THE SPECTRUM OF B CELL LYMPHOMAS AND LEUKEMIAS

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I. INTRODUCTION

B cell lymphomas are by definition malignant hematopoietic tumors that synthesize intact immunoglobulins (Ig) or fragments thereof. The purpose of my presentation today is to illustrate the extraordinary clinical variety of these tumors and to review some hypotheses dealing with their origin. At least eight distinct hematopoietic tumors have been shown to arise in the B cell lineage as judged by the criterion of Ig production (Table 1). These disorders differ markedly in clinical presentation, natural history, and response to treatment. A reasonable explanation for this unusual diversity emerges from studies of normal B cell development. According to this hypothesis, B cell lymphomas are composed of masses of cells arrested or frozen in various stages of differentiation and activation (transformation). The diversity of these tumors can accordingly be related to the complex pathways of B cell development (1).

The immunoglobulin in or on these cells provides a marker for testing whether the tumor mass is derived from a single cell. In almost all of these tumors that have been examined, the neoplastic cells all bear the same immunoglobulin light chain type, and immunoglobulin variable region structure, strongly suggesting origin from a single cell (2). This monoclonality does not exclude the possibility that two or more clones were involved at some time during the natural history of the tumor. Monoclonality merely implies that at some point, one clone gained a selective growth advantage. This monoclonal Ig, whether on the cell surface or secreted into the blood, provides a convenient marker for monitoring tumor burden in these patients (3,4).

II. NORMAL B CELL DIFFERENTIATION AND ACTIVATION

A. Differentiation

A current model of B lymphocyte differentiation is shown in Figures 1 and 2. Pluripotent hematopoietic stem cells in fetal liver and postnatal bone marrow, under unknown influences, become committed to the B cell lineage. The first recognizable cells in this lineage are large, rapidly dividing pre-B cells which contain sparse amounts of cytoplasmic mu immunoglobulin heavy chains (5,6). Pre-B cells develop surface IgM (SIgM) and migrate to peripheral lymphoid tissues (nodes and spleen). Here, the nascent B cells acquire surface IgD (SIgD), a molecule thought to be important in triggering subsequent steps in B cell maturation (7). Analysis of SIgM and SIgD on human chronic lymphocytic leukemia (CLL) cells provided strong evidence that within a single B cell clone, more than one heavy chain class can be associated with the same antibody combining site and light chain type (8). Other surface receptors are then acquired: Ia molecules, important in T-B and macrophage-B cell interaction; receptors for complement components; and receptors for immunoglobulin Fc domains (9). Up to this point, the development of B cells is not dependent upon contact with antigens or T lymphocytes. Subsequent steps in maturation occur in peripheral lymphoid tissues and are driven by antigen in conjunction with macrophages, and T lymphocytes (T helper cells) (10). Under these influences,

TABLE 1

MALIGNANT TUMORS OF THE B CELL LINEAGE (MODIFIED FROM LUKES/COLLINS CLASSIFICATION) AND THEIR EQUIVALENT DESIGNATIONS ACCORDING TO RAPPAPORT

Tumor	Rappaport Designation	
Pre-B cell acute lymphocytic leukemia	----	
Follicular center cell (FCC) lymphomas		
Small cleaved FCC -- 107 cases	Nodular PDL	(90%)
	Diffuse PDL	(10%)
Small noncleaved FCC -- 2 cases	Undifferentiated	
	Burkitt's	(1 case)
	Non-Burkitt's	(1 case)
Large cleaved FCC -- 11 cases	Nodular PDL	(9%)
	Nodular mixed L-H	(18%)
	Nodular histiocytic	(18%)
	Diffuse PDL	(9%)
	Diffuse histiocytic	(45%)
Large noncleaved FCC -- 51 cases	Nodular mixed L-H	(8%)
	Nodular histiocytic	(10%)
	Diffuse Histiocytic	(82%)
Immunoblastic sarcoma of B cells -- 6 cases	Diffuse histiocytic	(100%)
Chronic lymphocytic leukemia		
Small lymphocyte lumphoma	Diffuse WDL	
Waldenstrom's macroglobulinemia	Diffuse WDL	
Multiple myeloma	----	
Leukemic reticuloendotheliosis	----	

PDL -- poorly differentiated lymphocytic
L-H -- lymphocytic-histiocytic
WDL -- well-differentiated lymphocytic

(Ref. 47)

FIGURE 1

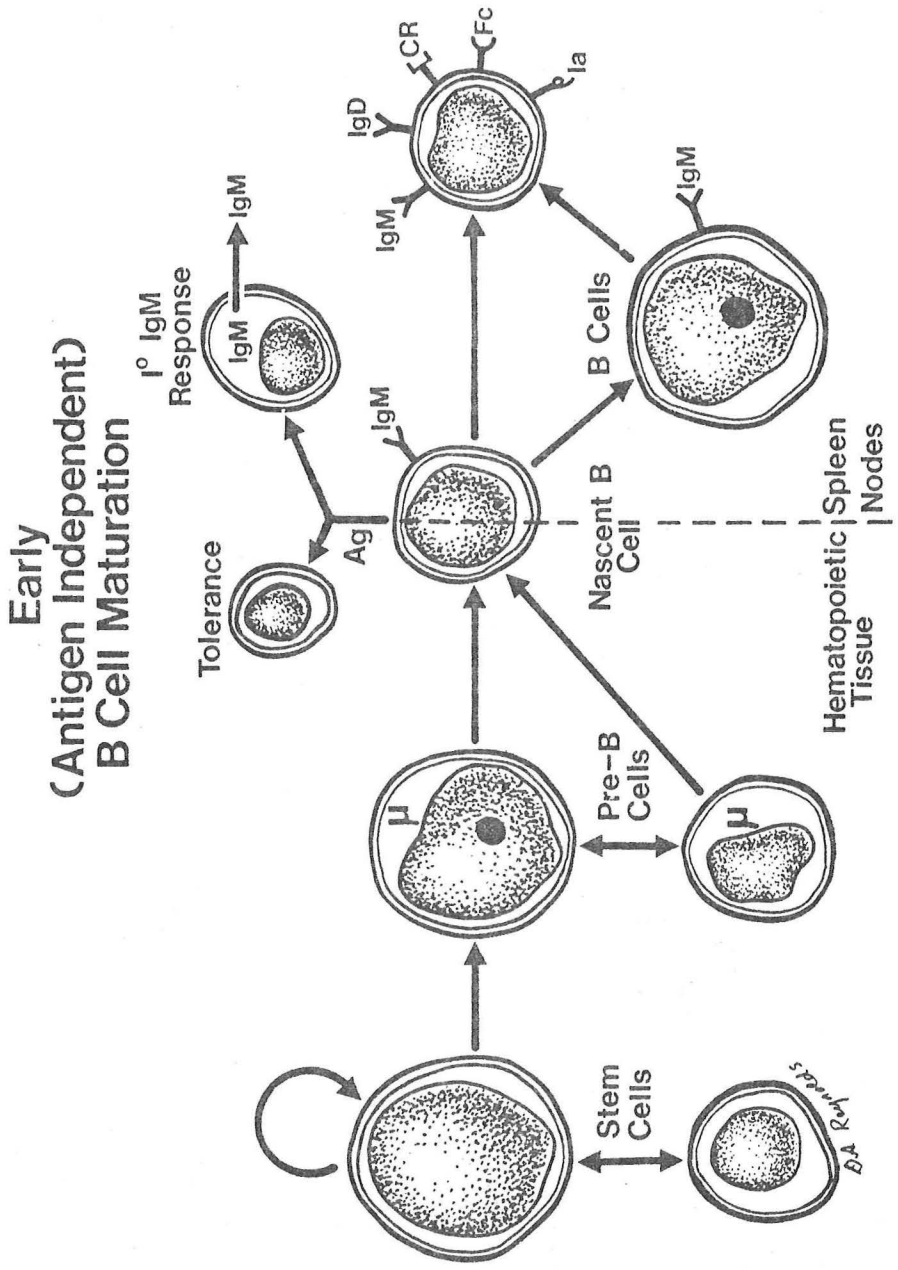
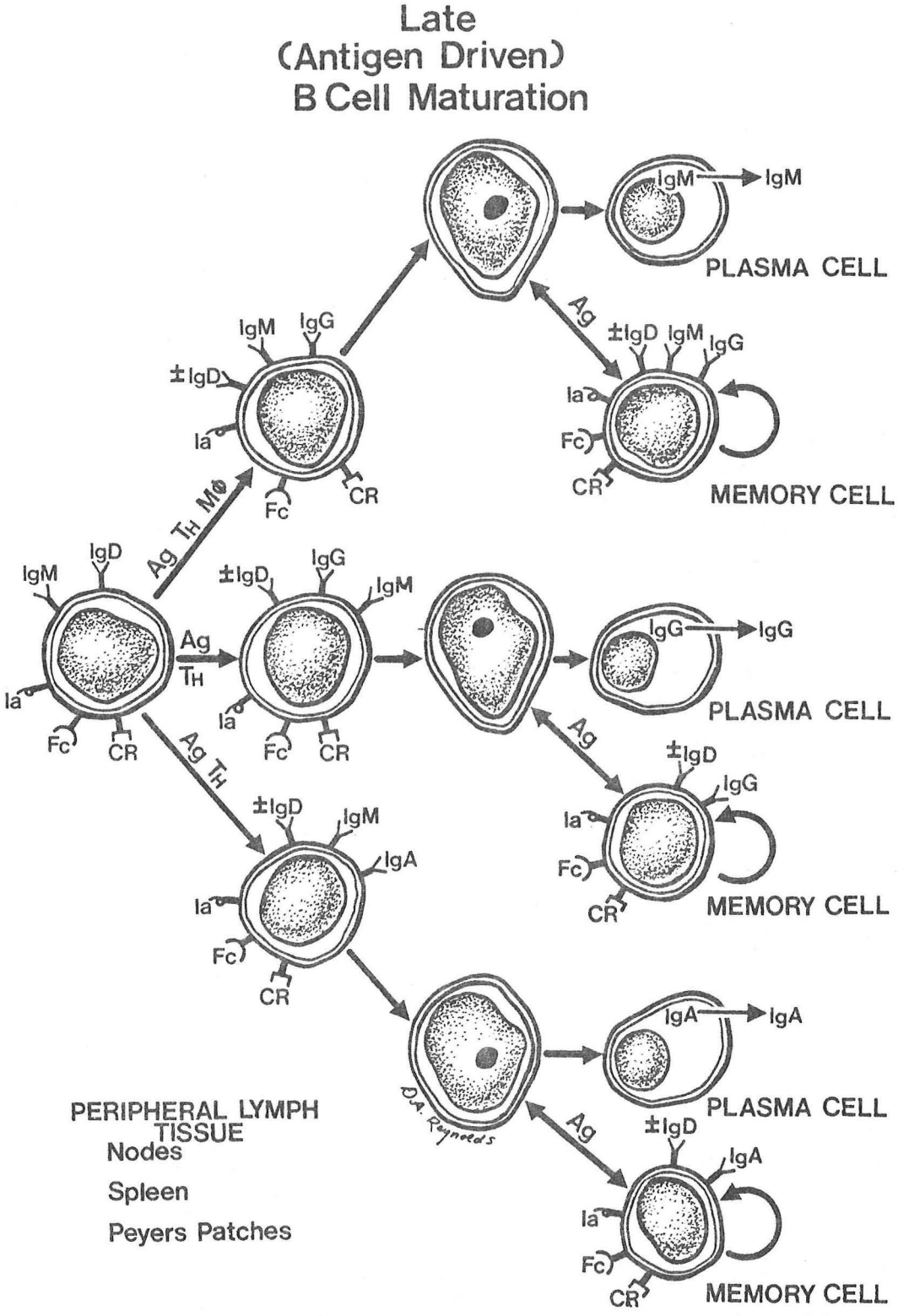

Early
(Antigen Independent)
B Cell Maturation
Stem Cells
Pre-B Cells
μ
μ
Tolerance
Ag
IgM
I° IgM Response
IgM
IgM
IgD
CR
Fc
Ia
IgM
B Cells
IgM
Nascent B Cell
Hematopoietic Tissue
Spleen
Nodes
D.A. Rowley

FIGURE 2


Late
(Antigen Driven)
B Cell Maturation
IgM
IgM
PLASMA CELL
Ag
±IgD
IgM
IgG
Ia
Fc
CR
MEMORY CELL
IgM
IgG
±IgD
Ia
Fc
CR
Ag TH MΦ
IgM
IgD
Ia
Fc
CR
Ag
TH
±IgD
IgG
IgM
Ia
Fc
CR
IgG
IgG
PLASMA CELL
Ag
±IgD
IgG
Ia
Fc
CR
MEMORY CELL
Ag TH
±IgD
IgM
IgA
Ia
Fc
CR
IgA
IgA
PLASMA CELL
Ag
±IgD
IgA
Ia
Fc
CR
MEMORY CELL
D.A. Reynolds
PERIPHERAL LYMPH TISSUE
Nodes
Spleen
Peyers Patches

cells with the appropriate immunoglobulin antigen receptors (SIgM and SIgD) diversify along pathways leading to enhanced synthesis and eventual secretion of IgM, IgG, and IgA. Thus, the heavy chain class undergoes further changes with differentiation, while the antibody combining site remains unchanged (11). During these steps of terminal B cell differentiation, two kinds of cells are generated: plasma cells, specialized for immunoglobulin secretion, and memory cells, specialized for rapid proliferation and differentiation towards secretory plasma cells upon subsequent exposure to antigen. Both plasma cells and memory cells are committed to synthesis of immunoglobulin of one heavy chain class. Memory cells are thought to bear surface immunoglobulin of the class that their progeny plasma cells are destined to secrete; however, more than one class of SIg may be found on memory cells (12).

B. Activation (transformation)

At multiple steps along this lineage map, cells undergo cycles of proliferation and quiescence. These cycles appear necessary to (a) expand the size of the clone; (b) permit certain steps in differentiation to proceed (coupled differentiation and proliferation); and (c) generate a pool of resting cells capable of further differentiation on subsequent contact with certain regulatory signals. Memory cells are an example of such resting cells. Activation of mature B cells by contact with antigens and T cells or by exposure to polyclonal mitogens results in an extraordinary transformation of cell structure and function (13). Morphologically, these activated lymphocytes may assume bizarre or anaplastic appearances, indistinguishable from the lymphocytes in certain lymphomas to be discussed below (14). After antigen- or mitogen-stimulated activation, the surface density of IgD declines.

Some of these B cells that can be triggered to proliferate and further differentiate may be true stem cells; that is, they are cells capable of self-renewal with very restricted developmental potential. Whether any of these cells are true stem cells is a very important question, since stem cells appear to be the targets for neoplastic change upon exposure to carcinogenic agents (15).

C. Homing and Recirculation

After early development in hematopoietic organs, nascent B lymphocytes migrate to peripheral lymphoid organs (spleen and nodes). Here they "home" to certain domains in these organs called primary or secondary follicles. These immature B cells do not re-enter the circulation until they have developed further. Most evidence suggests that recirculating B cells are very long-lived memory cells (12,15a). These cells are capable of homing to follicles, traversing and exiting lymphoid tissues, entering the thoracic duct and the blood, and re-entering lymphoid tissue through specialized venous endothelium (16). Thus, the properties of homing to certain domains in lymphoid tissue, and of recirculating in blood, lymphoid organs and lymph, are acquired with differentiation, just as are structural features such as SIgD. A better understanding of the structural basis of these physiologic properties is needed to understand the peculiar tendency of some B cell lymphomas to become leukemic, while others remain in nodes, spleen or marrow.

III. MALIGNANCIES OF THE B CELL LINEAGE -- CLINICAL FEATURES AND NATURAL HISTORY

A. Pre-B Cell Leukemias

Leukemic lymphoblasts that contain sparse amounts of cytoplasmic mu (μ) heavy chain determinants (cIgM) and lacking SIgM have recently been found to comprise a subset of about 20% of all cases of acute lymphocytic leukemias (ALL) (17). Except for the presence of cIgM, these "pre-B ALL's" have the same phenotype as a larger subgroup of 50-60% of ALL's known as "common ALL". In other words, pre-B ALL is a subset of common ALL. The similarities include the finding of similar membrane antigens and the nuclear enzyme terminal transferase (TdT) (18). At least some common ALL's as well as the subset pre-B cell ALL's apparently represent tumors arrested at very early points in B cell differentiation. In a group of 189 cases of pediatric ALL, the natural history and response to treatment of common and pre-B ALL were very similar (17) (Table 2). At the time of diagnosis, children with pre-B ALL and common ALL share similar age, sex and race distributions, physical findings, hematologic indices, and blast cell morphologies. Moreover, both of these diseases respond well to standard remission induction chemotherapy which includes vincristine, prednisone, and either Adriamycin or L-asparaginase. Preliminary observations suggest that, with optimal therapy, patients with pre-B ALL will have the same likelihood of long-term disease-free survival as the larger number of patients with common ALL whose blast cells do not contain cIgM (17). Survival in these two groups of patients is longer than survival in the group of 10-15% of ALL patients whose tumor cells express T cell markers (17).

About 25% of patients with chronic granulocytic leukemia (CGL) develop a lymphoblastic transformation (19). Except for the finding of the Philadelphia (Ph^1) chromosome in CGL cells, CGL lymphoblasts are indistinguishable from common ALL blasts; morphology and cell markers are identical (20,23,24). Preliminary surveys indicate that a subset of these patients with lymphoblastic CGL have a pre-B type leukemia (21). Other studies suggest that in some patients in the chronic phase of CGL, B or null lymphocytes are part of the neoplastic clone (22). Thus, the CGL defect can be expressed at various levels in the B lymphocyte lineage. These findings support the hypothesis that CGL is a neoplastic transformation of pluripotent hematopoietic stem cells that, under certain circumstances, may differentiate along erythroid, granulocytic, megakaryocytic, and B lymphocyte lineages. Patients with a lymphoblastic transformation of CGL may be identified by assay of tumor cells for certain common ALL markers (23). As a group, patients with lymphoblastoid CGL have a short survival. However, they may achieve worthwhile complete remissions when treated with vincristine and prednisone (23,24), the cornerstone of therapy in childhood ALL. Patients treated in this way may become severely pancytopenic for a prolonged period, in contrast to patients with ALL who ordinarily quickly recover normal hematopoiesis after treatment (23,24). This difference may reflect damage or depletion of normal hematopoietic stem cells in CGL.

B. Follicular Center Cell (FCC) Neoplasms

On the basis of histologic studies, Lukes and Collins proposed that a large class of lymphomas arise from various cells in the follicular (germinal) centers of

TABLE 2

CLINICAL FEATURES AND RESPONSE TO TREATMENT
OF CHILDREN WITH DIFFERENT TYPES OF ALL

	Common ALL	Pre-B ALL	T ALL
Frequency	67%	19%	12%
Mean age	4 years	4 years	8 years
Sex ratio (M/F)	∿1	∿1	>1
Mediastinal mass	<10%	0	>50%
Rate of remission	>85%	>85%	>85%
Relapse within 1 year	20%	20%	80%

(Reference 17)

lymph nodes (14,25,26). Although defined by morphologic criteria, most of these tumors can be shown to bear surface or cytoplasmic Ig, as would be expected of cells deriving from germinal centers (27-29). Normal FCC cells are B lymphocytes in various stages of activation or transformation. These cells may be either small or large and the nuclear contours may be either round or deeply cleaved (Figure 3).

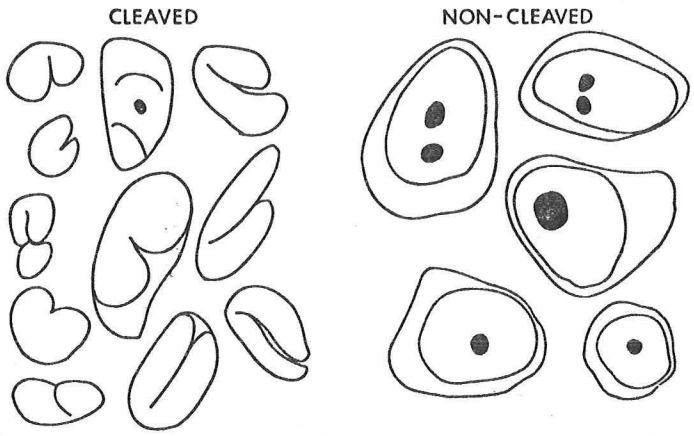


FIG. 1.—Camera lucida of normal follicular centre (FCC) cells shows a range of variations in size and configuration of cleaved cells and in the size and amount of cytoplasm of the non-cleaved cells.

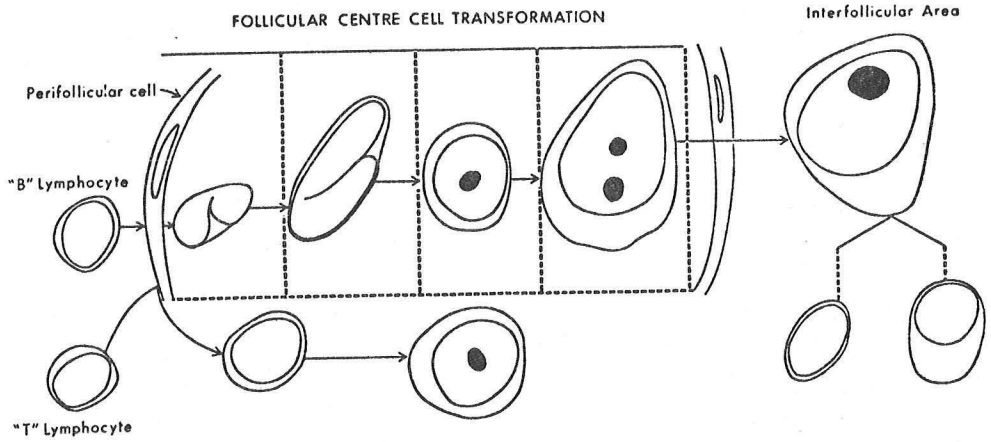


FIG. 2.—Schematic representation of normal transformation of follicular centre cells in comparison with the transformation of T cells.

(Ref. 14)

FIGURE 3

In the classification of Lukes and Collins, FCC lymphomas are divided into these four cell types on the basis of the predominant cell type. Within any given tumor a few cells of each of these four types may be present. The secretion of M-proteins by these tumors is unusual. These tumors, then, are arrested at various early stages of B lymphocyte activation.

Although most small cleaved FCC tumors are monoclonal B cells (29a), it is important to realize that only about 50% of large FCC tumors mark as B cells (reviewed in Ref. 47). The technical problems in these determinations are formidable, however. The B cell nature of the remaining large cleaved FCC tumors is inferred from morphologic studies but is not proven. Moreover, of all the large cell lymphomas (histiocytic lymphomas of Rapaport), only about 35% can definitely be identified as arising from monoclonal B cells (27,28).

1. Small cleaved FCC tumors

These tumors are a common subset of non-Hodgkins lymphomas in adults. They usually replace lymph nodes in a pseudofollicular or nodular pattern. In the Rapaport histologic classification, these tumors are classified as nodular poorly differentiated lymphocytic lymphomas. However, about 10-25% of small cleaved FCC tumors present as diffuse replacement or nodal architecture (47). These cells bear receptors for complement components (28,29). Clinically, small cleaved FCC tumors are usually widespread at diagnosis, with liver and bone marrow involvement seen frequently (Table 3). Atypical "cleaved" lymphocytes can be seen on blood films of up to 33% of patients (30). Using monoclonal SIg as a marker, we have shown that in at least 50% of these patients, circulating tumor cells can be detected (31,32). This finding may explain why these tumors are usually widespread at diagnosis: in most of the cases, subclinical leukemia is present. Frank leukemia is less common, occurring at some time during the course of the disease in about 5-10% of patients (30). In spite of this, these tumors typically follow an indolent course, with median survivals approximating 5-7 years. Since these tumors are usually well-tolerated for long periods of time, a conservative approach to treatment has been advocated. This includes observation alone for asymptomatic patients (33), alkylating agents for disease of intermediate mass and growth rate (34), and combination chemotherapy for rapidly progressive, compressive or symptomatic tumor masses (34,35) (Table 3). Radiotherapy has a definite role in the local management of bulky tumor masses, but the addition of total lymphoid irradiation to combination chemotherpay only adds toxicity without increasing the percentage of patients achieving a complete remission (34). In comparison to nonspecific supportive care, neither radiotherapy nor chemotherapy has yet been shown to prolong survival in large groups of patients. However, patients who achieved a complete remission with combination chemotherapy had a median survival of 8 years, while patients who achieved only a partial or negligable response survived a median of only 3 years (43). The principal difficulty in treating this disease is a very high relapse rate (Table 3). Nevertheless, most oncologists agree that the quality of life is definitely enhanced by the selective use of chemotherapy and radiotherapy.

The natural history of small cleaved FCC tumors, with or without therapy, commonly includes a change in the pace of the disease after several years

TABLE 3

SMALL CLEAVED FCC (NODULAR PDL) LYMPHOMAS:
CLINICAL FEATURES AND RESPONSE TO THERAPY

Clinical Features	Reference
Stage III or IV after pathologic staging -- 96%	40
Lymphangiogram positive -- 90%	40
Bone marrow biopsy positive -- 40%	40
Circulating abnormal cells -- 33%	30
Liver biopsy positive -- 27%	40

Response to Treatment (Ref. 34)

Therapy	Complete Remissions (%)	Disease Progression at 3 Years (%)	Median Survival
Single drug (CTX or CLB)	55	∿ 50	>5 years
Multiple drugs (CVP)	78	∿ 50	>5 years
Radiation + drugs (CVP-TLI)	65	∿ 50	>5 years

CTX - cytoxan
CLB - chlorambucil
CVP - cyclophosphamide, vincristine, and prednisone
TLI - total lymphoid irradiation

of slow progression. One or more lymph node masses may suddenly enlarge, symptoms may develop, organomegaly or abdominal masses may appear, or frank leukemia may emerge. Biopsy of rapidly growing tumor masses may then reveal histologic progression of one of two types: conversion from a nodular to a diffuse architectural pattern, or change from a small cell (lymphocytic) to a large cell ("histiocytic") lymphoma (36,37). Treatment is often ineffective after this type of progression, and survival is short (36,37). Although we have the impression that the treatment of this "transformed" tumor type is even less successful than therapy of de novo lymphomas of the diffuse or large cell type, this impression has not been confirmed in clinical trials.

To recap, small cleaved FCC tumors are usually widespread at diagnosis, are easy to treat but difficult to cure, and often progress to histologically and clinically more malignant disease. Median survival is approximately seven years (43).

2. Small noncleaved FCC tumors

These tumors are less common than the small cleaved FCC group. The tumor cells replace lymph nodes in a diffuse architectural pattern and are thought to be analogous to small transformed B lymphocytes (25-27). In keeping with this thesis, these tumors often have a high growth fraction. A subset of this group encompasses the Burkitt lymphomas of the African and American types. While African Burkitt's lymphoma commonly involves non-lymphoid tissues (jaw, ovaries, kidneys, CNS), American Burkitt's lymphoma usually involves peripheral nodes and the gastrointestinal tract (38,39). Burkitt tumors grow very rapidly and are initially remarkably sensitive to cyclophosphamide. Tumor lysis may lead to fatal hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia (38). Although 30-40% of patients may be cured, relapse and drug resistance are common (38,39).

3. Large FCC tumors

This is another common group of non-Hodgkins lymphomas that comprise approximately 60% of all the large-cell lymphomas ("histiocytic" lymphomas of Rappaport) (25-27). The vast majority of large FCC tumors replace lymph node architecture in a diffuse pattern. These tumor cells commonly bind serum immunoglobulins in nonspecific fashion, making identification of monoclonal SIg difficult (27). The relationship to normal follicular center cells and transformed lymphocytes is based primarily on morphologic evidence (14,25-27).

Systematic application of lymphangiography and staging laparotomy has shown that large cell lymphomas are more often stage I or II (31% of cases) than are small FCC (nodular) lymphomas (4% of cases) (40). Leukemia is very unusual in patients with large cell lymphomas.

In published results of clinical trials, response rates are not stratified according to the Lukes/Collins histologic classification. Therefore, the following data refer to all patients with diffuse large cell ("histiocytic") lymphomas.

In advanced stage disease (II, III or IV), large cell lymphomas were associated with a median survival of about 12-15 months prior to the introduction of aggressive programs of combination chemotherapy. The use of several combinations has been associated with complete remission rates in the 40-50% range (reviewed in Ref. 35) (Table 4). Of great importance is the observation that complete remissions are often associated with long-term disease-free survival, while partial responses do not prolong survival. Several attempts to identify prognostic factors have been made. Clinically, bulky disease (>10 cm in diameter in a single location), GI involvement, bone marrow infiltration, or poor performance status have all been associated with a poor prognosis (45). Histologically, preliminary evidence suggests that the large cleaved subtype carries a more favorable prognosis than the large noncleaved lymphomas (46,47). Further work is needed to identify histologic or biologic features that predict survival with current aggressive chemotherapy programs. In summary, these lymphomas are more difficult to treat than small cleaved FCC tumors because aggressive chemotherapy programs are toxic. The dividends of aggressive therapy are long-term disease-free survivals. It should be mentioned that localized (stage I) large cell lymphomas may be curable with surgery alone or with radiotherapy. The use of such therapy requires thorough staging to exclude advanced disease; at least half of all clinical stage I patients will be found to have more advanced disease after lymphangiography and pathological staging procedures (40). In our experience, large cell lymphoma presenting in the GI tract is rarely localized and, therefore, usually requires a systemic approach to therapy. The hazards of perforation of the GI tract during chemotherapy are well-recognized (45).

C. Immunoblastic Lymphoma (Sarcoma) of B Cells

These lymphomas, comprising about 10-20% of large cell lymphomas (25-27,47), are composed of cells with large round to oval noncleaved nuclei. Nucleoli are prominent. There is a moderate amount of cytoplasm which contains abundant RNA and protein and, therefore, stains deeply with methyl green pyronin. Thus, these cells resemble normal B cells in a late stage of terminal differentiation towards plasma cells. In fact, many of the tumor cells display an eccentric nucleus, amphophilic cytoplasm and pyroninophilia, clumping of chromatin near the nuclear membrane, features which are typical of plasma cells. These lymphomas are always diffuse in pattern, possibly reflecting an origin in B cells that have reached a post-follicular state of differentiation (25-27). Some of the tumor cells contain monoclonal Ig, further supporting a relationship to proliferating, terminally differentiating B lymphocytes (48). The histopathology of the condition closely resembles the appearance of a subset of normal B cells which have been activated with polyclonal stimulants such as pokeweed mitogen (PWM) (25-27). As in normal PWM-induced blasts (49), SIgD was not detected on the tumor cells (49).

Although immunoblastic sarcoma is becoming accepted as a discrete histopathologic entity, the clinical features of these patients are just beginning to be defined (50) (Table 5). In about 1/5 of patients, a history of a prior immunologic disorder or lymphoproliferative tumor is noted. About 2/3 of these tumors present in lymph nodes, 1/3 in extranodal sites with lung and GI tract being most common. More than half present with stage III or IV disease and about half have polyclonal hypergammaglobulinemia. Three-quarters of patients are

TABLE 4

COMBINATION CHEMOTHERAPY OF
DIFFUSE LARGE-CELL ("HISTIOCYTIC") LYMPHOMAS

Chemotherapy	Complete Remission (%)	Median Survival		Reference
		Patients Achieving CR	All Others	
COPP	46 (11/24)	>5 years	<1 year	41
COMA	40 (12/30)	>5 years	<1 year	42
BACOP	47 (15/32)	>5 years	<1 year	43
BACOP	56 (10/18)	>2 years	<1 year	44

COPP - cyclophosphamide, Oncovin®, procarbazine, prednisone
COMA - cyclophosphamide, Oncovin®, methotrexate, Ara-C®
BACOP - bleomycin, Adriamycin®, cyclophosphamide, Oncovin®, prednisone

TABLE 5

CLINICAL FEATURES OF IMMUNOBLASTIC SARCOMA OF B CELLS
(Reference 50)

Prior immunologic disorder -- 18%

- Celiac disease
- Chronic urticaria
- Life-long asthma
- Rheumatoid arthritis
- Sjogren's syndrome
- Hashimoto's thyroiditis
- Renal transplant recipients
- Immunoblastic lymphadenopathy

Prior lymphoproliferative disorder -- 12%

- Lymphocytic lymphoma
- CLL
- Waldenstrom's macroglobulinemia
- Alpha chain disease
- Hodgkin's disease

Clinical Presentation

Nodal	70%
Extranodal (lung and GI tract common)	30%

Clinical Stage

I and II	30%
III and IV	70%

Anemia	73%
Lymphocytopenia <1,000/μl	45%
Polyclonal hypergammaglobulinemia	44%

Prognostic Indicators

Favorable	Unfavorable
(median survival >30 months)	(median survival 5 months)
Stage I, II	Stage III, IV
Asymptomatic	B symptoms
Lymphocytes >1,000/μl	Lymphocytes <1,000/μl

anemic, and half are lymphocytopenic. As a rule, patients have responded poorly to chemotherapy, with a median survival of about 14 months. However, a trial of one of the aggressive drug combinations listed in Table 4, stratified to identify patients with this histology, has not been reported.

The observation that immunoblastic sarcoma follows various immunologic disorders raises the possibility that abnormal immunoregulation, perhaps including unusual antigenic stimulation, breakdown in self-tolerance, or failure of normal anti-idiotypic regulation may be involved in the pathogenesis of this malignancy (51-53). The tumor has frequently been observed to develop in sites of previous immunoproliferation; for example, in the salivary glands of patients with Sjogren's syndrome (54) and in thyroid glands of patients with chronic lymphocytic thyroiditis (55).

An extreme form of histologically benign immunoproliferation, termed immunoblastic or angioimmunoblastic lymphadenopathy (IBL) (56,57) may also progress to immunoblastic sarcoma (50,58). IBL is characterized by the sudden onset of lymph node enlargement, hepatosplenomegaly, skin rash, fever and weight loss. In one series, about 1/3 of the patients developed IBL after administration of a drug such as penicillin, Dilantin or a sulfonamide (57). Polyclonal hypergammaglobulinemia and Coombs positive hemolytic anemias are frequent findings. Histopathologically, IBL is characterized by a proliferation of branching blood vessels, immunoblasts (late-stage transformed B lymphocytes), and plasma cells interspersed with an amorphous PAS positive background material. More than half of the patients die of infection or inanition within one year. About 35% progress histologically to immunoblastic sarcoma (58). The disease occasionally remits spontaneously, or may be controlled with glucocorticoids. The immunoblastic proliferation appears to be polyclonal in nature (49,56,57). The occasional progression to immunoblastic sarcoma again suggests that antigenic stimulation may trigger an unusual immunoproliferative state in the setting of abnormal immunoregulation, and therefore that antigenic stimulation may be a co-factor in the development of an immunoblastic malignancy.

D. Chronic Lymphocytic Leukemia and Well-Differentiated Lymphocytic Lymphoma

Both of these tumors are composed of small lymphocytes with round, uniform nuclei. Morphologically, these cells resemble lymphocytes found in the parafollicular zones and the medullary cords of normal lymph nodes (14,25-27,29). The lymphocytes can in most cases be shown to bear SIgM and/or SIgD. The density of SIg on CLL cells is about 10-fold less than that on normal blood B cells (59) and in a significant fraction of cases cannot be demonstrated by ordinary fluorescence microscopy. SIgMD tumors are the commonest, followed by SIgM CLL's. SIgD and SIgG tumors are unusual (49,60) (Table 6). Just as with normal B cells, some of these tumor cells can be stimulated by allogeneic T cells and pokeweed mitogen to differentiate to Ig-secreting cells (61). Approximately 5% of patients with CLL have a monoclonal serum immunoglobulin, usually IgM or rarely IgG or IgA (62). Thus, CLL's in vivo resemble normal B cells frozen at various states of differentiation. in vivo resemble normal B cells frozen at various states of differentiation ranging from nascent B cells through memory cells and early secretory B cells. In vitro, the state of differentiation can be modulated by polyclonal mitogens and allogeneic T cells.

Clinically, a broad spectrum of aggressiveness is evident when large groups of patients are analyzed. Many patients survive ten years or more with few

TABLE 6

FREQUENCY OF SURFACE Ig ISOTYPES IN CLL

Isotypes	Preud'homme et al. (26) (55 cases)	Our Series (65 cases)
M	8	9
D	0	3
MD	35	24
G	10	2
MG	0	4
DG	0	3
MDG	1	10
Biclonal	1	0
	55	55
Undetectable or polyclonal	?	10

difficulties traceable to the disease, while others develop progressive mass disease, hypermetabolic symptoms, and cytopenias that lead to disability and death within two years or less. A staging system based on clinical features has been devised (63) (Table 7). This system has prognostic value for the prediction of survival. In a number of patients, disease progression is observed; that is, patients advance from one stage to the next. Patients then carry the prognosis appropriate to the higher stage (63). Stage 0 patients receive no specific therapy. Patients with mass disease (stages 1 and 2) are treated with alkylating agents, glucocorticoids, and/or radiotherapy to relieve compressive symptoms. Patients with cytopenias (stages 3 and 4) frequently respond to chemotherapy with an improvement in blood counts. Clinical trials with vigorous combination chemotherapy in patients with stage 3 and 4 disease are underway with the hope that survival time may be prolonged (64,65). Preliminary results suggest that complete responders may enjoy a prolonged survival (65).

Since CLL's display a broad spectrum of states of B cell differentiation and of clinical behavior, the question arises whether these two variables are related. We are currently studying the phenotypes of tumor cells in a series of patients to examine the possibility of such a relationship. Preliminary observations indicate that (a) higher SIg density and (b) a high ratio of density of SIgD to SIgM correlate with advanced stages of disease. These studies are potentially important since the accurate identification of patients destined to develop aggressive CLL could lead to trials of therapy designed to prevent disease progression.

Rarely, CLL may undergo a transition to a large cell lymphoma ("Richter's syndrome") or to a disorder morphologically indistinguishable from acute lymphocytic leukemia (66,66a-c). In both these circumstances, maintenance of the monoclonal SIg marker has been demonstrated (66a-c).

Well-differentiated lymphocytic lymphoma (WDLL) is the tissue analogue of CLL; that is, the cell type is similar but involvement of the marrow and blood is absent. The close relationship of the two diseases is evident from the similarity of cell type and the extension of WDLL to a leukemic phase in a proportion of patients (67). Likewise, CLL commonly involves nodes, spleen, and other tissues. The factors that determine whether this or other B cell tumors remain localized to nodes or become leukemic are not well understood. Recent studies in a guinea pig model suggest that the homing predisposition of B lineage lymphoma cells can change after reversible interactions with the host microenvironment (68). These changes may include the state of differentiation of the tumor cells (69).

E. Waldenstrom's Macroglobulinemia (WM) and Multiple Myeloma (MM)

Study of these disorders, representing monoclonal expansions of end-stage B cells, has revealed a remarkable wealth of information about immunoglobulin structure, normal B cell differentiation, and the pathogenesis of B cell malignancies. The cardinal diagnostic finding in WM is monoclonal serum IgM. Morphologic findings may vary and do not make the diagnosis. In MM, the demonstration of a monoclonal immunoglobulin (usually IgG or A) in the serum, or immunoglobulin light chains in the urine, is also required for the diagnosis (except for rare nonsecretory cases). Morphologically, sheets and clusters of plasma cells in the bone marrow are important diagnostic findings in MM.

TABLE 7

CLINICAL STAGING SYSTEM FOR CLL (Ref. 22)

Stage	Description	Median Survival (years)
0	Blood and marrow lymphocytosis only	>12.5
1	Enlarged lymph nodes	8.4
2	Hepatomegaly or splenomegaly	5.9
3	Anemia { Hb <11 g/dl, Hct <33% }	1.6
4	Thrombocytopenia (<100,000)	1.6

Blood and marrow lymphocytosis is common to all stages. Patients with stage 2 disease may or may not have lymph node enlargement. Patients with stage 3 or 4 disease may or may not have mass disease.

A comparison of the distinguishing features of WM and MM is given in Table 8. Although both diseases are not infrequently detected in asymptomatic individuals, skeletal pain, symptoms of anemia, unexplained renal failure or recurrent bacterial infections most commonly lead to the diagnosis of MM. Presenting findings in WM are typically related to the hyperviscosity syndrome: bleeding, visual disturbances, fatigue, headache, vertigo, decreased levels of consciousness, and congestive heart failure (72). Hypercalcemia, osteolytic bone lesions, Bence-Jones proteinuria, and renal failure are much more commonly due to MM than to WM. The indications and modes of therapy of these disorders have been reviewed in these Grand Rounds (70,71). Briefly, therapy in WM is indicated only when the serum IgM rises progressively, the hyperviscosity syndrome develops, or organ infiltration is marked. MM must be distinguished from nonprogressive plasma cell dyscrasias ("benign monoclonal gammopathies") (71). Once this distinction has been made, specific therapy is indicated. WM is treated by plasmaphoresis and chlormabucil, while standard therapy of MM is melphalan and prednisone (70,71). Approximately 75% of patients with MM respond to therapy with a clinically meaningful reduction in disease activity.

The morphologic findings in WM may span a broad spectrum, including lymphocytosis in the peripheral blood and bone marrow, small lymphocyte infiltration in the liver, spleen, and lymph nodes, and large cell lymphoma fulfilling the diagnostic criteria for immunoblastic sarcoma (29,50,70,73). Clinically, most patients present with the findings listed in Table 8. However, approximately 10% of patients present with a clinical and morphologic features indistinguishable from chronic lymphocytic leukemia. Occasionally, patients with osteolytic bone lesions and plasma cell infiltrates in the marrow are found to have IgM paraproteins (29). This broad range of clinical and morphologic expression reflects the spectrum of terminally differentiating B cells that can secrete IgM.

In the bone marrow of individual patients, lymphocytes bearing SIgM, SIgMD, and SIgD are found and are all part of the neoplastic clone. The density of SIg on clonal WM lymphocytes is more heterogeneous than in CLL (49).

A small group of patients with "double macroglobulin-myeloma gammopathy") have been reported (Table 9) (reviewed in Ref. 74). The tumors in most of these patients secreted both IgG and IgM. The different immunoglobulins usually shared the same light chain type and, in some instances, were shown to share idiotypic determinants. Immunofluroescence studies demonstrated that in some tumors, the same cell secreted both IgG and IgM, while in others, two separate populations of cells secreted the different isotypes. The clinical findings ranged from typical WM to typical MM, with frequent overlap of symptoms (74). These cases present unusual opportunities to investigate mechanisms controlling the switch in heavy chain production in clones of terminally differentiating B cells.

IV. RECAPITULATION -- RELATIONSHIP OF HISTOPATHOLOGY AND NATURAL HISTORY OF STATUS OF DIFFERENTIATION AND ACTIVATION OF TUMOR CELLS

The relationship between the morphology of B cell tumors and their divergent natural histories supports the general concept that tumor behavior is largely determined by the state of differentiation and activation achieved by the majority of the neoplastic cells. Thus, the clinical behavior of various B cell malignancies

TABLE 8

DISTINGUISHING CLINICAL AND LABORATORY FINDINGS IN WALDENSTROM'S MACROGLOBULINEMIA (WM) AND MULTIPLE MYELOMA (MM)

	WM	MM
Skeletal pain	Rare	Common
Hypercalcemia	Unusual	Common
Osteolytic bone lesions	Rare	Common
Renal failure	Rare	Common
Recurrent infections	Unusual	Common
Hemorrhage	Common	Unusual
Hyperviscosity syndrome	Common	Unusual
Hepatomegaly	Common	Rare*
Splenomegaly	Common	Rare*
Lymphadenopathy	Common	Rare
M-Protein	IgM	IgG, A; rarely M, D, E
Bence-Jones Proteinuria	10-20%	60-70%
Reduction in normal Ig	Common	Common
Amyloidosis	Rare (<5%)	10-15%

References 70 and 71.

*Except in amyloidosis

TABLE 9

DATA ON 21 PATIENTS WITH DOUBLE MACROGLOBULINEMIA-MYELOMA GAMMOPATHY

Reference	Age (yr) and Sex	M Components	Clinical Manifestations	Bone Marrow Findings
[3,4]	85,M	IgA(K), IgM(K)	Mild anemia, cystitis	Flame plasma cells, lymphocytosis
[3,4]	73,M	IgG(K), IgM(K)	High erythrocyte sedimentation rate, pancytopenia, cachexia, osteolytic lesions	Plasmacytosis, lymphocytosis
[5,6]	40 M	IgG, IgM	Multiple myeloma, osteolytic lesions	Plasmacytosis
[7]	52,M	IgG(K), IgA(K) IgM(λ)	Healthy person	Normal
[8]	64,M	IgG(K), IgG(λ), IgA(λ), IgM(λ)	Polyarthralgia, hepatosplenomegaly, anemia, lymphocytosis, hyperviscosity	Plasma cells increased, lymphocytes increased
[9]	76,F	IgG(K), IgM(λ)	Splenomegaly, osteolytic lesion, chronic thyroiditis, liver cirrhosis, melena, anemia	Lymphocytosis, atypical lymphocytes
[10]	48,F	IgG3(K),IgM(K)	Hepatosplenomegaly, lymphadenopathy, osteolytic lesions, anemia, lymphocytosis, proteinuria	Immature plasma cells, lymphocytosis
[11]	64,F	IgG(K), IgA(K), IgM(K)	Lymphadenopathy, arthralgias, myalgia, monocytosis, lymph node-lymphoplasmacytic infiltration	15–20% lymphocytes, 5–10% plasmacytes
[11]	68,M	IgG(λ), IgM(λ)	Petechiae; cryoglobulinemia, thrombocytopenia, monocytosis	5–20% lymphocytes
[11]	42,F	IgG(K), IgM(K)	Plasmacytoma of the base of the tongue, chronic bronchitis, monocytosis, liver: lymphocytic infiltration of portal zones	10–20% lymphocytes, 5% plasma cells
[12]	67,M	IgG3(λ), IgM(λ)	Retroperitoneal plasmacytoma	Not reported
[13]	88,M	IgA(K), IgM(K)	Paget's disease, splenomegaly, osteolytic lesions in the femur and humerus, anemia, thrombocytopenia, lymphocytosis	Diffuse plasmacytosis
[14]	64,F	IgM(K), Hγ chain	Plasma cell leukemia, anemia	Plasmacytosis
[15]	N.R.*	IgM(λ), IgG(K)	Waldenström's macroglobulinemia	Two populations of plasma cells
[16]	80,M	IgA, Hμ chain	Splenomegaly; ulcerating skin lesion of the left ear	8% plasmacytes; bizarre forms
[17]	78,M	IgA(K), IgM(K)	Lymphocytic lymphosarcoma	88% lymphocytes, some immature
[20]	61,M	IgG2(K), IgM(K)	Lymphadenopathy, anemia, lymphocytosis, hyperviscosity, proteinuria	75–85% plasma cells, mature; rest lymphocytes
Case 1	62,F	IgG4(K), IgM(K) 17S IgM(K) 7S	Hepatosplenomegaly, lymphadenopathy, anemia, eosinophilia, hyperviscosity, amyloidosis	Normal
Case 2	53,F	IgA(λ), IgM(λ)	Lymphadenopathy, fever, skin rash, polyarthralgia, anemia, leukopenia, plasmacytosis	Plasmacytosis
Case 3	70,F	IgG(λ), IgM(λ)	Plasmacytoma of the liver	A few immature plasmacytes
Case 4	79,M	IgG(K), IgM(K)	Lymphadenopathy, malignant diffuse histiocytic type lymphoma	Normal

* Not reported.

Ref. 74

should be predictable in part from a knowledge of the properties of normal B cells at various states of differentiation and activation and from the concept that the malignancies are monoclonal expansions of cells whose proliferation is not properly regulated by the host. A correlation between normal and malignant behavior of cells in the B lymphocyte lineage is given in Table 10. There is no simple relationship between the degree of malignancy of a tumor and its state of differentiation. At each state of differentiation a broad range of biologic behavior is observed. This variation relates to differences in activation or growth fraction of the tumor stem cells. Several small cell lymphoproliferative disorders including cleaved FCC tumors, Burkitt's lymphoma, CLL, and Waldenstrom's macroglobulinemia, may undergo clonal evaluation to biologically aggressive large cell neoplasms.

V. PATHOGENESIS OF MULTIPLE MYELOMA -- THE QUESTION OF STEM CELL IDENTITY IN B CELL MALIGNANCIES

The most prevalent tumor cell may not be the cell responsible for perpetuation of the tumor. Tumor stem cells, the self-renewing population of cells necessary to perpetuate or transplant a malignancy, may form a small fraction of the total neoplastic cell mass and may be considerably less differentiated than the bulk of the tumor cells. The delineation of the characteristics of tumor stem cells is of great practical importance since, if therapy eradicates only the most differentiated, nonself-renewing cell compartment, the tumor will persist. In the case of B cell neoplasms, for example, many investigators have suggested that the idiotypic antigenic determinants on the SIg molecules of the tumor cells may serve as tumor-specific rejection antigens and offer a target for the specific delivery of cytotoxic agents (53,75,76). This approach would not eradicate the tumor if its stem cells are SIg-negative B cell progenitors (although the emergence of SIg-bearing tumor cells might be blocked). It is particularly instructive to review current knowledge of the clonal origin of multiple myeloma with these questions in mind.

Studies in mice have shown that myeloma can be generated in certain inbred strains by the administration of hydrocarbon oils intraperitoneally (77). The genesis of myelomas in germ-free mice is far less frequent (78). Peritoneal fluid from animals treated with these oils contains factors derived from macrophages that promote the growth of plasma cells in vitro as well as in vivo (79). These observations suggested that nonspecific adjuvant or specific immunologic stimulation is important in the genesis of myeloma, and that genetic predisposition was also essential. Scant evidence is available to suggest that such factors play a role in the pathogenesis of human myeloma (80,81).

The availability of a clonal marker, the immunoglobulin idiotype, provides a means of scanning less differentiated members of the B cell lineage for clonal expansion in myeloma. Certain technical problems relating to the specificity of anti-idiotypic antisera and to nonspecific binding of serum paraprotein to normal cells appear to have been overcome in recent studies. Several investigators have reported that in the blood of patients with MM, normal (polyclonal) B lymphocytes are markedly decreased, while tumor idiotype-bearing B lymphocytes are strikingly increased (82-84). Recently, Kubegawa et al. (84) reported that idiotype-specific pre-B cells as well as B cells were markedly increased in the bone marrow of these patients (Table 11). Thus, clonal involvement in MM may extend backwards to the earliest recognizable state of B cell differentiation. These findings are consistent with many other animal studies showing that very primitive hematopoietic progenitor cells are the targets for many kinds of carcinogenic stimuli (85).

TABLE 10

TUMORS OF THE B CELL LINEAGE -- RELATIONSHIP TO NORMAL B CELLS

Tumor	Corresponding Normal B Cells	Properties
Pre-B cell ALL	$cIgM^+$ pre-B cells	High growth fraction; originate in bone marrow or fetal liver.
Small cleaved FCC lymphoma	Cells at early stage of maturation in germinal centers	Low growth fraction; commonly circulate in low numbers. "Home" to germinal centers. Dense SIgM,D. Do not secrete Ig.
Large cleaved FCC lymphomas	Cells at midpoint of maturation in germinal centers	Low to moderate growth fraction; do not commonly circulate. Do not secrete Ig.
Small/large noncleaved FCC lymphomas	Activated B cells in germinal centers	High growth fraction; occasionally circulate.
Immunoblastic sarcoma of B cells	Activated B cells with plasmacytoid differentiation; found in interfollicular regions	High growth fraction; low rate of Ig secretion. Loss of SIgD. Do not circulate.
CLL	Heterogeneous: Nascent B cells, long-lived B (?memory) cells or terminally differentiating B cells	Very low growth fraction; circulate to all areas of nodes. Increased production of short-lived (5 days) and long-lived (5 years) lymphocytes. Sparse SIgM, D; occasional G. Some secrete Ig.
Small lymphocyte lymphoma	Heterogeneous: ?Nascent B cells or terminally differentiating B cells	Very low growth fraction usually. Do not circulate. Sparse SIgM, D, occasional G.
WM	Very broad spectrum of terminally differentiating IgM-secreting cells: lymphocytes, immunoblasts, plasmacytoid lymphocytes and plasma cells	Entirely dependent on state of differentiation of majority of tumor cells. SIgM, D, of heterogeneous density. Usually significant circulation and marrow "homing".
Leukemic reticuloendotheliosis	Unknown	Phagocytic, cohesive. Circulate in small numbers; home to spleen and bone marrow.

TABLE 11

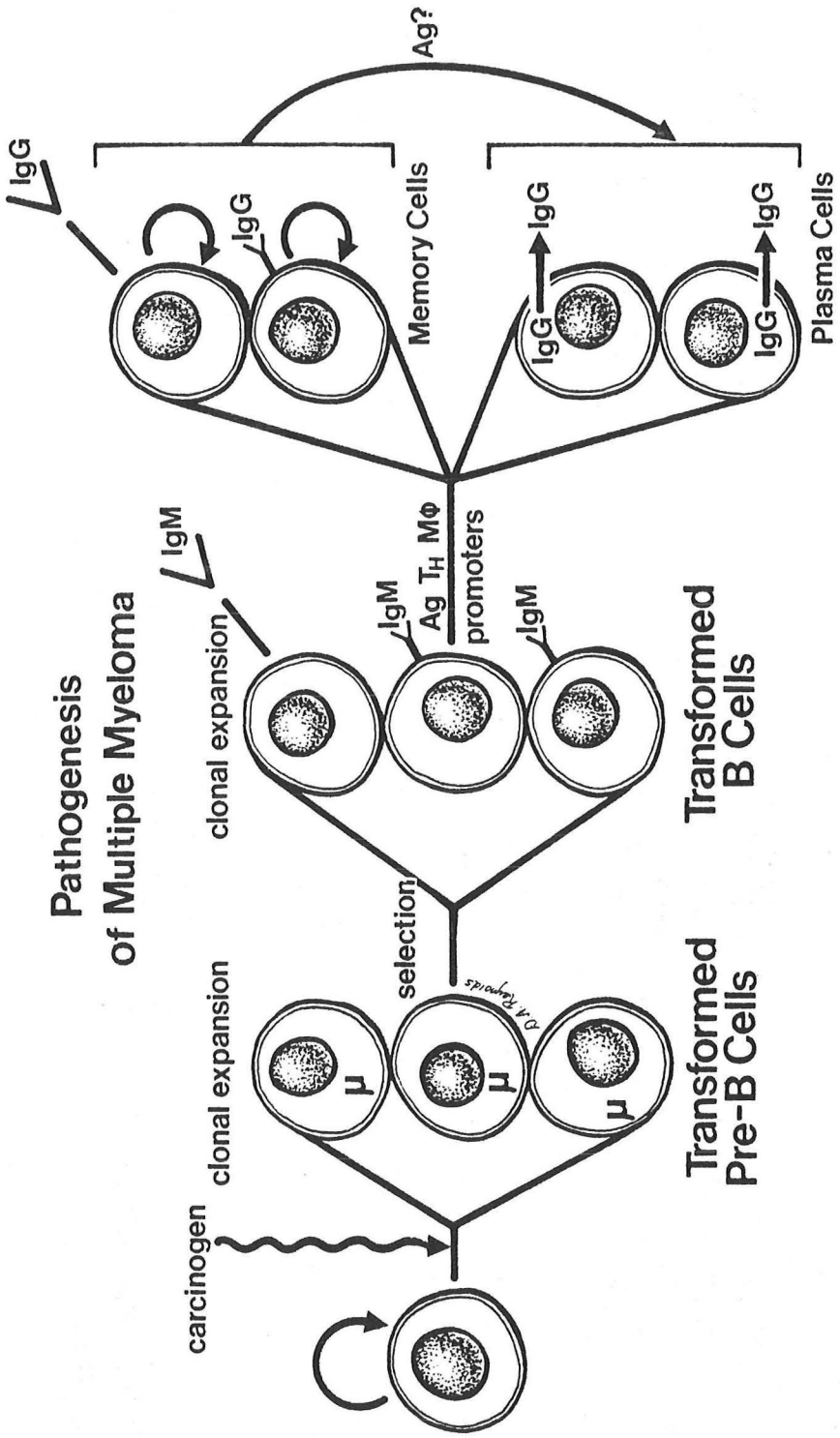
FREQUENCY OF PRE-B AND B LYMPHOCYTES OF THE MYELOMA CLONE IN NORMAL SUBJECTS AND TWO PATIENTS WITH IgA MYELOMA (from Ref. 84)

	Patient 1		Patient 2		Normal Controls	
	Pre-B	B	Pre-B	B	Pre-B	B
	(% of total pre-B or B cells)					
Myeloma idiotype 1	46	2.2-7.1	ND	ND	<0.3	<0.03
Myeloma idiotype 2	ND	ND	13	1.4	<0.6	<0.03

Pre-B cells were studied in the bone marrow, while B cells were studied in the peripheral blood. The presence of antigenic determinants peculiar to the individual myeloma proteins (idiotypic determinants) in or on cells was assayed by immunofluorescence. Idiotype-specific B cells were found amongst SIgM, SIgD, SIgG, and SIgA-bearing lymphocytes.

Based on these observations, a model for the pathogenesis of myeloma can be proposed (Figure 4). Carcinogens of unknown types, targeted on stem or early committed B cell progenitors, lead to an alteration in growth control which, in turn, expands the numbers of cells in one or more clones at this early stage of B cell maturation (86). In some of these cells, this genetic lesion is sufficiently minimal to permit subsequent steps in proliferation and differentiation to proceed to the early B cell level. Nonspecific and/or specific immunologic influences such as adjuvants, antigen or helper factors from T cells or macrophages may then lead to a dramatic increase in the size of the clone as well as to terminal differentiation along pathways leading to Ig secretion. These influences would be akin to tumor promotors (87). The basic lesion in the cell might account for resistance to normal immunoregulatory influences directed against idiotypic antigenic determinants (53). This model could be applied to other types of B cell tumors as well. At least three critical events would determine the nature of B cell tumors emerging after an initial carcinogenic stimulus: the type of genetic alteration in the B stem cell target, the presence or absence of "factors" promoting the growth and differentiation of B cells, and the efficacy of anti-idiotypic regulatory mechanisms. A clearer understanding of these factors might make it possible to manipulate the state of differentiation of the tumor cell mass and thereby alter the course of B cell malignancies (68). However, complete eradication of the tumor will require destruction of the stem cells which phenotypically may resemble very primitive B cell progenitors.

FIGURE 4


Pathogenesis
of Multiple Myeloma
carcinogen
clonal expansion
μ
μ
μ
selection
D.A Rearrangements
clonal expansion
IgM
IgM
Ag T_H MΦ
promoters
IgM
Transformed
Pre-B Cells
Transformed
B Cells
IgG
IgG
Memory Cells
Ag?
IgG
IgG
IgG
IgG
Plasma Cells

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