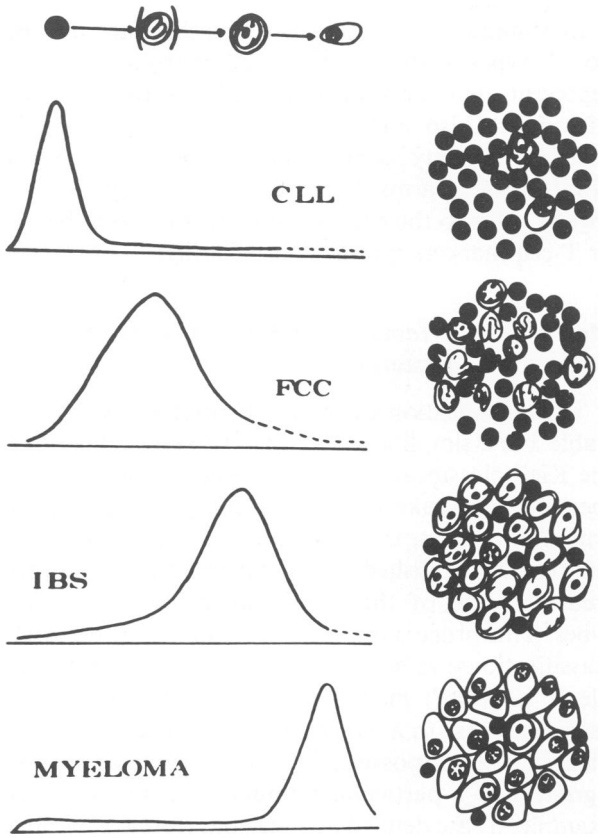


Figure 9—Interrelation of B-cell neoplasms and B-lymphocyte transformation and maturation to the plasma cell. *CLL*, chronic lymphocytic lymphoma; *FCC*, follicular center cell lymphoma; *IBS*, immunoblastic sarcoma (lymphoma); *Myeloma*, plasma cell lymphoma. The histologic appearances of four morphologically diverse neoplasms are represented; each is composed of the same three basic cytologic variants of the B-lymphocyte (small lymphocyte, immunoblast, plasma cell) that occur during different phases of the B-cell transformation maturation process (top of diagram). FCC lymphomas represent a partial exception, in that an additional B-cell variant is present, corresponding to the morphologic form shown by B cells in the intermediate stages of transformation within follicles. The different histologic appearances are entirely explained by variation in predominance of neoplastic cells at different phases of the cell cycle (represented at the top of the figure). The four designated histologic types clearly occupy arbitrary positions on a continuous spectrum. Other forms of B-cell neoplasia may be similarly explained by accumulation of neoplastic cells at various stages of "embryonic" development (eg, lymphoblastic), a kind of "neo-fetal" reversion that is common among other tumors.

Table 7—Summary of 70 Lymphoid Cell Neoplasms From BALB/c Female Mice*

Histologic diagnosis†	Number of lesions	Mean age, days ± SEM
Follicular center cell lymphoma		692.0 ± 26.6
Small cell type	3	678.7 ± 69.8
Large cell type‡	19	725.8 ± 42.9
Small and large cell type (ie, mixed FCC type)	20	662.0 ± 37.1
Immunoblastic lymphoma	5	697.0 ± 54.5
Lymphoblastic lymphoma	23	441.6 ± 49.3

* Eighty-eight untreated female BALB/cStCrl mice with spontaneous lymphoreticular tumors were killed at ages ranging from 101 to 1004 days. The BALB/cStCrl mice have been maintained and continuously inbred for at least 10 years at the National Center for Toxicologic Research (ie, BALB/cStCrlNctr). Eighty-one mice died as a result of terminal lymphoreticular neoplasms, whereas the remaining 7 were sacrificed as controls in ongoing studies at the National Center for Toxicologic Research. Animals were maintained under the guidelines set forth by the National Center for Toxicologic Research, Jefferson, Arkansas (72079).

† Complete autopsies were performed, and both gross and microscopic evaluations were done. Tissues were fixed in either formalin or Bouin's solution for 18–24 hours, blocked, and processed, and sections were cut at 4 μ. Sections were stained with hematoxylin and eosin or methyl green pyronin, or they were left unstained for the immunoperoxidase procedure (see Table 8). A total of 90 lymphoreticular neoplasms in 88 female BALB/c were evaluated. It was determined that 70 of 90 lesions were indeed lymphoid-cell-derived neoplasms, the remaining lesions being granulocytic (4 lesions) and true histiocytic (7 lesions) in nature. Nine lesions were considered unclassifiable because of inadequate fixation. Accordingly, stained sections of the lymphoid cell neoplasms (ie, 70 cases) were morphologically evaluated and classified by means of the Pattengale- Taylor classification for murine lymphoma/leukemia (Table 2). This classification was then compared with the earlier Dunn classification for murine lymphoreticular neoplasms (Table 3).

‡ Although cleaved or noncleaved types can predominate in large follicular center cell (FCC) lymphoma, it is common to observe mixtures of large cleaved and noncleaved cell types in this category of lymphoma (ie, FCC lymphoma, large cell type).

Mouse Non-B, Non-T Lymphoma/Leukemia

Table 10 depicts the problems related to the morphologic definition of non-B, non-T (null) lymphoid cell types. One such example of a non-B, non-T lymphoma/leukemia is observed in outbred, wild (feral) mice which spontaneously develop lymphoma/leukemia.[40] Since lymphoblastic, small lymphocytic, and immunoblastic lymphoid cell neoplasms of non-B, non-T type have been preliminarily observed in this wild mouse model,[40] it is important to define the stage of differentiation of these morphologically diverse nonmarking (ie, null) lymphoid cell types (ie, cells lacking *easily* detectable T- and B-cell markers). The available evidence in the wild-mouse-derived, retrovirus-induced NIH(S) system,[40] as well as the

Table 8—Heterogeneity of Murine Lymphoblastic Lymphoma

n	Mean age (days) ± SEM	Anterior mediastinal involvement* (no./total)	Presence of cytoplasmic immunoglobulin† (no./total)	Comments
7	607.4 ± 23.9	1/7‡	6/7§	Prominent central nucleolus, visible rim of MGP+ cytoplasm
16	638.3 ± 20.1	7/7	0/7	Nucleoli present
	159.6 ± 10.6	9/9	0/9	but usually not prominent; cytoplasm inconspicuous and not as prominent; weak MGP staining

MGP, methyl green-pyronin; SEM, standard error of the mean.

* Massive involvement of the thymus, pericardium, lung, and lymph nodes (includes parathymic and mediastinal). Although it is often difficult to identify discrete thymic tissue in old mice (ie, older than 20 months), the thymic area in the superior anterior mediastinum was massively involved with lymphoblastic lymphoma in the second group of 7 mice (ie, mean age of 638.3 ± 20.1 days).

† Demonstration of cytoplasmic Ig using the immunoperoxidase technique. Immunoperoxidase techniques were performed by means of the peroxidase-antiperoxidase method. In brief, rabbit anti-mouse sera (Litton Bionetics, Kensington, Md.) at varying titered concentrations (A, 1:200; G_1, 1:200; G_{2a}, 1:100; G_{2b}, 1:200; G_3, 1:50; M, 1:200; kappa, 1:400; and lambda, 1:400), swine anti-rabbit IgG (1:30), and rabbit peroxidase-antiperoxidase (1:200) were used sequentially with washes between each stage. Diaminobenzidine was used as the chromogen, giving a permanent brown reaction product that contrasted well with hematoxylin counterstain used. Normal rabbit and swine serums were used as controls. Antisera were titered for maximum positivity and specificity on both monoclonal-derived, mineral-oil-induced plasmacytomas in BALB/c mice and nonneoplastic reactive spleens and lymph nodes. The presence of cytoplasmic immunoglobulin was defined as 25% or more of the critical, neoplastic lymphoid cells containing easily detectable cytoplasmic heavy and/or light chain.

‡ Minimal anterior mediastinal involvement in a single case of cytoplasmic Ig+ (CIg+) lymphoblastic lymphoma.

§ The single case of CIg− lymphoblasts did not involve the thymus or anterior mediastinum.

spontaneous wild (feral) mouse systems,[40] strongly suggests that the individual neoplastic event(s) may occur within a rather diverse phenotypic array of non-B, non-T (null) lymphoid cell targets. Such targets might include true uncommitted stem cells, such as the conceptual hemocytoblast that in its proliferating mode may resemble, or may even be morphologically indistinguishable from, the immunoblast or the lymphoblast. By contrast, "resting" progenitor (stem) cells (lymphoid or otherwise), such as the granulocyte-monocyte (GM) precursor, may be morphologically indistinguishable from small lymphocytes. Cells that are committed to the B- or T-cell differentiation arms (ie, pre-T and pre-B cells) commonly exhibit lymphoblastic morphologic features. Presumably these represent the proliferating lymphoid stem cells; whereas resting stem cells, with inactive nuclei, would more closely resemble small lymphocytes.

It is of further interest that a small proportion of the wild mouse lymphoma/leukemias,[40] as well as the majority of the Abelson-retrovirus-induced lymphoma/leukemias are morphologically lymphoblastic in type,[42,45] and have small amounts of cytoplasmic immunoglobulin (ie, most commonly μ heavy chain).[41,43,44] These lymphoblastic lymphoma/leukemias of pre-B cells, may clinically and pathologically resemble acute lymphoblastic leukemias in man (ie, pre-B acute lymphoblastic leukemia [ALL]) and therefore may offer an important model for the study of these diseases.[54,55]

In summary, it is therefore possible that non-B, non-T types with lymphoid cell morphology may represent stem or progenitor cells (resting or proliferating). Also included would be lymphoid cells that are already committed to the T- or B-cell differentiation arms but are at that stage in ontogeny prior to the expression of *easily* detectable B- or T-cell markers (pre-B or pre-T cells).

Mouse Versus Human Lymphoma/Leukemia: Comparative Features

The classification of human lymphomas shown in Table 1 is a simplification of the Lukes-Collins[1] and the Kiel[2] classifications, and is rearranged to reflect the steps that take place in reaching a diagnosis of lymphoma. First, the tissue section is examined, the cell type is established, and the lymphoma is categorized into one of the morphologically defined cell types. This process in the Lukes/Collins[1] or the Kiel[2] classifications, as well as in the scheme shown in Table 1, is *entirely* morphologic in execution. Having assigned a case to a particular morphologic type, it is then sometimes possible to make a presumptive assignment to a particular immunologic division. For example, a case defined as a plasmacytoma or plasma cell lymphoma clearly belongs to the B-cell category, since plasma cells have not been observed to occur in the T-cells or non-B, non-T series. Similarly, in man, a classic convoluted lymphocytic lymphoma may be assigned to the T-cell category with some confidence, because these morphologic features have not been observed in the B-cell or non-B, non-T series. However, when possible, the morphologic division by cell type should be followed by immunologic confirmation.

The classification proposed for murine lymphomas (Table 2) was designed to parallel the human scheme (Table 1) for the purpose of better comparison with the human non-Hodgkin's lymphomas and related

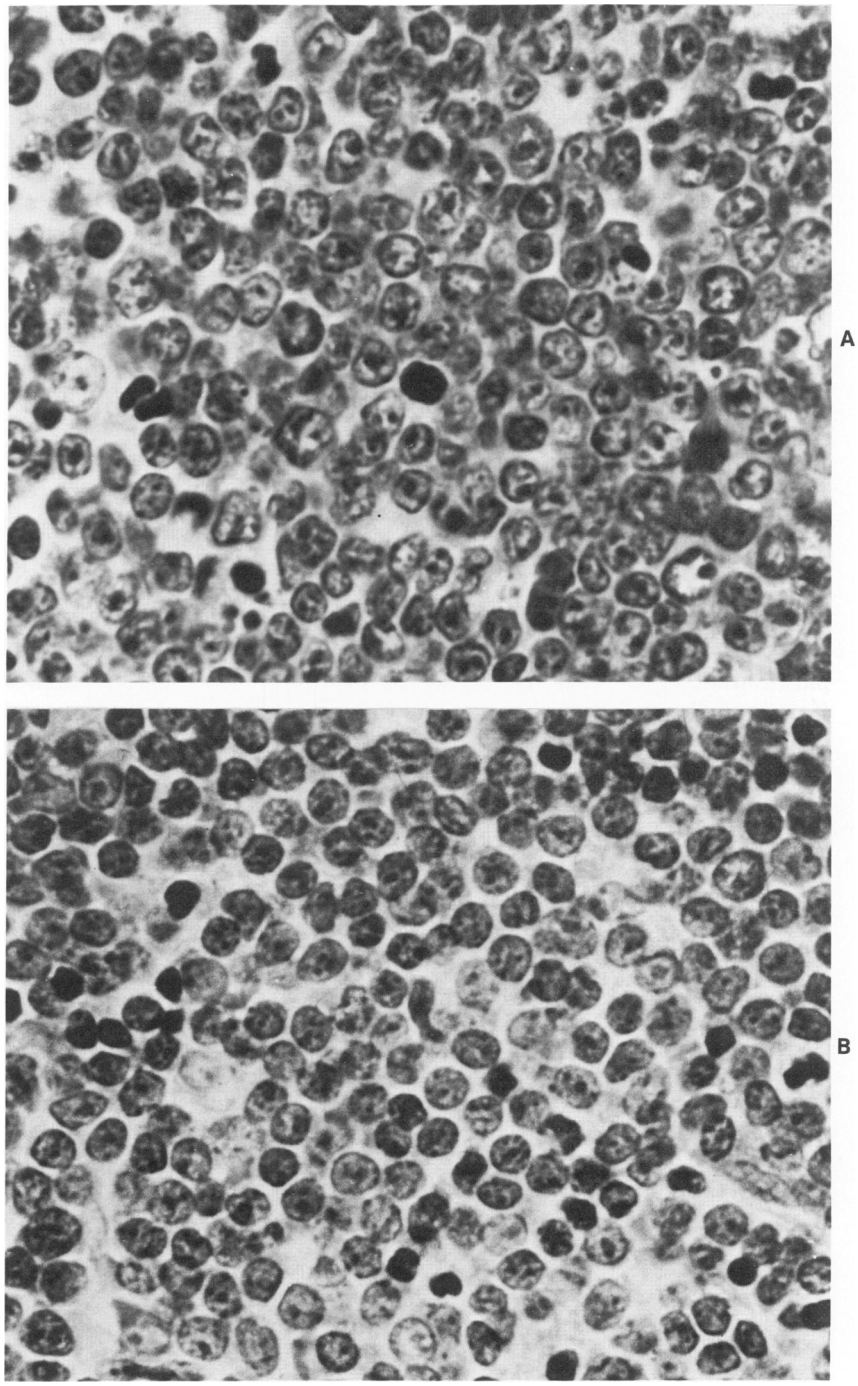
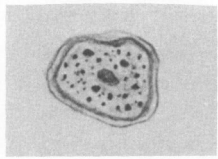


Figure 10A—Murine lymphoma of T-lymphoblasts (lymphoblastic lymphoma, T-cell type). Note the uniform, mitotically active, monomorphous population of intermediate-sized lymphoid cells with round to slightly irregular nuclei and delicate, finely dispersed, and stippled immature chromatin. These lymphoblasts stained positively for surface Thy-1 (fluorescence techniques). (H&E, thymus, radiation-leukemia virus-induced T-cell lymphoma in a C57BL/6 mouse, ×900) **B**—Human lymphoma of T-lymphoblasts, variously termed lymphoblastic lymphoma of T cells or convoluted lymphocytic lymphoma (Lukes-Collins), the latter designation emphasizing the presence of complex nuclear membrane folding that may be a conspicuous feature of this tumor. The nuclei have immature chromatin, cytoplasm is scanty, and mitoses are frequent. (H&E, human lymph node, ×900)

leukemias. In essence, close parallels of certain human B- and T-cell lymphoma types do occur in the murine systems (eg, compare Table 1 with Table 2, as well as Figures 1–8 and 10 [A versus B]). Other morphologic categories, such as the plasmacytoid B-lymphocyte and the small T-lymphocyte, T-immunoblast, Sézary-MF T-cell, and lymphoepithelioid T-cell types, do not occur or, more likely, have not yet been recognized.

Null cell lymphomas and leukemias do occur in mice and appear to show morphologic and immunologic resemblance to the ALL group in man, including cases that strictly are "nonmarking" and other cases that show some features ascribed to pre-B cells (ie, cytoplasmic μ chain). In man, ALL of B-cell type (termed L3 by the FAB classification)[56] and characterized by the presence of easily detectable surface immunoglobulin, is relatively uncommon but is con-

Table 9—Immunomorphologic Classification of Murine T-Cell Lymphoma/Leukemia*

	Morphologic T-cell type
	Lymphoblast†
	(Small lymphocyte)‡
	(Immunoblast)‡
	(Sézary-mycosis fungoides cell)‡
	(Lymphoepithelioid cell)‡

* A T cell is defined as having *easily* detectable surface Thy-1.
† T-lymphoblasts, on morphology alone, are difficult to distinguish from non-T, non-B cells as well as from B-lymphoblasts. There is some suggestion that T-lymphoblasts may exhibit a degree of nuclear irregularity and convolution and thus may be similar to the human lymphoblastic convoluted T-cell types[53] (see Table 1 and text).
‡ Expected but not yet observed.

sidered to be part of the Burkitt's lymphoma disease spectrum. Burkitt's lymphoma itself is a B-cell neoplasm that some think is related to proliferating (small noncleaved) FCCs[1] and others think is related to proliferating (nonfollicular) B-lymphoblasts.[2] We believe that the murine B-lymphoblastic lymphoma[16] may bear a close resemblance to the Burkitt's lymphoma/leukemia disease spectrum.

With regard to the FCC lymphomas, similarities do exist on an individual cell-to-cell basis between the murine lymphomas and the corresponding human diseases (see Figures 2–5). However, some differences, particularly the lack of a definitive nodal follicular pattern in the murine models, do exist. In man, subtypes of FCC lymphoma classically show early involvement of the bone marrow and peripheral blood (ie, the leukemic phase of FCC lymphoma).[57] It is not yet clearly established whether this is also true for subtypes of murine FCC lymphoma. Many of the FCC lymphomas of man are relatively indolent and clinically benign but are at the same time incurable. Despite chemotherapeutic and/or radiotherapeutic regimens, the disease always recurs after 5–10 years.[58,59] The availability of a relevant murine model for the purposes of designing a curative form of therapy would thus prove invaluable and would obviate the need for prolonged clinical trials that are the only recourse in investigating new treatment modalities in man.

Immunoblastic lymphoma (sarcoma) of B-cell type appears to occur both in mouse and in man with varying degrees of plasmacytoid differentiation. In contrast to the disease in man, murine plasmacytoma or plasma cell lymphoma is primarily an extramedullary neoplasm, occurring either spontaneously in the gut and/or lymph nodes[5,6] or occurring in the peritoneal cavity after induction with mineral oil.[27–29] Human plasma cell lymphoma, on the other hand, occurs primarily in the bone marrow and is therefore termed *multiple myeloma*. These conditions are clearly interrelated in terms of cellular derivation, but at this point the predilection for bone marrow involvement in man, as compared with the extensive extramedullary disease in the mouse, still remains an enigma.

With regard to lymphomas and related leukemias of the small B-lymphocyte, several comparative points deserve attention. Chronic lymphocytic leukemia of small B-lymphocytes (B-CLL) and its lymphomatous tissue counterpart (small lymphocytic lymphoma, B-cell type) have not been well-documented in murine systems. With the exception of the antigen-induced B-CLL model in the double congeneic 2^a4^b system[12] and the BCL_1 model,[13–15] which was derived from a spontaneously occurring BALB/c B-CLL, very little is known of lymphoma/leukemias involving the small B lymphocyte. With time, however, this should be better clarified, since aged stains (ie, more than 2 years of age) will be better and more extensively examined. We and others have begun to observe small B-cell lymphoma/leukemia in aged NFS/N congeneic, BALB/c, and nu/nu NIH(S) strains.[60,61]

Within the T-cell category, lymphoblastic lymphoma/leukemia appears to occur both in mouse and in man, with remarkable immunologic and clinicopathologic similarities. One distinctive difference, however, is the occurrence of easily identifiable nuclear convolutions in at least some cases of the human condition[53]; whereas similar features have not been consistently observed in murine T-cell lymphoblastic lymphoma.

In the future, the search for additional murine lymphomas, which resemble the human condition,

Table 10—Problems Related to the Immunomorphologic Classification of Non-B, Non-T (ie, Nonmarking or Null) Murine Lymphoma/Leukemia*

Morphologically defined Non-B, Non-T lymphoid cell types
Lymphoblast
Small lymphocyte
Immunoblast (hemocytoblast?)
Degree of differentiation
Stem cell
Progenitor cell
Pre-B cell
Pre-T cell

* Defined as *lacking* both *easily* detectable surface Thy-1 and Ig (surface and/or cytoplasmic). Pre-B cells, methodologically speaking, are thus not considered to be B cells because the cytoplasmic Ig (ie, usually small quantities of heavy chain) is usually *not easily* detectable.

will continue, and we have no doubt that other analogues will be discovered. The murine classification described here is meant merely to serve as a temporary framework that combines precise morphologic definition with precise immunologic definition. We are hopeful that this will lead to a more comprehensive and accurate classification of lymphoid cell neoplasms and to a more comprehensive investigation of etiologic factors, possible modes of therapy and pathogenesis (see Murine Prelymphoma, below). Furthermore, since the mouse is at present immunologically better defined than man, more precise immunologic resolution of the various murine morphologic subtypes is possible. Recognizing that certain murine and human subtypes are strikingly similar, we believe better immunologic definition of human subtypes should naturally follow. A good example, which relates to this concept of cross-fertilization from mouse to human lymphoid cell neoplasms, involves the careful delineation and documentation of B-cell differentiation stages using a battery of highly specific monoclonal antibodies. This already has been successfully performed in some murine B-cell lymphoma/leukemia systems by Warner and colleagues.[33,62] More detailed documentation and delineation of human B-cell systems is expected to follow. It should be stressed and cautioned, however, that the phenotypic evaluation of lymphoid cell neoplasms by monoclonal antibodies should be closely correlated with *immunomorphologic* criteria, so that some degree of contact is maintained between "newly defined phenotypic cells" and the morphologically defined traditional cell types.

In summary, it is of great interest, then, that the majority of the murine lymphomas and related leukemias (ie, the B, T, and non-B, non-T lymphoid cell types) have close clinicopathologic similarities to corresponding analogous human non-Hodgkin's lymphomas and related leukemias. The often stated dissimilarity between the B/T ratio and lymphoma/leukemia incidence (ie, more B-cell lymphomas than T-cell lymphomas in man; more T than B in the mouse) can be misleading, because many mouse strains, if allowed to age long enough, will spontaneously develop B-cell–derived non-Hodgkin's lymphomas.[16] If one then compares the B/T incidence in older mice with the B/T incidence in the adult human population, the differences do not appear to be very great (ie, approximate B/T ratio of 3–4:1).[16,63] Also in keeping with this observation is the finding of age and other clinicopathologic similarities between the lymphoblastic T-cell lymphoma/leukemia and the analogous childhood and young adult T-cell lymphoma/leukemia.[52]

Murine Models of Prelymphoma

Mouse Prelymphoma

Having defined the framework for mouse lymphoma/leukemia of the non-Hodgkin's type, we will attempt in this final section to focus on murine prelymphomatous states and to relate them to analogous human prelymphomatous states. A prelymphomatous state (prelymphoma) is defined as a conditioned, morphologically atypical, oligoclonal or polyclonal lymphoproliferation, which in time is superseded by the emergence of an autonomous monoclonal lymphoma. Since murine prelymphomatous states are experimentally accessible and allow for carefully performed prospective studies, they may provide valuable insight into analogous human conditions. We will further emphasize B-cell prelymphomatous states, not only because B-cell lymphoma/leukemia is more common than T-cell lymphoma/leukemia, but also because B-cell prelymphoma appears to be much more common than T-cell prelymphoma in both murine and human systems. This may relate to the fact that the B-cell system is more easily studied because of discrete morphologic compartmentalization (eg, follicular centers), morphologically demonstrable specialized cells (eg, plasma cells), and the availability of clonal markers (eg, Ig).

There is evidence that certain strains of mice, namely, New Zealand black (NZB), SJL/J, nu/nu NIH(S), and certain F_1 hybrids undergoing graft-versus-host (GVH) reactions, demonstrate prolonged B-cell stimulation when studied prospectively.[9,18,19,46,47,61,64] One is able to demonstrate a progression from simple, benign, follicular (B-cell) hyperplasia to an *atypical*, preneoplastic, follicular, and postfollicular B-cell hyperplasia. In time this atypical hyperplasia is eventually superseded by a lymphomatous B-cell proliferation (ie, most commonly a large FCC, B-immunoblastic, or plasma cell lymphoma).[9,61,64] Figures 11 and 12 illustrate representative examples of this process and depict, first, (Figure 11A) a lymph node showing the very prominent, active germinal centers characteristic of benign, exuberant follicular (B-cell) hyperplasia. Although this lymph node was obtained from a B-lymphotropic, retrovirus-infected C57BL/6 mouse,[51] identical histologic appearances are observed in SJL/J, NZB, nu/nu NIH(S), and certain GVH-induced F_1 hybrids. In contrast, a lymph node from an 8-month-old SJL/J mouse (Figure 11B) shows an atypical, somewhat bizarre, follicular hyperplasia, characterized by prominent B-cell follicular centers, which now exhibit near confluence and result in a subtotal effacement of the normal lymph node architecture. This process is justifiably consid-

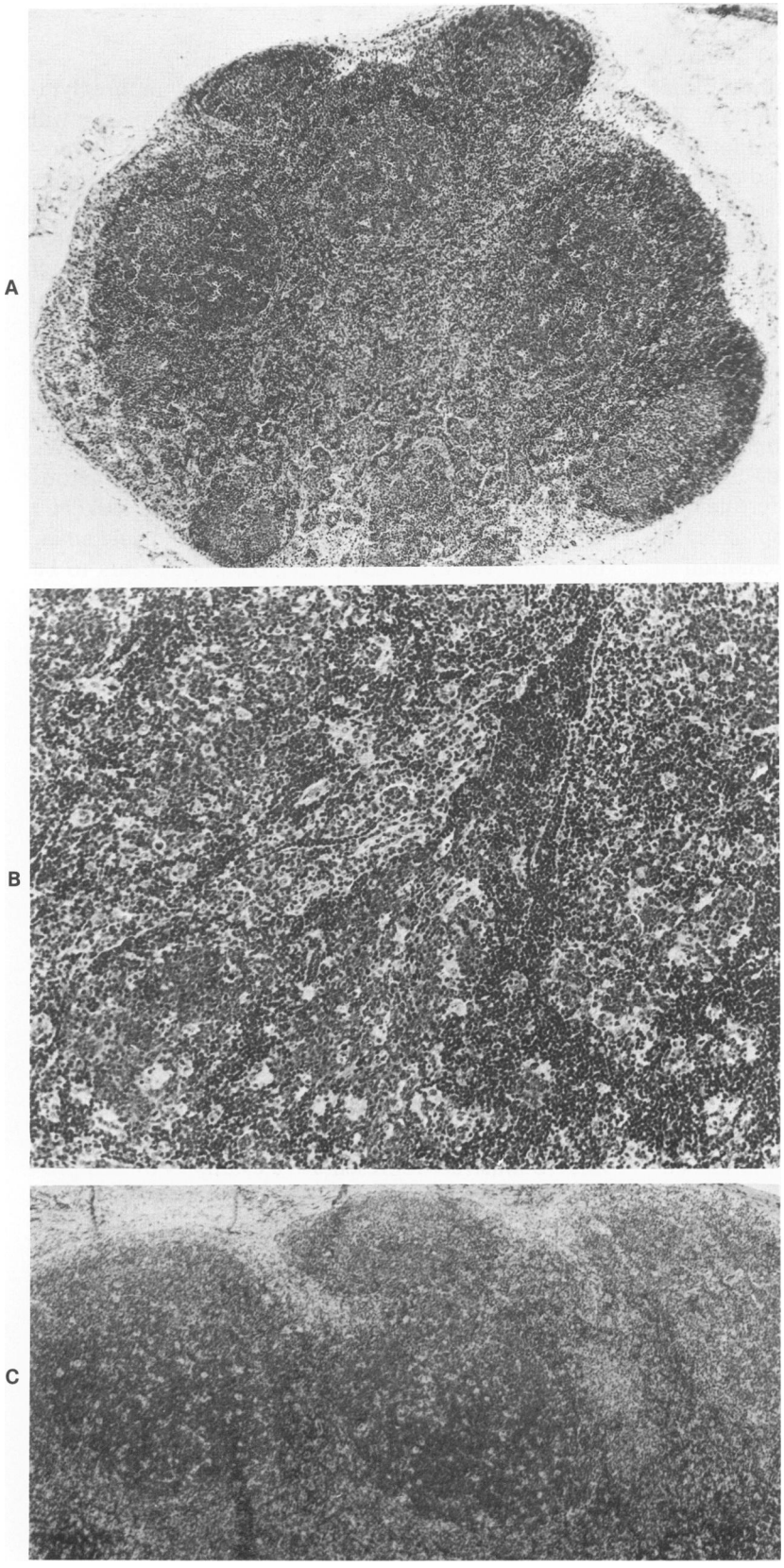


Figure 11A – Murine benign, exuberant, follicular hyperplasia. Notice the prominent active germinal (ie, follicular) centers and the surrounding mantle of smaller lymphoid cells. (H&E, lymph node, dualtropic murine leukemia virus-induced C57BL/6 mouse 1 week after injection, × 45) **B** – Murine atypical, prelymphomatous, follicular hyperplasia. Notice the still prominent B-cell germinal (ie, follicular) centers, which exhibit near confluence, resulting in subtotal effacement of the nodal architecture. (H&E, lymph node, 8-month-old SJL/J mouse, × 150) **C** – Human atypical follicular hyperplasia. Notice the prominent and active follicular centers, which have lost their mantle zones and which appear to be merging with one another. (H&E, lymph node, patient with the acquired immune deficiency syndrome [AIDS], × 80)

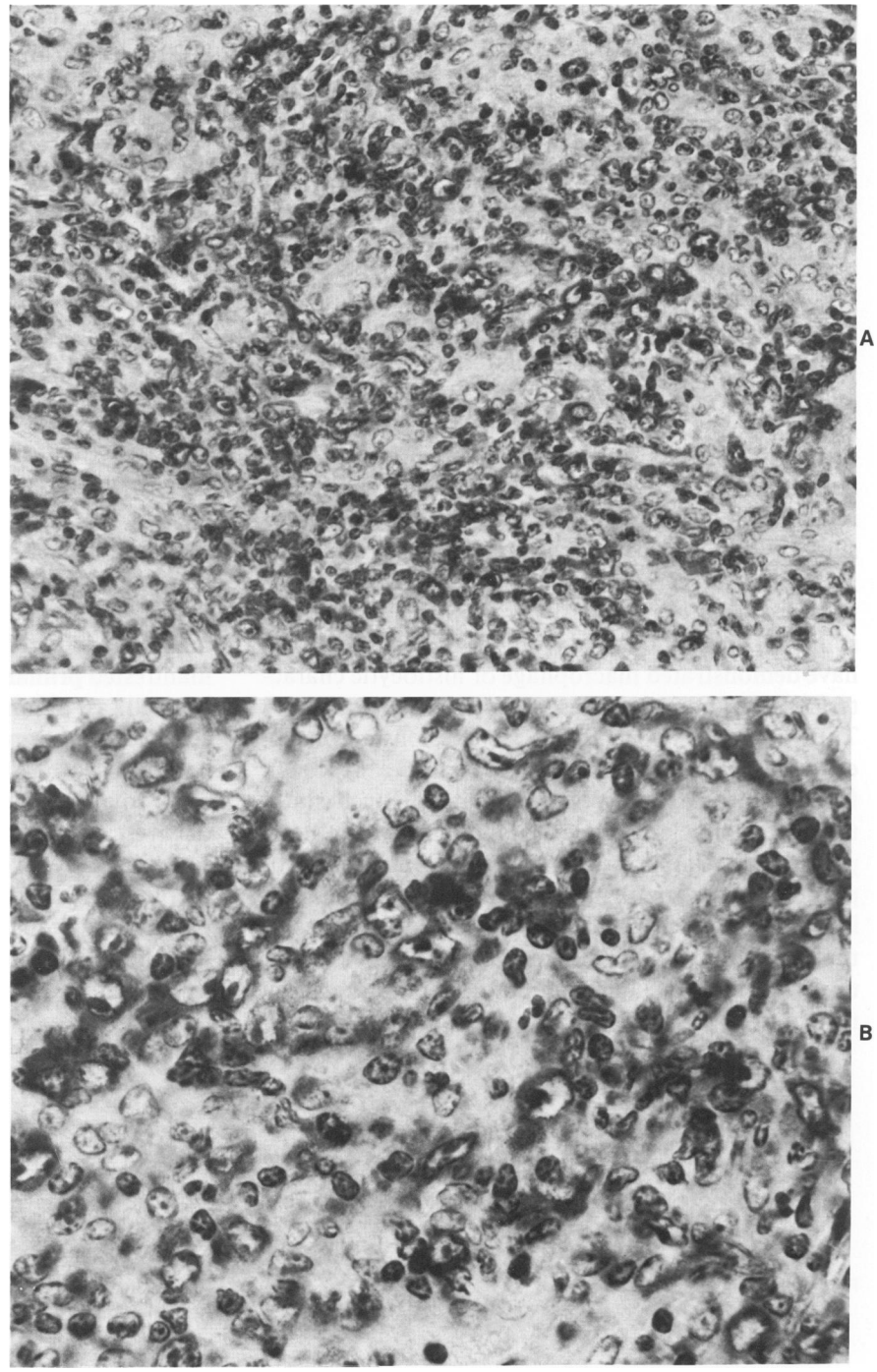


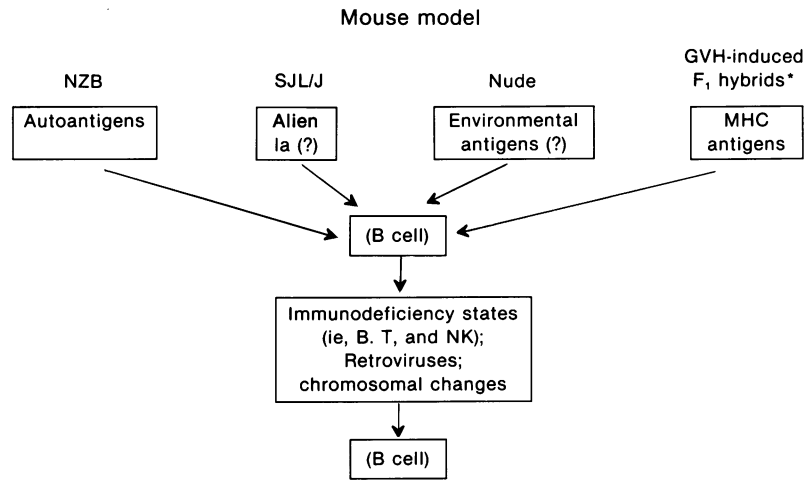
Figure 12—Murine large and small (mixed) follicular center cell (FCC) lymphoma. Notice that this section of lymph node is replaced by a diffuse, lymphomatous process (**A**), which, when seen at a higher power (**B**), is composed of a mixture of small and large (cleaved and noncleaved) FCCs. The black cytoplasmic staining in the large FCCs (**A** and **B**) represents positive staining for IgG, heavy chain. Further specific immunoperoxidase staining demonstrated the presence of intracytoplasmic κ light chain. (Immunoperoxidase stain counterstained with hematoxylin, mesenteric lymph node, 12-month-old SJL/J mouse; **A**, ×320; **B**, ×640)

ered to be preneoplastic (prelymphomatous), for at 12 months in the SJL/J mouse, there is progression to complete, diffuse replacement of the nodal architecture (Figure 12A) by a process that at higher power is composed of a spectrum of lymphoid cell types (Figure 12B). Although the most prominent (predominant) cell type is a large FCC with a round to oval, vesicular (noncleaved) nucleus with prominent nucleoli, there are varying mixtures of small, as well as large, cleaved (centrocytic) FCC types. These larger cells formerly were called pale reticulum cells; but with the use of the immunoperoxidase technique, it may be shown that a significant percentage of these large lymphoid cells contain intracytoplasmic immunoglobulin of the IgG_1-κ isotype, attesting to their B-cell nature (Figure 12B); this often correlates with a

serum monoclonal spike of the same IgG_1-κ isotype. This process in the SJL/J mouse, although called a reticulum cell neoplasm Type B by Dunn,[8] and classified by us as a mixed (large and small) FCC lymphoma, must be viewed with considerable caution when one applies more rigid biologic criteria for the evaluation of true, biologically malignant neoplasms (see Table 11 and below). A proportion of the SJL/J lesions appear to be true monoclonal malignant lymphomas of either FCC cells or monomorphic B-immunoblasts with corresponding serum monoclonal spikes[65,66] and B-cell homing patterns.[67] However, an equal if not larger percentage of the SJL/J lesions appears to represent lymphoproliferations composed of polymorphic collections of B-immunoblasts, plasmacytoid lymphocytes, and plasma cells, which correlate with oligoclonality or polyclonality, as measured by both intracytoplasmic and serum immunoglobulin. Furthermore, these latter prelymphomatous processes are not easily transplantable,[65,66] and some cell lines established from the "primary tumors" have demonstrated macrophage or histiocytic characteristics (ie, nonspecific esterases, phagocytosis).[68,69] Thus, it would appear that SJL/J lesions are markedly heterogeneous and may represent a spectrum from preneoplastic, prelymphomatous B-cell states to overt monoclonal B-cell lymphomas with a morphologically similar proportion of lesions being neoplasms of true (nonlymphoid) histiocytes. The finding that treatment with anti-μ antibody suppresses the development of the lesion supports the view that the process is B-cell–derived but does not necessarily rule out the possibility that the lesion is a neoplasm of non-B-cell type that requires B cells for its growth.[70] Because a measurable proportion of the primary tumor cells in SJL/J mice have a pre-B phenotype and are able to differentiate to more mature B cells *in vitro*,[71] one possible unifying hypothesis for SJL/J tumors of B-cell origin would be that the neoplastic event(s) occurs at the level of the B-cell progenitor (pre-pre-B or pre-B), which for unknown reasons is still capable of full differentiation (ie, through the entire B-cell morphologic spectrum—see Table 6) to the immunoglobulin-secreting plasma cell. In keeping with this hypothesis is the important finding of Murphy[72] that successfully transplanted primary SJL/J tumors exhibit lymphoblastic morphologic characteristics compatible with a pre-B cell origin (see Table 10).

Concomitant with the morphologic changes observed in these murine strains, one can also find evidence for disturbances in the immune system of the SJL/J, NZB, and nu/nu NIH(S) strains and in certain GVH-induced F_1 hybrids. These disturbances are manifested primarily among immunoregulatory cells, as well as among functioning B and T effector cells.[73-99] Abnormalities in natural killer cell activity have also been reported.[100-103] Such disturbances are often found to precede and antedate the development of overt lymphoma, and they accompany the observed, progressive, morphologic changes (simple hyperplasia → atypical hyperplasia → malignant lymphoma). It should be stressed that neither morphologic nor clinicopathologic observations are necessarily predictive of *true* malignant neoplasia, as defined by use of more rigid biologic criteria, such as clonal-

Table 11—Postulated Relationship of Conditioned B-Cell Prelymphomatous States to Autonomous B-Cell Malignant Lymphoma



* (BALB/cxA/J) F_1 mice given parental BALB/c spleen cells; (C57BL/6xDBA/2) F_1 mice given parental C57BL/6 spleen cells. Abbreviations used: GVH, graft-versus-host; MHC, major histocompatibility complex; NK, natural killer cell.

ity, transplantability, chromosome analysis, and autonomous growth.

Table 11 shows the postulated relationship of B-cell prelymphomatous states to the overt lymphomatous state in the NZB, SJL/J, nude outbred NIH(S), and the GVH-induced F_1 hybrid mouse models. The prelymphomatous state is defined as a *conditioned* premalignant state in which the observed, morphologically atypical B-cell proliferation is oligoclonal and/or polyclonal (ie, with respect to immunoglobulin), normal diploid (ie, on karyotypic analysis), and nontransplantable to nonimmunosuppressed syngeneic mice. The prelymphomatous state is believed to be "conditioned" by the presence of a persistent stimulus, and the cells are unable to grow autonomously. In time, however, this prelymphomatous state is superseded by the outgrowth of an autonomously malignant B-cell clone, which often exhibits nonrandom aneuploidy and is frequently characterized by translocations involving chromosomes coding for the immunoglobulin genes.[104,105]

In the case of the NZB mouse, the available evidence would implicate autoantigens[87] (ie, double-stranded DNA) as the persistent B-cell stimulus. In the semiallogeneic GVH-induced F_1 hybrid model, major histocompatibility complex (MHC) antigens of the other parent act as strong stimuli of lymphoproliferation.[84] The persistent stimulus in SJL/J mice is possibly a hybrid, alien Ia[106] molecule present either on B-lymphocytes and/or macrophage–histiocytes, which is capable of stimulating syngeneic T cells[92,107] and ultimately results in polyclonal activation of the B-cell series through a mechanism of back-stimulation. A similar pathogenesis of the B-cell prelymphomatous state has been postulated for the GVH-induced systems, since the GVH-induced B-cell lymphomas are principally of F_1 origin.[84] It has been hypothesized that the parental T cells respond to the MHC of the other parent (on F_1 cells), and subsequently back-stimulate F_1 B cells with allogeneic effect factor, which conditions the prelymphomatous B-cell state.[84] The stimulus in nu/nu NIH(S) mice is at present unknown, although it has been proposed that ubiquitous environmental antigens can exaggerate, overstimulate, and polyclonally push the B-cell system in the absence of adequate postthymic T-cell regulation.[60,61]

The common feature among these four examples is a prelymphomatous state characterized by a both polyclonal and diploid proliferation of nontransplantable, conditioned B cells. The additional necessary factors for conversion to the autonomous (ie, "true") malignant lymphomatous state would appear to be a combination of events, which may include retrovirus expression superimposed on chromosomal rearrangements, as well as a variety of coexisting immunodeficiency states, which ultimately result in the selection of an autonomous malignant clone. It is well known that these model strains have various types of immunodeficiencies that have been postulated as predisposing factors for the development of autonomous ("true") malignant lymphoma.[73–103] One should be cautioned that an equally tenable hypothesis would be that the immunodeficiencies merely coexist in parallel with the development of malignancies and, in fact, are not predisposing factors. Similarly, the relationship of retroviruses in these four murine models to B-cell lymphoma appears, at the present time, to be by association only, with no evidence of direct causation, if one uses Koch's postulates.

In summary, the postulated models of B-cell lymphoma in Table 11 have an eventual clinical outcome that is commonly monoclonal; when studied prospectively, this monoclonal outcome is preceded by a persistent polyclonal or oligoclonal response (with respect to immunoglobulin phenotype), which closely correlates with the presence of B-cell atypia, by using morphologic criteria.

By way of comparison, the B-cell lymphoproliferative state induced in C57BL/6 mice by dualtropic, murine leukemia viruses (ie, dualtropic MuLV) is also polyclonal with respect to immunoglobulin phenotype, but progression to the monoclonal state has not been clearly documented.[51] In this condition the serologic finding of *poly*clonality (Figure 13A) is accompanied by a morphologic picture of an immunoblastic lymphoma (Figure 13B) composed of B-immunoblasts and associated plasmacytoid cells; this polymorphic, B-cell lymphoproliferative state in C57BL/6 mice is *poly*clonal, normal diploid, and unable to be transplanted and requires the presence of a conditioning stimulus (ie, dualtropic MuLV);[51] clinically and pathologically, however, this process is judged to be malignant, since sarcomatous lesions are found in visceral organs.[51] Thus it would appear that dualtropic MuLV is able to produce a conditioned, B-cell lymphoproliferative state in which the additional necessary factors for conversion to the autonomous, true malignant lymphomatous state are not present. It will be of great interest to determine experimentally the necessary factors for conversion of this presumptive prelymphomatous state to an overt monoclonal lymphoma of B cells.

Mouse Versus Human Prelymphoma: Comparative Features

The dualtropic MuLV-induced B-cell lymphoproliferation in C57BL/6 mice[51] as described above is

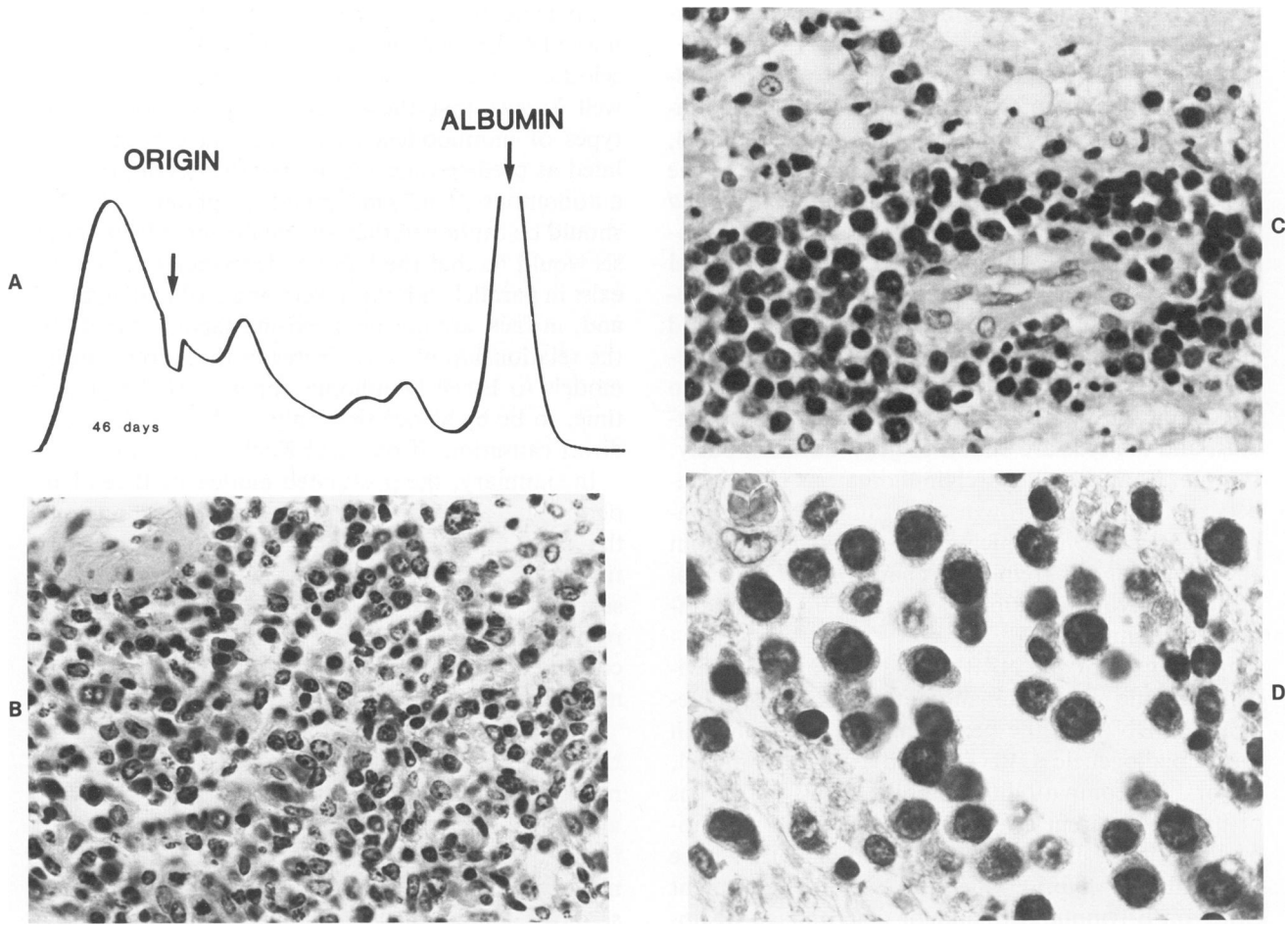


Figure 13A – Serum protein electrophoresis from a C57BL/6 mice given an injection of dualtropic murine leukemia virus (MuLV) 46 days before. Notice the marked polyclonal gammopathy. **B** – Murine polymorphic, postfollicular B-cell lymphoproliferation. Notice the presence of immunoblasts admixed with a prominent component of plasmacytoid cells. Although staining polyclonally for intracytoplasmic immunoglobulin, (Ig), this prelymphomatous state was widespread and clinically aggressive, as evidenced by infiltrative, destructive lesions in visceral organs. (H&E, kidney, young adult C57BL/6 mouse given an injection of dualtropic MuLV 10 weeks before, ×400) **C** and **D** – Human polymorphic B-cell lymphoproliferation in a young male with the X-linked lymphoproliferative syndrome (XLP). Although morphologically diagnosed as an immunoblastic lymphoma (ie, sarcoma) of B cells, this process was found to be polyclonal with respect to Ig isotype (ie, IgA, IgG, IgM, κ and λ), but with a prominence of IgM-κ-containing cells. Note the large lymphoid cells as well as the smaller plasmacytoid cell component. There is a lack of morphologic quality due to the fixation of autopsy material in formalin. (H&E, central nervous system; **C**, ×200; **D**, ×700)

analogous to the Epstein-Barr virus (EBV)-induced B-cell lymphoproliferation observed in certain young males (Figure 13C and D). This entity, called the X-linked lymphoproliferative syndrome (XLP), is found to occur in susceptible immunodeficient young males who lack the ability to produce EBV-specific antibody.[108-112] Defects in natural killer activity have also been found in these patients with XLP,[113] and other deficiencies in T-cell function have been postulated. One would predict from this model that the proliferating B cells in these patients would be polymorphic, polyclonal, and normal diploid, because the B-cell trophic EBV[114-116] is able to induce a polymorphic, polyclonal, B-cell proliferation of normal diploid immunoblasts and associated plasmacytoid cells *in vitro*.[117] Although the number of cases is small, some of the available evidence is in support of this prediction.[109,118,119] Similar viral conditioning stimuli (ie, possibly EBV-related) have been postulated to be present in immunosuppressed patients undergoing renal transplants who subsequently develop B-cell polymorphic lymphomas of the central nervous system.[120,121] Preliminary evidence would suggest that such processes are initially polyclonal with respect to Ig phenotype and in fact are EBV-related.[122] Other examples of EBV-related, polyclonal, polymorphic B-cell immunoblastic proliferations, such as those sometimes seen in Sjogren's syndrome

and other autoimmune diseases, are beginning to emerge. In addition, preliminary evidence strongly suggests that a proportion of immunosuppressed renal transplant recipients have a propensity to develop superimposed monomorphic, monoclonal B-cell lymphomas that are aneuploid and that contain characteristic marker chromosomes involving the immunoglobulin genes.[123]

An analogous series of events may occur in male homosexual and other patients with acquired immune deficiency syndrome (AIDS) in whom malignant B-cell lymphomas later develop.[124,125] As seen in Figure 11C, there is atypical follicular hyperplasia, with the loss of recognizable mantle zones and the merging of follicular centers.[125] This atypical B-cell hyperplasia is reminiscent of that observed in the SJL/J and other inbred strains (see Figures 11A and B for comparison), which exhibit antecedent morphologic and immunologic abnormalities before evolving to a malignant B-cell lymphoma. The relationship of a viral agent (eg, EBV or CMV) to the development of malignant B-cell lymphomas in patients with AIDS remains to be determined.

Although angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)[126] and immunoblastic lymphadenopathy (IBL)[127] are considered to be human B-cell prelymphomatous states, these states remain undefined in murine systems, to the best of our knowledge. Lymphadenopathy containing a prominent vascular and immunoblastic component has been described, however, in the hamster.[128]

Although there is no clinically recognizable prodrome in Burkitt's lymphoma, there is nonetheless evidence of persistent stimulation by environmental malarial antigens; and in time, a truly malignant, autonomous B-cell lymphoma develops.[129] The conversion to B-cell lymphoma may require additional factors, such as the presence of EBV and a nonrandom, persistent, 8/14 translocation (ie, the 14g+ marker).[104,130] It should be stressed, however, that the majority of human non-Hodgkin's lymphomas and related leukemias (eg, primarily FCC types) are unrelated to EBV or to other known viruses and seemingly do not develop out of antecedent prodromal, prelymphomatous states. This is somewhat discouraging from the standpoint of identification of patients at risk, although in-depth prospective studies involving inbred mouse strains, which have a high spontaneous incidence of FCC lymphoma (eg, BALB/c[16] and others), may be helpful in elucidating prelymphomatous states that may be applied to analogous human diseases. In this respect the murine B-cell lymphomas and prelymphomas are anticipated to be excellent immunopathologic models for certain subtypes of human B-cell lymphoma/leukemia.

Future Experimental Directions

One of the most exciting molecular discoveries in recent years is the finding of cellular oncogenes (termed *c-onc genes*), which are highly conserved in evolution.[131] This remarkable finding was made possible because there exist oncogenic retroviruses of short latency whose genomes contain cross-hybridizable nucleic acid sequences, which were closely related, if not identical, to the nucleic acid sequences in c-onc genes. Presumably these oncogenic retroviruses of short latency, such as the Abelson MuLV, which rapidly induces a pre-B type of lymphoblastic lymphoma, acquired the oncogenic sequences (termed *v-onc genes*) through a mechanism of recombination and capture. Some oncogenic retroviruses of long latency, which lack viral oncogenes (such as the avian leukosis virus), appear to function by inserting their DNA proviral sequences close to cellular oncogenes (ie, c-myc), thereby producing malignant B cells through a mechanism of "downstream promotion."[132]

These exciting molecular discoveries engendered considerable enthusiasm among both tumor biologists and geneticists, since it was also becoming clear that both human and mouse neoplastic lymphoid cells possessed persistent, nonrandom chromosomal changes (primarily trisomies and translocations), which involved chromosomes coding for cellular oncogenes and/or chromosomes coding for the immunoglobulin genes.[105,133-136] One of the original observations was the presence of a highly specific 8/14 translocation in cases of classical Burkitt's lymphoma.[104,105,130] Further molecular analysis has demonstrated that c-myc sequences are present on human Chromosome 8 and are translocated to the region of human Chromosome 14, which is known to code for the Ig heavy chains.[133,134] Translocations from human Chromosome 8 to human Chromosome 2 (κ light chain) and to human Chromosome 22 (λ light chain) have also been observed in Burkitt's lymphoma.[105] An analogous situation is found in certain murine plasma cell lymphomas, in which translocations involving c-myc sequences on murine Chromosome 15 and Ig heavy chain genes on murine Chromosome 12 are observed to occur.[133,135,136] In a recent study it was shown that neoplastic plasma cells from a mineral-oil-induced plasmacytoma (plasma cell lymphoma) of the IgA type contained rearranged c-myc sequences, which were now present in the α

switch region of the nonproductivity rearranged chromosome (ie, murine Chromosome 12).[135,136] Since c-myc sequences normally map to mouse Chromosome 15 in nonneoplastic, somatic cells, the presence of a 15/12 translocation within the neoplastic B cells is theoretically of considerable importance. The causal relationship of these translocated cellular oncogenes, as well as other hitherto unidentified cellular and/or viral transforming genes, to the pathogenesis of lymphoma/leukemia remains to be established.

In summary, this review stresses the *close* immunomorphologic and clinicopathologic similarities between mouse and human lymphoid cell neoplasia. In the future, it will be of great importance to further combine these immunomorphologic criteria with cytogenetic and molecular parameters. In this manner, and with time, a distinct mechanistic approach, in addition to the present descriptive approach, may be possible. This may first be feasible in the murine system, since precise immunologic, genetic, and molecular approaches can be effectively combined with statistically meaningful, *prospective* studies involving well-defined clinicopathologic entities. It seems to us that this prospect alone is sufficient reason for attempting to develop a parallel approach for human and murine lymphomas, so that in the future, new observations made in the murine model may more rapidly be translated to the corresponding human condition.

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