Distribution of T-Cell Subsets in Follicular and Diffuse Lymphomas of B-Cell Type

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The authors examined the number and distribution of cells reacting with monoclonal antibodies to T-cell subsets in frozen tissue sections of B-cell lymphomas (30 follicular and 17 diffuse lymphomas). In five diffuse lymphomas (two lymphocytic, three small cleaved cell) the neoplastic B-lymphocytes reacted with the monoclonal antibody anti-T1. In all other cases, the monoclonal antibodies to T-cell subsets reacted only with small lymphocytes concentrated between the follicles of follicular lymphomas and distributed randomly in diffuse lymphomas. The distribution of T cells and the $T4^+/T8^+$ ratio in follicular small cleaved and mixed lymphomas was similar, although not identical, to that seen in hyperplastic lymphoid follicles. Fewer T cells and a decrease in the $T4^+/T8^+$ ratio were seen in follicular large cell lymphoma and in diffuse large cell lymphomas. The number and distribution of T cells in follicular lymphomas is consistent with the hypothesis that there is a functional interaction between neoplastic B cells and benign T cells. No tumors were found in which the neoplastic B cells reacted with anti-T3, anti-T4, or anti-T8. (Am J Pathol 1983, 113:172–180)

NORMAL-APPEARING small lymphocytes are frequently observed in tissue sections in non-Hodgkin's lymphomas of all histologic types. They are often numerous in follicular lymphomas[1,2] and are also present in many diffuse lymphomas. It may be impossible to determine by routine histologic techniques whether these small lymphocytes are part of the neoplastic proliferation or whether they are reactive or residual benign cells. With the development of immunologic surface marker techniques, it has become apparent that in suspensions prepared from B-cell lymphomas a variable population of T cells may be seen in addition to the monoclonal Ig-bearing B-cell population.[3,4] In addition, on the basis of enumeration of cells in suspension, several lymphomas thought to express simultaneously both T- and B-cell surface markers have been recently described.[5] The development of immunohistologic techniques for the detection of lymphocyte-associated antigens in frozen tissue sections permits localization of various subsets of lymphoid cells in normal lymphoid tissue and tissues involved by lymphoma.[6–15] Using this technique, Stein et al[9] and Dvoretsky et al[15] recently reported that the number and distribution of T-lymphocytes in follicular lymphomas was similar to that seen in reactive lymphoid tissues. In this study, using a panel of antibodies to T-cell associated antigens as well as antibodies to immunoglobulin isotypes, we have assessed the number and distribution of T cells in both follicular and diffuse lymphomas of B-cell type and also evaluated the staining of neoplastic B cells with the antibodies to T-cell subsets.

Materials and Methods

Biopsy specimens were frozen in OCT (Miles, Naperville, Ill) in a cryostat, cut at 6 μ, air-dried, fixed 10 minutes in acetone, and stained by an indirect immunoperoxidase technique as previously described.[8,11] Sections were examined without counterstain. The monoclonal antibodies used in this study were anti-T1 (pan-T-cell), anti-T3 (pan-T-cell), anti-T4B (helper T-cell) and anti-T8 (suppressor/cytotoxic T-cell); the preparation and characterization of these antibodies as well as their staining patterns in normal lymphoid tissues have been previously described.[8,10,11,16,17] (Monoclonal antibodies were kindly supplied by Drs. Ellis Reinherz and Stuart

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Schlossman.) All cases were also stained with antibodies to immunoglobulin heavy and light chains: γ, α, μ, δ, κ, and λ (DAKO, Accurate Chemical and Scientific Co., Westburn, NY). The specificity of the antiserums was assessed by staining lymphomas or myelomas with secreted immunoglobulins of known isotype. A total of 53 lymphomas and 11 reactive lymph nodes with nonspecific follicular hyperplasia were stained.

Lymphomas were classified according to the classification of Rappaport[18] and the Working Formulation for Non-Hodgkin's Lymphomas.[19]

Because of the difficulty of enumerating lymphocytes in sections of lymphoid tissues, we did not attempt accurate quantitation of positive cells. An estimate of the proportion of cells staining with the various anti-T-cell reagents was made both by scanning the slides visually and by counting the total number of positive cells in five high-power ×40, microscopic fields. An estimate of the $T4^+/T8^+$ ratio was based on the number of cells stained with each reagent on serial sections. In the follicular lymphomas, positive cells in five high-power fields were counted both outside and inside the neoplastic follicles. Similar counts were made in the paracortex and germinal centers of reactive lymph nodes.

Results

Reactive Lymph Nodes

The staining of reactive lymph nodes with antibodies to T- and B-cell markers was similar to previously reported results[9-13] (Figure 1A–D). Antibodies to μ and δ stained follicle mantle zone lymphocytes and scattered interfollicular lymphocytes. Antibodies to μ and γ stained germinal center cells and amorphous extracellular and/or cytoplasmic deposits within germinal centers. Antibodies to κ and λ light chains produced staining that was a composite of the patterns seen with the heavy chain antibodies.

T cells that reacted with the monoclonal antibodies anti-T1, anti-T3, and anti-T4B constituted the majority of cells present in the interfollicular zones of reactive lymph nodes (Figure 1B and C). $T8^+$ cells were also present in this area but were always less numerous than $T4^+$ cells (Figure 1D). $T1^+$, $T3^+$, and $T4^+$ cells were also present in germinal centers. These ranged from only a few cells to a substantial minority of cells but never constituted a majority of cells. In some germinal centers, a crescent of $T4^+$ cells was present just inside the B-cell mantle zone, as previously described.[10,11] In addition to small lymphocytes, anti-T4B antibody stained the cytoplasm of some large cells in some germinal centers, which appeared to be histiocytes (macrophages). $T8^+$ cells were very rare in germinal centers and were always less than 10 per high-power field. The estimated $T4^+/T8^+$ ratio in the paracortical regions ranged from as low as 2 to 4 or more, while within germinal centers the $T4^+/T8^+$ ratio was usually higher, in the range of 10 to 20.

Follicular (Nodular) Lymphomas

Thirty follicular lymphomas were stained: 18 small cleaved cell (poorly differentiated lymphocytic), 7 mixed small cleaved and large cell (mixed lymphocytic and histiocytic), and 5 large cell (histiocytic). The majority of cells in all except 3 cases reacted with antibody to a single light chain (κ or λ) and one or two heavy chains. One case had no heavy chain, and 2 cases had no detectable immunoglobulin. In most cases, as previously reported, a follicular pattern could be recognized in sections stained for immunoglobulin (Figures 2A and 3A). Cells with restricted (κ or λ) light chain staining were concentrated in follicles but were also dispersed to varying degrees throughout the interfollicular areas in most cases.

The monoclonal antibodies anti-T1, anti-T3, anti-T4B, and anti-T8 stained small lymphocytes scattered among the neoplastic cells (Figures 2B–D and 3B and C). In most cases, dense aggregates of T-lymphocytes alternated with areas containing fewer T cells. Thus, the distribution of T cells defined a follicular pattern, in which areas with few T cells corresponded to the areas containing dense collections of cells bearing monotypic immunoglobulin. The absolute number of T cells varied greatly from one case to another, but usually half or more of the cells in the interfollicular areas were T cells (more than 100 per high-power field). In contrast, the follicles usually contained a minority of T cells, ranging from only 2 or 3 scattered cells per follicle to as many as 75 cells per high-power field. In contrast to the results in reactive lymphoid follicles,[10,11] a crescentic arrangement of $T1^+$, $T3^+$, and $T4^+$ cells was only rarely observed within the neoplastic follicles. In addition, the absolute number of T cells of all subsets was usually less both inside and outside the follicles of lymphomas than in reactive lymph nodes.

$T4^+$ cells were at least twice as numerous as $T8^+$ cells in 27 of 30 follicular lymphomas, both in the interfollicular area and within the follicles. In the majority of cases the estimated $T4^+/T8^+$ ratio was 4 or more. The $T4^+/T8^+$ ratio was similar outside and inside the follicles in follicular lymphomas. This differed from the results in follicular hyperplasia, in

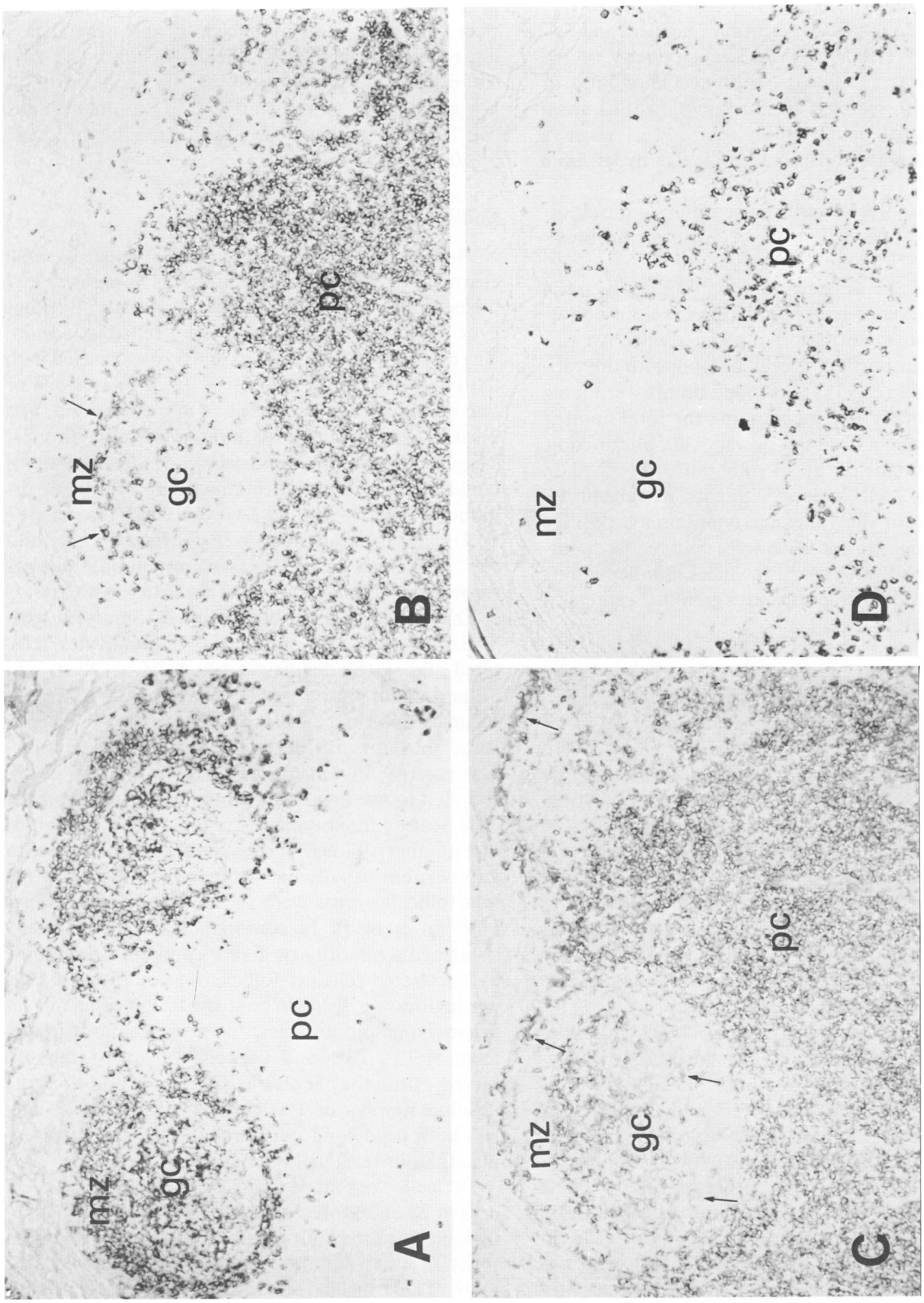

Figure 1 – Reactive lymph nodes with two reactive follicles. **A** – Anti-μ heavy chain. There is staining of mantle zone (*mz*) and germinal center (*gc*) lymphocytes. The paracortex (*pc*) contains few positive cells. **B** – Anti-T3. The majority of paracortical lymphocytes are stained. Numerous positive cells are present within the germinal centers, concentrated in crescentic fashion at the capsular pole, between the germinal center and the mantle zone (*arrows*). Similar staining was seen with anti-T1. **C** – Anti-T4B. The majority of paracortical cells are stained. In addition, there is cytoplasmic staining of some large cells in the germinal center and subcapsular sinus (*arrows*). **D** – Anti-T8. A minority of the cells in the paracortex are stained. Only rare cells are present in the germinal centers. (×160)

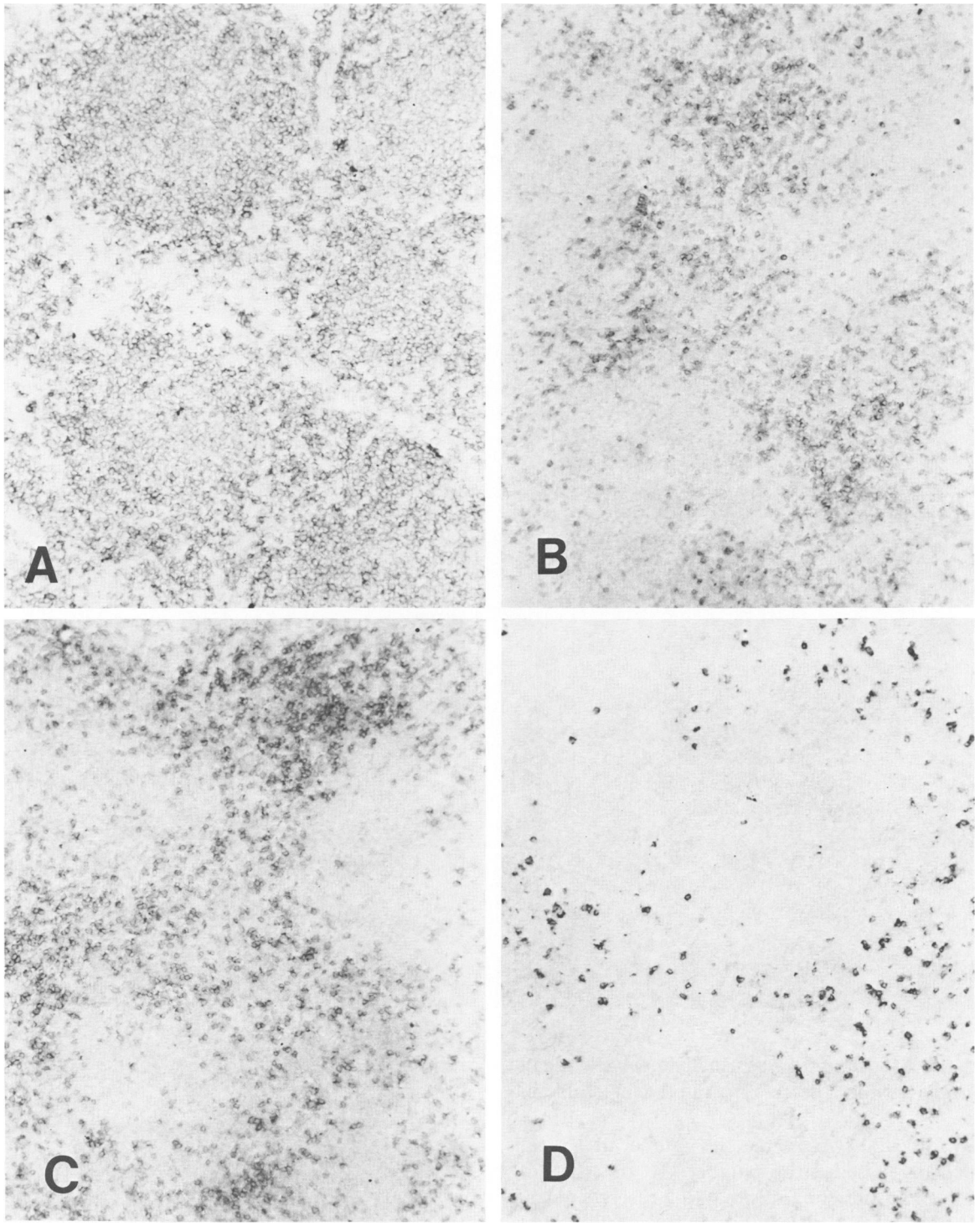

Figure 2—Follicular lymphoma, small cleaved cell type, with neoplastic cells not restricted to follicles. **A**—Anti-μ heavy chain. Positive cells are concentrated within the follicles but are also present in the interfollicular area. Identical staining was observed with anti-λ light chain. **B**—Anti-T3. Many positive cells are present between and within follicles. **C**—Anti-T4B. The staining is similar to that seen with anti-T3. **D**—Anti-T8. Many fewer cells are present. (×160)

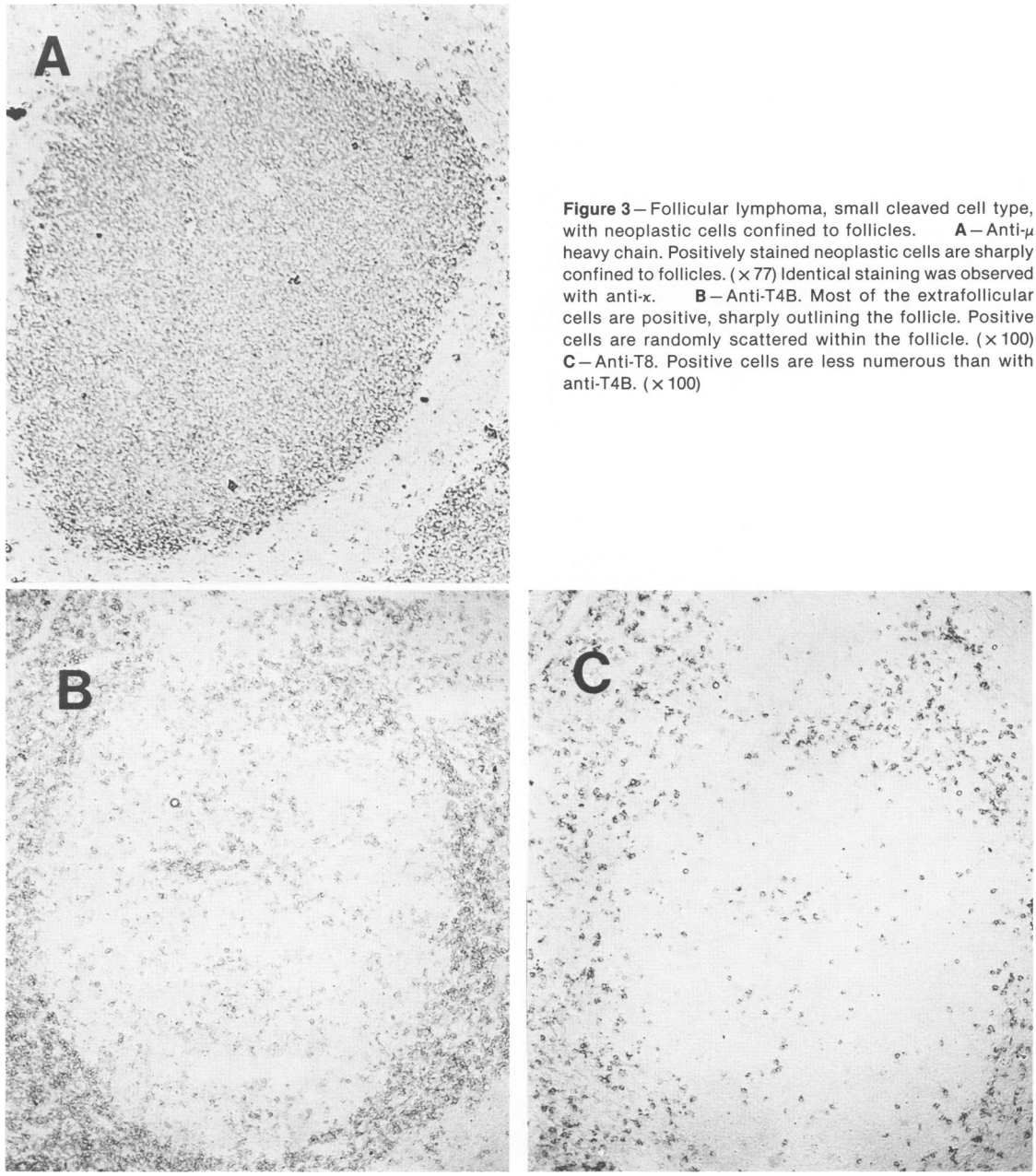

Figure 3—Follicular lymphoma, small cleaved cell type, with neoplastic cells confined to follicles. **A**—Anti-μ heavy chain. Positively stained neoplastic cells are sharply confined to follicles. (×77) Identical staining was observed with anti-κ. **B**—Anti-T4B. Most of the extrafollicular cells are positive, sharply outlining the follicle. Positive cells are randomly scattered within the follicle. (×100) **C**—Anti-T8. Positive cells are less numerous than with anti-T4B. (×100)

which the $T4^+/T8^+$ ratio was usually markedly greater within the germinal centers than in the interfollicular areas.

In 3 follicular lymphomas the number of $T8^+$ cells equaled or exceeded the number $T4^+$ of cells both outside and inside the follicles. All 3 cases were large cell lymphomas; 3 of 5 follicular large cell lymphomas had a $T4^+/T8^+$ ratio of 1 or less, while all 20 small cleaved cell and mixed lymphomas had a $T4^+/T8^+$ ratio of 2 or more.

Five of the follicular lymphomas were from extranodal sites. The number, distribution, and $T4^+/T8^+$ ratio in these cases was similar to that seen in nodal tumors.

Diffuse Lymphomas

Twenty-three diffuse lymphomas were stained: 3 small lymphocytic (well-differentiated lymphocytic), 4 small cleaved cell (poorly differentiated lymphocytic), 11 large cell (histiocytic), and 5 small noncleaved cell (undifferentiated). Tumor cells in all cases reacted with antibodies to a single light chain (κ or λ) and one or more heavy chains. (Immunoglobulin

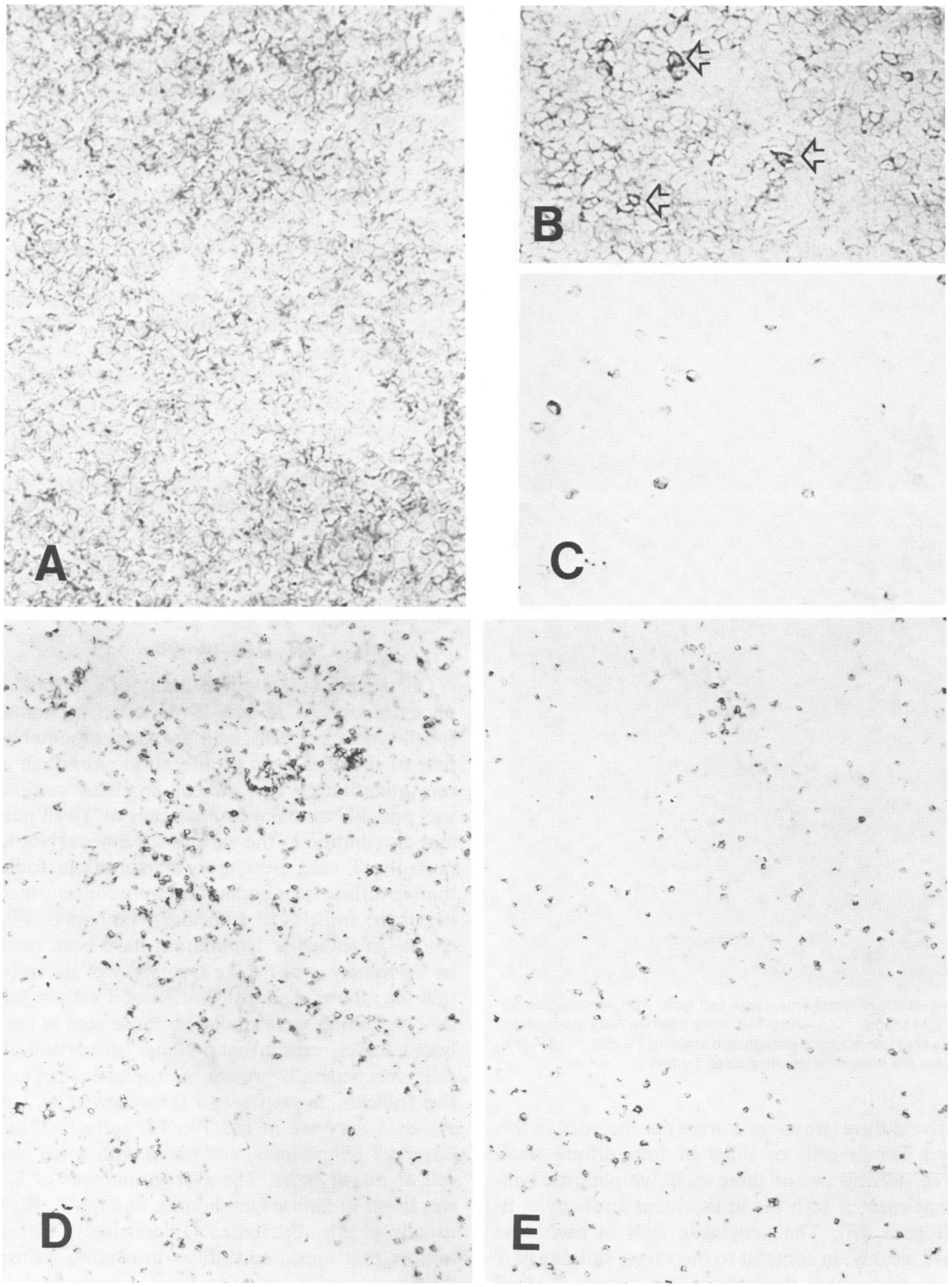

Figure 4 — Diffuse lymphoma, small cleaved cell type. **A** — Anti-μ. The majority of cells are stained in a diffuse pattern. The same result was obtained with anti-κ. **B** — Anti-T1. Most of the cells are faintly stained; occasional cells, thought to be reactive T cells, stain strongly (*arrows*). **C** — Anti-T3. Most of the cells are negative. Scattered positive cells are present, comparable to the strongly stained cells in **B**. (**A–C**, × 400) **D** — Anti-T4B. Scattered positive cells delineate vague nodularity, despite the diffuse pattern seen with anti-μ. (× 160) **E** — Anti-T8. There are fewer positive cells than with anti-T4B. (× 160)

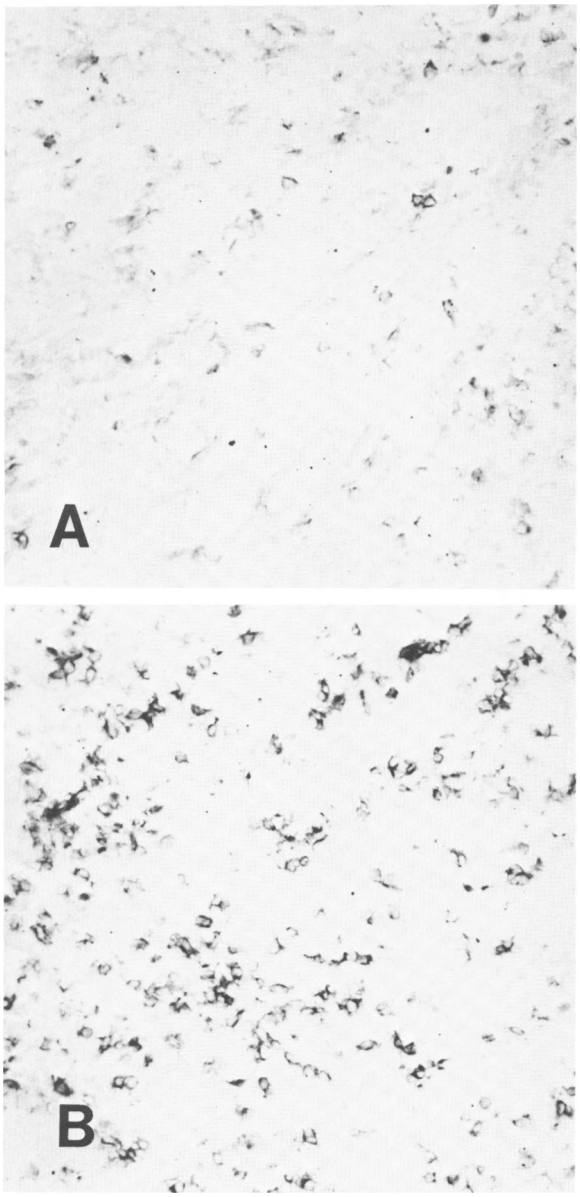

Figure 5—Diffuse lymphoma, large cell type, with immunoglobulin of the IgM-λ type. **A**—Anti-T4B. Rare positive cells are present. There is some nonspecific background staining. (×256) **B**—Anti-T8. There are numerous positive cells. (×256)

negative diffuse lymphomas were not included in this study.) Tumor cells of three of four diffuse small cleaved cell and two of three small lymphocytic lymphomas reacted with the monoclonal antibody anti-T1 (Figure 4B). The neoplastic cells in each case stained weakly, in contrast to the strong staining of T cells present within the tumor. The 2 cases (1 small cleaved and 1 small lymphocytic) that were T1-negative both had plasmacytoid differentiation. There was no staining of the neoplastic cells in any of the cases with anti-T3, T4B, or T8 antibodies. Reactive histiocytes in some diffuse lymphomas showed cytoplasmic staining with anti-T4B.

T cells were in general less numerous in diffuse lymphomas than in nodular lymphomas. In the 7 small cell (3 lymphocytic, 4 small cleaved cell) diffuse lymphomas T cells ranged from 14 to 50 per high-power field, while among the large cell and undifferentiated lymphomas only 5 of 16 had five or more T cells per high-power field and many had less than one. In most cases, T cells were scattered randomly throughout the tumor, but in 3 of the 7 small cell tumors and in 2 of the 16 large cell lesions, there were regularly spaced clusters of T cells that appeared to delineate vague nodularity within the tumors (Figure 4D). In the small cell lymphomas, the $T4^+/T8^+$ ratio was greater than 1 in 4 cases and close to 1 in 3. In contrast, $T8^+$ cells equaled or exceeded $T4^+$ cells in 12 of 14 large cell lymphomas (Figure 5). In only 2 large cell lymphomas was the $T4^+/T8^+$ ratio clearly greater than 1.

Five of the diffuse lymphomas were from extranodal sites. The number and distribution of T cells in these cases were similar to those seen in the nodal lymphomas.

Discussion

Our results indicate that many of the small lymphocytes present in non-Hodgkin's lymphomas of B-cell type are T cells, and are thus presumably not part of the neoplastic proliferation. Although accurate quantitation was difficult in tissue sections, it was possible to make comparisons of T-cell number and distribution in the various specimens. Not unexpectedly, T cells were more numerous in follicular than in diffuse lymphomas and were concentrated between the follicles of follicular lymphomas. Similar studies in follicular lymphomas have been reported by Dvoretsky et al.[15] Like Dvoretsky et al, we found that the number and distribution of T cells in follicular lymphomas were similar to those seen in reactive lymph nodes, except that a higher proportion of $T8^+$ cells were generally present in neoplastic than in reactive follicles. In contrast to Dvoretsky et al, we observed a decrease in the $T4^+/T8^+$ ratio in follicular large cell lymphomas, compared with small cleaved cell or mixed types. The average number of T cells was lower in diffuse lymphomas, and the T cells were usually evenly distributed. Interestingly, in several tumors that appeared diffuse on routine stains, the distribution of T cells suggested a vague nodularity of the tumor. The relationship of this vague nodularity to the well-formed follicles of most follicular lymphomas is not clear. As in the follicular lymphomas, the $T4^+/T8^+$ ratio was decreased in the large cell lymphomas compared with the small cell types. The $T4^+/T8^+$ ratio in the majority of the diffuse large cell lym-

phomas was markedly lower than that in the follicular lymphomas.

The role of the large number of T-lymphocytes in follicular lymphomas is not clear. At least three possible interpretations may be suggested: 1) The T-lymphocytes are residual elements of the normal lymph node, occupying that part of the node not replaced by nodules of neoplastic cells. 2) The T cells are present as part of an immunologic response against the tumor; follicular lymphomas may be more "antigenic" than diffuse lymphomas and thus incite a greater T-cell response. 3) There is a specific interaction between neoplastic follicular center B-lymphocytes and nonneoplastic T-lymphocytes, which is a recapitulation of the normal interaction between these two cell types in the immune response.

The presence of large numbers of T-lymphocytes in extranodal follicular lymphomas argues against the first interpretation. Although it is not possible to rule out the second hypothesis, there are several lines of evidence that suggest that the neoplastic B cells of follicular lymphomas retain the ability to interact functionally with nonneoplastic cells of the immune system.

Germinal centers are the site of B-cell proliferation in response to antigenic stimuli. In addition to follicular center B-lymphocytes, germinal centers contain T-lymphocytes (predominantly of the $T4^+$ or helper subset), dendritic reticulum cells, and phagocytic cells (so-called "starry sky" histiocytes), and are surrounded by a mantle zone of smaller B-lymphocytes. Both B- and T-lymphocytes are necessary for germinal center development.[20,21] $T4^+$ lymphocytes are known to facilitate B-cell proliferation and differentiation to plasma cells in response to certain stimuli *in vitro*[22] and may perform this function in germinal centers. The dendritic reticulum cell is thought to function in antigen presentation[23]; the function of the "starry sky" histiocytes in the immune response is not known. Normal B-lymphocytes have been shown to "home" preferentially to the follicles of lymphoid organs.[24]

The neoplastic B cells of follicular lymphomas have been shown to retain some of the functions of their normal counterparts. They produce immunoglobulin, and they appear to retain the capacity to home to normal B cell regions.[7,13] In addition to neoplastic B lymphocytes, the neoplastic follicles of follicular lymphomas have been shown to contain both dendritic reticulum cells[25] and nonneoplastic B-lymphocytes, which may be arranged in a mantle zone around the neoplastic follicles, similar to germinal centers.[13] The presence of these nonneoplastic cells in lymphomatous follicles suggests that the neoplastic B cells retain some ability to interact normally with other cell types.

We postulate that the T cells in follicular lymphomas, like the dendritic reticulum cells and the mantle zone B-lymphocytes, are benign cells that are induced by the neoplastic cells to participate in the formation of a neoplastic structure: the follicle. If the large lymphoid cells of diffuse large cell lymphomas lack the ability to interact with $T4^+$ cells, this might explain the relative lack of $T4^+$ cells in tumors of these types. It is intriguing to speculate whether the T cells present in follicular lymphomas may assist in maintaining the follicular architecture and/or provide a continued stimulus for proliferation or differentiation of the neoplastic B cells. If functionally normal T-lymphocytes are involved in promoting the formation of follicles by neoplastic B-lymphocytes, this may in part explain the preponderance of diffuse lymphomas in immunocompromised hosts.[27-30] It would be interesting to know whether there are differences in the number or functional capacity of circulating $T4^+$ cells in patients with follicular lymphomas, compared with those of patients with diffuse lymphomas.

Reactivity of the neoplastic B-lymphocytes of chronic lymphocytic leukemia, small lymphocytic lymphoma, and diffuse small cleaved cell lymphoma with the 65,000-dalton antigen recognized by the monoclonal antibody anti-T1 has been previously reported.[31,32] We found this antibody to react with 2 of 3 cases of small lymphocytic lymphoma and 3 of 4 cases of diffuse small cleaved cell lymphoma in our series. Interestingly, both T1-negative cases had plasmacytoid features. Similarly, Royston[31] reported that the 65,000-dalton antigen recognized by T101 was absent from peripheral blood lymphocytes of patients with monoclonal gammopathy, in contrast to those of patients with chronic lymphocytic leukemia without monoclonal gammopathy. The difference in reactivity of follicular and diffuse small cleaved cell lymphomas with anti-T1 may reflect a more fundamental difference between these tumors than has been appreciated on morphologic grounds alone. Further studies will be necessary to determine the usefulness of this reagent in subclassifying small cell lymphomas.

In contrast to the results of Aisenberg et al,[5] we found no other B-cell tumors in which the neoplastic cells reacted with anti-T1 and no B-cell lymphomas in which the neoplastic cells reacted with anti-T3, anti-T4, or anti-T8. Case 1 of their report was included in this series; in tissue sections cells which reacted with the monoclonal antibodies anti-T1, anti-T3, and anti-T4B were numerous but were concentrated in the interfollicular regions. Although scattered cells reactive with these antibodies were present within the follicles, most of the monotypic immunoglobulin-positive neoplastic cells within the follicles did not react (Figure 3). Although double staining techniques

were not used, the striking compartmentalization of the cells reactive with anti-immunoglobulin antiserums from those reacting with anti-T cell antibodies suggests that they are distinct populations. The immunoperoxidase technique on frozen sections, while not ideal for accurate quantitiation of cells, provides information about tissue architecture that cannot be duplicated with suspension studies.

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