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NEW APPROACHES TO THE CLASSIFICATION OF THE LYMPHOMATA

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Summary.—Our recently proposed functional approach to and classification of the malignant lymphomata based upon the T and B cell systems, lymphocyte transformation and their development as blocks or a " switch on " in lymphocyte transformation has been reviewed. This functional classification contains 5 major groups: (a) U cell or undefined for those proliferations without specific markers; (b) T cell; (c) B cell; (d) histiocytes as macrophages; (e) unclassifiable for those technically insufficient for specific cytological classification.

Retrospective study of several case populations indicates that the majority of non-Hodgkin's lymphomata exhibit features of follicular centre cell (FCC) lymphomata of either cleaved or non-cleaved types. The prognostically favourable status of nodular lymphomata seems to result from the retained capability of follicle formation by FCC types with limited abnormality.

Lymphomata of large cell types previously classified as histiocytic lymphoma or reticulum cell sarcoma predominantly resemble transformed lymphocytes and rarely exhibit features of histiocytes as macrophages. They are designated " immunoblastic sarcoma " when they occur as large transformed lymphocytes and may have either T or B cell immunological markers. Immunoblastic sarcoma has been observed to develop in individuals with chronic abnormal immune states, Sjögren's syndrome, alpha chain disease, in patients on immunosuppression therapy for graft rejection and in senescence.

There is accumulating evidence of lymphomata of T cells but none are firmly established. These include Sézary's syndrome, mycosis fungoides and the convoluted lymphocyte type, previously included designated as acute lymphocytic leukaemia with mediatinal mass.

The results of initial functional studies provide support for the proposed classification and indicate that the modern pathological investigative approach requires the collection of fresh lymphomatous tissue and an integrated immunocytochemical and morphological approach for the precise characterization of human lymphoma cell types.

IN THE PAST decade there has been remarkable progress in our understanding of basic immunology, but little advance in the field of malignant lymphomata, the neoplasms of the immune system. Furthermore, the traditional classifications and terminology bear no relationship to modern immunology. The commonly used terms of past decades, reticulum cell sarcoma and lymphosarcoma, have both been demonstrated to include a number of cytological types and have achieved a meaningless status in communication (Gall, 1958; Lukes, 1967, 1968). The approach of Rappaport (1966) questioned the existence of follicular lymphoma and demonstrated the prognostic importance of nodular lymphomata. It provided needed emphasis on the cytological character of nodular proliferation but obscured any relationship to follicles. The nodular lymphomata and

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cytological types of Rappaport (1966), though shown to be of prognostic significance (Dorfman, 1973*a*, *b*) preceded the modern advances in immunology and are lacking in conceptual relevance. Through the past decade Lennert has maintained that follicular lymphoma is a distinctive morphological entity, as he has indicated elsewhere in this symposium, and that it is a special tumour of germinal centre cells for which he uses the term " germinoblastoma " (1971, 1973).

Since 1971 in a series of major meetings, we have proposed a new functional approach and classification for the malignant lymphomata (Collins and Lukes, 1971; Lukes and Collins, 1973, 1974*a*, *b*). The morphological findings were related to the B and T cell systems and lymphocyte transformation, and a new approach for the ultimate immunocytochemical characterization of malignant lymphomata was outlined. A follicular centre concept was presented on the following basis: (1) follicular centre cells (FCC) are plasma cell precursors and B cells; (2) the follicular centre is the site of normal B cell transformation; (3) lymphomata of FCC occur in both follicular and diffuse histological patterns and represent cytological types of lymphomata; (4) the lymphomata of large cells, previously interpreted as histiocytic lymphoma or reticulum cell sarcoma, with few exceptions are transformed lymphocytes, most commonly of B cell type. The previous follicular lymphoma concept regarded the follicular structure as lymphomatous. The follicular centre cell concept is concerned with lymphomata of follicular centre cell types that commonly retain some degree of follicle formation but may evolve to a diffuse pattern while maintaining the same cytological type. The majority of non-Hodgkin's lymphomata from our survey of several case series morphologically appear to fall within the cytological types of the B cell group. The number of cytological types in the T cell group is uncertain but Sézary's syndrome, mycosis fungoides and Hodgkin's disease all seem likely candidates. There is also evidence that the convoluted lymphocytic type, a new morphological type we have observed that is often associated with mediastinal masses and acute lymphocytic leukaemia of adolescent children and young adults, also may be of T cell type. The results of immunological membrane marker studies that have become available since our initial proposals in 1971 and 1972 have provided support for our functional approach, the existence of lymphomata of the B and T cell systems and the rarity of " true " histiocytic lymphoma.

In this presentation we will briefly review (1) the immunological and (2) morphological basis of our approach, (3) the supportive functional studies, (4) the functional classification and (5) the definition of the cytological types.

IMMUNOLOGICAL BASIS OF PROPOSAL

Lymphocytic systems.—Two lymphocytic systems are now generally accepted to exist in man. This is based on the observations of human congenital immune deficiencies and the ablation experiments in the murine and avian systems (Good and Finstad, 1968). They are (a) the T cell or thymic dependent and (b) the B cell or the bursal equivalent (thymic independent) systems. A group of lymphocytes without membrane markers is also recognized, the so-called null cells, that appears to represent a third lymphocytic system of non-B or T cells for which we have suggested the term U cells (undefined cells) (Lukes and Collins, 1973, 1974*a*, *b*). The T and B cells are distributed in a consistent manner. The T cells occupy the paracortical area of lymph nodes, perivascular region of the spleen and small foci in the lamina propria of the gastrointestinal tract. The B cells concentrate in the follicular centres of lymph nodes, spleen, the lamina propria of the gastrointestinal tract and wherever follicles occur; they also are found interspersed in the marrow.

Plasma cells, apparently the mature or functioning cells of the B cell system, typically are located in the medullae of lymph nodes, perivascular areas of the spleen and bone marrow and in chronic system reactions throughout lymphoid tissue and inflammatory sites of chronic reaction. T cells circulate 4–6 times a day, and represent normally 70% of the lymphocytes in the peripheral blood, while 20–25% are B cells and U cells the remainder. There is a highly selective "homing" phenomenon in the complex daily traffic of lymphocytes that relates to the preferential anatomical distribution of lymphocytes.

Lymphocyte transformation.—Pathologists are beginning to become aware of the morphological expressions of the remarkable phenomenon, lymphocyte transformation in lymphoid reactions and in lymphomatous processes. Previously, these large cells in histological sections of lymphoid tissue were interpreted as an expression of reticulum cells or histiocytes. From *in vitro* studies it has become apparent that normal lymphocytes, apparently of both B and T cell systems, under the influence of plant mitogens and antigens to which the individual previously has been exposed, transform from small lymphocytes to large dividing forms. Phytohaemagglutinin (PHA) and concanavalin seem to be selective mitogens for T cells while pokeweed transforms both B and T cells. A highly selective mitogen for B cells in man has not been established as yet. We believe that small lymphocytes and large transformed cells both are expressions of lymphocytes and represent dormant and metabolically active states respectively, rather than, as in the past, variations in the degree of differentiation. The fully transformed normal lymphocyte (immunoblast) typically is 3–4 times the size of the normal small lymphocyte. The transformed lymphocytes grow in cohesive clusters, have primitive appearing large nuclei with finely distributed chromatin network, and one large or several small nucleoli. The cytoplasm is abundant, pyroninophilic and deeply azurophilic in Romanowsky stained sections. In histological sections of aggregated clusters of normal *in vitro* transformed lymphocytes, there is a wide variation in cell size and the transformed lymphocytes present a primitive neoplastic appearance with numerous mitoses. Because of this dramatic *in vitro* experience, a search for the benign and neoplastic counterparts of transformed lymphocytes of B and T cell type was undertaken. We have found large transformed lymphocytes (immunoblasts) consistently in small numbers in the interfollicular tissue in typical benign lymphoid reactions of lymph nodes. They occur with dramatic frequency in the interfollicular tissue both in the regional lymph nodes of smallpox vaccination and in infectious mononucleosis. On the basis of our morphological observations (Lukes, Tindle and Parker, 1969; Tindle, Parker and Lukes, 1972), the process in infectious mononucleosis has every appearance of marked activation of lymphocyte transformation to the immunoblast that in the late stage of the process is associated with numerous plasmacytoid cells. In addition, in infectious mononucleosis we consistently have found binucleated immunoblasts in the interfollicular tissue indistinguishable from diagnostic Reed–Sternberg cells of Hodgkin's disease (Lukes, Tindle and Parker, 1969; Tindle, Parker and Lukes, 1972). In reactive follicular centres, transformed lymphocytes are found in varying numbers, depending on the degree of reactivity. They are demonstrated most effectively in methyl green pyronine or Giemsa stained sections (Lukes and Collins, 1973, 1974*a*, *b*). The large pyroninophilic cell of the follicular centre is presumed to be the transformed B cell since follicular centres are regarded as B cell regions on the basis of the absence of follicles in Bruton's sex linked congenital immune defect of the B cell system (Good and Finstad, 1968) and this view has been

supported by recent immunological membrane marker studies (Jaffe *et al.*, 1974). Immunoblasts of both T and B cell systems probably occur in the interfollicular tissue, but their differentiation is unestablished in histological sections, though the transformed B cell probably is larger, has more cytoplasm and at times has plasmacytoid features. The demonstration of cytoplasmic immunoglobulin in paraffin sections by Taylor and Mason (1974) may prove to be an effective method of identification of immunoblasts of the B cell system in histological sections (Bennett and Millett, 1969).

MORPHOLOGICAL BASIS OF PROPOSAL

T cell lymphomata.—In recent years Hodgkin's disease, mycosis fungoides and Sézary's syndrome have been suspected of being disorders of T cell type, but definitive evidence from membrane marker studies has lately become available only in Sézary's syndrome (Brouet, Flandrin and Seligman, 1973). Recently we proposed that a lymphoma of convoluted lymphocytes, previously regarded as one type of acute lymphocytic leukaemia that is associated with a mediastinal mass, may be of T cell type (Barcos and Lukes, 1974*a*, *b*; Lukes and Collins, 1974*a*, *b*). Several reports of membrane marker studies on these cases have provided support for this proposal (Borella, Sen and Green, 1974; Kersey *et al.*, 1973*a*, *b*; Leech *et al.*, 1974; Smith *et al.*, 1973).

A fundamental lymphocyte abnormality in Hodgkin's disease has long been suspected because of the frequent abnormality observed in delayed hypersensitivity responsiveness, delayed graft rejection, increased susceptibility to certain infections and the frequent development of lymphocyte depletion with disease progression. The nodular sclerosing type, with its mediastinal orientation, also raises the question of a thymic relationship in Hodgkin's disease. In addition, the initial foci of involvement of lymph nodes in the paracortical region presents evidence of thymic dependent lymphoid tissue selectively. Our morphological approach to the natural history of Hodgkin's disease and the associated histological types are based on the suspected interrelationship of lymphocytes and Reed–Sternberg cells (Lukes, Butler and Hicks, 1968; Lukes and Butler, 1966; Lukes, 1971). The hypothesis on the development of Hodgkin's disease, recently proposed by Order and Hellman (1972), is based on a defective T cell surveillance system that permits the formation of Reed–Sternberg cells from reticulum cells. We have proposed a variation of this hypothesis in which the Reed–Sternberg cell develops as modified or polyploid transformed lymphocyte under the permissive state of a defective T cell surveillance system. This view evolved from our studies of the morphology of Hodgkin's disease during the past decade and the demonstration of Reed–Sternberg cells in infectious mononucleosis (Lukes *et al.*, 1969; Tindle *et al.*, 1972). From this experience we suggested that Reed–Sternberg cells may be polyploid expressions of transformed lymphocytes or immunoblasts, rather than the malignant reticulum cell as traditionally believed. In this modified hypothesis the defective T cell surveillance proposed by Order and Hellman (1972) would permit the polyploid immunoblasts (Reed–Sternberg cells) that develop in the course of viral infections such as infectious mononucleosis, to persist, eventually increase in number, disseminate and produce clinical disease. This hypothesis is consistent with our initial proposal that the basic process in Hodgkin's disease represents the attempted induction of malignant neoplasia and the clinical manifestations of Hodgkin's disease reflect the struggle between the host (the T cells) and the induction of Reed–Sternberg cells (Lukes *et al.*, 1966; Lukes and Butler, 1966; Lukes, 1971).

Recently we have observed a distinctive clinical and morphological entity

that in the past has been designated as acute lymphocytic leukaemia with mediastinal mass (Barcos and Lukes, 1971*a*, *b*; Lukes and Collins, 1974*a*, *b*). We proposed the term convoluted lymphocytic lymphoma and suggested that it may involve a T cell proliferation. It was observed initially in a group of 22 patients predominantly in the adolescent age group who commonly presented with a mediastinal mass composed of a proliferation of distinctive convoluted lymphocytes. The marrow at the time of diagnosis was frequently uninvolved, but after a brief period (1–8 months) during therapy the marrow usually became diffusely leukaemic. The convoluted lymphocytes are non-cohesive, primitive appearing cells that present as infiltrative masses or as partially involved lymph nodes. These lymphomatous cells range in size from 1–3 lymphocytes in diameter and most commonly have a regular configuration. The nuclei have finely distributed primitive chromatin, small nucleoli, and the cytoplasm is scanty or indistinct. The convoluted appearance of the nuclei results from a variable number of fine linear subdivisions that are most common in the larger cells and typically impart a " chicken footprint " appearance. Mitoses are usually numerous. This cellular proliferation is steroid and radiation sensitive and is similar to the immunologically incompetent cell of the thymus. The initial functional studies on a few reported cases have provided some support for the T cell character of this neoplasm (Borella *et al.*, 1974; Kersey *et al.*, 1973*a*, *b*; Leech *et al.*, 1974; Smith *et al.*, 1973). The association of leukaemia and a tumour mass, frequently in the mediastinum, was reported by Sternberg (1916). The cases of his report, however, seem to represent several cytological types of leukaemia, including both acute granulocytic and acute lymphocytic leukaemia. The term " Sternberg sarcoma " (Smith *et al.*, 1973; Sternberg, 1916) in our view is inappropriate since a term ideally should emphasize the morphological character and derivation of the neoplastic cell. In addition, 4 of our patients presented with a leukaemic marrow and enlarged nodes without a mediastinal mass and one with inguinal lymphadenopathy only. We are proposing, therefore, the descriptive cytological term, convoluted lymphocytic lymphoma, possibly of T cell type, until the precise characterization of the cell is definitely established.

Another type of T cell lymphoma with membrane markers has been observed by Berard (1974) and Leech *et al.* (1974) and we have identified 2 additional cases. Morphologically, the proliferation exhibits a wide range of lymphocytes, from the small dormant forms to the large cytoplasmic transformed cell, apparently with representation of all intermediate stages in T cell transformation.

B cell lymphomata.—Malignant lymphomata of the B cell system include (1) the lymphomata of plasma cell precursors of the immunoglobulin producing system, the follicular centre cells (FCC) and (2) lymphomata associated with abnormal immunoglobulin production. Chronic lymphocytic leukaemia, the leukaemic counterpart of the lymphoma of small lymphocytes of the classification described in this presentation, already appears established as a B cell neoplasm from a number of membrane marker studies (Aisenberg and Bloch, 1972; Green, 1974; Grey, Rabellino and Pirofsky, 1971; Piessens, Schur and Moloney, 1973).

Follicular centre cell concept

The normal cells of the follicular centre are considered components of the B cell system on the basis of: (1) the ablation experiments of the avian pouch of Fabricius that produce agammaglobulinaemic animals without follicles or plasma cells; and (2) Bruton's agammaglobulinaemia, the human congenital sex linked immune deficiency that is manifested morphologically by an absence

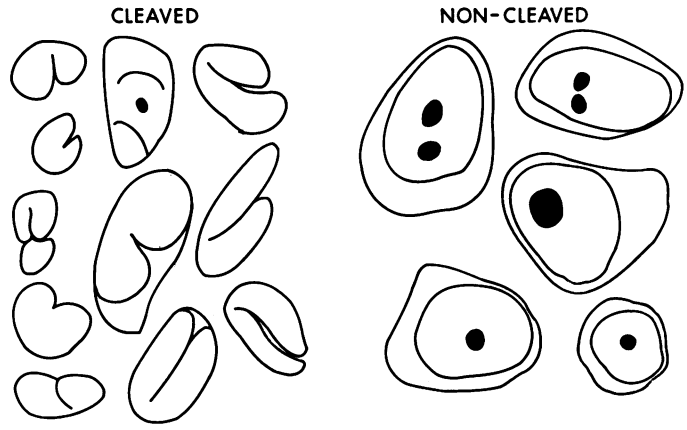


FIG. 1.—Camera lucida of normal follicular centre (FCC) cells shows a range of variations in size and configuration of cleaved cells and in the size and amount of cytoplasm of the non-cleaved cells.

of B cells, follicles and plasma cells (Good and Finstad, 1968). In the normal human follicular centre we have found 4 types of cells: (a) the cleaved nucleated cell with scanty cytoplasm; (b) the non-cleaved nucleated cell with prominent pyroninophilic cytoplasm; (c) the tingible body macrophage or so-called "starry-sky" phagocyte; and (d) the dendritic reticular cell (Lukes and Collins, 1973*a*, *b*). The cleaved and non-cleaved cells are the predominant cells of the normal follicular centre and the cytological types with which we are concerned in the lymphomata of FCC. Their relative frequency in normal follicles varies with the degree of immunological activity of the follicle. From our camera lucida studies of normal follicular reaction centres shown in Fig. 1, there is a wide variation in the size and the relative frequency of cleaved and non-cleaved cells. A similar variation in the degree of nuclear cleavage is noted in the cleaved cell. The cytoplasm of the cleaved and non-cleaved cells is pyroninophilic, but it is scanty in the cleaved cell and moderate to abundant in the non-cleaved cell. In general, the amount of cytoplasm is proportional to size of nucleoli. From our experience with the morphology of the normal follicular centre and lymphocyte transformation, we proposed that the follicular centre is a site of normal lymphocytic transformation in the B cell system in which the small round lymphocyte in the lymphocytic mantle changes gradually through cleaved cell stages to the large non-cleaved cell in the follicular centre. From the observation of Nossal *et al.* (1968), antigen is trapped within the follicular centre, principally on the surface of dendritic reticular cells, in close association with lymphocytes and induces blast transformation in lymphocytes. This phenomenon is illustrated schematically in Fig. 2. The small B lymphocyte under the influence of antigen and a dendritic reticular cell, shown as a perifollicular cell, is induced to begin transformation and undergoes nuclear cleaving. Gradually, the cleaved cell enlarges, acquires a narrow rim of pyroninophilic cytoplasm as it reaches the large cleaved cell stage which is similar in size to the nucleus of a non-cleaved cell. Nuclear cleavage disappears in the next stage as the nucleus becomes round or oval, nucleoli appear and enlarge as the amount of pyroninophilic cytoplasm reaches a prominent degree. The non-cleaved cell continues in its enlargement and achieves a size 4 or more times the original small lympho-

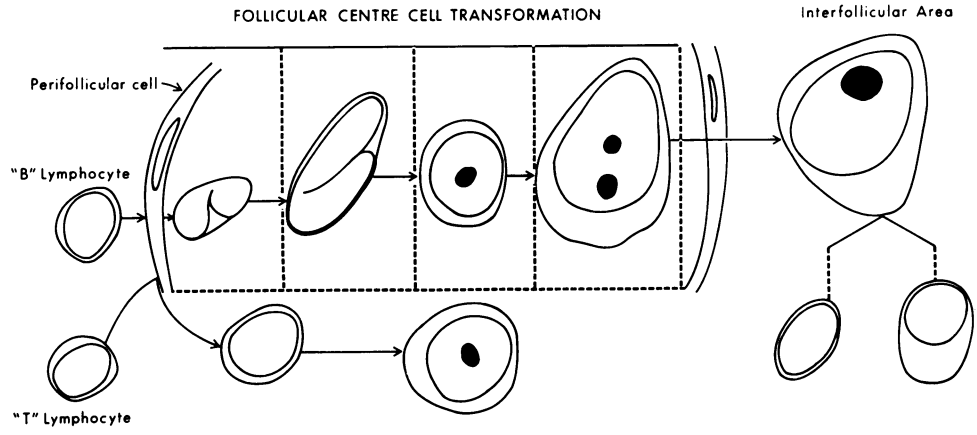


FIG. 2.—Schematic representation of normal transformation of follicular centre cells in comparison with the transformation of T cells.

cyte. With increase in the quantity of cytoplasm the nucleoli become prominent and distinctive, typically with 2 situated at the nuclear membrane on the short axis of an oval nucleus. The non-cleaved cell is the dividing cell of the follicular centre while the cleaved cell is the non-dividing form. In histological sections some of the large non-cleaved cells are found at the margin of the follicular centre and in the lymphocyte mantle, as they seem to move out into the interfollicular tissue. In the interfollicular tissue, they may continue to proliferate as immunoblasts of B cells and provide daughter cells that eventually become plasma cells. Apparently with disappearance of the stimulus, the immunoblast may return to the dormant state as small memory lymphocytes. The small T cell probably undergoes a parallel transformation in the interfollicular tissue, but without nuclear cleavage. The proposed direction of *in vivo* transformation of B lymphocytes in the follicular centre from a small lymphocyte to a large non-cleaved cell is in direct contradiction to the commonly held view of differentiation. This proposal was developed from our long experience with *in vitro* transformation of peripheral blood lymphocytes, in which transformation occurs from the small dormant lymphocyte to the large, metabolically active, dividing form; a parallel direction of transformation in the follicular centre of B cell system seems most likely to us. Bi-directional transformation or modulation *in vivo* also is acknowledged as a possibility and may account for the differences in views. The studies of DNA synthesis of follicular centre cells in the human tonsil by Mitrou *et al.* (1969) provides evidence in support of our proposed direction of transformation.

Follicular centre cell (FCC) lymphomata

The majority of nodular and diffuse human non-Hodgkin's lymphomata present as cleaved or non-cleaved follicular centre cell (FCC) types in our retrospective morphological studies at 3 medical centres. The results of survival studies of these case series will be reported separately. In addition, our camera lucida studies of numerous cases of nodular (follicular) lymphomata revealed that the nodules were composed predominantly of cleaved or non-cleaved cells, or in varying mixtures. These cells were essentially similar to normal follicular centre cells shown in Fig. 1, with variations only in the degree of nuclear cleavage and cell size. The majority of diffuse non-Hodgkin's lymphomata also consist of similar FCC, though they exhibit a

greater range in cell size and frequency of pleomorphism. The lymphomata of follicular centre cells (FCC) can be divided into the following 4 categories based on the size of the 2 follicular centre cell types: (a) small cleaved; (b) large cleaved; (c) small non-cleaved; and (d) large non-cleaved. Designation of the cytological type depends essentially upon the numerically predominant cell type. In general, the prognostically unfavourable large non-cleaved cell is the determining factor. If the process is focally dominated by non-cleaved cells or the number exceeds 25% throughout, it is regarded as the non-cleaved type. The FCC proliferations, however, fundamentally are mixtures of cleaved and non-cleaved cells, though the degree of mixture is usually minor. Most commonly the frequency of non-cleaved cell component in a small cleaved FCC lymphoma ranges from 1 to 10%. When the non-cleaved cell component increases significantly in number, it rapidly dominates the process, apparently because it is the dividing cell of the follicular centre. When the proliferation appears mixed, there is usually a significant component of large cleaved cells, possibly as a result of a block at the large cleaved cell stage of transformation. All cytological types of FCC are observed in follicular (nodular) or diffuse histological patterns. All other B and T cell types are diffuse in growth pattern. With few exceptions, those with follicular patterns are of the small or large cleaved cell types. The small and large non-cleaved FCC lymphomata are usually diffuse and exhibit partial or minimal follicularity in a small proportion of cases, apparently as a result of their rapid rate of growth and development.

The clinical and histological behaviour of the FCC lymphomata in general reflects the cytological activity of their normal counterparts. The lymphomata of the non-cleaved cells as the dividing cell of the follicular centre appear to have a high proliferative and turnover rate, a diffuse histological pattern and a rapidly progressive course. Clinically they are manifested by rapidly enlarging masses and aggressive symptomatic disease with short median survivals. The small cleaved cell lymphomata involve the non-dividing cell of the follicular centre and are manifested usually by some degree of attempted follicle formation and slow progression. The small cleaved cells exhibit little cellular cohesion, may be found in the peripheral blood as cleaved nucleated cells and account for the widespread "seeding" to the marrow, spleen and liver, possibly as a result of the normal "homing tending" of B cells to these sites. This "seeding" phenomenon accounts for the occurrence of clinical Stage IV disease in patients who are asymptomatic and seem to have limited disease. The small cleaved cell lymphoma is a slowly progressive process with median survivals often in excess of 5 years. The course commonly changes in aggressiveness with the appearance of a prominent, large, non-cleaved cell component as the processes change from the small, cleaved cell proliferation of low aggressiveness to the highly aggressive non-cleaved cell lymphoma. Recognition of this change requires sequential lymph node biopsies, particularly with any dramatic change in the clinical manifestations of the disease. On occasions we have observed lymph node biopsies from 2 sites at the time of initial evaluation, one a diffuse non-cleaved FCC type and the second a small cleaved FCC type with follicular pattern. The progression was rapid and related to the highly aggressive non-cleaved FCC type. The small cleaved cell proliferation was found in the lymph nodes that had been present for years and suggest a long-standing quiescent, undiagnosed lymphoma. This dual expression of the FCC lymphomata in our experience reflects the apparent natural evolution of the process from the predominance of the cleaved FCC to the transformed or non-cleaved FCC. The large cleaved cell is more commonly

associated with a diffuse histological pattern but exhibits a tendency to sclerosis and more limited extent of disease similar to the sclerosing lymphoma described by Bennett and Millett (1969).

From our experience in a retrospective morphological evaluation of case series from 3 medical centres, the majority of non-Hodgkin's lymphomata exhibit features of follicular centre cell types, can be related to the stages of FCC transformation shown in Fig. 2 and appear to develop from either a block of a " switch on " of lymphocyte transformation. The lymphoma of small lymphocytes, which we regard as the tissue manifestation of chronic lymphocytic leukaemia, seems to represent a block at the dendritic reticular cell, shown in Fig. 2 as the perifollicular cell. It appears unable to transform and form cleaved FCC or follicles. This lymphoma is characterized histologically by an apparent inability to form follicles and is associated with a lack of plasma cells and the frequent finding of hypogammaglobulinaemia with advanced disease. A similar block at the small cleaved cell stage is almost always associated with some degree of follicle formation. The block at the large cleaved cell stage is more variable and both small and large cleaved cell components commonly occur together. The majority of all lymphomata with follicles are a variation of the cleaved cell types. The lymphoma of small non-cleaved cells includes 2 variants: (a) the typical lesion of the Burkitt lymphoma as defined in the World Health Organization Conference Report (Berard *et al.*, 1969) that is composed of uniform small non-cleaved cells, and (b) a second type that is composed of a variable size, small non-cleaved cell. Both types have pyroninophilic cytoplasm, closely resemble transformed lymphocytes and for this reason, appear to represent a " switch on " of lymphocyte transformation. They are observed in a wide age range and when large and variable in size are commonly beyond the fifth decade. When small and uniform in size they are observed usually in children and fulfil the morphological criteria of the Burkitt lymphoma (Berard *et al.*, 1969). The large non-cleaved FCC type of lymphoma is more variable in character, usually monomorphous, but on occasion has a residual cleaved cell component. On several occasions we have observed monoclonal immunoglobulin production with this lymphoma and the closely related type, immunoblastic sarcoma type, that will be discussed in a subsequent section.

The evolution of follicular centre cell lymphomata (FCC)

The evolution of both the histological pattern and the cytological types in the FCC lymphomatous process seems apparent from our experience in the past few years of a large volume of consultative material and retrospective review of a case series from 3 medical centres that will be reported separately. The variations in the histological pattern are shown schematically in Fig. 3, and the relationship of histological pattern and cytological types in the evolution of FCC in Fig. 4. There are 4 types of follicular histological patterns that are designated descriptively according to the degree of follicle formation by the following terms: (a) intrafollicular; (b) infiltrative follicular; (c) partially follicular and (d) minimally follicular. These terms were developed from the observation that nodular lymphomatous proliferations are follicles composed of FCC that can be identified both inside and outside of follicles. In the *intrafollicular* type, the lymphomatous cells are limited to follicular centres. In the *infiltrative follicular* type, the follicles extend throughout the lymph node and often into the capsule, the lymphomatous cells being found both within follicles and interfollicular tissue, and usually the capsule. The *partially follicular* and *minimally follicular* types descriptively quantitate the number of

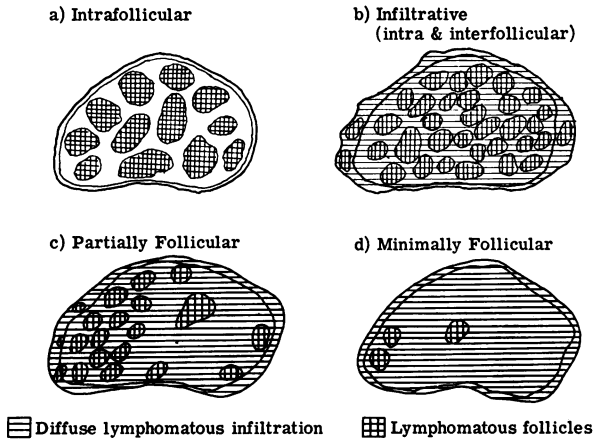


FIG. 3.—Variations in follicular pattern in malignant lymphoma of follicular centre cell types.

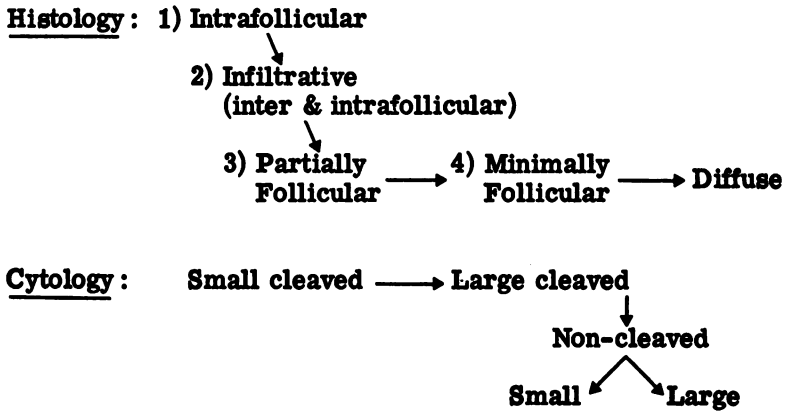


FIG. 4.—Evolution of lymphomata of follicular centre cells. Relationship of histological pattern and cytological types.

follicles in a diffusely infiltrated lymph node. The former indicates that the follicles occupy more than half and the latter less than one-half of the histological section of the lymph node. Frequently, the minimally follicular type is an indication that only a few residual follicles remain in a diffusely involved lymph node. From examination of Fig. 3, it becomes clear that FCC are not confined to follicles in the last 3 types but extend diffusely throughout the lymph node. That the small cleaved FCC of the interfollicular tissues is lymphomatous has not been appreciated because it is smaller than the FCC of the follicular centres. This small cleaved cell is the size of a small lymphocyte but is irregular in configuration and often has less obvious nuclear cleavage. This infiltrating small cleaved FCC appears non-cohesive, is identical usually with the lymphomatous cellular nodules found in the marrow and, for this reason, is believed to be the cell responsible for the seeding phenomenon to the bone marrow, spleen and liver. The evolution of the histological process is apparent from the 4 follicular patterns after appreciating the significance of the infiltrative, small cleaved FCC component. The FCC limited to the centre of the follicles

in the intrafollicular type possibly represent the earliest recognizable stage in the development of the process. In the infiltrative follicular pattern, the infiltrate between the follicles and in the capsule evidence a more aggressive infiltrative phase even though follicles are distributed throughout the node. In the next 2 phases the terms partial and minimally follicular indicate the loss of follicle forming capability and an advanced change to a diffuse pattern. All FCC may occur in the diffuse histological pattern.

A relationship appears to exist, from our retrospective studies, between the type of FCC and the character of the histological pattern. Lymphomata of small cleaved FCC most commonly exhibit some degree of follicular pattern, the majority being infiltrative or partially follicular. The lymphomata of large cleaved FCC are quite variable, most are diffuse, but commonly they are partially or minimally follicular. The non-cleaved FCC are diffuse in pattern, with the exception of a few cases in which the pattern is partially or minimally follicular. Appreciation of the histological evolution of the process is of particular importance in the comparative study of sequential biopsies or a comparison of the initial biopsy and follow-up autopsy material. During the evolution of the process, the small cleaved cell type and some degree of follicular pattern tend to be maintained in patients with slowly progressive disease. With change in the aggressiveness of the disease and under the influence of therapy, the small cleaved cell diminishes in frequency and the transformed (FCC), the non-cleaved cell, becomes prominent. It commonly dominates the process found in the aggressive phase and the tissue examined at autopsy.

IMMUNOBLASTIC PROLIFERATIONS AND IMMUNOBLASTIC SARCOMA

The term immunoblast was initially proposed for the conceptual precursor of cellular immune proliferations. Recently, we have defined its morphological features as those of transformed lymphocytes though the distinction morpholoigcally between T and B immunoblasts has not been established (Tindle *et al.*, 1972). In histological evaluations, we have used the term to designate the transformed lymphocyte of the interfollicular tissue in benign reactions while acknowledging that it probably includes both T and B cell types. The transformed lymphocyte of benign reactive follicular centres and lymphomatous follicles are designated as large non-cleaved FCC to indicate that they are transformed B cells of FCC type, as shown in Fig. 2. The term immunoblastic sarcoma refers to lymphomata of transformed lymphocytes that may be either T or B cell type. Those presenting evidence of FCC relationship, either from a previous biopsy or a cleaved FCC component, are designated large non-cleaved FCC.

From these considerations we have developed 3 types of immunoblastic proliferations: (a) immunoblastic reaction, the type found typically in varying degrees in the interfollicular tissue of lymph node in immune reactions and in severe form in infectious mononucleosis and post-vaccination lymphadenitis; (b) immunoblastic lymphadenopathy, a hyperimmune disorder usually of progressive type resembling Hodgkin's disease that is characterized by 3 morphological features, a non-neoplastic appearing immunoblastic and plasma cell proliferation, a distinctive arborizing vascular proliferation and the deposit of an amorphous acidophilic, interstitial material, that combine to obliterate the lymph node architecture. Clinically, it is characterized by generalized lymphadenopathy, frequently hepatosplenomegaly, fever, weight loss, polyclonal hyperglobulinaemia, and at times, a haemolytic anaemia and initial sensitivity to therapeutic agents. The prominent proliferation of plasma cells, plasmacytoid immunoblasts and the associated polyclonal hyperglobulinaemia sug-

gest that this is a hyperimmune process of the B cell system. This new entity appears similar to the one presented elsewhere in this symposium by Dr Dumont. The results of our study will be published in detail elsewhere (Lukes and Tindle, 1974); (c) immunoblastic sarcoma, a lymphoma of transformed T or B cells.

In the course of our review of large case series, the development of lymphomata of immunoblasts in monomorphous form have been observed in individuals with long-standing abnormal immune disorders such as severe rheumatoid arthritis, systemic lupus erythematosus and the late stage of macroglobulinaemia for which the term "immunoblastic sarcoma" seems appropriate (Lukes and Collins, 1973, 1974*a*, *b*). They are regarded as immunoblastic sarcoma of B cells because of the type of abnormal immune disorder, the frequency of plasmacytoid features and evidence on occasions of a monoclonal gammopathy. The process we initially recognized developing in chronic immune disorders of prolonged duration were manifested by the dramatic appearance of rapidly enlarging nodes or masses and a rapidly progressive course that terminated fatally within 2–3 months. There are numerous reports in the literature of lymphomata developing in similar conditions, but under the term "reticulum cell sarcoma". We suspect that upon review these will prove to be lymphomata of transformed lymphocytes (immunoblastic sarcoma). These include the reticulum cell sarcomata reported in Sjögren's syndrome (Talal, Sokoloff and Barh, 1967), in graft recipients during immunosuppressant therapy (Penn, Halgrimson and Starzel, 1971), the lymphomata in alpha chain disease (Rappaport *et al.*, 1972), and in congenital immune defects (Good and Finstad, 1968). We have had the opportunity to study material representative of these disorders and, with the exception of one case with a congenital immune defect of T cell type, these lymphomata have exhibited the features of transformed lymphocytes (immunoblastic sarcoma). Morphologically similar lymphomata have been encountered in older patients, without monoclonal gammopathy or apparent evidence of an abnormal immune state other than senescence. From this observation, it is suggested that immunoblastic sarcoma may develop in abnormal, damaged or even senescent immune systems following chronic antigenic stimulation. So far, the majority of immunoblastic sarcomata have presented morphological features suggestive of the B cell type. In a recent case, however, functional studies revealed conclusive evidence of a T cell transformed lymphocyte following a 3-year period of lymphomatous proliferation without morphological evidence to suggest a B cell lymphoma.

HISTIOCYTIC LYMPHOMA

The recognition of lymphomata of transformed lymphocytes necessitates a redefinition of histiocytic lymphoma as a neoplasm of "true" histiocytes or macrophages or identifiable reticulum cells using immunocytochemical techniques. Lymphomata of histiocytes with morphological features of macrophages have been rare in our recent review of case series. The cytochemical studies of Leech *et al.* (1974) and Yam and Tavassoli (1974) and our own experience support this observation. In the past histiocytic lymphomata or reticulum cell sarcomata were identified on the basis of large cell size, amount of cytoplasm and pleomorphism. The lymphomata previously classified under these terms, upon review, present the morphological features of transformed lymphocytes either as large non-cleaved FCC, often with a component of cleaved cells, or as immunoblastic sarcoma, often with plasmacytoid features. The recent demonstration by Stein, Lennert and Parwaresch (1972) of abnormal tissue immunoglobulin also represents evidence of B cell proliferation in lymphomata classified as reticulum

cell sarcoma according to previous criteria. At the present time, identification with certainty of the " true " histiocyte as a macrophage in histological sections is impossible. Redefinition of histiocytic lymphoma is essential and specific evidence for identification of neoplastic histiocytes as macrophages as listed in Table I should be required.

TABLE I.—*Techniques for Identification of T and B Cells and Histiocytes*

	T cells	B cells	Histiocytes-monocytes
Membrane bound Ig*	−	+	−
Anti-T cell serum (?)	+	−	−
Sheep RBC rosettes			
E	+	−	−
EAC (IgM)	−	+	+
EA (IgG)	−	−	+
Tissue Ig	−	+	−
Alpha naphthol acetate esterase	−	−	+
Immunoperoxidase for cytoplasmic immunoglobulin	−	+	−

* T cells have a small amount of surface Ig.

SUPPORTIVE FUNCTIONAL STUDIES

A variety of immunological techniques developed for the identification of T and B cells in the murine system in the past decade are now being applied to the study of human malignant lymphomata and have yielded significant results in support for our original proposal. Several of these will be discussed in detail elsewhere in the symposium. Sheep erythrocyte rosette formation with T and B cells and histiocytes has been demonstrated to be helpful in distinguishing these cells when employed alone or with antibody or complement, apparently reacting with specific membrane receptor sites (Green, 1974). Spontaneous sheep erythrocyte rosette formation (E) occurs with T cells, sheep erythrocyte rosette formation with antibody (IgM) and complement (EAC) occurs with B cells, histiocytes and monocytes. Histiocytes and monocytes, however, also form rosettes with sheep erythrocytes with antibody (EA) IgG, but do not require complement and therefore are distinguishable from B cells. Specific receptor sites for heavy and light chains of immunoglobulin on B cells are considered to provide reliable identification for B cells (Aisenberg and Bloch, 1972; Aisenberg and Long, 1974; Green, 1974; Grey *et al.*, 1971; Leech *et al.*, 1974; Piessens *et al.*, 1973; Shevach, Jaffe and Green, 1973). The nonspecific esterase of alpha naphthol acetate esterase is also considered reliable for the identification of histiocytes or monocytes in tissue imprints or frozen sections (Leder, 1967; Yam, Li and Crosby, 1971). The immunoperoxidase technique for the identification of specific cytoplasmic immunoglobulins in formalin fixed paraffin embedded tissue has been reported recently by Taylor and Mason (1974) and may prove effective in histological identification of B cells (Taylor, 1974). These techniques are listed according to their cellular identifying characteristics in Table I, together with several others that have provided useful information in the study of lymphoreticular neoplasms.

The follicular nature of nodular lymphoma now has been established by the ultrastructural studies of Kojima, Imai and Mori (1973) and Lennert (1973) and the EAC rosette studies on frozen sections by Jaffe *et al.* (1974). The results of the presently available functional studies support the identification of the majority of the lymphomata proposed for the B and T cell systems and the cell types in the various stages outlined in the follicular centre cell concept as B cells. The lymphomata with a follicular (nodular) pattern have been demonstrated to be of B cell type on the basis of the EAC and EA rosette techniques on frozen sections (Jaffe *et al.*, 1974). Using the membrane immunoglobulin markers technique, and sheep erythrocyte rosette techniques on lymphomatous cell suspensions, Leech *et al.* (1974) have shown that lymphomata of FCC type with follicular (nodular) histological patterns are of B cell type and have monoclonal markers,

most commonly IgM Kappa. With similar techniques, Aisenberg and Long had the same results on lymphomata classified according to the terminology of Rappaport (1974). Using the alpha naphthol acetate esterase, lymphomata of histiocytes as macrophages, in our experience are rare and Yam and Tavassoli (1974) have found that every case proposed as of histiocytic type is cytochemically similar to a transformed lymphocyte.

Diffuse lymphomata identifiable morphologically as FCC types have also been shown to have B cell markers by Leech *et al.* (1974), in a study of cell suspensions of biopsied lymph node with the membrane marker techniques cited above. In this combined functional and morphological study of non-Hodgkin's lymphomata, approximately 70% of the cases exhibited morphological features of FCC type with either follicular (nodular) or diffuse patterns, have B cell membrane markers (1974). Burkitt's lymphoma, which we regard as small non-cleaved (transformed) FCC type, was demonstrated by Fialkow *et al.* (1973) to have B cell markers and to produce immunoglobulins by Fahey *et al.* (1966). Lymphomata interpreted as reticulum cell sarcoma, based on morphological criteria of the past, contained monoclonal immunoglobulin in the tumour tissue in the study of Stein *et al.* (1972) and provided further evidence that these neoplasms are commonly of B cell type, most likely transformed lymphocytes. Chronic lymphocytic leukaemia (CLL) that we regard as the leukaemia manifestation of the lymphoma of small lymphocytes, now appears established as a B cell process on the basis of membrane marker characteristics (Aisenberg and Bloch, 1972; Green, 1974; Grey *et al.*, 1971: Piessens *et al.*, 1973). The plasmacytoid lymphocytic type of lymphoma, which includes Waldenstrom's macroglobulinaemia, is closely related to CLL, if not an identical process, and is presumed to be of B cell type on the basis of the monoclonal IgM production and plasmacytoid features.

There is evidence supporting the existence of several types of diffuse T cell lymphoma, but none with a nodular (follicular) pattern. The lymphocytes from patients with Sézary's syndrome, the entity closely related to mycosis fungoides, has been reported with T cell membrane characteristics (Borella *et al.*, 1974). The lymphoma of convoluted lymphocytes that is frequently associated with mediastinal masses and acute lymphocytic leukaemia in teenage children, which we have described in an earlier section, has also been reported to have T cell membrane markers in several cases (Kersey *et al.*, 1973*b*; Leech *et al.*, 1974; Smith *et al.*, 1973). A third type of T cell lymphoma with similar markers has been observed by Berard (1974) and Leech *et al.* (1974), but there is an insufficient number of cases at the present time to establish this entity as a T cell type. We have observed several somewhat similar cases with functional studies supportive of T cells. The proliferation represents a spectrum of cells from a slightly irregular small lymphocyte to a large, pale cytoplasmic cell with cohesive cell borders. The nucleus has finely distributed chromatin and usually a large single nucleolus. The range of cell size, together with the nuclear characteristics, are suggestive of cells in varying stages of T cell transformation. Hodgkin's disease also is a candidate for a T cell process, but no conclusive evidence is available from functional studies at this time to substantiate this commonly held view. Our cytochemical studies do not support the long held view of the histiocytic nature of the Reed–Sternberg cell, but fit with our proposal of a polyploid transformed lymphocyte (Tindle *et al.*, 1972).

A FUNCTIONAL CLASSIFICATION OF NON-HODGKIN'S LYMPHOMATA

In 1971 at the Japanese–American Lymphoma Conference we outlined the follicular centre cell concept and the

B cell types (Lukes and Collins, 1973), and at the South-west Germany Radiology Society Meeting in 1972 we proposed a functional approach to the classification of malignant lymphomata (Lukes and Collins, 1974*a*). These reports were based at the time of presentation entirely on our morphological experience with malignant lymphomata and lymphocyte transformation. In the intervening 2 years the results of functional studies, summarized briefly in the previous section, have become available and supported the classification of lymphomata according to the T and B cell systems and the position of each cytological type in this schema. Unquestionably further functional studies and new *in vitro* techniques may necessitate the addition of new types or possibly even modifications. The terms for the cytological types, with the exception of the immunoblast, are descriptive and were selected to convey for the pathologist the most distinctive morphological features.

The classification of lymphomata is listed in Table II according to the following major groups: (a) U cell (undefined); (b) T cell; (c) B cell; (d) histiocytic and (e) unclassifiable. The U cell is essentially hypothetical but provides for a group of cellular proliferations that lack discriminating membrane markers or cytochemical indicators. It presumably will include proliferations of lymphocytes suspected to be true marrow stem cells, such as those found in some cases of acute lymphocytic leukaemia of childhood, that at the present time do not have apparent markers. Possibly in the future, with the development of new techniques, specific markers may be demonstrated and the precise classification established. The unclassifiable group is designed for those proliferations that appear to be lymphomatous, but for technical reasons the cytological features are indistinct or obscured and the process cannot be classified precisely according to the new systems.

TABLE II.—*Functional Classification of Malignant Lymphoma*

- I. U cell (undefined cell) type
- II. T cell types
  - (1) Mycosis fungoides and Sézary's syndrome
  - (2) Convoluted lymphocyte
  - (3) Immunoblastic sarcoma of T cells
- III. B cell types
  - (1) Small lymphocyte (CLL)
  - (2) Plasmacytoid lymphocyte
  - (3) Follicular centre cell (FCC) types (follicular, diffuse, follicular and diffuse, and sclerotic)
    - (a) small cleaved
    - (b) large cleaved
    - (c) small non-cleaved
    - (d) large non-cleaved
  - (4) Immunoblastic sarcoma of B cells
- IV. Histiocytic type
- V. Unclassifiable

DEFINITION OF CYTOLOGIC TYPES OF MALIGNANT LYMPHOMA

The morphological appearance of each of the cytological types will be described briefly in the following section. These descriptions will be limited to the non-Hodgkin's lymphomata of B and T cell types. Sézary's syndrome and mycosis fungoides are included in the T cell group but will not be defined cytologically. No description will be attempted for the U cell group.

I. *T cell types*

1. *Convoluted lymphocyte* (*Fig.* 5).—This is a diffuse proliferation of non-cohesive primitive appearing cells that present as infiltrative masses or with partially or totally involved lymph nodes. The cells are of variable size, ranging from the nucleus of a small lymphocyte to that of a reactive histiocyte. The nuclei, regardless of cell size, have finely distributed chromatin and at times a small central nucleolus. The nuclei of the small cell component are round, while the larger component has deep subdivisions of varying prominence typically resembling a "chicken footprint" and usually some irregularity. In general, the subdivisions resemble a convolutional phenomenon or even lobation though usually the cell maintains a round con-

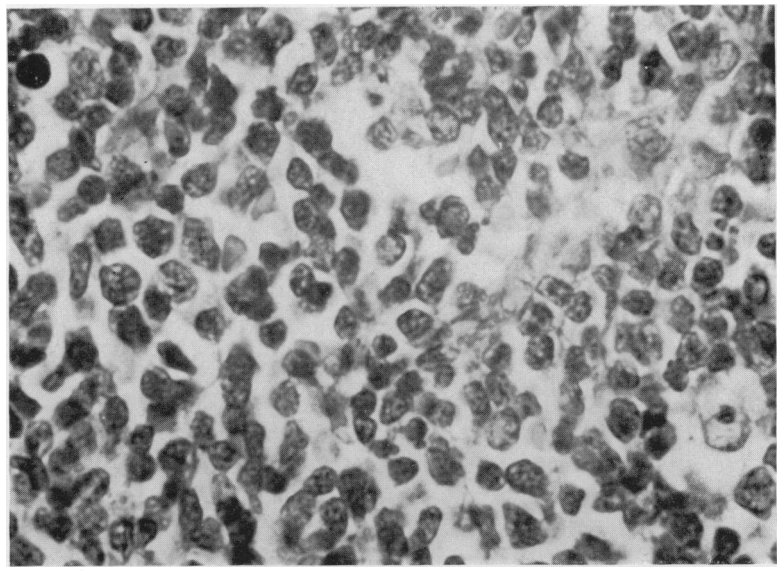


FIG. 5.—Convoluted lymphocytic lymphoma: This is a proliferation of non-cohesive cells of variable size with indistinct cytoplasm and round nuclei with primative chromatin and numerous fine linear subdivisions. RMH 2986–66. H. and E. ×850.

figuration. In a few cases the convolutions exhibit a striking degree and the cells present a dramatically irregular convoluted nuclear surface. The proportion of small and large cells varies in each case and at times from area to area. When the number of large cells is prominent, mitoses are numerous (5–7/h.p.f.). The cytoplasm is scanty or indistinct and apparently relates to their non-cohesive character.

A lymphoma of small lymphocytes of T cell type may also exist but there is insufficient evidence at this time.

II. *B cell types*

1. *Small lymphocyte* (*Fig.* 6).—This is a diffuse and uniform proliferation of small lymphocytes that extends throughout lymph nodes. The nuclei are small, round and regular without nuclear cleavage. The chromatin is compact, nucleoli are inconspicuous and mitoses are rare. Cytoplasm is scanty. Normal reactive follicles are absent and plasma cells are rare or absent. Small foci of larger cells resembling transformed lymphocytes are found at times and apparently represent proliferating foci. On occasions, particularly when the patient is in an accelerated phase of the disease, the lymphocytes are of intermediate size, have somewhat finely distributed chromatin, a central small nucleolus and a moderate amount of cytoplasm. Both forms are regarded as the tissue manifestation of chronic lymphocytic leukaemia.

2. *Plasmacytoid lymphocyte* (*Fig.* 7).—This proliferation closely resembles the lymphoma of small lymphocytes since it is usually composed predominantly of small round lymphocytes. There is, however, also a variable number of plasmacytoid lymphocytes and cytoplasmic lymphocytes with suggestive plasma cell features. Large globular intranuclear PAS-positive inclusions are typically found in a variable proportion of cells. This proliferation is commonly associated with macroglobulinaemia but on occasion no gammopathy is observed and PAS-positive cytoplasmic inclusions may be present in large numbers (Kaiserling, Stein and

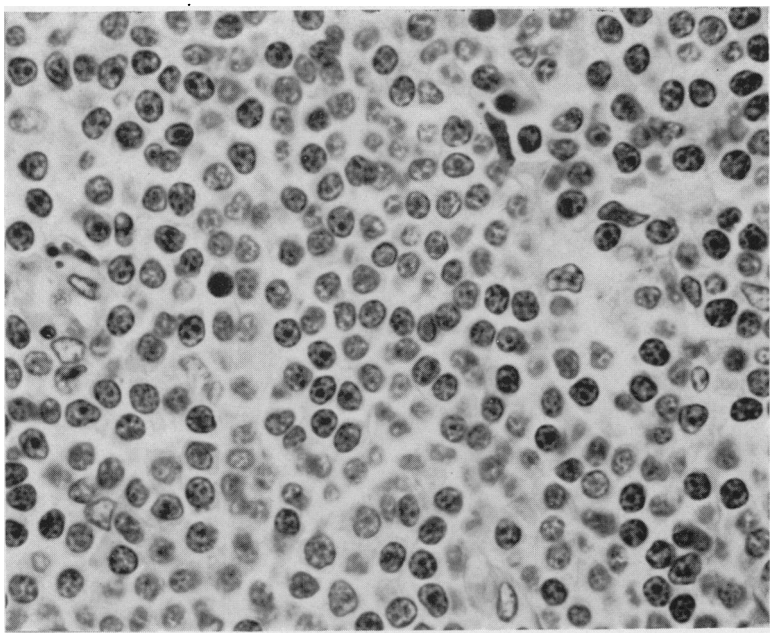


FIG. 6.—Small lymphocytic lymphoma: This lymphoma consists of uniform non-cohesive small round cells with scanty cytoplasm and compact nuclear chromatin. No plasma cells or follicles are found. RJL 372–74. H. and E. ×850.

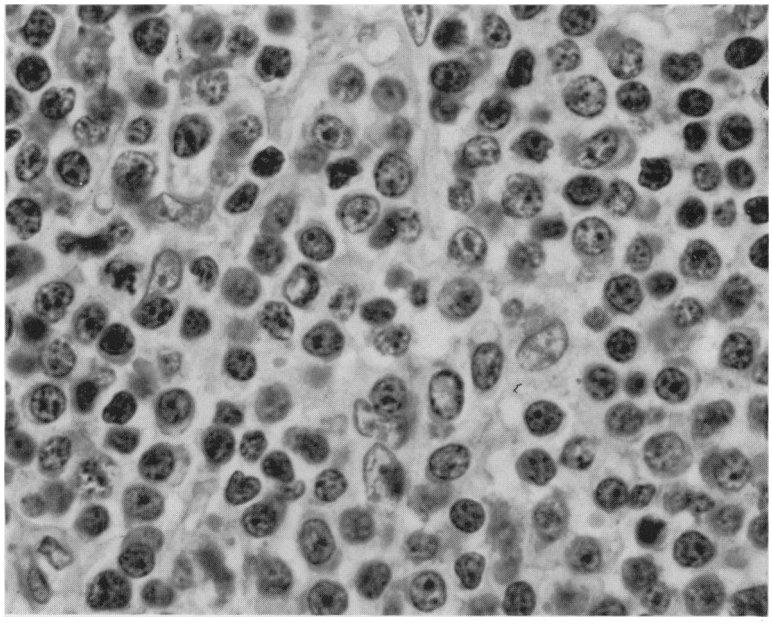


FIG. 7.—Plasmacytoid lymphocytic lymphoma: In this proliferation the cellular composition is variable but predominantly composed of small lymphocytes. Plasmacytoid cells with nuclei resembling those of lymphocytes are readily found. A centrally situated cell contains an acidophilic intranuclear body that is typically positive in PAS stains. RJL 363–74. H. and E. ×850.

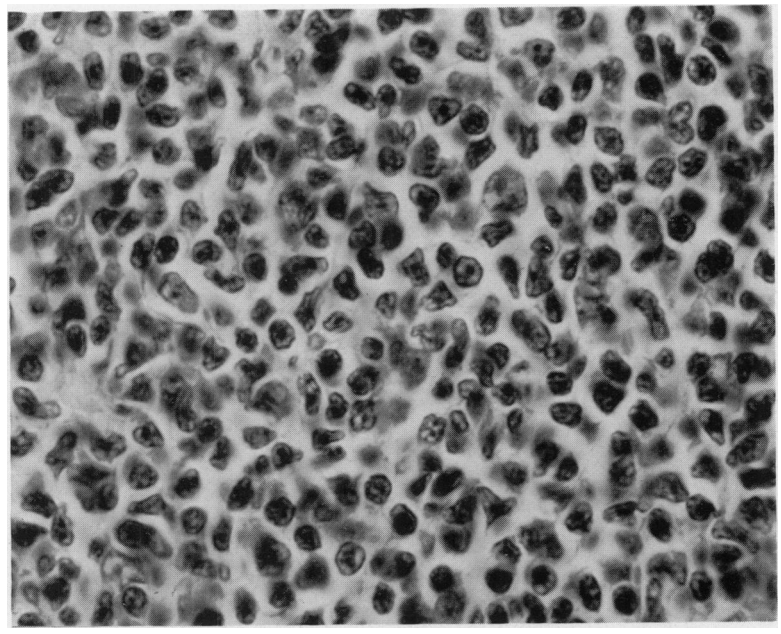


FIG. 8.—Small cleaved follicular centre cell lymphoma: This proliferation is primarily composed of small irregular cells with a limited amount of cytoplasm. Many of the nuclei have a single linear cleavage plane that accounts for the nuclear irregularity. On functional studies this proliferation exhibited a monoclonal IgM Kappa membrane marker. RJL 420–74. H. and E. ×850.

Lennert, 1973). Reactive follicles are absent.

3. *Follicular centre cell (FCC) types.*—All FCC cytological types may be observed in follicular (nodular) or diffuse histological patterns, though the small cleaved cell type is usually follicular in pattern and the non-cleaved cell types are almost always diffuse in growth pattern. Sclerosis is an additional qualifying feature that has been proposed as being prognostically significant (Bennett and Millett, 1969).

(a) Small cleaved cell (Fig. 8): This lymphomatous proliferation usually exhibits some degree of follicular (nodular) pattern and the cells range in size from a small lymphocyte to that of a histiocyte nucleus. The nuclei are of variable configuration, exhibiting the typical nuclear cleavage of normal cells shown in Fig. 1, but commonly in more exaggerated degree. The smallest cleaved cell has a minor degree of cleavage and frequently the nucleus appears irregular in configuration. The chromatin is compact and the nucleoli are small or inconspicuous. Mitoses are rare. Cytoplasm is indistinct or scanty and the cells appear non-cohesive when the cleaved cell is the size of a small lymphocyte. When intermediate in size there is a small amount of cytoplasm that is pyroninophilic and the cells seem cohesive. In those proliferations with follicular pattern, the cleaved cell within the follicles is frequently of the cohesive intermediate size while those infiltrating the interfollicular and capsular tissues are the small cleaved type with scanty cytoplasm that is often mistaken for a non-lymphomatous lymphocyte.

(b) Large cleaved cell (Fig. 9): This proliferation is typically variable in composition with a wide range of cellular size and configuration that often presents

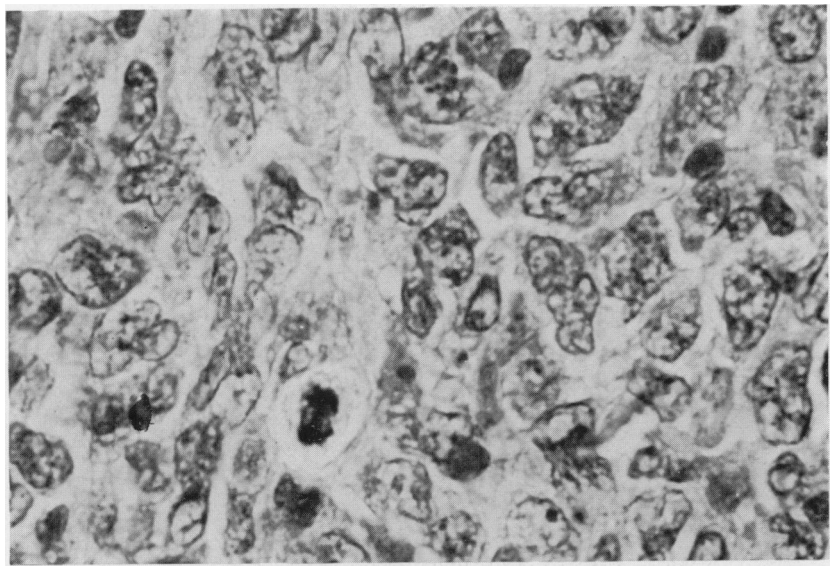


FIG. 9.—Large cleaved follicular centre cell lymphoma: This proliferation is composed of considerably larger cells with more irregularity of the nuclei and more prominent cytoplasm than the small cleaved FCC of Fig. 8. In areas the nuclei were equal in size to the nucleus of a phagocyte. RMH 5042–71. H. and E. ×850.

the appearance of a mixed proliferation. The nucleus of the large cleaved cell is as large as, or larger than, the nucleus of a benign histiocyte or non-cleaved cell but it has a variable configuration. On occasion, there is extreme exaggeration of cleavage with multinucleated appearing forms that may suggest Reed–Sternberg cells. Small cleaved cells of variable size and non-cleaved cells commonly occur with the large cleaved cell proliferations. The majority of the larger cells, however, on close examination still retain some degree of cleavage. Mitoses are variable and relate to the number of non-cleaved cells. The proliferation of large cleaved cells is diffuse in the majority of cases but some follicularity is frequent though usually partial or minimal in degree.

(c) Non-cleaved cell (Fig. 10): This proliferation of the dividing cell of the follicular centre is, with few exceptions, diffuse in character and typically extends broadly throughout the lymph node or mass without leaving evidence of residual architecture. The non-cleaved cell type varies widely in size, similar to its normal counterpart shown in Fig. 1 and is subdivided into small and large types according to the size of the nuclei. If the majority of the cells have nuclei smaller than the nucleus of the benign "starry-sky" histiocyte commonly found in the proliferation, it is placed in the small non-cleaved group. If the majority of the nuclei are equal to or larger than the benign histiocyte nucleus it is classified as the large non-cleaved type. The cytoplasm of the non-cleaved cell is prominently pyroninophilic and varies in amount, usually with the size of the nucleus and the prominence of the nucleoli. The cell borders often appear interlocking and cohesive. The nuclei of the small type tend to be round, have finely distributed chromatin and small nucleoli, while the large type has an oval nucleus, finely distributed, pale staining chromatin, a single large or 2–3 medium size nucleoli arranged in a typical fashion often on the nuclear membrane.

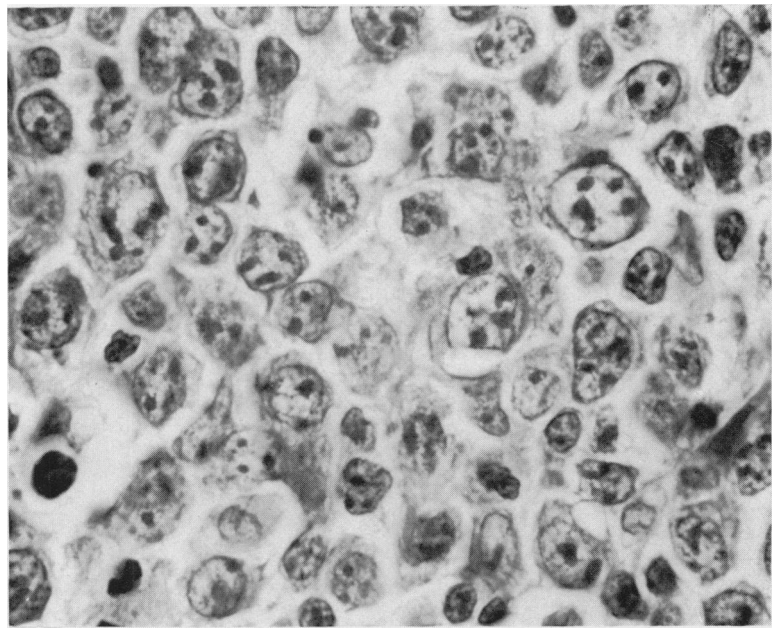


FIG. 10.—Large non-cleaved follicular centre cell lymphoma: The cells of this lymphoma closely resemble the transformed lymphocyte and have a large round or oval nucleus with finely distributed chromatin, one prominent or 2–4 small nucleoli often situated on the nuclear membrane. The cytoplasm is amphophilic and variable in amount and the cellular borders are irregular. A few scattered small cleaved FCC are evident. H. and E. × 850.

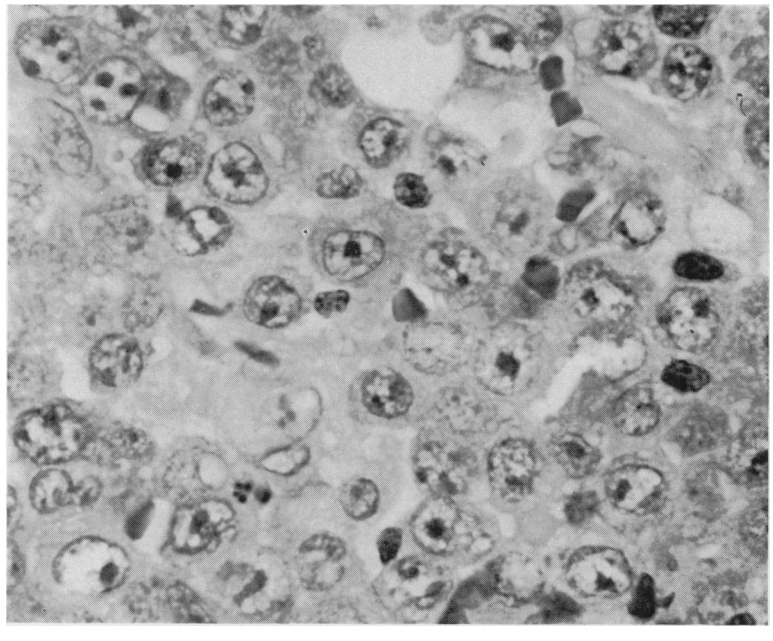


FIG. 11.—Immunoblastic sarcoma: This proliferation also resembles the transformed lymphocyte but the cells are usually larger than the non-cleaved FCC and may exhibit plasmacytoid features. The nuclei are round to oval, the chromatin is finely dispersed and one or more nucleoli are prominent. The cytoplasm is abundant and amphophilic with irregular cell borders and several cells exhibit plasmacytoid features. RJL 320–74. H. and E. × 850.

Mitoses are numerous and reactive phagocytes of the so-called " starry-sky " type are commonly prominent. The typical Burkitt lymphoma as defined in the W.H.O. report (Berard, 1974) exhibits the characteristic features of the small non-cleaved cell and is composed of cells of uniform size, with small inconspicuous nucleoli. The so-called " undifferentiated " lymphoma of non-Burkitt type observed in the U.S.A. also appears to be a non-cleaved cell type but is variable in size, has prominent nucleoli and a definite component of large non-cleaved cells. The lymphoma of large non-cleaved cells has similar cytological features to its small counterpart but is larger, more variable and at times pleomorphic or multinucleated. It has abundant pyroninophilic cytoplasm, a large oval nucleus with finely distributed chromatin and a larger prominent nucleolus than the small non-cleaved cell.

4. *Immunoblastic sarcoma of B cells* (*Fig.* 11).—This lymphoma is closely related to the large non-cleaved cell type since the normal immunoblast occupies an adjacent position in the FCC transformation sequence outside the follicular centre, as shown in Fig. 2. The immunoblast as the next stage in transformation in the B cell series, is larger than the large non-cleaved cell, has more abundant pyroninophilic cytoplasm and may have plasmacytoid features. The morphological distinction between normal B and T cell immunoblasts is uncertain. At the present time on morphological characteristics alone, immunoblastic sarcoma is defined as a monomorphous proliferation of large cells with pyroninophilic cytoplasm that resemble their normal counterparts to varying degrees. They are generally larger than the large non-cleaved FCC, have more abundant amphophilic cytoplasm in H. and E. stained sections with irregular cellular borders. The large nucleus is commonly oval in shape, has finely distributed, pale staining chromatin and usually 2 or 3 nucleoli similar to the large non-cleaved FCC. The proliferation of immunoblasts may diffusely or partially involve lymph nodes. The single case of T cell type that we have observed exhibited a range of cells from a small lymphocyte to a medium size immunoblast, was monomorphous in areas and lacked plasmacytoid features.

III. *Histiocytic type* (*Fig.* 12)

At the present time, this lesion is identified in histological sections primarily by exclusion, though the alpha naphthol acetate esterase (Leder, 1967; Yam *et al.*, 1971) and immunological membrane marker (Jaffe *et al.*, 1974) permit the distinction from large non-cleaved FCC or immunoblastic sarcoma in freshly collected tissue. As indicated previously, a redefinition of the " true " histiocyte lymphoma is needed and the use of immunocytochemical methods is essential.

DISCUSSION

Malignant lymphomata are neoplasms of the immune system but the presently employed terminology and classifications bear no relationship to the modern concepts of immunology. In our recent proposals, however, we have shown that it is possible to recognize a number of distinctive morphological entities within the malignant lymphomata and to predict their likely relationship to the T and B cell systems and alterations in lymphocyte transformation. The results of subsequent studies using cytochemical and recently developed immunological membrane marker techniques applied to freshly collected biopsy tissue, have provided strong support for our proposed concepts and the morphological entities reviewed in this presentation. These morphological entities of the T and B cell systems appear to develop from a block or a " switch on " (derepression) of lymphocyte transformation. These observations raise the possibility that lymphomata represent masses of immunologically abnormal or defective cells at

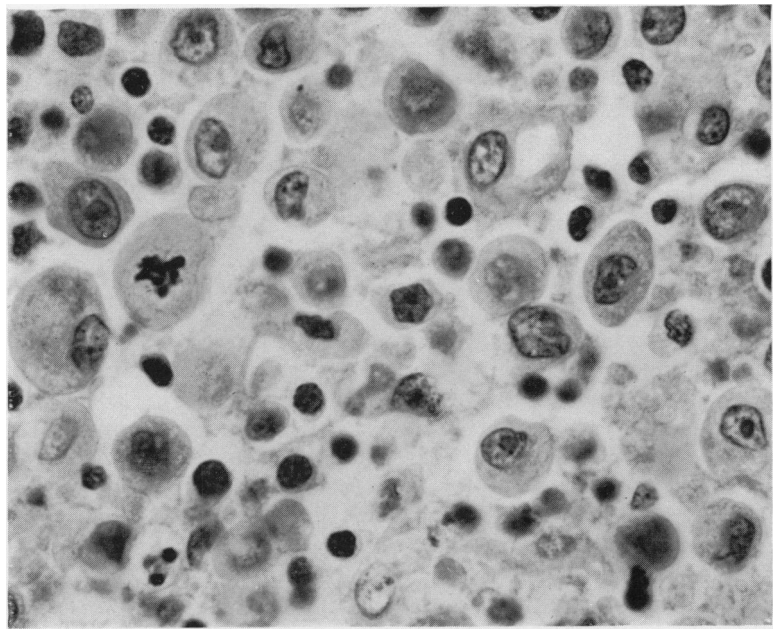


FIG. 12.—Histiocytic lymphoma: The cells of this lymphoma are large and differ in appearance from the transformed lymphocyte. They have abundant acidophilic amorphous cytoplasm and the nuclei vary in size and configuration. The cytoplasm was strongly positive in alpha naphthol acetate esterase stains. RJL 416–70. H. and E. ×850.

levels of developmental abnormality parallel to the pure congenital immune defects.

From the results of the functional studies, it seems likely that within a short time the general use of at least a few selected techniques will greatly enhance the accuracy and reproducibility of the classification of the lymphomata. To achieve this important goal, two major changes are essential. The first involves the surgical biopsy procedure and the second the need for the pathologist to collect tissue fresh for functional studies. These steps require a total change in the philosophical approach for both surgeon and pathologist. The surgeon must be aware that abundant tissue is required and that the most representative node, usually the largest and deepest lymph node, must be obtained. No longer will the biopsy of a small node in the periphery of a lymphomatous mass suffice. It is necessary for the clinician, the surgeon and the pathologist to develop a close collaboration on the selection of the most appropriate lymph node or biopsy site. Because of the change in the character of the cellular proliferation with the evolution of the process and the frequency of generalized lymphadenopathy, at least two biopsy sites are required to characterize the process. A single lymph node may represent either the rapidly progressive new phase or the slowly aggressive phase that may have existed subclinically for years. Frequently from a careful clinical history, the two types of enlarged nodes can be identified and both should be biopsied. Sequential biopsies, searching for change in the cellular character of the proliferation, are considered necessary for ideal case assessment. The surgeon's responsibilities are thus to provide the largest and most representative lymph nodes, and often from several sites, if generalized lymphadenopathy exists. In addition he must be certain that the pathologist receives the tissue fresh, immediately for the functional studies that are to be

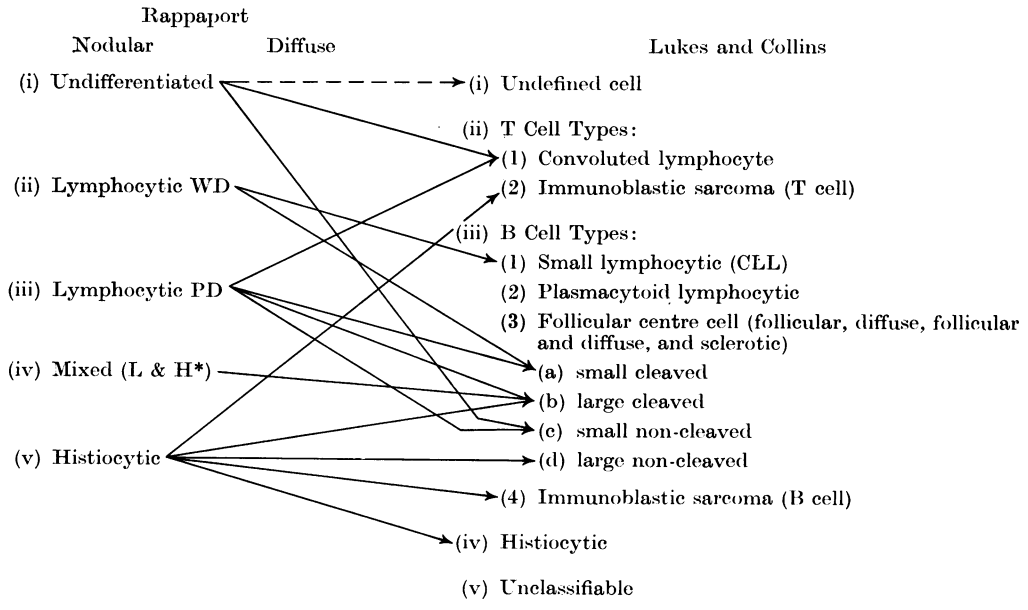
performed on live cells. The pathologist's role is greatly expanded. In order to succeed it requires considerable preparation and experience, depending upon the number and complexity of procedures to be performed. Regardless of the number of procedures, lymph node biopsies ideally should be sent to the pathologists immediately in order to prepare tissue imprints (touch preparations) and to achieve the most ideal fixation possible for morphological evaluation. The number of techniques that will ultimately be required for an accurate classification and characterization of lymphoma cells is uncertain in this definitional phase of investigation. It is dramatically apparent that the approach of the past, both of selecting the site of biopsy and the number of nodes removed, will not be adequate for the modern immunological approach for lymphomata.

The proposed classification can be applied on the basis of morphological criteria only, but it requires ideal fixation, processing and one-cell thick sections for effective usage. Touch imprints are an important asset and certain cytochemical procedures, particularly the alpha naphthol acetate esterase for identification of the true histiocytic lymphoma, will be a minimum requirement. Undoubtedly several years of investigation will be necessary before the essential requirements for effective accurate diagnosis and classification can be established. The majority of the cytological types in the proposed functional classification can be identified with instruction and experience. Several areas have not been entirely resolved and necessitate further functional studies. These areas involve principally the unestablished number and variations in T cell lymphomata, the differential diagnostic criteria of immunoblastic sarcoma of B and T cell types and whether a lymphoma of small T cells exists.

Retrospective morphological evaluation of three case populations using routine histological sections only are essentially complete. The preliminary results reveal that the majority of non-Hodgkin's lymphomata present features of FCC types, either cleaved or non-cleaved types. In addition, all cases with a follicular pattern exhibit the FCC types and with few exceptions are the small or large cleaved cell. The available survival data of the follicular (nodular) pattern coincide with that of the small and large cleaved cell types. The relatively favourable course associated with nodularity seems to be a function of the FCC types, reflected by their ability to produce a follicular pattern. The non-cleaved FCC have a median survival of less than a year but a small group of approximately 20% continue to survive beyond 2 years, either because the disease was of limited extent or conceivably as a result of selective sensitivity of the lymphoma cells to therapeutic agents. The cases of convoluted lymphocytic type that we have had the opportunity to study have a median survival of 8 months and only 3 cases have survived one year.

Comparison of the classification of Rappaport (1966) with the functional approach of the authors is shown in Table III. It reveals 4 principal differences: (a) a multiplicity of B and T cell types are included in Rappaport's types; (b) all cytological types of Rappaport are classified as nodular and diffuse; (c) a relationship to follicular origin is avoided; (d) a practical and conceptual basis for the approach to the investigation of lymphomata is provided in the functional classification of the authors and lacking in Rappaport's approach. The arrows present a criss-cross pattern between the 2 classifications as an indication that multiple cytological types of B and T cells are included in most of the cytological types of Rappaport. This situation results from the cytological types of Rappaport being based largely on cell size. The histiocytic type as a large cytoplasmic cell includes the large cells of all our types, *i.e.*, the large cleaved FCC, the large non-cleaved FCC, immunoblastic sarcoma of both B and T cells,

TABLE III.—*Comparisons of Classifications*



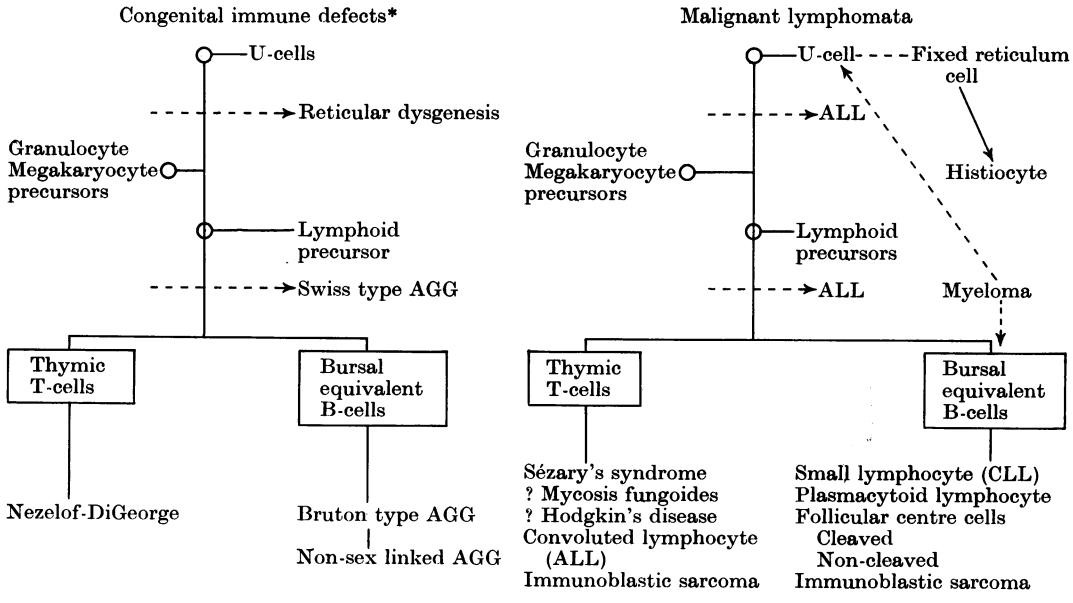
* Lymphocytic and histiocytic.

large cleaved FCC as well as the " true " histiocyte. Similarly the lymphocytic poorly differentiated type includes 3 or more types, depending on the observer: *i.e.*, the convoluted lymphocyte, the small cleaved cell and some of the large cleaved cell cases. Some observers also might include the small non-cleaved cell and the U cells. Both the undifferentiated and the well differentiated lymphocyte also include several cell types. The mixed type, because of its variable content and appearance, presents a special problem of precise classification and individual observer variation that depends upon the observer's evaluation of the degree of mixture of 2 or more cell types.

The malignant lymphomata as neoplasms of the immune system represent proliferations of abnormal or defective immune cells. As such, they may be functionally defective and in a sense are comparable with the congenital immune defects. In Table IV the pure congenital immune defects are arranged according to the level of developmental defect in the stem cell (U cell), B and T cell systems according to Good and Finstad (1968). The lymphomata have been arranged according to these systems in a parallel fashion according to the types of defective immune cells.

The pure congenital immune defects represent developmental abnormalities of the immune system at various levels according to the system involved. If the level of defect is at the stem cell (U cell) level, as in reticular dysgenesis, neither the marrow nor the lymphoid systems develop. In a defect of the lymphoid precursor cells of the Swiss type of agammaglobulinaemia, the marrow is normal but the T or B cell systems fail to develop. Similarly, in the Nezelof–DiGeorge type, the T cell system fails to develop but the marrow and B cell system are normal. The B cell system may be defective in 2 ways: (a) the sex linked agammaglobulinaemia of Bruton type that becomes apparent early in life in which no B cells are found and (b) the

TABLE IV.—*Comparison of Apparent Level of Lymphoid Defects in Congenital Immune Deficiencies and Malignant Lymphomata*



* Modified after R. Good (1969).
AGG—Agammaglobulinaemia.

late developing non-sexlinked type of agammaglobulinaemia. The former has no follicles or plasma cells and the latter has follicles and B cells but no plasma cells, and raises the possibility of a follicular defect.

From our functional proposal, the position of the various lymphomata of the U, B, and T cell systems can be predicted. Only a few of the most apparent counterparts will be considered. The lymphoma of small lymphocytes, the tissue manifestation of chronic lymphocytic leukaemia, presents an excellent prototype for these comparisons. It is the close counterpart to Bruton's agammaglobulinaemia. In the Bruton's immune defect, however, no B cells are found while in the lymphoma of small lymphocytes (CLL), there is a tremendous accumulation of defective B cells that are either unable to function or are functionally defective. In both processes there is a lack of follicles and plasma cells, and in the disseminated form (CLL) commonly there is hypogammaglobulinaemia and poor antibody production capability similar to Bruton's defect.

Lymphomata of follicular centre cells (FCC) may represent a close counterpart to the non-sex linked, late developing agammaglobulinaemia. In both conditions defective follicles may be formed and attributed to a block in the transformation of FCC that prevents the formation of effective plasma cell precursors. In many of the other lymphomata our knowledge is too limited to make a detailed comparison but approaching the lymphoma cells from this immunological aspect may yield important information. The lymphomata of large transformed cells in both systems, including immunoblastic sarcomata of T and B cell type, may be considered the defective transformed and dividing cell of the system. Myeloma with its typical monoclonal immunoglobulin production is ac-

cepted as a B cell neoplasm. Its remarkable association with bone marrow, however, indicates to the authors that some basic marrow factor is relevant in myeloma and it deserves separate consideration from the lymphomata.

The recognition of the convoluted lymphocytic lymphoma as a possible T cell type previously included within ALL, obviously indicates that there is more than one type of ALL and that an immunological classification may be appropriate. The results of initial functional studies suggest that many cases of ALL lack membrane markers and are U cells. The type at the U cell level would account for lack of membrane markers in one type and the failure to develop precursors of both marrow and lymphoid systems. Another type from this consideration theoretically may be at the lymphoid precursor level, the marrow may be unaffected and the leukaemic cells may have a definite lymphoid appearance, yet lack T or B cell markers. Finally, in this consideration the counterpart of ALL in the B cell system may be represented by the small non-cleaved FCC that presents as the Burkitt lymphoma.

In time, the parallelism of the lymphomata to the congenital immune defects may become more obvious as the lymphoma cells are investigated from an immunological approach. We suspect that the converse may also result. The study of lymphoma cells as masses of defective immune cells may enable the development of a better understanding of the normal immune system, just as the investigation of the coagulation defects have revealed most of the basis for our modern concepts of normal coagulation.

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