NON-HODGKIN’S LYMPHOMA
Analysis of the relationship between morphology and clinical features, based on a survey of 302 cases.

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av
PER LENNER
med. lic.

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ABSTRACT

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Per Lenner, M.D., Department of Oncology, University of Umeå, S-901 87 Umeå, Sweden.

Non-Hodgkin’s lymphomas are neoplasms of the immune system. Recent progress in knowledge about the immune system and its functions has led to a lot of new classifications of non-Hodgkin’s lymphomas. One of the new classifications (Lukes-Collins) was applied to a retrospective patient series. The Lukes-Collins system is based on both morphologic and functional characteristics and had to be somewhat modified since the present work was based on pure morphology.

The patient series encompassed 302 cases with histologically proven non-Hodgkin’s lymphoma. Data on clinical and histological variables were collected and analysed for correlations and interrelations. With Lukes-Collins classification as basis, the material could be divided into groups with distinct clinical features.

Small cell morphology implied a considerable tendency to dissemination of diffuse, or leukemic, character, but nevertheless a comparably favourable prognosis. Systemic symptoms were rare and these lesions showed little evidence of proliferation.

Mixed small/large cleaved cell morphology was associated with a favourable survival, a relatively small propensity for dissemination, and a low frequency of systemic symptoms.

Large cell morphology was accompanied by aggressive clinical behaviour with short survival, a pronounced tendency to (non-leukemic) dissemination, a high frequency of systemic symptoms, and a high proliferative capacity.

Lymphoblastic morphology implied strongly an unfavourable clinical course with short survival, a high propensity for leukemic spread, systemic symptoms in high frequency, and evidence of pronounced proliferative capacity.

Growth pattern was of great importance, since a nodular pattern was associated with a significantly more favourable prognosis than if the same cells were growing diffusely.

The further theoretic and clinical implications of the findings were discussed. A proposal for a simplified view on the non-Hodgkin’s lymphomas, based on modern concepts about the immune system, was set forth. The general conclusions concerning clinical management were discussed on the basis of the present findings.

Key words: Non-Hodgkin’s lymphoma, retrospective analysis, morphological classification, Lukes-Collins classification, clinico-pathologic correlation, clinical implications.
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To

Eva

Per-Erik, Johan and Niklas
"Nowhere in pathology has a chaos of names so clouded clear concepts as in the subject of lymphoid tumours".

-R. Willis, 1948.
This thesis is based on the following papers:


In the text these papers will be referred to by their Roman numerals.
INTRODUCTION
The immune system is essential for life in a vertebrate organism, serving to protect it from pathogenic influences such as foreign substances or altered cellular constituents of the own organism. To perform these functions the immune system has a highly specialized and complicated structure and function. One of the main units in this structure is the lymphocyte, a remarkable cell which is highly reactive to the appropriate stimulus.

Malignant lymphomas are neoplasms originating from cells of the immune system. Knowledge about this system has been profoundly deepened in the last decades. Several new methods have been developed to study lymphoid cells. These methods have also been applied to the study of malignant lymphomas, thus broadening the insight into the biology of these tumours. The newly gained knowledge has resulted in several new classifications, which, however, have not made the situation easier for clinicians and pathologists that are dealing practically with lymphoma patients. To quote Taylor (1978), "the problem with regard to existing histological classifications of lymphoma is not that there are too few, but rather that there are so many".

Neither has the practical and clinical usefulness of modern classifications been fully settled yet. Decisions about therapy should be based on as accurate knowledge as possible of the biologic behaviour of the neoplastic process. Since modern classifications could be supposed to be conceptually more correct than older classifications, it could also be hoped that newer systems should be more useful as tools for the clinician.

This work could be regarded as an attempt to elucidate the value of one of the new classifications (Lukes-Collins) as applied to clinical routine biopsies, in predicting clinical behaviour of the tumour. Furthermore, the intention was to achieve a synthesis of important clinical and histological features in order to get a simplified
and comprehensible view on the non-Hodgkin's lymphomas that might be useful as a basis in the clinical management of these patients.

To get the appropriate background a short summary of modern concepts about the lymphoreticular system and its functions is required.
SOME ASPECTS OF THE IMMUNE SYSTEM OF RELEVANCE FOR THE STUDY OF MALIGNANT LYMPHOMA

The lymphoreticular system can, for practical reasons, be separated into two parts; the lymphoid cell series, and the mononuclear phagocytic series.

The lymphoid series

The lymphoid system includes cells differing in ontogeny, distribution and function (Raff 1970, Unanue et al 1971). The distinct types of lymphocytes cannot be distinguished by conventional morphologic techniques, but are identified by immunological and/or cytochemical methods (reviewed by Kersey & Gajl-Peczalska 1975). All lymphocytes probably derive from precursors located in the bone marrow (Raff 1973), as demonstrated in Fig 1.

Fig. 1. Simplified scheme on the structure and function of the immune system.
The predominant type in peripheral blood is the T lymphocyte, which undergoes differentiation and attains immunologic competence in the thymus. The second main type, the B lymphocyte, undergoes differentiation and functional commitment in the bursa of Fabricius in birds and in mammals in an unknown equivalent to the bursa (Craddock et al 1971, Raff 1973).

The ontogeny and functions of non-T, non-B cells are less well known. It seems conceivable that these cells are progenitor cells that have not gained immunologic competence by passing through thymus or the bursa equivalent. However, it also seems to exist subgroups of functioning lymphocytes not belonging to the B or T cell lineages, e.g. some cells with cytolytic (killer) capacity (Katz 1977).

On proper antigenic or mitogenic stimulation, small lymphocytes transform into large cells characterized by intense proliferation. These transformed cells, sometimes termed immunoblasts, may develop into small lymphocytes ("memory"cells), or different forms of functionally active cells (reviewed by Roitt et al 1969).

"Virgin" lymphocyte (Fig. 1) is the accepted term for a lymphoid cell that has gained immunologic competence, but not encountered its appropriate antigen, and hence it has never been transformed. These cells are somewhat hypothetical, deduced from theoretical considerations and not clearly defined. They may, however, be of importance when discussing origin cells for the non-Hodgkin's lymphomas.

The scheme in Fig. 1 gives an oversimplified view on a highly complex system. For example, interactions exist between cells. Macrophages may have stimulatory or inhibitory actions on lymphocytes. There are subsets of T cells with stimulatory ("helper") or inhibitory ("suppressor") effects on antigen-initiated lymphoid proliferation (Katz 1977). There are a few studies indicating that
such interactions may be of importance in the genesis or progression of malignant lymphomas (Krüger 1971, Bluming et al 1979).

T and B cells have different anatomical distributions. There is a normal "traffic" of lymphocytes with "homing" to different parts of the lymphoid system (Ford & Gowans 1969, Craddock et al 1971). B cells reside primarily in the follicular centres of the lymphoid tissues, where active proliferation and production of B cells is taking place. The migrating descendants of these cells, immunoblasts and plasma cells, are found in interfollicular areas and medullary cords. Primary and secondary lymphoid follicles can be found, except in lymph nodes, in the Malpighian bodies of the spleen, the lamina propria of the gastrointestinal tract, and interspersed in the bone marrow. The T cell system is distributed in the paracortical areas of lymph nodes, in perivascular regions of the spleen and in small foci in the gastrointestinal tract. The skin also seems to be a predilection site for T lymphocytes (reviewed by Streilein 1978).

The preferential "homing" of different forms of lymphocytes to certain organs and structures seems to be of relevance for the understanding of dissemination patterns in malignant lymphomas, since the neoplastic cells might be expected to spread and localize in a similar way as their normal counterparts (Pilgrim 1972).

The mononuclear phagocytic series
Mononuclear phagocytes (tissue macrophages and histiocytes and their precursors, the circulating blood monocytes) are involved in antigen processing. They interact with, and activate, lymphoid cells (Nossal & Ada 1971, Gery & Waksman 1972, Schrader 1973). They also serve as effector cells (Van Furth et al 1972). Excessive levels of macrophages are inhibitory for lymphocyte proliferation (Kurland et al 1977).
Previously, when the process of lymphocyte transformation was not yet recognized, immunoblasts or other large transformed cells were considered as histiocytes on purely morphologic grounds. In analogy, large cell lymphomas were classified as histiocytic lymphomas (reticulum cell sarcomas) (Rappaport 1966). However, modern immunologic techniques have demonstrated that most of these tumours are composed of large, transformed lymphocytes of B or T cell origin (Braylan et al 1975, Morris & Davey 1975, Schaefer et al 1975, Habeshaw & Stuart 1975, Rappaport & Braylan 1975, Bloomfield et al 1976, Brouet et al 1976, Davey et al 1976, Taylor 1976, Habeshaw et al 1977, 1979, Bom-van Noorloos et al 1978, Epstein et al 1978, Filippa et al 1978, Li & Harrison 1978, Lukes et al 1978a, b, Pinkus & Said 1979). To recognize a true histiocytic lymphoma, cytochemical or immunochemical methods are required (Braylan et al 1975, Habeshaw & Stuart 1975, Brouet et al 1976, Jaffe et al 1977, Pinkus & Said 1979). Since such methods were not used in the present study, the true histiocytic lymphomas, which seem to be very rare (Braylan et al 1975, Habeshaw & Stuart 1975, Brouet et al 1976, Jaffe et al 1977), will not be discussed further.
MORPHOLOGIC CLASSIFICATION OF NON-HODGKIN'S LYMPHOMA

The historical terms "lymphosarcoma", "reticulum cell sarcoma" and "giant follicular lymphoma" are reviewed elsewhere (Mann et al 1979) and will not be further commented in this presentation. This old terminology was abandoned as the Rappaport classification (Rappaport et al 1956, Rappaport 1966) gained acceptance.

Rappaport classification

Currently most practicing pathologists and clinicians rely on the Rappaport classification. This classification is based on two principal features; the cell morphology, and the histologic pattern. Five distinct cell types are recognized (Table 1). Three of these may have either a diffuse or a nodular growth pattern. The remaining two types are seen only in a diffuse pattern.

<table>
<thead>
<tr>
<th>Table 1. Rappaport classification of non-Hodgkin's lymphoma</th>
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<tbody>
<tr>
<td>Nodular (follicular)</td>
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<tr>
<td>Lymphocytic, poorly differentiated</td>
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<tr>
<td>Mixed lymphocytic-histiocytic</td>
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<tr>
<td>Histiocytic</td>
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<tr>
<td>Diffuse</td>
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<tr>
<td>Lymphocytic, well differentiated</td>
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<tr>
<td>Lymphocytic, poorly differentiated</td>
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<tr>
<td>Mixed lymphocytic-histiocytic</td>
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<tr>
<td>Histiocytic</td>
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<tr>
<td>Undifferentiated</td>
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</table>

This classification, developed before recent progress in immunology, is based on presumed origins of the neoplastic cells, which in many instances have been shown to be erroneous, as mentioned above concerning the so called histiocytic lymphomas, the majority of which are composed of transformed lymphocytes of B or T cell origin. There are also some recent reports showing that a subdivision of "histiocytic" lymphomas may have clinical and prognostic significance (Nathwani et al 1978, Strauchten et al 1978, Armitage et al 1979, Meusers et al 1979).
The group termed "lymphocytic, poorly differentiated" has been shown to comprise tumours with different origin and biology; partly lesions with small lymphoid cells with pleomorphic appearance, partly tumours composed of medium sized cells with immature features, sometimes termed "lymphoblasts" (Nathwani et al 1976).

Lukes-Collins classification

Several new classifications of non-Hodgkin's lymphoma have been proposed during recent years (Bennett et al 1974, Dorfman 1974, Gerard-Marchant et al 1974, Lukes & Collins 1974a, Mathé et al 1976). As regards the different classifications the interested reader is referred to the work of Nathwani (1979). As Lukes-Collins classification was used in the present study, a presentation of this classification seems to be warranted.

Table 2. Lukes-Collins classification of non-Hodgkin's lymphoma

<table>
<thead>
<tr>
<th>B cell</th>
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<tbody>
<tr>
<td>Small lymphocyte (CLL)</td>
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<tr>
<td>Plasmacytoid lymphocyte</td>
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<td>Follicular center cell (FCC)</td>
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<tr>
<td>- small cleaved</td>
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<tr>
<td>- large cleaved</td>
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<tr>
<td>- small non-cleaved</td>
<td></td>
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<tr>
<td>- large non-cleaved</td>
<td></td>
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<tr>
<td>Immunoblastic sarcoma</td>
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<tr>
<td>Hairy cell leukemia</td>
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</table>

<table>
<thead>
<tr>
<th>T cell</th>
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<tbody>
<tr>
<td>Small lymphocyte</td>
<td></td>
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<tr>
<td>Convoluted lymphocyte</td>
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</tr>
<tr>
<td>Sézary - Mycosis fungoides</td>
<td>(Cerebriform lymphocyte)</td>
</tr>
<tr>
<td>Immunoblastic sarcoma</td>
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<table>
<thead>
<tr>
<th>U cell</th>
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<tbody>
<tr>
<td>Histiocytic</td>
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</table>

*Maurer et al 1979

**Follicular or diffuse, with or without sclerosis
This classification (Lukes & Collins 1973, 1974a, b, 1975, 1977, Lukes et al 1978a, b, Maurer et al 1979) was elaborated on two premises: 1. The separation of the immune system into different functional compartments, i.e. T, B, and U cell (undefined cell, i.e. non-T, non-B cell) compartments, and 2. The process of lymphocyte transformation after antigenic or mitogenic stimulation, when the cell undergoes profound changes morphologically and functionally. Lukes & Collins also postulated that the cells of lymphoid neoplasms more or less retain the functional and morphologic properties of normal lymphoid cells, and that there is a freezing of the cells in one or more stages of the normal lymphocyte development.

Accordingly, the Lukes-Collins classification (Table 2) divides the non-Hodgkin's lymphomas into three main groups; T, B, and U cell tumours, which are further divided into subentities. Most of these groups can be recognized morphologically. There are, however, some entities that beside morphology also require immunological methods to be diagnosed. Therefore, in a morphological study like the present one, a modification of Lukes-Collins scheme was required. This question is further discussed under "Material and methods".

Some comments concerning nodularity

Nodularity in non-Hodgkin's lymphomas has for long time been a matter of controversy. It is well known that tumours growing with a nodular pattern are accompanied by a more favourable prognosis than those with a diffuse pattern (Rappaport et al 1956, Lumb & Newton 1957, Jones et al 1973, Patchefsky et al 1974, Schein et al 1974). The interpretations of this phenomenon have, however, been quite divergent. Some, notably European, authors (Robb-Smith 1938, 1947, 1964, Lennert 1964, 1967, 1973) have regarded nodular lymphomas as a separate and distinct disease entity. Other, preferably American authors (Rappaport et al 1956, Rappaport 1966), have favoured the view that tumours with the same cell picture can grow with either a nodular or diffuse pattern. Lukes (1977) claimed that growth pattern is secondary to cell type and of no primary prognostic
significance. This approach is in direct opposition to the opinion of Rappaport, who considers the pattern to be of primary importance for the biological behaviour of the tumour.

Paper II in this investigation was intended as an attempt to contribute to the resolution of this question.

Cytologic entities
Distinct subgroups according to cell types are recognized in all morphological classifications. It is to large extent possible to translate the different classifications into each other. In the following the different cell types will be discussed one by one with comments for each of the Rappaport (1966) and Lukes-Collins (1975) classifications. The Rappaport classification is indicated by (R) and Lukes-Collins by (L-C).

Lymphocytic, well differentiated (R)
Small lymphocytic (L-C)
Size: 6-9 microns.
Nucleus: Round or oval with compact chromatin. Nucleoli inconspicuous.
Cytoplasm: Pale, scanty.

The same cell is found in CLL (chronic lymphocytic leukemia), and this lymphoma may be regarded as the tissue manifestation of CLL (Lukes 1967, Huber et al 1974, Peter et al 1974, Aisenberg & Long 1975, Braylan et al 1975, 1976, Brouet et al 1975). Fig. 2.

Lymphocytic, poorly differentiated (R)
Small cleaved FCC (L-C)
Size: 6-12 microns.
Cytoplasm: Indistinct and scanty.
Pattern: Nodular or diffuse. Noncohesive growth.
Leukemic variant also known as "lymphosarcoma cell leukemia" (Schnitzer 1978), or leukemia composed of "notched nucleus cells" (Anday & Schmitz 1952, Spiro et al 1975) or "hematogones" (Rosenthal et al 1952). Fig. 3.

Mixed lymphocytic-histiocytic (R)
Mixed small/large cleaved (L-C)
This tumour, which can grow with a nodular or diffuse pattern, is not recognized as a separate entity in Lukes-Collins original scheme. It is, however, included in the present work, defined as a lesion composed of a mixture of small and large cleaved cells, 1/3 or more of each. Fig. 4.

Histiocytic (R)
Large cleaved FCC (L-C)
Size: 20-40 microns
Nucleus: Prominently irregular. Nucleoli absent or inconspicuous.
Cytoplasm: Moderate, pyroninophilic.
Pattern: Mainly diffuse, but occasionally nodular. Rather cohesive growth. Fig. 5.

Histiocytic (R)
Large non-cleaved FCC (L-C)
Size: 20-40 microns.
Nucleus: Round or oval. Chromatin finely dispersed. Nucleoli often prominent, characteristically situated at the nuclear membrane on short axis of an oval nucleus.
Cytoplasm: Rather abundant.
Pattern: Diffuse, but occasionally with some tendency to nodular pattern. Cohesive growth. Fig. 6.
Histiocytic (R)
Immunoblastic (L-C)

Size: 20-40 microns.

Nucleus: Round or oval. Chromatin often condensed at the nuclear membrane, giving a "vesicular" appearance. One or two, often prominent, central nucleoli.

Cytoplasm: Often abundant, pyroninophilic.

Pattern: Diffuse. Cohesive growth.

According to Lukes & Collins (1975, 1977), this tumor typically arises in chronic abnormal immune states. Numerous reports have described lymphoma development in such states, e.g. immunoblastic lymphadenopathy (Lukes & Collins 1974b, Bamberg et al 1979), systemic lupus erythematosus (Schleissner et al 1976, Green et al 1978), Sjögren’s syndrome (Talal et al 1967), in immunosuppressed patients (Penn et al 1971), and in certain congenital disorders (Good & Finstad 1968). It is not known, however, how often these lymphomas were of the immunoblastic type, since most of these reports were based on older classifications. In a recent survey, however, Banks et al (1979) reported that only one of 29 patients with lymphoid neoplasia following connective tissue disease had immunoblastic cell type. Fig. 7.

Histiocytic (R)
Immunoblastic with plasmacytoid features (L-C)

Morphologic picture as immunoblastic, but plasmacytoid features are evident.

Pattern always diffuse. Less cohesive than immunoblastic?

Fig. 8.
Lymphocytic lymphoma with dysproteinemia (R)
Plasmacytoid lymphocytic (L-C)
Morphologically as small lymphocytic but some cells show plasma cell differentiation. PAS-positive intranuclear and/or cytoplasmic immunoglobulin may be present. This cell morphology, combined with IgM monoclonal macroglobulinemia, gives the clinical syndrome of Waldenström's macroglobulinemia.
Pattern: Diffuse. Non-cohesive growth. Fig. 9.

Lymphoblastic, convoluted or non-convoluted
These entities were not recognized in Rappaport's original scheme. The convoluted variety was first described by Barcos & Lukes (1975). Later, the non-convoluted form was described by Nathwani et al (1976).
Size: 10-20 microns.
Nucleus: Irregular (convoluted), or round or oval (non-convoluted). Chromatin finely stippled and evenly distributed. Nucleoli inconspicuous.
Cytoplasm: Scanty.

The immature-appearing cells are indistinguishable from cells of ALL (acute lymphoblastic leukemia), and this lymphoma represents the tissue manifestation of ALL. Fig. 10.

Additional entities

Mycosis fungoides and Sézary's syndrome
Cytoplasm: Scanty.
Affinity for skin, but often progression to involvement of nodes and other internal organs. Sézary's syndrome might be regarded as the

**Hairy cell leukemia**
Nucleus: Round or oval. Finely granular chromatin. Nucleoli absent or inconspicuous.
Cytoplasm: Abundant, pale. In well-fixed material sharply demarcated and interlocking cell borders with prominent acidophilic intercellular zone. In smears and imprints abundant, finely granular cytoplasm and poorly defined margins with hairlike processes.

**Burkitt’s lymphoma**
Included among small non-cleaved FCC in Lukes-Collins classification, among the undifferentiated lymphomas according to the Rappaport scheme.

Nucleus: Round. Chromatin finely dispersed. One to three small nucleoli.
Cytoplasm: Moderate, pyroninophilic.
Pattern: Diffuse, but nodularity has been reported in a few cases (Mann et al 1976). "Starry sky" pattern characteristic due to intermingled reactive histiocytes. Cohesive growth.

**Plasmocytoma**
A pure proliferation of plasma cells in a solitary lesion, i.e. the solitary equivalent to multiple myeloma.
Fig. 2. Lymph node: Well differentiated lymphocytic lymphoma (R), or small lymphocytic lymphoma (L-C). (H & E, x500).

Fig. 3. Lymph node: Poorly differentiated lymphocytic lymphoma (R), or small cleaved FCC lymphoma (L-C). (H & E, x500).
Fig. 4. Lymph node: Mixed lymphocytic and histiocytic lymphoma (R), or mixed small/large cleaved FCC lymphoma (L-C). (H & E, x500).

Fig. 5. Lymph node: Histiocytic lymphoma (R), or large cleaved FCC lymphoma (L-C). (PAS, x500).
Fig. 6. Lymph node: Histiocytic lymphoma (R), or large non-cleaved FCC lymphoma (L-C). (PAS, x500).

Fig. 7. Lymph node: Histiocytic lymphoma (R), or immunoblastic sarcoma (L-C). (PAS, x500).
Fig. 8. Lymph node: Histiocytic lymphoma (R), or immunoblastic sarcoma with plasmacytoid differentiation (L-C). (PAS, x500).

Fig. 9. Lymph node: Lymphocytic lymphoma with dysproteinemla (R), or plasmacytoid lymphocytic lymphoma (L-C). (H & E, x500).
General comments on classification of non-Hodgkin's lymphoma

Clinicians treating lymphoma patients are today employing a highly differentiated spectrum of therapy methods. The therapy must rely on an accurate morphologic diagnosis. In order to compare results of treatment the classification should be reproducible between different centres. The reproducibility of the Rappaport classification has been shown to be insufficient in some respects (DeVita et al 1968, Jones et al 1977, Ezdinli et al 1979). This factor is probably one of the main reasons for current controversy about the non-Hodgkin's lymphomas.

From a clinical point of view it is a great advantage if a classification is logic, comprehensible and simple to apply in practical work. It should have descriptive, well defined terms. To be clinically useful it must correlate to clinical course and give good prediction of prognosis.
A classification should be scientifically valid, i.e. based on current knowledge about the normal cells of origin. The knowledge of the immune system has expanded greatly during recent decades, which has obviously made previous classifications inadequate.

Thus, it was considered of interest to study the usefulness and clinical relevance of Lukes-Collins classification, which is based on modern concepts concerning the origin and nature of the lymphoma cells.
PRESENT INVESTIGATION

Material and methods
During the period 1959 to 1975, 823 patients with a verified or suspected diagnosis of malignant lymphoma (Hodgkin and non-Hodgkin) were referred to the Department of Oncology. Histopathological material was available and evaluable in 586 cases. The reasons for exclusion of cases are shown in Fig. 11, which also demonstrates the distribution of diagnoses among cases with adequate histologic slides. 302 patients with histologically proven non-Hodgkin's lymphoma in tissues other than bone marrow were found. These cases were further analysed. Clinical and histologic data were recorded and stored in a computer.

Clinical review. Pretreatment clinical stage was recorded according to principles in the Ann Arbor staging classification (Carbone et al 1971). The staging was, in this study, based on physical examination, simple roentgenological methods such as chest and bone films, and bone marrow puncture with cytologic and histologic evaluation. Lymphography was performed on 27 patients. The results of this procedure were, however, not taken into account, in order to make these cases comparable to the other patients. Staging laparotomy was not performed in any case.

The peripheral blood was regarded as leukemic when more than 5000 lymphocytes per microlitre, or other pathologic cell forms of lymphoma type, were present.

Treatment was recorded in general terms, i.e. radiotherapy and/or chemotherapy, or no tumour-specific therapy. Whether the patient achieved a complete remission (CR) or not was evaluated by the same simple methods as in the pretreatment evaluation. Time and site of first relapse were recorded. All patients were followed to death or to completion of follow-up, i.e. the end of 1976 (paper I, II and III), or the end of 1978 (paper IV). Thus, the minimum observation time for living patients was one and three years, respectively. No patient was lost to follow-up.
Fig. 11. Schematic figure demonstrating how the non-Hodgkin's lymphoma patient series was collected.
Histological review. Hematoxylin and eosin sections of the original diagnostic specimens were reviewed with knowledge of basic patient data such as age and sex. New sections were made in 30% of the cases because of bad technical quality. Twentyfour cases had to be rejected for the same reasons (Fig. 11). In most cases also periodic acid-Schiff and methyl green pyronine staining were performed.

All sections were independently reviewed by a pathologist (E. Lundgren) and the author. On disagreement, the sections were reexamined until one diagnosis could be agreed upon. In 28 cases there were only bone marrow specimens available, and these cases were excluded from the series (Fig. 11).

Cell types. The criteria posed by Lukes and Collins for description of the different cell types were generally found to be distinct and easy to follow. However, this classification is based on both morphological and functional criteria. In this retrospective study on a clinical, routinely collected material it was therefore necessary to slightly modify the original scheme to adapt it to purely morphologic application (Table 3). The main differences between the modified and original schemes are the following.

The discrimination into B, T and U cell types based on immunocytochemical methods was not possible to make in this retrospective analysis. Thus, a distinction of immunoblastic sarcomas into B and T cell types was impossible. However, as a morphologic indication of B cell origin some of these tumours may have distinct plasmacytoid features (Lukes & Collins 1975). Hence the distinction was made into immunoblastic lymphomas with and without plasmacytoid differentiation.

The distinct clinico-pathologic entity termed "convoluted lymphocytic lymphoma" was first described by Barcos & Lukes (1975). Later, the term "lymphoblastic lymphoma" was proposed for these tumours by Rappaport's group (Nathwani et al 1976). The reasons for the term "lymphoblastic" were the immature appearance of the cells and their close resemblance to cells of acute lymphoblastic leukemia morpho-
logically and clinically. The existence of a clinico-pathologically almost identical group, but without convoluted nuclei, was also pointed out. In another paper, Nathwani et al (1978) reported that the "non-convoluted lymphoblastic lymphomas" seemed to be equivalent with the U cell entity of Lukes-Collins. The entities of Nathwani et al seemed to be morphologically well defined and were adopted in the present study.

True histiocytic lymphomas can only be identified by immunologic methods and not with certainty in histological sections (Lukes & Collins 1975). Hence this entity was not distinguished in the present work. These rare tumours were, if present in this series, probably classified as immunoblastic or large cell FCC lymphoma.

Table 3. Modified Lukes-Collins scheme for morphological classification of non-Hodgkin's lymphoma

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<th>Lymphoblastic</th>
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<tr>
<td>convoluted</td>
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<tr>
<td>non-convoluted</td>
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<tr>
<td>Small lymphocytic (CLL)</td>
<td></td>
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<tr>
<td>Plasmacytoid lymphocytic</td>
<td></td>
</tr>
<tr>
<td>Follicular centre cell types</td>
<td></td>
</tr>
<tr>
<td>small cleaved</td>
<td></td>
</tr>
<tr>
<td>large cleaved</td>
<td></td>
</tr>
<tr>
<td>small non-cleaved</td>
<td></td>
</tr>
<tr>
<td>large non-cleaved</td>
<td></td>
</tr>
<tr>
<td>Immunoblastic sarcoma</td>
<td></td>
</tr>
<tr>
<td>with plasmacytoid differentiation</td>
<td></td>
</tr>
<tr>
<td>without plasmacytoid differentiation</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable</td>
<td></td>
</tr>
</tbody>
</table>


Growth pattern can be recognized as diffuse or nodular. Nodular patterns were, in the present study, subdivided into three degrees based on the relative amount of nodular areas in the specimen. Grade I was recorded when the neoplastic cells were growing in a distinct nodular fashion without, or with only minute, areas with diffuse growth. In grade II there were both nodular and diffuse areas without distinct preponderance for either. Grade III was recorded when the process was predominantly diffuse, but still with discernible nodule formation.

Proliferation was estimated by a simple quantitation of the frequency of mitoses. This frequency was for every specimen recorded in terms of "few" or "numerous", i.e. less or more than one mitosis per three high power (12,5x40) view fields.

Statistical analysis. The statistical significance of differences in the clinical variables, except survival, was tested with the two-tailed proportional test (Colton 1974). For analysis of dependency between different variables the chi-square test was employed (Colton 1974). Survival curves were generated as described by Peto et al (1976, 1977). Differences in survival were tested with the log-rank test (Peto et al 1976, 1977). A p-value less than or equal to 0.05 was considered as significant.
Results

Dissemination (Papers I, III and IV). The tendency to dissemination for the different subgroups was measured in three ways; by recording pretreatment clinical stage (Table 4) and frequency of bone marrow and peripheral blood involvement (Table 5), and by recording relapse rates after therapy of stage I and II disease (Table 6). A great propensity for leukemic spread was found for the small cell lymphomas, especially the small lymphocytic and plasmacytoid lymphocytic subtypes, and for the lymphoblastic lymphomas. A very high relapse rate was found for the small cleaved FCC subgroup. The small cell lymphomas were often in advanced stages on admission. Large cell tumours had a low propensity for bone marrow and peripheral blood involvement, but some of them, notably the immunoblastic lymphomas, were often in stage III or IV at admission. Relapse rates were generally lower for large cell than for small cell lymphomas. The mixed small/large cleaved FCC tumours appeared to have a comparably low tendency for dissemination, with a low frequency of stage III-IV disease, a low rate of bone marrow and peripheral blood involvement, and a relatively low relapse rate after therapy of localized disease.

Systemic symptoms (Paper I). Systemic symptoms were common in the lymphoblastic, immunoblastic and large non-cleaved FCC lymphomas (Table 4), whereas such symptoms were infrequent among patients with the small lymphocytic and plasmacytoid lymphocytic tumours. The small cleaved, mixed small/large cleaved and large cleaved FCC subtypes constituted an intermediate group in this respect.

Proliferation (Paper III). A correlation was found between cell types and frequency of mitoses as measured in terms of "few" or "numerous" (Table 7). The large cell (large cleaved, large non-cleaved and immunoblastic) and lymphoblastic subgroups showed evidence of high proliferative capacity. The small cell types
(small lymphocytic, plasmacytoid lymphocytic and small cleaved) had no, or a low number of cases with "numerous" mitoses. The mixed small/large cleaved subgroup took an intermediate position in this respect.

Table 4. Clinical stage at admission by cell type

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Advanced disease (stage III-IV)</th>
<th>Systemic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/total number of each cell type</td>
<td>Per cent</td>
</tr>
<tr>
<td><strong>FCC type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cleaved</td>
<td>48/84</td>
<td>57</td>
</tr>
<tr>
<td>Mixed small/large cleaved</td>
<td>12/31</td>
<td>39</td>
</tr>
<tr>
<td>Large cleaved</td>
<td>13/42</td>
<td>31</td>
</tr>
<tr>
<td>Large non-cleaved</td>
<td>22/51</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>95/208</td>
<td>46</td>
</tr>
<tr>
<td><strong>Non-FCC type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>35/43</td>
<td>81</td>
</tr>
<tr>
<td>Plasmacytoid lymphocytic</td>
<td>5/7</td>
<td>71</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>15/25</td>
<td>60</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>8/11</td>
<td>73</td>
</tr>
<tr>
<td>Total</td>
<td>63/86</td>
<td>73</td>
</tr>
</tbody>
</table>
Table 5. Bone marrow and peripheral blood involvement by cell type at admission

<table>
<thead>
<tr>
<th></th>
<th>Bone marrow involvement</th>
<th>Peripheral blood involvement</th>
<th>Bone marrow and peripheral blood involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/number evaluable</td>
<td>Per cent</td>
<td>n/number evaluable</td>
</tr>
<tr>
<td><strong>FCC type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cleaved</td>
<td>28/80</td>
<td>35</td>
<td>13/84</td>
</tr>
<tr>
<td>Mixed small/large cleaved</td>
<td>4/27</td>
<td>15</td>
<td>0/29</td>
</tr>
<tr>
<td>Large cleaved</td>
<td>0/38</td>
<td>0</td>
<td>1/42</td>
</tr>
<tr>
<td>Large non-cleaved</td>
<td>4/38</td>
<td>11</td>
<td>1/50</td>
</tr>
<tr>
<td>Total</td>
<td>36/183</td>
<td>20</td>
<td>15/205</td>
</tr>
<tr>
<td><strong>Non-FCC type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>31/40</td>
<td>78</td>
<td>27/43</td>
</tr>
<tr>
<td>Plasmacytoid lymphocytic</td>
<td>5/7</td>
<td>71</td>
<td>4/7</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>1/22</td>
<td>5</td>
<td>0/25</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>5/11</td>
<td>45</td>
<td>3/11</td>
</tr>
<tr>
<td>Total</td>
<td>42/80</td>
<td>53</td>
<td>34/86</td>
</tr>
</tbody>
</table>
Table 6. Relapse rates after therapy of stage I and II disease

<table>
<thead>
<tr>
<th></th>
<th>No. relapses/No. complete remissions</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cleaved</td>
<td>23/33</td>
<td>70</td>
</tr>
<tr>
<td>Mixed small/large cleaved</td>
<td>7/17</td>
<td>41</td>
</tr>
<tr>
<td>Large cleaved</td>
<td>9/19</td>
<td>47</td>
</tr>
<tr>
<td>Large non-cleaved</td>
<td>7/17</td>
<td>41</td>
</tr>
<tr>
<td><strong>Non-FCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small and plasmacytoid lymphocytic</td>
<td>2/9</td>
<td>22</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>3/6</td>
<td>50</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>1/1</td>
<td>100</td>
</tr>
<tr>
<td><strong>Nodular FCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18/37</td>
<td>49</td>
</tr>
<tr>
<td><strong>Diffuse FCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28/49</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 7. Distribution of cases with numerous mitoses (more than 1 per 3 high magnification view fields) by cell type

<table>
<thead>
<tr>
<th></th>
<th>Number with numerous mitoses</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total number within each cell type</td>
<td></td>
</tr>
<tr>
<td>Small cleaved</td>
<td>16/84</td>
<td>19</td>
</tr>
<tr>
<td>Mixed small/large cleaved</td>
<td>22/31</td>
<td>71</td>
</tr>
<tr>
<td>Large cleaved</td>
<td>33/42</td>
<td>79</td>
</tr>
<tr>
<td>Large non-cleaved</td>
<td>42/50</td>
<td>84</td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>0/43</td>
<td>0</td>
</tr>
<tr>
<td>Plasmacytoid lymphocytic</td>
<td>1/7</td>
<td>14</td>
</tr>
<tr>
<td>Immunoblastic</td>
<td>24/25</td>
<td>96</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>9/11</td>
<td>82</td>
</tr>
</tbody>
</table>
Fig. 12. Actuarial survival for patients with favourable prognosis. Within parantheses at the end of the curves the number of patients after 10 years observation time.

Fig. 13. Actuarial survival for patients with unfavourable prognosis.
Survival (Papers I, III and IV). Two main groups were recognized according to cell type. One group, with a relatively favourable prognosis (Fig. 12), corresponded to small or mixed small/large cell morphology (small lymphocytic, plasmacytoid lymphocytic, small cleaved and mixed small/large cleaved cell types). Large cell size (large cleaved, large non-cleaved and immunoblastic), on the other hand, was associated with short survival (Fig. 13). In this group were also the lymphoblastic lymphomas included. In the large cell group, however, there was a small proportion of patients with long-term survival. These patients could probably be considered as cured from the disease.

Growth pattern (Papers II, III and IV). FCC tumours frequently showed a tendency to grow in a nodular manner. A clear correlation was found between cell type and propensity for nodular growth, the small cleaved cell type showing the most pronounced tendency, followed by the mixed small/large cleaved subtype, whereas the large cleaved and large non-cleaved cell types had a rather low propensity for nodular growth. These observations were valid both when regarding the frequency of nodular growth on the whole, and when regarding the degree of nodularity (Table 8).

Table 8. Distribution of pattern by cell type

<table>
<thead>
<tr>
<th></th>
<th>Nodular</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I</td>
<td>Grade II</td>
<td>Grade III</td>
<td>Diffuse</td>
<td>Total</td>
</tr>
<tr>
<td>Small cleaved</td>
<td>5</td>
<td>20</td>
<td>22</td>
<td>37</td>
<td>84</td>
</tr>
<tr>
<td>Mixed small/ large cleaved</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Large cleaved</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>Large non-cleaved</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>26</td>
<td>45</td>
<td>130</td>
<td>208</td>
</tr>
</tbody>
</table>
Survival was correlated with growth pattern, patients with nodular FCC tumours having significantly longer survival than those with corresponding diffuse FCC tumours. The difference was valid even when analysing the different cell types separately (Table 9), but proved to be statistically significant only within the group of small cleaved FCC lymphomas. There was also a correlation between degree of nodularity and prognosis, grade I being associated with the most favourable survival, and grade III with the most unfavourable (Fig. 14). Statistical significance was found when testing the difference between grade II and III, and between grade III and diffusely growing tumours.

Systemic symptoms and involvement of Waldeyer's ring were more frequent among diffuse lymphomas than among their nodular counterparts. Bone marrow involvement was more common among nodular FCC tumours. The distribution of nodular versus diffuse FCC neoplasms did not differ with respect to age, sex, and clinical stage at admission. Relapse rates after therapy of localized disease were approximately the same for nodular and diffuse lymphomas (Table 6), but both relapse-free survival and survival were significantly more favourable for patients with nodular lesions.
Fig. 14. Actuarial survival for patients with tumours of different degrees of nodularity.

Summary of results. The results are summarized in Table 10. Four main groups were recognized regarding cell type. These groups were differing according to systemic symptoms, dissemination, proliferation and survival.

Nodular growth pattern can be recognized in FCC tumours, particularly the small cleaved and mixed small/large cleaved subtypes. When present, it was a strong indicator of a better prognosis than if the same cells were growing diffusely.

Lukes & Collins (1974a) proposed a scheme for lymphoid cell development based on their experience on camera lucida studies of normal
lymphocyte transformation after antigenic or mitogenic stimulation. It is apparent that the different morphologic expressions of lymphoid cells are accompanied, normally and in neoplasia, by certain biologic properties. For B cell neoplasms these properties may be summarized as in Fig. 15.

Table 10. Summary of results

<table>
<thead>
<tr>
<th></th>
<th>Small cell</th>
<th>Mixed small/large cleaved cell</th>
<th>Large cell</th>
<th>Lymphoblastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic symptoms</td>
<td>Seldom</td>
<td>Seldom</td>
<td>Frequently</td>
<td>Frequently</td>
</tr>
<tr>
<td>Dissemination</td>
<td>Leukemic</td>
<td>Metastatic</td>
<td>Metastatic</td>
<td>Leukemic</td>
</tr>
<tr>
<td>Proliferation rate</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Survival</td>
<td>Long</td>
<td>Long</td>
<td>Short</td>
<td>Short</td>
</tr>
</tbody>
</table>
Fig. 15. Summarizing scheme on the relation between cell morphology and important biologic features in B-cell non-Hodgkin's lymphoma.
GENERAL DISCUSSION

A simplified view on non-Hodgkin’s lymphoma
Thirty years ago Videbaek (1949) wrote an article entitled "Do malignant lymphomas represent varying differentiation of the same growth?". The intervening years have seen many classifications and changing concepts concerning the non-Hodgkin’s lymphomas. Today, in the era of modern experimental immunology and cell research, the time seems to have come to return to the concept proposed by Videbaek, which was largely based on simple clinical observations.

Today we regard the malignant lymphomas as neoplasms of the immune system with origin in a neoplastically transformed lymphocyte. A simplified cellular scheme based on knowledge of development of cells in different compartments of the immune system has been proposed by Lennert (1978). A similar, but not identical view will be presented here (Fig. 16).

Lukes & Collins (1975) proposed that lymphomas composed of cells neither with B nor T markers should be referred to as U cells lymphomas. These cells may represent immature lymphocytes, neoplastically transformed at a stage where the cells have not developed B or T cell markers. This view fits well with the fact that the majority of cases with childhood ALL lack detectable surface markers (Tsukimoto et al 1976). They possess, however, an enzyme, terminal deoxynucleotidyl transferase (TdT), which seems to be a marker for immature T cells, as it is detected in large amounts in human thymocytes, but not in peripheral T cells (McCaffrey et al 1975). Lymphoblastic lymphoma cells are morphologically, immunologically, cytochemically and clinically very similar to lymphoblasts of ALL (Kaplan et al 1974, Kersey et al 1974, Barcos & Lukes 1975, Sen & Borella 1975, Coccia et al 1976, Jaffe et al 1976, Nathwani et al 1976, Stein et al 1976, Tsukimoto et al 1976, Donlon et al 1977, Dow et al 1977, Jaffe & Berard 1978, Rosen et al 1978, Weinstein et al 1979). The convoluted
Fig. 16. A proposal for a simplified scheme of the non-Hodgkin's lymphomas based on morphogenesis and functional properties of the origin cells.
variety is often of T cell type (Barcos & Lukes 1975, Stein et al 1976, Rosen et al 1978). In a series studied by Koziner et al (1977) the majority of non-convoluted lymphoblastic lymphomas were of the U cell type, but some had T cell markers. Both the convoluted and non-convoluted varieties have a predilection to be located in mediastinum (Nathwani et al 1976) and have thus been associated to thymus.

The place of Burkitt's lymphoma in this scheme represents a problem. It has been demonstrated that Burkitt's lymphoma cells express B cell characteristics (Fialkow et al 1973). Lukes & Collins (1975) have suggested that Burkitt's tumour is of FCC type (small non-cleaved). This hypothesis has support in the observation that foci of Burkitt's lymphoma cells were often confined to germinal centres in lymph nodes and Peyer's patches (Mann et al 1976). However, from a clinical standpoint Burkitt's tumour is a distinct entity, clearly separated from other lymphomas of FCC type. It cannot be excluded that Burkitt's lymphoma may be a tumour from "virgin" B lymphocytes, a hypothesis that does not exclude the possibility that the tumour cells sometimes may express functional characteristics of FCC cells. This view is, however, not confirmed immunochemically or in any other way. It seems realistic to place Burkitt's lymphoma separately in a scheme of non-Hodgkin's lymphomas until one or another hypothesis is confirmed.

The further stages in the transformation process represent the neoplasms that comprise the majority of non-Hodgkin's lymphomas, i.e. all FCC types, B-immunoblastic, small lymphocytic (B-CLL), plasmacytoid lymphocytic and plasmocytoma subclasses among B cell types; mycosis fungoides, T-immunoblastic and T-CLL along the T cell lineage.

Some ideas concerning pathogenesis

An antigenic stimulation of a committed small lymphocyte implies a transformation into large, cycling cells, which expand the clone of immunologically active cells and memory cells (Fig. 17). When the stimulus has faded and the proliferation stops, it leaves an expanded clone of circulating memory cells that have the potential to become re-stimulated on a new antigenic challenge.
Small lymphocytes have the physiological function to circulate, and it has been demonstrated that the recirculation from blood into lymphoid tissue and back to the blood has a cycle time which is measured in hours (Ford & Gowans 1969). The average life span of non-dividing small lymphocytes is several weeks. Thus each small lymphocyte may be exchanged between the blood and lymphoid tissue many times during its lifetime.

Salmon & Seligmann (1974) proposed that lymphoid neoplasms were generated by an "oncogenic event" occurring in a population of antigenically stimulated lymphocytes. The oncogenic event produced maturation arrest and allowed clonal expansion of the affected B cells. This evolution seems to be promoted by deficiencies in T cell function (Krüger 1971, Gershwin & Steinberg 1973, Louie & Schwartz 1978,
This idea is consistent with the well established fact that most lymphoid tumours are monoclonal, i.e. derived from a single malignant cell, which has been demonstrated by studies on Ig on or in the tumour cells (Mårtensson 1963, Preud'homme & Seligmann 1972, Levy et al 1977) and on certain enzymes in tumour cells from women heterozygous for X-linked isoenzymes (Friedman & Fialkow 1976).

As Taylor (1978) recently pointed out, a malignant lymphoma can be regarded as monoclonal, but polymorphous, implying that the process develops from a small lymphocyte, but the expressions of different morphologic features depend on growth kinetics in the tumour cell population. In other words, large cell morphology is an expression of high proliferative rate (cells in cycle stages G₂ and M), whether small cells are equivalent to non-proliferating cells (G₀ or G₁). This view is well consistent with findings in kinetic studies on malignant lymphomas (Cooper et al 1968, Peckham & Cooper 1970, Peckham & Steel 1972, Fried et al 1976, Huber et al 1977, Sandritter & Grimm 1977, Silvestrini et al 1977, Braylan et al 1978, Meyer & Higa 1979, Shackney & Skramstad 1979).

Thus, a lymphoid tumour may be regarded as a monoclonal process with varying cellular expressions. The clinical and pathological features of the tumour are direct functions of the proportion of cells in different compartments (Fig. 17). When composed of large, actively dividing cells, the neoplasm becomes clinically evident as a large cell lymphoma, frequently accompanied by an aggressive behaviour and a rapid natural course. On the other hand, when composed of small, "memory" or functionally active cells, it attains the well known appearance of chronic lymphocytic leukemia or small cell lymphoma. The characteristic features of these neoplasms are their widespread, diffuse dissemination, which is well consistent with the properties of the normal counterparts of these cells.
This concept is applicable to neoplasms of the B or T cell lineages (Fig. 18). It can also be applied to different classifications, e.g. the schemes of Rappaport and Lukes-Collins in Fig. 18. Burkitt's tumour and lymphoblastic lymphoma have been omitted from the scheme, since the places for these tumours are not yet fully determined (vide supra).

Clinical implications


Thus, it appears to be firmly established that both pattern and cell type are of relevance for prognosis in malignant lymphoma. Which one of the two factors that is most important seems to be an unsolved question and a matter of controversy. The extremes in this controversy may be examplified by the opinions posed by Nathwani and Lukes, respectively.

Nathwani (personal communication) claims that, since pattern recognition is perhaps the only reproducible morphologic feature, it constitutes an overriding concern that compels us to separate non-Hodgkin's lymphomas on the basis of pattern into nodular and diffuse. On the other hand, Lukes (1977) claimed that pattern is secondary to cell type, and of no primary prognostic significance.
Fig. 18. Non-Hodgkin's lymphomas subdivided according to predominant cell type. For further explanation see text.
In the present investigation (paper II) it was demonstrated that pattern is strongly correlated with cell type. However, even within the same cell type, nodular lesions were associated with better survival than their diffuse counterparts. These results could thus be regarded as a compromise between the opinions of Nathwani and Lukes, strongly supporting the view that both pattern and cell type must be considered in a classification.

However, since cell type governs pattern, and not the opposite, the cell type should, for logical reasons, be considered as primary, and thus should the main division of entities in a classification of non-Hodgkin's lymphoma be made according to this factor. In the following discussion the main subdivision will be made according to cell type.

Favourable cell type. When regarding lymphomas with a relatively favourable prognosis (small cell) there seems to be a relatively slow, but constant slope of the survival curve. Relapses occur rather randomly with time, and virtually all patients get a relapse sooner or later, or have a slowly progressing disease that ultimately proves fatal (Stein et al 1974, Schein et al 1975a, Rudders et al 1979, Rosenberg 1979). Extensive staging procedures from several institutions have also established that a majority of these patients have widespread disease at the time of initial presentation (Jones et al 1972a, Goffinet et al 1973, Kim & Dorfman 1974, Chabner et al 1975, 1976, 1977, Johnson et al 1975, Rosenberg et al 1975, Stein et al 1976, Castellani et al 1977, Coller et al 1977, Menon & Buchanan 1979, Ribas-Mundo & Rosenberg 1979). This observation has further support in the known high frequency of systemic relapse following radiotherapy for apparently localized disease (Jones et al 1973b, Fuks et al 1975). In addition, recent reports have described a high incidence of previously unsuspected monoclonal B lymphocytes in peripheral blood of lymphoma patients with tumours of favourable histology, thought to have no abnormal blood cells according to standard morphologic techniques (Ault 1979,

Histologically, there is often in these tumours areas or clusters of large, dividing cells (Lukes & Collins 1975, Lennert 1976, Rausing 1976). The majority of cells are, however, of small cell type. This cell appears to have the retained physiological function of circulation through the body. Therefore it is reasonable to assume that these tumours are often widely disseminated even early in the clinical course. It might also be reasonable to suspect that the dissemination, i.e. the true stage of disease cannot be fully mapped out, even with extensive staging procedures.

Although these malignancies are often very sensitive to treatment, it seems realistic to assume that not every neoplastic cell throughout the body can be eradicated by therapeutic means, which may be the explanation for late relapses in this group of tumours. An alternative explanation for late relapses may be a renewed neoplastic transformation of small cells remaining after therapy. Thereby the neoplastic stimulus, whatever it may be, reactivates the process and promotes a clinically apparent relapse. This explanation is consistent with the hypothesis recently proposed by Habeshaw (1979), that non-Hodgkin's lymphomas have many features of an abnormal immune response to some as yet undefined, chronic or repeated antigenic stimulation.

It has been reported that patients with malignant lymphoma occasionally have two different histologic types occurring simultaneously in different sites (Kim & Dorfman 1974). It is also well established that during the course of a lymphoma with favourable histology, a
"transformation" into a more aggressive process can take place (Richter 1928, Gall & Mallory 1942, Jackson & Parker 1947, Custer & Berhard 1948, Symmers 1948, Rappaport et al 1956, Dorfman 1973, Long & Aisenberg 1975, Spiro et al 1975, Jones et al 1978, Cullen et al 1979, Risdall et al 1979). This change is typically accompanied by a shift from nodular to diffuse pattern, or from small cell to large cell morphology. The reason for the change is unknown, but there is strong evidence supporting the view that the second, more aggressive process represents an evolution of the same clone as the initial, more "benign" process (Woda & Knowles II, 1979).

The clinician's conclusion concerning lymphomas with "favourable" histology leads, curiously enough, to a state of despair. With conventional methods of treatment we seem to have little chance to cure the patient from the disease. Further research, cell biological and clinical, is urgently needed. Since the process is always, or nearly always, generalized at admission, it appears to be of minor importance to perform extensive staging procedures (Lenner 1980). Neither should the treatment, with methods that are available today, be aggressive, since the outlook for cure seems to be absent or very minute in the long perspective (Rosenberg 1979), and hazards with extensive treatment must be weighed against the potential advantage of the therapy.

Unfavourable cell type. This group includes large cell (large cleaved, large non-cleaved, immunoblastic), lymphoblastic, and Burkitt's lymphomas. The clinical management of the two last mentioned entities is beyond the scope for this presentation. The following discussion will thereby refer to only the large cell lymphomas. These tumours demonstrate a survival curve with an initial rapid slope, but with a fraction of patients with long term survival. These patients are probably cured from the disease (DeVita et al 1975, Coltman et al 1977, McKelvey 1978). As demonstrated in several studies (Luce et al 1973, Schein et al 1974, 1975b, 1976b, Berd et al 1975, DeVita et al 1975, Durant et al 1975,

The large cell lymphomas can to a large extent be compared with other solid tumours. They have the same type of survival pattern. They are often sensitive to treatment and are potentially curable. Since they hypothetically are lacking small, diffusely disseminating cells, they have no propensity for leukemic spread throughout the organism. They have, however, obviously the capability to disseminate, but the mechanism seems to be in accordance with other solid tumours, i.e. by metastasis.

The clinician's conclusion concerning these "unfavourable", often fulminant tumours must, after all, be somewhat optimistic, implying an aggressive approach, with the decisive aim of curing the patient from the disease.

Mixed small/large cleaved cell type. These tumours had, in the present series, a smaller tendency to disseminate than the small cell lymphomas (paper I), and a more favourable survival than large cell lymphomas (paper I and IV). Thus, they should probably be treated separately in the clinical management. This group was, however, in the present series rather small, and before any firm conclusions are drawn the results should be confirmed in a larger patient series.

Proposal for a clinically useful classification of non-Hodgkin's lymphoma.

The present investigation was intended as an attempt to contribute to the resolution of some unsolved questions in a field of oncology and pathology that is regarded as controversial. It is sincerely hoped that the work will not add to current controversies. The
The proposed classification should be regarded as a modification of a current one (Lukes-Collins), elaborated from a clinical and morphologic point of view, with the purpose to be of potential value for those who diagnose and treat patients with non-Hodgkin's lymphoma. The proposed classification appears in Table 11.

Table 11. Proposed morphological classification of non-Hodgkin's lymphoma

<table>
<thead>
<tr>
<th>Favourable cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small lymphocytic (may have plasmacytoid differentiation)</td>
</tr>
<tr>
<td>Small cleaved FCC</td>
</tr>
<tr>
<td>Mixed small/large cleaved FCC</td>
</tr>
<tr>
<td>Mycosis fungoides and Sézary's syndrome</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unfavourable cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large cleaved FCC</td>
</tr>
<tr>
<td>Large non-cleaved FCC</td>
</tr>
<tr>
<td>Immunoblastic (may have plasmacytoid differentiation)</td>
</tr>
<tr>
<td>Burkitt's tumour</td>
</tr>
<tr>
<td>Lymphoblastic (convoluted or non-convoluted)</td>
</tr>
</tbody>
</table>

Unclassifiable

* Nodularity may be subdivided in three degrees.
GENERAL SUMMARY AND CONCLUSION

Non-Hodgkin's lymphomas are neoplasms originating from the immune system. Recent progress in knowledge about the immune system and its functions has led to new classifications of the non-Hodgkin's lymphomas. One of the new classifications (Lukes-Collins) has been applied to a retrospective patient series. This classification is based on both morphologic and functional characteristics and had to be somewhat modified since the present investigation was based on pure morphology.

The patient series comprised 302 patients with histologically proven non-Hodgkin's lymphoma. Data on clinical and histological variables were collected and analysed for correlations and interrelations. With the Lukes-Collins classification as a base, the material could be subdivided into groups with distinct clinical features.

Small cell morphology implied a considerable tendency to dissemination of a diffuse, or leukemic, character, but nevertheless a relatively favourable prognosis. Systemic symptoms were rare and these tumours showed little evidence of proliferation.

Mixed small/large cleaved cell morphology was associated with a favourable survival curve, a relatively small propensity for dissemination, and a low frequency of systemic symptoms. This group was intermediate in terms of proliferation.

Large cell morphology was accompanied by aggressive clinical behaviour with short survival, a pronounced tendency to (non-leukemic) dissemination, a high frequency of systemic symptoms, and a high proliferative capacity.
Lymphoblastic morphology implied strongly an unfavourable clinical course, with short survival, a strong propensity for leukemic spread, frequently systemic symptoms, and evidence for pronounced proliferative capacity.

Growth pattern was shown to be of great importance, since a nodular pattern was associated with a more favourable prognosis than if the same cells were growing diffusely.

The further theoretic and clinical implications of the findings were discussed. A proposal for a simplified view on the non-Hodgkin's lymphomas, based on modern concepts of the immune system, was set forth. General conclusions concerning clinical management were discussed on the basis of the findings.

Conclusion
The present work has demonstrated that the Lukes-Collins classification of non-Hodgkin's lymphoma is, somewhat modified, well applicable to morphologic classification, as used in an ordinary histopathologic laboratory. The classification has well defined disease entities with descriptive names, and it gives significant information about clinical behaviour and course. It is based on current state of knowledge about the cells of origin. The classification has the potential to be the basis for a deeper biologic understanding of these disorders. It is strongly believed that this, or some equivalent, classification, combined with the distinction into nodular versus diffuse pattern, will form the morphologic basis for clinical management of patients with non-Hodgkin's lymphoma in the future.
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