Lymphoproliferations in the bone marrow: identification and evolution; classification and staging

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SUMMARY Bone marrow biopsies from 3229 patients with lymphoproliferative disorders and 1156 patients with benign or reactive lymphoproliferations were investigated and criteria for distinguishing between them are given. Bone marrow involvement was found in 89% of multiple myeloma, 64% of non-Hodgkin’s lymphomas and 8% of Hodgkin’s disease. According to the predominant proliferative cell type there were five major entities in multiple myeloma and non-Hodgkin’s lymphomas: (1) plasmacytic; (2) lymphocytic; (3) hairy cell; (4) immunocytic; (5) centrocytic. These were further classified into distinct subtypes each of which had independent prognostic significance. The mode of spread of the lymphoproliferative disorders in the bone marrow showed one of six architectural patterns, which together with the quantity of infiltration in the biopsy (reflecting the tumour cell burden) had significant predictive value. These results demonstrate the value of bone marrow biopsies in the identification, classification and staging of lymphoproliferative disorders, as well as in monitoring the course of disease and the response to therapy.

It is over a decade since the value of bone marrow biopsies in the staging of non-Hodgkin’s lymphomas has been recognised.1 They are now taken routinely in the initial investigation of patients with non-Hodgkin’s lymphomas to estimate the progression of disease at time of presentation (staging) and to type the mode of proliferation (growth pattern) in the bone marrow.2–8 A bone marrow biopsy may be diagnostic in patients without peripheral lymphadenopathy,8 and may aid classification when inconclusive or divergent histologies are found at other sites. A bone marrow biopsy also provides information on the extent of tumour cell burden (volume percentage) and on the function and response to therapy of the residual marrow and of the neoplasia. A bone marrow biopsy thus offers insight into the biological behaviour of the disease process in the individual patient. The aim of this study was to provide a comprehensive survey of lymphoproliferations in the bone marrow based on a retrospective and prospective analysis of bone marrow biopsies in 4385 cases.

Patients and methods

Initial pretreatment bone marrow biopsies were taken (after informed consent had been obtained) from 3213 patients diagnosed by the established criteria on lymph node biopsies as suffering from one of the lymphoproliferative disorders and from 512 patients during follow-up periods of one to 10 years. In 270 patients the diagnosis of non-Hodgkin’s lymphoma (subsequently confirmed) was first made by bone marrow biopsy. In addition, 1156 biopsies from patients with reactive plasmacytosis, benign monoclonal gammopathies, benign lymphoid nodules, reactive lymphocytosis and non-specific granulomas, were also evaluated. Normal bone and bone marrow values were obtained from 160 biopsies of individuals without evidence of disease taken.

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during investigation for other conditions. All biopsies were obtained under local anaesthesia from the iliac crest, fixed, dehydrated, and embedded in methacrylate without decalcification, cut and stained as previously described.\textsuperscript{10-12} In 186 cases immunohistological reactions (FITC and PAP) were performed on fresh frozen cryostat sections of one half of the longitudinally cut biopsy core.\textsuperscript{13-15} The histological and morphometric variables investigated in 2186 biopsies were used for multivariate data analysis by selected BMDP programs.\textsuperscript{16}

Results

RECOGNITION AND EVOLUTION OF LYMPHOPROLIFERATIONS IN THE BONE MARROW

The overall division of the biopsies into the different entities is shown in Table 1; the different types of lymphoid tumour evolution in the bone marrow are summarised in Fig. 1.

Plasmacytosis and multiple myeloma

To provide criteria for distinguishing between reactive and neoplastic plasmacytosis, bone marrow biopsies of the following clinical groups were analysed: patients with chronic inflammatory diseases (group RP, 210 cases), patients with benign monoclonal gammopathy (group BMG, 164 cases), and patients with early multiple myeloma (group EMM, 69 cases). In all three groups plasma cells, singly or in twos and threes, were located around capillaries (Fig. 2a) or loosely dispersed among haematopoietic and fat cells. In addition group EMM exhibited small, tight clusters of plasma cells in paratrabecular and periarterial regions which were not seen in groups RP and BMG (Fig. 2c). The histological growth pattern thus proved the most reliable characteristic for distinguishing reactive from malignant plasmacytosis. Only very early (albeit rare) cases of multiple myeloma required immunohistology for the identification (Fig. 2b). With progression of disease

<table>
<thead>
<tr>
<th>Lymphoproliferations</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign</strong></td>
<td></td>
</tr>
<tr>
<td>Reactive plasmacytosis</td>
<td>210</td>
</tr>
<tr>
<td>Benign monoclonal gammopathy</td>
<td>164</td>
</tr>
<tr>
<td>Reactive lymphocytosis</td>
<td>110</td>
</tr>
<tr>
<td>Benign lymphoid nodules</td>
<td>566</td>
</tr>
<tr>
<td>Reactive granulomas</td>
<td>106</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>813</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphomas</td>
<td>1351</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>1011</td>
</tr>
<tr>
<td>Angioimmunoblastic lymphadenopathy</td>
<td>54</td>
</tr>
</tbody>
</table>

Table 1  Lymphoproliferations

Fig. 1  Tumour evolution of lymphoproliferative disorders in the bone marrow.
the small plasma cell aggregates expanded to form nodules, "multiple myelomas", both inter- and paratrabecular with a tendency to confluence into densely packed masses (myelomatous pattern) which progressed eventually to the "packed marrow" with virtual replacement of haematopoietic...
and fat tissues and accompanied by osteoporotic-osteolytic bone lesions (Fig. 2e, f). Only four cases showed osteosclerotic bone lesions (Fig. 2d). The activity of the bone cells, particularly osteoclasts, correlated with the plasma cell burden (Fig. 3). There was also a statistically significant correlation between the volume ratio of fat/haematopoiesis and the plasma cell mass in the pre- and post-treatment biopsies (Fig. 4). Cytotoxic therapy reduced but did not eradicate the myeloma, as residual cells were always present in sequential biopsies of 112 treated patients (Fig. 4).

**Lymphocytosis, benign lymphoid nodules, and malignant lymphomas**

Lymphocytes normally may comprise up to 20–25% of the population of nucleated cells in the bone marrow, itself an organ of lymphopoiesis. Increases may occur either absolute, or relative due to reduction in haematopoietic elements. The distinction of these cases from early lymphocytic lymphomas with interstitial spread may not be possible by histology alone. Benign lymphoid nodules, found in 8% of 7080 bone marrow biopsies investigated, occur more frequently in the older age groups (36% in patients over 70 yr). They are classified into four types according to Hashimoto et al.\(^\text{17}\): type A = nodules with germinal centres 5%; type B = sharply demarcated nodules 30%; type C = well defined nodules 45%; type D = small aggregates of lymphocytes 22%. The size of the nodules varies from 0-1 to 2 mm (average 0-4 mm). They consist of small lymphocytes, some plasma cells and occasional histiocytes and capillaries within a reticular fibre network. Though usually single, multiple nodules occur in a quarter of the cases; and the question of recognition as benign or malignant arose when they were large and/or numerous. In these cases immunohistology was required and of 14 such cases investigated, six revealed a monoclonal cell population indicating non-Hodgkin's lymphoma immunocytic and the other eight cases were polyclonal (reactive lesions). All other bone marrows of patients with non-Hodgkin's lymphoma low grade malignancy were not equivocal and six bone marrow patterns were observed at presentation: nodular (151 cases), interstitial/nodular (466 cases), interstitial (359 cases), paratrabecular (39 cases), patchy/focal (165 cases), and packed marrow (455 cases) (Table 2, Fig. 5). In the first type, the nodules expanded as the disease progressed to form multinodular areas. In the interstitial type the lymphocytes, loosely dispersed among the haematopoietic and fat cells and around the blood vessels, may not initially be evident on low power examination. Subsequently they form a dense homogeneous infiltration, the packed marrow pattern. Infiltrates which initially appeared as paratrabecular foci extended to envelop the cancellous bone and inwards to replace the

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**Fig. 3** Correlation between myeloma cell mass and osseous remodelling in the bone marrow (pretreatment patients). Osteoclastic index (OC) = number of osteoclasts per 100 mm trabecular circumference. Osteoblastic index (OB) = percentage of trabecular circumference covered by cuboidal osteoblasts.

**Fig. 4** Quantitative evaluation of sequential biopsies in a patient with multiple myeloma (68 years old, male, IgD lambda, Bence-Jones negative).
Lymphoproliferations in the bone marrow: identification and evolution, classification and staging

Table 2  Growth patterns of lymphoproliferative disorders in the bone marrow (at time of initial diagnosis)

<table>
<thead>
<tr>
<th>Growth patterns</th>
<th>Median survivals* (months)</th>
<th>MM</th>
<th>CLL</th>
<th>HCL</th>
<th>IC</th>
<th>CC</th>
<th>CB/CC</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular</td>
<td></td>
<td>58</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>n = 151, 9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial/nodular</td>
<td></td>
<td>28</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>n = 466, 29%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial</td>
<td></td>
<td>23</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>n = 359, 22%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paratrabecular</td>
<td></td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>n = 39, 2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patchy focal</td>
<td></td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>n = 165, 10%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed marrow</td>
<td></td>
<td>16</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>n = 455, 28%</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*From time of biopsy to death or date of last contact.

MM = multiple myeloma
CLL = chronic lymphocytic leukaemia
HCL = hairy cell leukaemia
IC = immunocytoma
CC = centrocytic lymphoma
CB/CC = centroblastic/centrocytic lymphoma
HD = Hodgkin’s disease

haematopoietic and fat tissues and thus eventually also presented a packed marrow. Finally the patchy growth pattern with a tendency to confluence also showed a packed marrow in the later stages. At presentation of patients with non-Hodgkin’s lymphoma high grade malignancy only the focal (sarcomatous)
Fig. 5 Growth patterns of non-Hodgkin's lymphomas in the bone marrow. Gomori ×10. (a) nodular pattern in immunocytic lymphoma, (b) interstitial/nodular pattern in immunocytic lymphoma, (c) interstitial pattern in chronic lymphocytic leukaemia, (d) paratrabeular pattern in centrocytic lymphoma, (e) patchy/focal pattern in hairy cell leukaemia, and (f) packed marrow pattern in non-Hodgkin's lymphoma high grade malignancy.
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Granulomas and Hodgkin's disease: (a) large noncaseating epithelioid-cell granuloma with giant cells in a patient with Hodgkin's disease, nodular sclerosis, stage II. Gomori ×100; (b) small focus (arrow) of Hodgkin's disease in the bone marrow. Gomori ×40; (c) Hodgkin's disease with complete replacement of the bone marrow and osteoclastic osseous reaction (arrow). Gomori ×40; (d) osteoclastic resorption of a trabecula surrounded by lymphogranulomatous tissue. Gomori ×250.

Granulomas and Hodgkin's disease
Granulomas were encountered in 106 cases (4% of 2650 biopsies investigated). Single or multiple, they ranged in size from small to large (0.1 to 2.3 mm) usually with but occasionally without multinucleated giant cells, and consisted of epithelioid cells, histiocytes, small vessels, reticulin fibres, and variable numbers of lymphocytes as well as occasional macrophages and eosinophils (Fig. 6a). When large, the distinction between such non-specific granulomas, angioimmunoblastic lymphadenopathy, malignant histiocytosis, systemic mastocytosis and Hodgkin's disease in the bone marrow may not be possible on histology alone. Nevertheless for the initial diagnosis of Hodgkin's disease, Reed-Sternberg cells within a characteristic stromal environment are mandatory, while the presence of mononuclear Hodgkin cells within such a setting suffices for confirmation of bone marrow involvement, when Hodgkin's disease is already documented elsewhere (Ann Arbor). Minimal lesions of Hodgkin's disease were small, usually paratrabeicular foci with Hodgkin or Reed-Sternberg cells (Fig. 6b). Large intertrabecular areas of lymphogranulomatous tissue

Fig. 6 Granulomas and Hodgkin's disease: (a) large noncaseating epithelioid-cell granuloma with giant cells in a patient with Hodgkin's disease, nodular sclerosis, stage II. Gomori ×100; (b) small focus (arrow) of Hodgkin's disease in the bone marrow. Gomori ×40; (c) Hodgkin's disease with complete replacement of the bone marrow and osteoclastic osseous reaction (arrow). Gomori ×40; (d) osteoclastic resorption of a trabecula surrounded by lymphogranulomatous tissue. Gomori ×250.
were observed in 51% and complete infiltration of the marrow in 31% of involved biopsies (Fig. 6c). There were variations in fibrosis, vasculature and cellular composition of the involved marrow both in the same biopsy and from patient to patient. The structure of the trabeculae was normal when the lesions were small, but varied from osteosclerotic to osteoporotic/osteolytic when the foci were large and confluent. Osseous remodelling showed primarily osteoblastic activity including primitive bone production in oedematous, hypocellular spaces, and marked osteoclastic resorption in hypercellular lymphogranulomatous areas, rich in Hodgkin and Reed-Sternberg cells (Fig. 6d).

CLASSIFICATION AND STAGING OF LYMPHOPROLIFERATIVE DISORDERS IN THE BONE MARROW

The criteria of the Kiel classification for lymph node histology were applied and the overall distribution of the patients with bone marrow involvement is given in Table 3. There were five major entities according to the predominant proliferative cell type: (1) plasmacytic; (2) lymphocytic; (3) hairy cell; (4) immunocytic; (5) centrocytic. Each of these was further subclassified on the basis of bone marrow histology and cytological features, and the results are shown in Tables 4, 5 and Figures 7–10. The amount of infiltration in the biopsy, that is the tumour cell burden (volume percentage), was estimated in the initial bone marrow biopsy of all untreated patients. Three cut off points were utilised: less than 20 vol % of the bone marrow biopsy area occupied by the infiltration, 20–50 vol %, and more than 50 vol % as shown in Table 6.

Multiple myeloma
Multiple myeloma in the bone marrow was divided into two broad groups: (1) plasmacytic, primarily mature plasma cells, and (2) plasmablastic, mainly immature cells (Fig. 7, Table 4).

(1) Plasmacytic
A spectrum of plasma cells was usually present in any one biopsy. These were subdivided into three types. Type 1: mature Marschalko type plasma cells, indistinguishable from normals, with excentric cartwheel nuclei, perinuclear hof and basophilic cytoplasm; few had nucleoli. Type 2: mainly round or notched small (lymphoplasmacytoid) type plasma cells with little cytoplasm. Type 3: a polymorphous population consisting of types 1 and 2. All infiltrations had a fine reticulin network, and the residual marrow showed an increase in fat cells, reduction in haematopoiesis and maturation arrest of erythropoiesis. Increased remodelling of the cancellous bone was almost invariably present. Disease progression was accompanied by anaemia, infections and bone-related problems. The frequency of a leukaemic blood picture (plasma cell leukaemia) was highest in patients with type 2 and this had an unfavourable prognosis. The prognostic value of the initial plasma cell burden is shown in Table 6.

(2) Plasmablastic
The infiltration consisted of large, polymorphic, often multinuclear plasma cells with prominent central nucleoli, moderate to large amounts of cytoplasm and frequent mitotic figures. Dispersed among them were mature plasma cells, lymphocytes and immunoblasts. As the most frequent growth pattern was the packed marrow type, fat and haematopoiesis were scant. Increased osseous remodelling especially pronounced osteoclastic activity was frequent. The patients showed a rapid downhill course (Table 4), aggravated by hyper-

| Table 3 Frequency of bone marrow involvement in lymphoproliferative disorders (at time of initial diagnosis) |
|-------------------------------------------|----------------|----------------|
| **Histological group** | **Patients** | **Positive biopsies (%)** |
| **Multiple myeloma** | 813 | 89 |
| Plasmacytic | 546 | 94 |
| Plasmablastic | 267 | 79 |
| **Non-Hodgkin’s lymphomas** | | |
| Lymphocytic | 1351 | 64 |
| Hairy cell | 286 | 99 |
| Immunocytic | 152 | 95 |
| Centrocytic | 253 | 85 |
| Centroblastic/cytic | 92 | 71 |
| "Blastic" (sarcomatous) | 260 | 20 |
| Unclassifiable | 272 | 25 |
| **Hodgkin’s disease** | | |
| Nodular sclerosis | 1011 | 3 |
| Lymphocyte predominance | 363 | 6 |
| Mixed cellularity | 154 | 9 |
| Lymphocyte depletion | 346 | 22 |

*Diagnosed only by lymph node histology.*
Table 4  Classification of lymphoproliferative disorders by bone marrow histology (at time of initial diagnosis)

<table>
<thead>
<tr>
<th>Histological groups</th>
<th>Predominant cell type</th>
<th>Patients, % in each group</th>
<th>Median survival* (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmacytic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmacytic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marschalko</td>
<td>(1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, round</td>
<td>(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, notched</td>
<td>(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorphous</td>
<td>(1-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmablastic</td>
<td>(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, round</td>
<td>(1)</td>
<td></td>
<td></td>
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<tr>
<td>Small, notched</td>
<td>(2)</td>
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<td>Large</td>
<td>(3)</td>
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</tr>
<tr>
<td>Prolymphocytic</td>
<td>(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>(5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hairy cell</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hairy cell</td>
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<tr>
<td>Ovoid</td>
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<td>Indented</td>
<td>(3)</td>
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</tr>
<tr>
<td>Immunocytic</td>
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<td></td>
</tr>
<tr>
<td>Immunocytic</td>
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<td>Lymphoplasmacytic</td>
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</tr>
<tr>
<td>Immunoblastic</td>
<td>(4)</td>
<td></td>
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<tr>
<td>Centrocytic</td>
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<td></td>
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</tr>
<tr>
<td>Large, cleaved</td>
<td>(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorphous</td>
<td>(1-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centroblastic/cytic</td>
<td>(3, 1)</td>
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<tr>
<td>Centroblastic</td>
<td>(3)</td>
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</tr>
<tr>
<td>HD, low content of lymphocytes</td>
<td>(3, 4, 2, 1)</td>
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<td></td>
</tr>
<tr>
<td>HD, high content of lymphocytes</td>
<td>(1, 2, 3, 4)</td>
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<td></td>
</tr>
<tr>
<td>HD, high content of epithelioid cells</td>
<td>(2, 1, 3, 4)</td>
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<td></td>
</tr>
<tr>
<td>AILD</td>
<td>(1-5)</td>
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</tr>
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</table>

*From the time of biopsy to death or date of last contact.
AILD = angioimmunoblastic lymphadenopathy.
Table 5  Frequency of bone marrow patterns and their prognostic relevance in lymphoproliferative disorders (at time of initial diagnosis)

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Patients</th>
<th>Nodular</th>
<th>Interstitial/ nodular</th>
<th>Interstitial</th>
<th>Paratrabecular</th>
<th>Patchy focal</th>
<th>Packed marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple myeloma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmacytic</td>
<td>513</td>
<td>4% (50)</td>
<td>39% (29)</td>
<td>36% (40)</td>
<td></td>
<td></td>
<td>21% (16)</td>
</tr>
<tr>
<td>Plasmablastic</td>
<td>211</td>
<td>50% (12)</td>
<td>20% (21)</td>
<td></td>
<td></td>
<td></td>
<td>30% (5)</td>
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<tr>
<td><strong>Non-Hodgkin's lymphomas</strong></td>
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<td></td>
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<tr>
<td>Lymphocytic</td>
<td>283</td>
<td>32% (107)</td>
<td>42% (36)</td>
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<td></td>
<td>26% (25)</td>
</tr>
<tr>
<td>Hairy cell</td>
<td>144</td>
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<td></td>
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<td>25% (18)</td>
</tr>
<tr>
<td>Immunocytic</td>
<td>215</td>
<td>41% (74)</td>
<td>33% (56)</td>
<td>6% (34)</td>
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<td></td>
<td>20% (12)</td>
</tr>
<tr>
<td>Centroyctic</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
<td>60% (29)</td>
<td></td>
<td>40% (19)</td>
</tr>
<tr>
<td>Centroblastic/cytic</td>
<td>52</td>
<td>80% (56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20% (12)</td>
</tr>
<tr>
<td>&quot;Blastic&quot; (sarcoma type)</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100% (5)</td>
</tr>
<tr>
<td><strong>Hodgkin's disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low content of lymphocytes</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62% (17)</td>
<td>38% (12)</td>
</tr>
<tr>
<td>High content of lymphocytes</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80% (60)</td>
<td>20% (42)</td>
</tr>
<tr>
<td>High content of epithelioid cells</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60% (63)</td>
<td>40% (52)</td>
</tr>
<tr>
<td><strong>Angioimmunoblastic lymphadenopathy</strong></td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76% (34)</td>
</tr>
</tbody>
</table>

% = percentage in each histological type.
( ) = median survival time (months) from time of biopsy to death or date of last contact.

Fig. 7  Classification of multiple myeloma based on bone marrow histology. Giemsa x400: (a) multiple myeloma plasmacytic, Marshalko type; (b) multiple myeloma plasmacytic, small round type; (c) multiple myeloma plasmacytic, small notched type; (d) multiple myeloma plasmacytic, polymorphous type; (e) multiple myeloma plasmablastic; (f) multiple myeloma plasmablastic, pleomorphous type.
Lymphoproliferations in the bone marrow: identification and evolution, classification and staging

Non-Hodgkin's lymphomas

(1) Lymphocytic
The infiltrations consisted of typical small lymphocytes showing three growth patterns each with prognostic significance: (1) interstitial; (2) interstitial/nodular; (3) packed marrow (Table 5). Nodules with follicular centres were present in 25% of the biopsies. There was some variation in lymphocytic size and numbers of nucleated cells, a higher proportion of which indicated a poorer prognosis (Table 4). Fat and haematopoietic tissue were progressively reduced as the tumour cell burden increased and this constituted a reliable prognostic factor (Table 6). Six cases had somewhat larger lymphoid cells with nucleoli, moderate amounts of cytoplasm and a positive acid phosphatase reaction (prolymphocytic).18

The bone marrow was extensively replaced with a corresponding reduction in normal elements and the prognosis was poor (Table 4). In 58 cases the lymphocytes had slight notches or indentations (Fig. 8b) corresponding to the B1 lymphocyte.31 45 These also had a more unfavourable prognosis.

(2) Hairy cell
There was a patchy to complete replacement of the marrow by hairy cells having abundant cytoplasm with lateral extensions, and rodlike inclusion bodies in 45% of the cases. The hairy cells were widely dispersed within a reticulin fibre network which also contained plasma cells, lymphocytes, mast cells and extravasated erythrocytes. The hairy cell nuclei displayed a wide morphological spectrum comprising three main configurations, one of which usually predominated in each biopsy and had predictive value. Type 1: in 47% of the cases small ovoid nuclei; type 2: in 37% of the cases medium sized convoluted nuclei; and type 3: in 16% of the cases large indented nuclei usually with a prominent nucleolus (Table 4). Hairy cell involvement of the bone marrow occurred in three patterns: (1) multiple small patches; (2) large confluent areas; (3) complete replacement. The survival times correlated significantly with the amount of tumour cell burden (Table 6). A high incidence of inclusion bodies in any of the subtypes also indicated a poor prognosis. Splenectomy significantly prolonged survival in patients with both the ovoid and convoluted types.

(3) Immunocytic
The specific infiltration consisted mainly of small lymphocytes with variable numbers of mature plasma cells, plasmacytoid cells and mast cells in a hypocellular marrow. Most cases had some lymphoid cells with cytoplasmic or nuclear PAS-positive inclusions. As in the lymph nodes three prognostically different subtypes were distinguished: (1) the lymphoplasmacytid in 49% showing mainly a nodular pattern and clinical splenomegaly; (2) the lymphoplasmacytoid in 46% with numerous plasma and mast cells and a combined interstitial and nodular pattern, and clinical lymphadenopathy; (3) the polymorphous subtype in 5% consisting of lymphocytes, plasma cells, centrocytes, centroblasts and immunoblasts and exhibiting the packed marrow pattern with clinical lymphadenopathy, splenomegaly and pancytopenia. The infiltrated areas showed a fine reticulin fibrosis, and haematopoietic precursors were found within the infiltrations as well as in areas between them. The tumour burden in the initial biopsy correlated with the survival times (Table 6). Clinically 89% of the patients had IgM paraproteinaemia, the disease thus corresponding to Waldenström's macroglobulinaemia.

(4) Centrocytic
Most of the involved bone marrows showed paratrabeclular infiltrations of small to medium sized lymphoid cells with cleaved nuclei and narrow rims of cytoplasm. Fibres radiating out from the trabeculae formed a reticulin network within the infiltrations. Between the paratrabeclular seams the marrow spaces were occupied by fat cells and residual haematopoietic precursors. The size and nuclear morphology of the infiltrating cells were used for subtyping: small cleaved 46%, large cleaved 43%, and polymorphous 11%. The subtype classification and the extent of infiltration in the biopsy both showed significant correlations with survival (Tables 4, 6).

(5) Centroblastic/centrocytic
This lymphoma showed a strictly nodular pattern frequently of follicles with germinal centres consisting of lymphocytes, centrocytes and centroblasts within a fine reticulin network. Between the nodules the marrow had a normal aspect both in structure and cellular composition. It was not possible to subtype this lymphoma which with 50 months had the longest median survival of all the malignant lymphomas with bone marrow involvement.

(6) Lymphoblastic (only sarcoma type, 16 cases), Centroblastic (8 cases), and Immunoblastic (5 cases)
Each of these groups showed similar clinical and histological features. All involved marrows had a packed marrow pattern, with only isolated residual haematopoietic elements. All had a very unfavourable course with median survivals of about 5 months.
Fig. 8 Classification of non-Hodgkin's lymphomas based on bone marrow histology (I). Giemsa ×400. 
(a) non-Hodgkin's lymphoma lymphocytic, small round type; (b) non-Hodgkin's lymphoma lymphocytic, small notched type; (c) non-Hodgkin's lymphoma lymphocytic, large type; (d) non-Hodgkin's lymphoma hairy cell, ovoid type; (e) non-Hodgkin's lymphoma hairy cell, convoluted type; (f) non-Hodgkin's lymphoma hairy cell, indented type; (g) non-Hodgkin's lymphoma immunocytic, lymphoplasmacytoid type; (h) non-Hodgkin's lymphoma immunocytic, lymphoplasmytic type; (i) non-Hodgkin's lymphoma immunocytic, polymorphous type.
Fig. 9  Classification of non-Hodgkin's lymphomas based on bone marrow histology (II). Giemsa ×400. (a) non-Hodgkin's lymphoma centrocytic, small type; (b) non-Hodgkin's lymphoma centrocytic, large type; (c) non-Hodgkin's lymphoma centroblastic/centrocytic; (d) non-Hodgkin's lymphoma lymphoblastic; (e) non-Hodgkin's lymphoma immunoblastic; (f) non-Hodgkin's lymphoma centroblastic; (g) non-Hodgkin's lymphoma prolymphocytic; (h) perivascular infiltration in a patient with mediastinal T cell lymphoma. Giemsa ×400; (i) nodular infiltration of T lymphocytes in immunocytoma. PAP ×100.
(7) Unclassifiable
In 36 patients with non-Hodgkin’s lymphomas we had problems classifying merely on the basis of bone marrow histology. However, 29 of them could be categorised as non-Hodgkin’s lymphoma of high grade malignancy and the remaining seven cases as non-Hodgkin’s lymphoma of low grade malignancy.

(8) Mediastinal lymphomas
Bone marrow biopsies taken in a few cases of mediastinal lymphomas (subsequently shown to be of T cell type) had a sparse interstitial and a somewhat more dense perivascular infiltration with preservation of haematopoietic tissue (Fig. 9h). This type of spread did not correspond to any of the distinct patterns described above, though it could well represent an early phase of the packed marrow type.

**Hodgkin’s disease and angioimmunoblastic lymphadenopathy**
Bone marrow involvement in Hodgkin’s disease has been described above. Reed-Sternberg cells were found in 62% and mononuclear Hodgkin cells in 95% of the involved cases. It should be noted that the extent of the infiltration (volume percentage or tumour cell burden) as used above does not apply to Hodgkin’s disease in which the actual amount of tumour cell burden or putative malignant cells may be very low if by malignant cells is meant the number of Reed-Sternberg or Hodgkin cells. The rest of the infiltration consists of stromal elements contributed by the host. Nevertheless the degree of lymphocytic infiltration constituted a significant predictive factor. A low content of lymphocytes indicated a shorter life expectancy than a high con-
Lymphoproliferations in the bone marrow: identification and evolution, classification and staging

Table 6  Staging of cumulative lymphoproliferative disorders by bone marrow histology (at time of initial diagnosis)

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Patients</th>
<th>Infiltration volume in the biopsy (vol%)*</th>
<th>Survival statistics†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stage I (&lt;20)</td>
<td>Stage II (20–50)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmacytic</td>
<td>546</td>
<td>40% (48)</td>
<td>40% (29)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>283</td>
<td>17% (78)</td>
<td>44% (38)</td>
</tr>
<tr>
<td>Hairy cell</td>
<td>144</td>
<td>7% (30)</td>
<td>44% (20)</td>
</tr>
<tr>
<td>Immunocytic</td>
<td>215</td>
<td>43% (75)</td>
<td>30% (57)</td>
</tr>
<tr>
<td>Centrocytic</td>
<td>65</td>
<td>25% (42)</td>
<td>40% (30)</td>
</tr>
</tbody>
</table>

*Volume percentage of the whole biopsy core.
†Breslow- and Mantel-Cox test; ++ = < 0.01.
% = Percentage in each histological type.
() = Median survival time (months) from time of biopsy to death or date of last contact.

tent—median survival of 15 and 55 months respectively (Table 4, Fig. 10a, b). Five patients had bone marrow involvement with a high degree of epithelioid cells correlating with a more favourable prognosis (Fig. 10c).

In our material, of 40 cases with angioimmunoblastic lymphadenopathy diagnosed by lymph node histology, bone marrow involvement was found in 24 cases. However, in another 14 patients a positive bone marrow was the only detected manifestation of angioimmunoblastic lymphadenopathy, without lymphadenopathy even during the course of disease. Involvement of the bone marrow was characterised by multiple, partly confluent foci with a heterogeneous cell population consisting of immunoblasts, lymphocytes, centrocytes, plasma cells and eosinophils. There were hyperplastic, occasionally arborising capillaries within a reticulin framework and interstitial deposition of PAS-positive material (Fig. 10e, f). Patients with angioimmunoblastic lymphadenopathy and bone marrow involvement had systemic symptoms in 85%, hepatosplenomegaly in 80% and a relatively short life expectancy with a median survival of 28 months. Conversion to haematological neoplasms was observed in only two cases (immunoblastoma, acute myeloid leukaemia).

HISTOLOGICAL VARIATION OF LYMPHOPROLIFERATIVE DISORDERS IN THE BONE MARROW

Two types of histological variations were observed: (1) simultaneous detection of different cell types and/or growth patterns within the same biopsy (coexistence) and (2) subsequent detection of different types and/or architectural patterns in follow-up biopsies (conversion, metamorphosis, transformation, progression). Furthermore myeloproliferative disorders or acute leukaemias developed in 62 cases as shown in Table 7.

Coexistence of lymphoproliferative disorders in the bone marrow

Double lymphoproliferative disorders at initial biopsy were observed in 16 cases (multiple myeloma 4, non-Hodgkin’s lymphomas 10, Hodgkin’s disease 2), and the combinations are given in Table 7. Co-

Table 7  Histological variation of lymphoproliferative disorders in the bone marrow

<table>
<thead>
<tr>
<th>Multiple myeloma</th>
<th>Lymphocytic</th>
<th>Hairy cell</th>
<th>Immunocytic</th>
<th>Centrocytic</th>
<th>Centroblastic/centrocytic</th>
<th>Non-Hodgkin’s lymphoma‡</th>
<th>Hodgkin’s disease</th>
<th>Myeloproliferative disorders</th>
<th>Acute myeloid leukaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>2 (2)*</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>1</td>
<td>9 (10)</td>
<td>7</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td></td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>6 (6)</td>
<td>1</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Hairy cell</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>1</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Immunocytic</td>
<td>2 (3)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>7 (7)</td>
<td>1</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Centrocytic</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>1</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Centroblastic/centrocytic</td>
<td></td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>7 (7)</td>
<td>1</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>7 (7)</td>
<td>1</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Simultaneous detection at initial biopsy; in brackets subsequent detection at follow-up biopsies.
‡Of high grade malignancy.
existing lymphoproliferative and myeloproliferative disorders in the same bone marrow biopsy (Fig. 11) were detected in 25 cases; in 8 of these polycythaemia vera was found together with multiple myeloma. Differences in architectural pattern were occasionally observed in a single biopsy, in which case the predominant pattern was used for categorising.

Conversion of lymphoproliferative disorders in the bone marrow
Five hundred and twelve sequential biopsies were used to monitor the effects of therapy both on the infiltrations and on the haematopoietic tissues. Biopsies were also taken for restaging and for recategorisation if clinical conversion was suspected. These serial biopsies demonstrated a change in lymphoid cell type in 31 cases, and conversion to a myeloid neoplasia in 37 cases (myeloproliferative disorders 29, acute myeloid leukaemia 8). Two patients with polycythaemia vera developed chronic lymphocytic leukaemia, 4 and 5 years respectively after the onset of disease. The growth patterns in the lymphoproliferative disorder remained stable in follow-up biopsies in most cases, thus reflecting the basic proliferative cell system as well as the tumour cell burden. In chronic lymphocytic leukaemia, nodularity correlated with a favourable prognosis, and transformation to a diffuse pattern signalled a faster disease progression. On the other hand, a switch from a diffuse to a nodular pattern was not observed in our series.

Discussion
Recognition of lymphoproliferations in the bone marrow
With increasing use of bone marrow biopsies as a diagnostic tool in internal medicine and oncology, lymphocytes and lymphoid nodules are more frequently encountered, as their presence in the bone marrow may be reactive to a variety of non-haematological and haematological conditions. Their recognition as benign or malignant is of considerable clinical importance especially as the benign infiltrates are more common, though prolonged follow-up is required for their recognition. Moreover the number of plasma cells as well as that of benign lymphoid nodules increases in the older age groups while the overall cellularity in the iliac crest, from which bone biopsies are usually taken, tends to decrease with age. Coincidentally the peak incidence of the non-Hodgkin's lymphomas also occurs in the higher age groups. In addition normal lymphocytes may be present together with neoplastic lymphoma cells, for example T lymphocytes in a B cell neoplasm such as follicle centre cell lymphoma or B-CLL, or the lymphocytes in the cellular infiltrates in Hodgkin's disease. The distinction between minimal benign and...
neoplastic accumulations of lymphocytes and plasma cells can best be made by means of immunological markers and clearly benign lymphoid hyperplasia must be excluded when involvement of the bone marrow is suspected in an elderly patient with a lymphoproliferative disorder. These observations support the hypothesis that the presence of a lymphoid neoplasm may be symptomatic of a widespread disturbance affecting the immune system as a whole and indicating defective immuneregulation, rather than being the expression of a single malignant cell clone. The wide range of detection of bone marrow involvement reported in the literature over the past decade is probably due to inclusion of unequal proportions of patients with early and advanced disease, as well as to technical aspects such as differences in biopsy size and preparation. Plastic embedded large single biopsies have proved their value in detection of minimal and focal lesions in the bone marrow.

**Growth patterns of lymphoproliferations in the bone marrow**

The results presented here have confirmed and extended previous observations on the mode of spread of the lymphoproliferative disorders in the bone marrow as well as on the prognostic significance of the different patterns. The more favourable course of a nodular as opposed to a diffuse spread was first recognised by Rappaport for lymph nodes and recently confirmed by Damber et al and by Straus et al. It is not known what factors influence lymphoid cells to assume certain architectural arrangements in the bone marrow though these might include an inherent behavioural tendency to aggregate; a propensity to form architectural structures as in the lymph nodes; some local topographic influence or a chemotactic attraction to specific areas in the bone marrow. Why the centrocytic lymphomas should show a paratrabecular predilection is unclear, perhaps an association with the paratrabecular sinus is involved. It might be significant that whereas red and white cell and platelet precursors have preferred topographic localisations in the bone marrow none is known for lymphopoiesis. Nevertheless the chronic lymphoproliferative disorders exhibit characteristic modes of spread which provide independent information and should therefore be included in any classification system of lymphoproliferative disorders in the bone marrow.

The presence of a lymphoproliferative disorder in the bone marrow almost invariably has some effect on the bone. The most extensive and serious complications are generally seen in multiple myeloma, though osteolytic bone lesions with accompanying hypercalcaemia may occur in any lymphoproliferative disorder. An early bone biopsy will give warning of increased activity so that measures may be taken to avoid osteolysis and hypercalcaemia.

**Histological classification of lymphoproliferative disorders in the bone marrow**

General agreement on classification of the non-Hodgkin’s lymphomas has not been achieved in spite of publication of the International Working Formulation. In the United States the Lukes-Collins classification is widely used while in Europe there is a tendency for the Kiel classification to be employed. One explanation is that though the modern trend is towards an immune based functional classification morphology remains the foundation of histopathology. In many cases the differentiation between B and T lymphomas may be made on that basis alone as their morphological features have now been well defined and in most instances are characteristic. Moreover, in recent prospective studies the histopathological grading of malignancy (low or high according to the Kiel classification) emerged as a powerful independent prognostic factor. The results of this study utilising the Kiel criteria show that classification by bone marrow histology is feasible, reproducible and has prognostic significance.

In the B cell lymphomas, histological assessment also requires estimation of the cellular composition which reflects the diverse structural forms of the neoplastic clone, as cells in each of the stages of the developmental pathway (lymphocytes, follicle centre cells, immunoblasts and plasma cells) are represented though their relative proportions vary in the different entities. This explains the mixed populations of cells seen in the involved bone marrows which enabled subtype recognition. Moreover recent work indicates that the different entities within the lymphoproliferative disorders are not sharply separated as shown for example by circulating lymphocytes bearing the same idioype determinants as the plasma cells in patients with multiple myeloma or cytoplasmic inclusions containing immunoglobulins in chronic lymphocytic leukaemia cells. Likewise a strict categorisation to specific steps in the maturation pathway itself has not been confirmed by electron microscopic observation of lymphocytes during transformation by studies of immunoglobulin secretion showing that centrocytes may precede or follow centroblasts and by demonstration of acid hydrolases in immature as well as in mature lymphocytes. Thus the presence of variable populations may help to account for unequal responses to therapy of patients with a superficially similar chronic lymphoproliferative
disorder and this may apply to pattern as well as to cell type.\textsuperscript{79–81}

**Staging and evolution of lymphoproliferative disorders in the bone marrow**

Clinical staging procedures\textsuperscript{82–87} attempt to estimate the spread and quantity of the tumour cell burden which in some cases is reflected in the volume percentage in the biopsy. But there are differences between the entities which may be roughly divided into three groups:\textsuperscript{2} (1) the cumulative lymphomas such as chronic lymphocytic leukaemia, immunocytoma and hairy cell leukaemia with a systemic presentation in which stage is indicated by the amount of infiltration in the bone biopsy, (2) the primarily regional lymphomas with a centrifugal spread in which bone marrow involvement indicates stage IV, and (3) lymphomas with a sarcomatous (metastatic) growth indicating systemic disease, though not necessarily wide spread.

Recent reports have confirmed earlier ones on the occurrence of histological progression, conversion and transformation in the chronic lymphoproliferative disorders.\textsuperscript{88–99} Since blasts, as shown in this survey, are normally present in the chronic lymphoproliferative disorders in the bone marrow, a transformation such as Richter’s in chronic lymphocytic leukaemia\textsuperscript{100} or to immunoblastic sarcoma in multiple myeloma or immunocytoma\textsuperscript{101–103} or diffuse large cell from nodular lymphocytic lymphoma\textsuperscript{104} may point to a shift in proliferation advantage of a cell type already present over another. Alternatively, the ability to mature is steadily decreased. Whether this is analogous to the blastic transformation as seen in chronic myeloid leukaemia or represents an additional mutation, or is treatment-induced, cannot be decided at present. However, reports of acute leukaemia supervening in untreated cases of lymphatic malignancies are extremely rare\textsuperscript{105} in contrast to plasma cell neoplasias.\textsuperscript{106} Zalberg and coworkers\textsuperscript{107} have shown that chronic lymphocytic leukaemia may arise after multiple myeloma and that two different clones are involved. On the other hand evolution of one lymphoma from another—for example, Sézary’s syndrome in the course of hairy cell leukaemia—has also been described.\textsuperscript{108} Moreover, coexistent lymphoproliferative and myeloproliferative disorders have been documented suggesting an expansion from a common abnormal pluripotent stem cell.\textsuperscript{109} The high frequency of lympho/myeloproliferative disorders diagnosed either simultaneously or subsequently, found in this study, supports this unifying concept of haematological neoplasias. We have demonstrated by means of serial biopsies taken during extended follow-up periods of both treated and untreated patients that the bone marrow was not entirely cleared of lymphoma. Other long term follow-up studies have emphasised the fatal outcome of patients treated conservatively.\textsuperscript{49} This underlines the question put by Longo \textit{et al}\textsuperscript{110} “What is so good about the good prognosis lymphomas?” since they cannot be cured. Indeed a chance for eradication might arise when conversion to a more malignant histology occurs—provided the cells had not previously been made resistant to therapy. This idea has led, in some centres, to the “watch and wait” approach.\textsuperscript{112} Different aspects have been stressed in recent critical studies of staging and prognostic factors in the multiple myelomas and lymphomas. Some have emphasised the importance of the plasma cell mass in the bone marrow and its maturity as indicated by labelling indices.\textsuperscript{111–116} These correspond to the infiltration volume and subtypes with nucleolated cells as shown in this study. Moreover cases with immature cells were prone to develop an aggressive terminal phase with emergence of a blastic type of multiple myeloma.\textsuperscript{102,103} Other investigators have stressed clinical parameters such as haemoglobin, blood urea and $\beta_2$-microglobulin levels;\textsuperscript{114,117} and the predictive value of some was confirmed in this study also. Nevertheless in a recent survey of patients surviving for more than 10 years,\textsuperscript{118} the response to therapy was the most important factor in recognising long term survivors though this was not mentioned in the recent results of the Medical Research Council’s Working Party on long term survival in myelomatosis (patients followed for up to 12 years).\textsuperscript{119} Our own study shows that estimation of the tumour cell burden and of the cytological subtypes in the bone marrow biopsy are reliable prognostic indicators in multiple myeloma. Likewise in the cumulative variants of non-Hodgkin’s lymphomas (chronic lymphocytic leukaemia, hairy cell leukaemia, immunocytic and centrocytic lymphomas) the infiltration volume in the biopsy reflects the tumour size and proved to be a reliable parameter for histological staging.\textsuperscript{34,38,70} In chronic lymphocytic leukaemia, Rozman \textit{et al} interpreted the different architectural patterns as variations in the amount of lymphoid accumulation during the natural course of disease.\textsuperscript{85} However, we have shown that nodularity in the bone marrow in chronic lymphocytic leukaemia indicates a favourable prognosis and thereby reflects the intrinsic “malignancy” rather than the “stage” of the tumour.\textsuperscript{38}

Bone marrow biopsy is now an integral part of staging in Hodgkin’s disease since bone marrow involvement is one of the criteria for systemic disease, i.e. stage IV, indicating haematogenous spread.
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(as the bone marrow has no lymphatics) and an unfavourable prognosis.108120,122. Furthermore the degree of Hodgkin's disease infiltration assessed in large scale biopsies proved to be a prognostic factor though not so significant as in the cumulative, primarily systemic lymphoproliferative disorders.123 Angioimmunoblastic lymphadenopathy is regarded as a "hyperimmune entity resembling Hodgkin's disease"1124 or a "defectively regulated immune response to an unidentified antigen(s)".1125,126 The high frequency of bone marrow involvement previously reported127,128 has been confirmed in this study, suggesting a primarily systemic onset. However, in about a third of the cases exhibiting the histologic picture of angioimmunoblastic lymphadenopathy in the bone marrow, no lymphadenopathy was evident during the course of disease: these cases were called "angioimmunoblastic myelopathy". The differentiation of these granulomatous reactions from those occurring in Hodgkin's disease (without Hodgkin or Reed-Sternberg cells) and in rheumatic or allergic conditions is not always possible.20

In conclusion, bone marrow biopsy has proved its value not only for identifying, classifying and staging of lymphoproliferative disorders at presentation, but also for monitoring and restaging during the course of disease. Progression, metamorphosis as well as consequences of therapy—success or failure—may be quantitatively and qualitatively evaluated by serial biopsies. Thus, in the bone marrow biopsy the clinician has a tool at his disposal which supplies decisive information on the diagnosis and therapy of any given patient with lymphoproliferative disorders.

The authors would like to express their gratitude to all colleagues who referred patients or sent biopsies. This work was supported by the Gesellschaft für Strahlen- und Umweltforschung mbH, Munich.

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Requests for reprints to: Professor Dr med Reiner Bartl, Abteilung für Knochenmarksdiagnostik an der Medizinischen Klinik Innenstadt der Universität München, D-8000 München 2, Ziemssenstrasse 1, Germany.


Book Reviews


There is a wealth of reliable information and wise guidance in this potentially useful book. After a short introduction it begins with a 28 page survey of the more important and available antibiotics, then continues with chapters on their use (mainly therapeutic) in the various branches of surgery. The last chapter, on the choice of antibiotics and the assessment of new ones, is especially sound but might have been better combined with chapter 2 so that the general principles of antimicrobial therapy could be found all in one place. There is some advice on the prophylactic use of antibiotics in the various specialist chapters, but a general discussion of the principles of antibiotic prophylaxis would have been useful. There is a reference list at the end of each chapter but the inquiring reader will have difficulty in relating this to specific topics because there are no references in the text.

Rarely have I reviewed a book in which there was so little to fault in the scientific matter; but rarely have I reviewed one of similar size that took me so long to read—because it was such hard reading. Essential material, for which a reader will long search without the help of a good index, is entangled in a tautological forest of awkward and unclear sentences that call for frequent rereading. If there is to be another edition of this book, and I hope that there is, skilled editing would reduce it to little more than half the present size without loss of facts but with great gain in clarity and accessibility of content.

ROBERT BLOWERS


This slim paperback volume is part of the World Health Organisation Technical Report Series, and was produced by a committee of distinguished authorities including clinicians, epidemiologists, and pathologists. It is written in a clear, concise, and didactic style, and an enormous amount of useful information is contained in its 80 pages. The emphasis is mainly towards clinical aspects of trophoblastic disease, and discussion of the pathology, although comprehensive, is not surprisingly rather superficial. Nevertheless, this is an excellent report, right up to date, and with a good reference list. At just over £2 it represents tremendous value and I recommend every department which deals with gynaecological pathology to buy it.

CW ELSTON

Some new titles

The receipt of books is acknowledged, and this listing must be regarded as sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits.


Notice

Supraregional assay service booklets—further copies

The supraregional assay service (SAS) set up by the DHSS in January 1974 is still very active. Provided it receives the requests via consultants in pathology departments it undertakes certain difficult, infrequently requested assays free of charge. The repertoire is contained in the SAS booklet, which was sent to all those who are registered users of the SAS.

It has been decided to make copies of the SAS booklet available for educational purposes, and for information for those who are not registered users. However, any requests for SAS tests have to be made through the consultant or top grade scientist in charge of the laboratory, to whom results are initially sent. Requests should not be made directly by any other member of the NHS staff to the SAS.

Copies of the SAS booklet are available, and the cost is greatly reduced if a cheque is made payable to Westminster Medical School and sent direct with the order to: Professor JR Hobbs, Westminster Hospital, 17 Page Street, London SW1P 2AR.

They can be purchased as follows:

1 copy ....... £7.00
2 copies ....... £12.00
3 copies ....... £17.00
4 copies ....... £22.00
5 copies ....... £27.00

This arrangement avoids the costs of further correspondence and invoicing. The booklets will be despatched direct to whoever sends the order with the cheque.

Those preparing for the MCB or MRCPath will find very useful guidelines in this booklet with regard to the investigation of patients.

Correction

We apologise to Professor Bartl and his colleagues for the error which occurred in their paper in the March 1984 issue (p 233).1 Owing to a printer's error figure 2 appeared as a mirror image.

Reference