Distribution of malignant lymphoid cells

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About two-thirds of tumours of adult human lymphoid tissue originate from B cells; one-fifth derive from T cells; one-eighth are undefinable, using markers currently available; and fewer than one in a 100 are truly histiocytic, showing markers associated with monocytes (Lukes et al., 1978). B cells can be demonstrated in suitable tissue sections since they possess either surface or intracytoplasmic immunoglobulin. Evidence of monoclonality can be deduced from the pattern of immunoglobulin light chain staining (Warnke and Levy, 1978). Techniques are not yet available to enable similarly detailed studies to be performed on human T cells in tissue sections where structural relationships can be defined. The emphasis in this paper consequently is on B cell malignancies.

B cell malignancies

To understand the complexities of distribution of cells in these diseases the heterogeneity of physiological B cells must be considered first. Precursor B cells develop in the bone marrow (Davies, 1969), and, in experimental animals, in the fetal liver (Cooper, 1975). Recently these cells have been shown to contain intracytoplasmic IgM, and to be able to reconstitute animals which have been deprived of more mature B cells. After leaving the sites of primary B cell development the cells are found to exhibit surface immunoglobulin (Cooper et al., 1977). Many of these B cells form part of the pool of small lymphocytes, which are engaged in a constant recirculation via the lymph and blood between the secondary lymphoid organs (lymphoid follicles and Peyer’s patches of the lamina propria of the gut, lymph nodes, and white pulp of the spleen) (reviewed by Ford, 1975).

Some B-cells, however, are situated in sites where migration is less obvious—for example (1) the marginal zone of the spleen as well as in the equivalent areas in lymph nodes and gut-associated lymphoid tissue, and (2) the secondary follicles (or ‘germinal centres’). The second of these is of particular clinical interest, because follicle centre cell tumours are relatively common and appear to represent neoplastic transformation of germinal centre B cells (Lukes and Collins, 1973).

The final stage of B cell development follows stimulation by antigen whereby the cells mature into antibody-producing cells (Reviewed by Lennert, 1978). These cells are either lymphoplasmacytoid in appearance or true plasma cells. They appear to be static and are mostly found in the lamina propria of the gut, lymph node medullary cords, splenic red pulp, the bone marrow, and sites of chronic inflammation. The production of these end-stage, antibody-producing cells involves the elastic transformation of small B lymphocytes. This transformation appears to occur mainly in the secondary lymphoid organs through which the recirculating pool of small lymphocytes traffic. The developing immunoblasts then migrate via the lymph and blood to the final site of metamorphosis to mature antibody-producing cells.

Heterogeneity of B cell neoplasia

These considerations—dealt with in detail by Prof. W. L. Ford (p. 63)—provide the basis for interpreting the heterogeneity of B cell neoplasia. With this in mind, three proposals are made, which will be discussed.

(1) Neoplastic transformation arising in cells with a physiological capacity to migrate

There are four main types of B cell neoplasm that can be distinguished where neoplastic transformation appears to have occurred in cells which have a physiological capacity to migrate: (a) histologically diffuse lymphocytic lymphomas (including chronic lymphatic leukaemia; (b) lymphomas of follicle centre cell origin; (c) lymphoblastic lymphoma; and (d) some immunoblastic tumours.

It is argued that these tumours are by nature widely distributed and that the patterns of infiltra- tion are far from haphazard. Consequently, clinical staging as for Hodgkin’s disease is inapplicable.

(2) The stage at which neoplastic transformation has occurred may not be obvious at presentation

Some diffuse lymphocytic lymphomas contain a
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proportion of cells with the capacity to mature into antibody-producing cells. In such tumours a paraprotein may be detected in the serum or urine.

The converse is seen in some cases presenting as multiple myeloma. In these the lymphocytic component can be detected by demonstrating idiotypic immunoglobulin synthesis by a clone of circulating small lymphocytes (Mellstedt et al., 1974; Abdou and Abdou, 1975).

3) Metastasis of end-stage B cell tumours
Localised tumours may arise from B cells after they have reached the end point of their migration. The tumours may be classified morphologically as lymphoplasmacytoid, or plasma cell tumours, or as immunoblastic sarcoma. They may metastasise to characteristic secondary sites. In this instance a I to IV clinical staging has prognostic and therapeutic implications.

LYMPHOCYTIC LYMPHOMA
Early in the disease patients present typically with nodal or splenic enlargement. The overall architecture is preserved but there is a selective increase in numbers in one cellular component. In the case of B cell neoplasms this can often be demonstrated by sensitive immunoperoxidase techniques (Taylor and Mason, 1974) (Fig. 1).

T cell lymphocytic lymphoma, which in England and America is much rarer than the B cell equivalent, may similarly show expansion in areas predominantly populated by T cells—for example, the periarteriolar lymphatic sheath in the spleen. In the case of T cells early involvement is difficult to detect because there

![Fig. 1](a). Part of Malpighian corpuscle in spleen weighing 2870 g from a man aged 45 with a 4½-year history of chronic lymphatic leukaemia. The circulating lymphocytes showed surface IgMA. Section stained by immunoperoxidase for lambda light chains with haematoxylin counterstain. Few immunoglobulin-negative periarteriolar lymphoid sheath cells remain, surrounded by a wide band of lambda-positive CLL cells. The marginal zone is not involved. × 300. (b). Higher power of (a). The clone of malignant cells produces a dark band because of positive intracytoplasmic staining for lambda light chains. Kappa light chain staining reveals very few positive cells in this zone although mature plasma cells, staining either for kappa or lambda, are present in the red pulp and outer edge of the marginal zone. × 500.
are no markers of clonality that can satisfactorily be applied to sections. The diagnosis rests on the demonstration of rosettes formed by the circulating cells, or cells separated from the tissues, and sheep red cells. The diagnosis in early disease is not clear-cut because the neoplastic clone of cells is mingled with large numbers of other subsets of physiological cells. In general, detailed histological descriptions of lymph nodes affected in T cell chronic lymphatic lymphoma appear to be lacking (Rilke et al., 1978).

The T cells of mycosis fungoides may represent another example of homing. In this condition tumour often invades multiple areas of skin and many years may elapse before lymph node or visceral involvement becomes evident. It is generally held that the Sezary syndrome is a leukaemic variant of mycosis fungoides. In this context it is of interest that a number of cases of T cell lymphocytic leukaemia that show a predilection for skin have been reported (Brouet et al., 1975). To what extent T cells home physiologically to skin is at present speculative.

**PLASMA CELL TUMOURS AS NEOPLASTIC TRANSFORMATION OF LYMPHOCYTIC CELLS**

In rare instances chronic lymphocytic leukaemia has been shown to develop into plasma cell leukaemia (leukaemic myelomatosis)—for example, case 3 in Zawadzki et al. (1978), who cite 10 other cases with simultaneously existing chronic lymphatic leukaemia and multiple myeloma. Rather more often circulating small lymphocytes have been shown to carry the idiotypic immunoglobulin of the paraprotein and to be able to resynthesise it after its removal by trypsin digestion (Mellstedt et al., 1974; Abdou and Abdou, 1975).

If sections of the marrow aspirate in multiple myeloma are examined one of the following three patterns is evident: (1) a diffuse increase, spread throughout the marrow, of plasmacytoid cells of the immunoglobulin type of the paraprotein; (2) tumour cells are arranged in solid clusters, displacing other marrow cells; or (3) there may be a combination of the two (Fig. 2).

Very much more rarely fewer plasma cells of the paraprotein light chain type may be present than of the alternative light chain. This has been noted also by others (Taylor et al., 1978). Such an appearance may indicate suppression of physiological plasma cells with light chains of the myeloma type in a sample taken from an unaffected area. In the cases of the diffusely distributed malignant cells it is more difficult to envisage such a pattern arising from division within the marrow than the possibility that the cells have migrated into the marrow at various points as more immature forms.

Results such as these suggest that some B cell neoplasms may be monoclonal but polymorphous. Taylor et al. (1978) suggest a variation of morphological types occurring within a single neoplastic clone in multiple myeloma, related to B lymphocyte transformation and maturation to the plasma cell.

![Fig. 2](http://jcp.bmj.com/)
If some cases of multiple myeloma arise in extra-medullary B cells it is surprising that bony tumours are so common compared with gut plasma cell neoplasms, particularly since about 20% of myelomas produce IgA paraprotein. About 36,000 plasma cells/mm³, of which 90% contain IgA, are physiologically present in the lamina propria (Crabbé and Heremans, 1966), yet in only three rectal biopsies from 214 myeloma patients has there been evidence of involvement, while random sternal aspirates have shown unequivocal involvement in 95% of cases.

In contrast, other B cell neoplasms presenting outside the gut often show tumour involvement in random rectal mucosal biopsies. In the Oxford non-Hodgkin's lymphoma series this is currently highest for follicle centre cell tumours at about 40% with an incidence of around 20% overall in non-Hodgkin's lymphoma.

**Follicle centre cell tumours**

Lukes and Collins (1973) proposed that some tumours, often described by others as 'nodular lymphomas', might represent the neoplastic equivalent of reactive, secondary follicles. Follicle centre cell tumours, they suggest, are composed of 'defective immune cells that function in, migrate to, and arise in tissues similar in varying degrees to their normal counterparts' (Lukes et al., 1978) (Fig. 3).

Warnke and Levy (1978) studied 22 patients with follicular lymphoma by analysis of the light and heavy chains on the tumour cells. They review the evidence that a single cell could give rise to progeny that produce immunoglobulin of different heavy chain classes, but that the products of one clone all show a single variable segment of both heavy chains and a single light chain-constant region of either kappa or lambda type. They conclude that monoclonality may be inferred from the uniformity of light chain type.

All but two out of these 22 patients showed positive immunofluorescent staining for immunoglobulin within the follicles. There was light chain restriction in each case, which was regarded as evidence of monoclonality in the tumour. Just over half of their cases showed a normal ratio of about 2:1 kappa to lambda positive cells in the interfollicular regions. Just under a half showed diffuse areas of infiltration by cells of the same light chain type as those in the neoplastic follicles, although not always to the total exclusion of cells showing the alternative light chain.

Our experience with the immunoperoxidase technique applied to routinely processed paraffin sections is broadly similar, although there may often be doubt about the significance of the low level of follicular staining and interfollicular monoclonal infiltration is rare.

![Fig. 3](http://jcp.bmj.com/content/3-1/70.1/10.1136/jcp.s3-13) Asymptomatic gut involvement, found incidentally by rectal biopsy, in woman aged 70 provisionally diagnosed as case of stage 1a follicular lymphoma. Both the cervical lymph node and nodules in the rectal biopsy showed a similar follicle centre cell tumour, with small cleaved cells predominating. Haematoxylin and eosin × 40.
Warnke and Levy (1978) analysed 10 different tissue sites in four patients. In three of them the spleen was available for analysis. In each case multiple sites showed identical light and heavy chain staining of the lymphoma nodules. They concluded that the neoplastic cells of follicular lymphoma arise from a single clone or dominant clone whose progeny home to the centre of lymphoid follicles and may eventually displace the normal B lymphocytes in the mantle zones.

Rosenberg (1975) has shown that the bone marrow is involved in presentation in as many as 85% of patients with follicular lymphoma. Goudie et al. (1974) drew attention to published reports of patients with symmetrical deposits of lymphoma 'which can most readily be explained on the basis that these tumours consist of a clone of neoplastic lymphocytes which enter the circulation and show ecotaxis of a highly tissue-specific nature.' They also cite experimental evidence that neoplastic lymphoid cells display ecotaxis. For example, virus-induced feline neoplasms show selective localisation in B or T cell compartments. In certain cases the B cell lesions predominantly involve the gut-associated lymphoid tissue.

**METASTASIS IN END-STAGE TUMOURS**
Clinicians treating lymphoma know of cases, often presenting in extra-nodal sites with large-celled tumours showing considerable mitotic activity, in which with local excision and local radiotherapy the patient is subsequently free from disease for considerable periods. It is as though sarcomatous transformation, with local invasion and destruction, has occurred in an end cell. Nevertheless, in any series the numbers are small, and different series are not comparable because of uncertainty in the terminologies used in classifying this type of tumour.

Metastatic spread from a single focus occurs in some cases of intestinal true histiocytic lymphoma associated with malabsorption. Isaacson and Wright (1978a) studied 18 such patients and noted that when the tumour spread to mesenteric nodes the tumour cells were predominantly intranuclear, much in the way one might expect an epithelial tumour to spread via the lymphatics. Nevertheless, the disease appeared to have metastasised widely by presentation in two-thirds of the cases 'usually consisting of subtle intranuclear infiltrates in bone marrow, liver and spleen'. A suggestion to account for a focal origin (or possibly multifocal origins) of the tumours is that the 'sequence of progressive hyperplasia and plasma cell proliferation in the gut (in coeliac disease) appears to induce malignancy in the histocytes of the lamina propria rather than the plasma cells' (Isaacson and Wright, 1978b).

**Conclusions**
Recent immunological advances have enabled malignant non-Hodgkin's lymphomas to be closely defined in a significant proportion of cases. However, the success of therapy lags far behind that for Hodgkin's disease, in which the nature of the malignant cell is much less certain. The implication for the histologist is that biopsies early in well differentiated lymphoid neoplasms may not show outright features of malignancy. Possibly a combination of immunopathological techniques and careful analysis of morphology, along the lines suggested by Robb-Smith (1974), could be used to demonstrate selective replacement within certain areas of nodes showing 'progressive hyperplasia'. For the therapist the implication is that not all tumours composed of large rapidly dividing cells are necessarily widespread at presentation and careful staging with adequate local treatment may be successful. Conversely, many tumours reported as being well differentiated with a low mitotic activity may be widespread by presentation and be difficult to treat adequately.

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**References**
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