

## IMMUNOLOGICAL ASPECTS OF NON-HODGKIN'S LYMPHOMAS

JOHN BOSCO MBBS, FRACP"

### INTRODUCTION

Over the last ten years major changes have occurred in our concepts about the non-Hodgkin's lymphomas. New classifications incorporating deeper knowledge of the immune system have appeared. This is a summary of the Lukes-Collins (immunological) classification of the non-Hodgkin's lymphomas.

### Some Considerations of the Immune System

Various cell groups participate in the immune response and the lymphocytes constitute a large proportion of these. Lymphocytes are derived from bone marrow stem cells which differentiate in the bone marrow or the thymus gland to form two major sub-groups, B (bone marrow derived) cells which are precursors of antibody forming cells and T (thymus derived) cells required for cell mediated immunity. These two lymphocyte populations can be distinguished by surface membrane markers or receptors. B cells have the following on their surface membrane — immunoglobulin, Fc receptor, C3 receptor and histocompatibility molecules. T cells on the other hand can be identified fairly easily by their ability to form rosettes with sheep red blood cells. They too have other differentiation antigens and histocompatibility molecules on their surface.

Following differentiation, lymphocytes undergo a complex circulatory pattern which involves recirculation between blood, lymph and lymphoid organs including the mucosal associated lymphoid tissue (MALT) (Fig. 1). In the lymph node lymphocytes are distributed mainly into two areas, the superficial cortex and the deep cortex. The superficial cortex consists of closely packed accumulation of lymphocytes called follicles which are made up predominantly of B lymphocytes. The deep

cortex and the interfollicular areas consist mainly of T lymphocytes. The lymph node is the major site of antigen recognition and following antigen recognition a series of events takes place that includes morphologic changes of the lymphocyte and destruction or removal of antigen.

### Follicular Cell Concept and Lymphocyte Transformation

In a series of papers since 1971, Lukes and Collins have employed the newly acquired knowledge about the dynamic processes within the immunological network including the T and B cell sub-groups to provide an understanding of one of the common abnormalities of the immune system namely, the **lymphomas**.<sup>1,2</sup>

They proposed the follicular centre cell concept by linking 'new' knowledge of the physiology and anatomy of the immune system to what was known about lymphocyte transformation, which was first described by Nowell and associates in 1960.<sup>3</sup> In brief, when a mitogen eg. phytohemagglutinin (PHA) is added to lymphocytes in culture *in vitro*, there are morphologic and metabolic alterations of the lymphocytes which lead to a change in their appearance with cytoplasmic and nuclear enlargement. By corollary *in vivo*, transformation by an antigen of a follicular B lymphocyte leads to the formation of a small cleaved cell followed by a large cleaved lymphocyte, then to a smaller non-cleaved cell and finally a non-cleaved cell. Then it either reverts to a mature 'memory' lymphocyte or progresses to an immunoblast and finally a plasma cell. In the lymph node this leads to the formation of a 'germinal centre' i.e. an enlarged follicle with a central area with large proliferating cells. T cells, too, undergo transformation to form **immunoblasts**, **cytotoxic cells** and memory cells (Fig. 2).

\* Associate Professor, Department of Medicine,  
Faculty of Medicine, University of Malaya,  
Kuala Lumpur (Address for reprint requests).

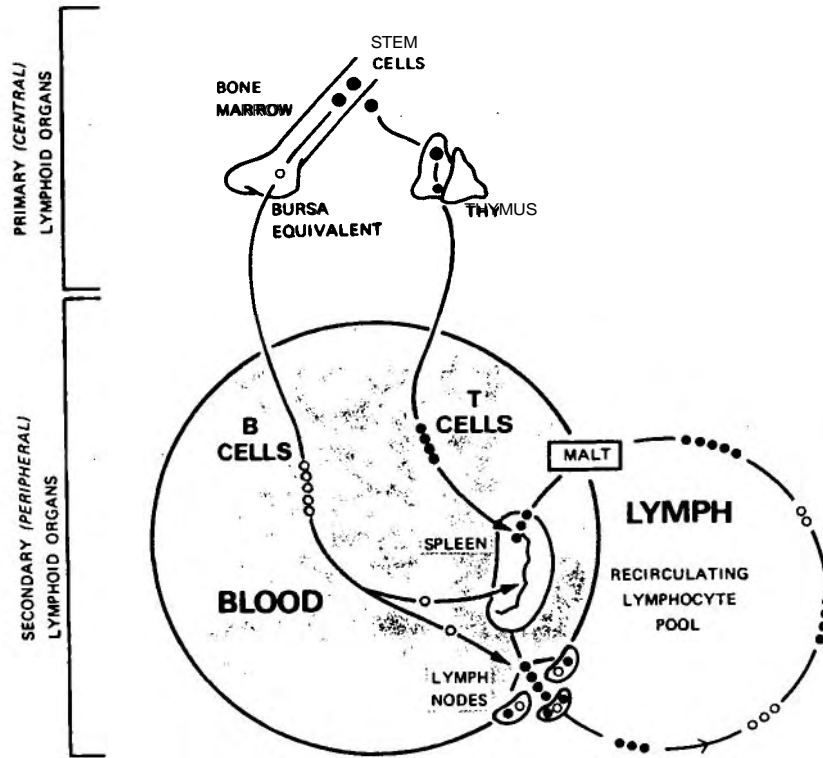


Figure 1. BASTEN(1979)

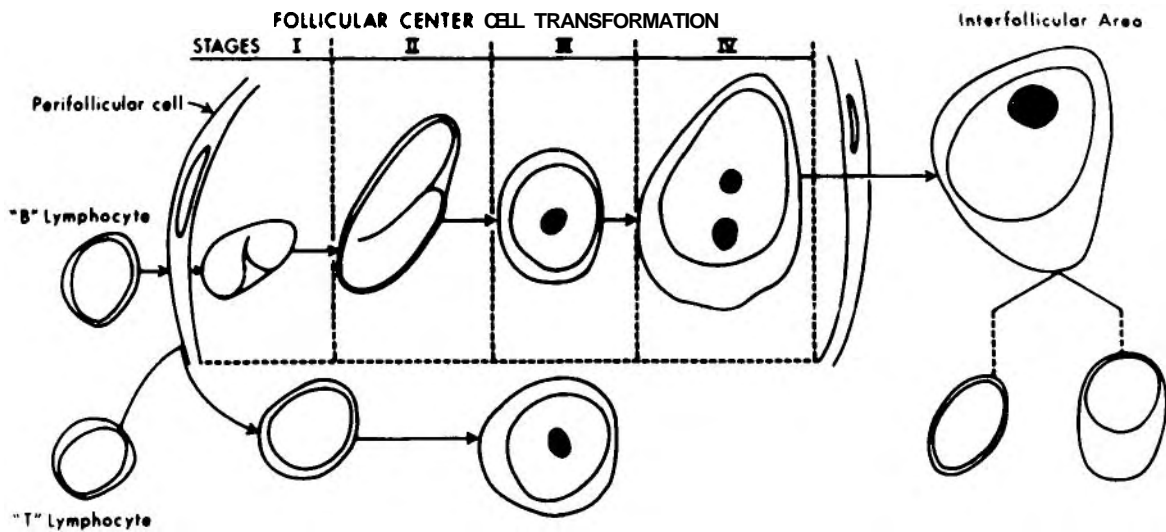


Figure 2. Schematic representation of normal transformation of FCC in comparison with transformation of T cells. (I) Small cleaved cell; (II) large cleaved cell; (III) small noncleaved transformed cell; (IV) large noncleaved transformed cell, gives rise to a B immunoblast, which may revert to a small lymphocyte or become a plasma cell. T immunoblast results from T lymphocyte transformation. Lymphomas appear to develop from either a "block" in or a "switch on" of this lymphocyte transformation in vivo (LUKES 1978).

Using camera lucida studies, electron microscopy, cytochemistry, immunofluorescence, immuno-peroxidase and cell surface receptor techniques and comparison of sections of transformed lymphocytes with sections of normal reactive and malignant lymphoid tissues, Lukes et al/ proposed that lymphomas represent proliferation of cells that were blocked or "switched on" (**derepressed**) at a particular stage of transformation in the various lymphatic systems e.g. block and proliferation at the large non-cleaved cell stage lead to the development of large non-cleaved cell lymphoma etc. This gave rise to the follicular centre cell concept which is as follows:-

- (i) Cells of the lymph node follicle are B cells and these give rise to plasma cells.
- (ii) The normal follicle is a site of B cell transformation.
- (iii) Nodular lymphomas of Rappaport are lymphomatous follicles consisting of cleaved and non-cleaved cells.
- (iv) Diffuse lymphomas are made up of cells which actually originate in the follicles. These malignant cells replace other lymphocytes in the lymph node by proliferation and infiltration.
- (v) With rare exceptions, lymphomas previously regarded as reticulum cell sarcomas or histiocytic lymphomas are in fact lymphomas made up of transformed lymphocytes. They had been labelled "histiocytic" only because of the morphologic resemblance of histiocytes to transformed lymphocytes.

Employing the follicular centre cell concept Lukes et al/ reclassified non-Hodgkin's lymphomas into four major groups:-

- (i) B cell,
- (ii) T cell,
- (iii) Truly histiocytic, and
- (iv) U cell where the 'U' cell represents an unidentified cell group with no specific or immunologic or cytochemical markers.

In a recent study of 425 patients with lymphomas, 70% of the lymphomas were noted to be of B cell origin, while 15% were T cell in type and only 1% was truly histiocytic; the rest were **unclassifiable**.<sup>4</sup> Other immunologic stu-

dies have also indicated that follicular lymphomas apparently arise from a single dominant or 'malignant' clone whose progeny 'home' to the centre of lymphoid follicles and may eventually displace the normal B lymphocytes in the cortical zones.'

## CONCLUSION

The explanation and classification of lymphomas as expressed by Lukes and Collins and others is an attempt to provide a link between knowledge about basic cell functions, the immune system and malignant transformation. It is also an attempt to overcome the Rappaport classification, which although is reproducible by many pathologists and predicts prognosis, is scientifically inaccurate because many of the different cellular types mentioned in the classification are indeed different morphologic expression of B cell differentiation and this is not accounted for.

Although the Lukes and Collins classification may be a little more biologically accurate, it at the moment lacks extensive clinical and therapeutic correlations unlike the Rappaport classification and therefore will be reluctantly accepted by the clinician. For the pathologist, the methods employed are technically cumbersome and difficult to reproduce including the need for fresh specimens and plastic embedding.

However, for both the pathologist and the clinician the immunological approach to this group of tumours may provide an improved understanding of basic biological process of malignancy and perhaps lead to the design of more rational and effective therapy of malignant diseases.

## REFERENCES

1. Lukes RJ, Collins RD. Immunologic characterization of human malignant lymphomas. *Cancer* 1974; 34 : 1488-503.
2. Lukes RJ, Collins RD. New approaches to the classification of the lymphomata. Symposium on non-Hodgkin's lymphomata. *Br J Cancer (Suppl)* 1975; 31 : 1-28.
3. Nowell PC. Phytohemagglutinin : an initiator of mitosis in cultures of normal hu-

- man leukocytes. *Cancer Res* 1960; 20 : 462-6.
4. Lukes RJ, Parker JW, Taylor CR, Tindle BH, Cramer AD, Lincoln TL. Immunologic approach to non-Hodgkin lymphomas and related leukemias. Analysis of the results of multiparameter studies of 425 cases. *Semin Hematol* 1978; 15 : 322-51.
  5. Warnke R, Levy R. Immunopathology of follicular lymphomas. A model of B-lymphocyte homing. *N Engl J Med* 1978; 298 : 481-6.