Lymph Node Smears in the Diagnosis of Lymphadenopathy: A Review

By P. F. Lucas

EXCISION of a lymph node has for many years been the final arbiter in the diagnosis of lymphadenopathy. This often leads to considerable expense and delay in treatment because general anesthesia and admission to hospital may be necessary, apart from the time taken to fix and stain sections. The importance of establishing a diagnosis before treatment has led to increasing use of aspiration and punch biopsies by a variety of different techniques. All these methods have advantages of ease and speed of application over excision of a node; several nodes can be examined and, in case of doubt, further specimens are easily obtainable. It must be allowed that section of the small amount of tissue obtainable is inferior to section of a whole node, although many authors prefer this method to examination of smears. It cannot be emphasized too strongly that analysis of smears is more easily undertaken by those trained in examination of the similar smears from bone marrow than by those most experienced in the histology of lymph nodes. By the smear method, the paucity of tissue obtained and its detachment from its surroundings are of little importance; cytologic abnormalities are usually generalized by the time a node is large enough to puncture; a simple needle and syringe is adequate, and preparation of specimens is quicker. It has been suggested that detectable cytologic abnormalities precede histologic change.1-4 The accuracy of these methods must be viewed against the accuracy of excision,5-6 but failure can always be followed by excision of a node as suggested by Martin and Ellis7 and Stewart.8 Aspiration biopsy has been condemned on the ground that it disseminates disease, but there is little evidence that this danger is greater than after excision.

Guthrie9 was the first systematically to use this technic but gave little information on his findings. Forkner10 was the first to describe the cytology of lymph nodes; he used a barbed dental broach to obtain tissue and confined his descriptions to supravitally stained smears. Martin and Ellis7 reported puncture of 1844 cervical tumors and Stewart8 confirmed their high opinion of the method, especially in the diagnosis of malignancy. Pavlovsky's11 monograph contains details of the cytology of diseases of lymph nodes and did much to stimulate further work in this field. Since its publication in 1934, seven other monographs have been published,12-19 the most recent of which contains the fullest account of the method in English.19 Berman20 has compared smears with sections of lymph nodes; this important work confirms that the two methods should be regarded as complementary. Morrison et al.21 and Tempka and Kubiczek22 have also pub-
lished important studies apart from many other papers on various aspects of lymph node cytology in the European and South American literature, reference to which is made in the course of this paper.

There is less information on the cytology of normal lymph nodes. Dreyfus' monograph contains the most detailed description but gives little indication of the frequency of the cells described. Some authorities describe puncture of normal nodes in vivo, but it seems that such nodes are hyperplastic, and this suggestion is confirmed by finding hyperplastic features in a node thought to be “within normal limits” (see below). Others have published differential cell counts of small numbers of normal nodes with little comment on the findings.

These reports agree on the value of the method for diagnosis although criteria for diagnosis vary and differences in terminology make comparisons difficult. Many authors have not controlled their studies by normal nodes and there are few carefully documented series in which the diagnosis has been checked by other means.

The purpose of this paper is to describe the cytology of lymph nodes in health and disease, based on 15 normal and 85 pathologic nodes (table 1), and to assess the diagnostic value of lymph node aspiration biopsy on 85 consecutive successful aspirations.

**Table 1.—Final Diagnoses in 85 Consecutive Cases of Lymphadenopathy. Figures in parentheses give the numbers in which a diagnosis was made by aspiration.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Numbers in Parentheses</th>
<th>Total Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>18 (8)</td>
<td>85 (52)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>3 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>3 (2)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Glandular fever</td>
<td>2 (1)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>1 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Erythrodermia</td>
<td></td>
<td>3 (2)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6 (1)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Reticulosis</td>
<td>43 (23)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>17 (5)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Lymphoid follicular reticulosis</td>
<td>1 (--)</td>
<td>1 (--)</td>
</tr>
<tr>
<td>Reticulum cell medullary ret's</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sarcoid</td>
<td>1 (--)</td>
<td>1 (--)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Lymphatic leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chronic</td>
<td>19 (13)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Monocytic leukemia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>? Myeloid leukemia</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>24 (21)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>13 (10)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Secondary carcinoma</td>
<td>8 (8)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Secondary melanoma</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Salivary tumor</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

**Total:** 85 (52)
LYMPH NODE SMEARS IN DIAGNOSIS OF LYMPHADENOPATHY

MATERIAL AND METHODS

Examination of sections and smears suggests that nodes larger than 0.75 cm. in diameter usually show hyperplastic or frankly pathologic features, whereas those smaller do not. Such small nodes cannot be punctured in vivo and autopsy material autolyzes too quickly. These 15 normal nodes were obtained at operations; all were less than 0.5 cm. in diameter. The nodes were held between finger and thumb and aspirated in the same way as the pathologic nodes. Imprints were also made from the cut surfaces but there was little difference between the two types of smear. Tissue was obtained from the pathologic nodes by aspiration biopsy using an 18 gauge needle and a 20 cc. syringe. When nodes were excised for histology, imprints were made in addition but for purposes of diagnosis only aspirated specimens were used.

Smears were stained by the May-Grunwald-Giemsa technic. Complete examination under the one-sixth inch objective of the microscope was followed by assessment of abnormal cells under the oil immersion lens. Differential counts of 1000 consecutive cells were made. Cells were measured with a micrometer eyepiece and the figures given are the average maximum diameter of 100 cells. The diagnosis was confirmed histologically in all the pathologic nodes except in syphilis, glandular fever, herpes zoster, 11 of the leukoses and 2 carcinomata.

TERMINOLOGY OF NORMAL CELLS

This section consists of a description of the cytology of the 15 normal nodes (table 2) and gives an opportunity to define the terms used. These terms are purely descriptive although there is good evidence for the classification adopted which is in accordance with most of the modern work on this subject.

In the absence of accumulation of pigment and aggregation of granules, the following features are taken as the most reliable indicators of maturity: (1) Presence of nucleolus. (2) Fine, pale-staining chromatin distributed in an even, open network without clumps or thickenings. (3) A nucleus which is relatively large for the size of the cell. (4) The large size of the cell. (5) Cytoplasm which is basophilic without granules or inclusions.

I. Multipotent stem cells

The term hemohistioblast is used as synonymous with the primitive, undifferentiated, totipotent, embryonic, mesenchymal cell of Maximow; it can form all blood and tissue

<p>| Table 2.—Differential Cell Counts of 1000 Consecutive Cells From 15 Normal Lymph Nodes |
|-----------------------------------------------|----------|----------|</p>
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Range</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemocytoblast</td>
<td>0-0.1</td>
<td></td>
</tr>
<tr>
<td>Histocyte</td>
<td>0-2.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Mast cell</td>
<td>0-0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Lymphoblast</td>
<td>0.1-0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Prolymphocyte</td>
<td>5.3-16.4</td>
<td>10.7</td>
</tr>
<tr>
<td>Differentiated lymphocyte</td>
<td>67.8-90</td>
<td>83.5</td>
</tr>
<tr>
<td>Total lymphocytes</td>
<td>87.0-99.2</td>
<td>94.2</td>
</tr>
<tr>
<td>Monoblast</td>
<td>0-0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Promonocyte</td>
<td>0-0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Monoctyes</td>
<td>0.2-4.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Total monocytes</td>
<td>0.2-5.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Plasmoblast</td>
<td>0-0.1</td>
<td></td>
</tr>
<tr>
<td>Proplasma cell</td>
<td>0.0-0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>0-4.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Total plasma cells</td>
<td>0-5</td>
<td>2.3</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>0-2.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>0-0.3</td>
<td></td>
</tr>
<tr>
<td>Basophil</td>
<td>0-0.2</td>
<td></td>
</tr>
</tbody>
</table>
Figs. 1.—Normal node. Lymphocytes, some of which show marked chromatin clumping, a plasmoblast (bottom center), a monoblast (upper right) and the naked nucleus of a reticular cell (lower left). X750.

cells. The hemocytoblast is one stage further differentiated, being potent for blood cells only. These two cells and the histiocyte are included in the generic term reticulum cell.

1. The hemohistioblast (fig. 4) is oval in shape, 25-30 microns in diameter, with broad lilac-colored cytoplasm often without any clear cell membrane—the "tissue hemohistioblast" of Dreyfus. The chromatin strands are finer and more evenly and widely spaced than those of any other cell seen in lymph nodes. One to three large blue nucleoli are always present.

2. The hemocytoblast (fig. 2) is round and rather smaller than the hemohistioblast (diameter 24 microns). The cytoplasm is scanty and moderately basophilic. The chromatin is fine and closely-packed, and blue-staining nucleoli are always present as many as six in number. These cells are often partially differentiated to other blast cells which accounts for the varied descriptions of them in the literature.

Both these cells were seen in each of these normal nodes and in each of five nodes, one hemocytoblast was seen in the differential count. Other figures for the frequency of hemocytoblasts are 0.74 per cent and 0.026 per cent. This great difference may be a matter of terminology which is so prodigious that attempts to correlate it are fruitless.

II. Histiocyte Series

1. Histioocytes (figs. 2, 5 and 6) are usually classified separately from monocytes although some observers believe the two cells to be identical.

Cells in the resting phase are 14-36 microns in diameter, those containing inclusions may measure 50 microns. The nucleus is of almost constant size (diameter 13 microns) but of variable shape. The chromatin is evenly-distributed in long, brightly-staining strands with
thickenings at points of intersection. As many as three small blue nucleoli may be present, but none may be visible in dry smears; this has led to their subdivision into histiocytes and histioblasts. Bi- and even tri-nucleated cells are occasionally seen in normal nodes. Inclusions vary from nuclear fragments to masses of pigment and vacuoles. They do not give the oxydase reaction. De Renzi and Michelazzi\textsuperscript{2} gave 0.74 per cent and Fortezza Bover\textsuperscript{14} 0.004 per cent for their frequency. They may be increased in all types of inflammation, especially in erythrodermia in which an average of 5.6 per cent was found in my three cases. Fat phagocytes are increased in necrosis.

2. **Tissue Mast Cells** (fig. 4) are 12-20 microns in diameter and contain much cytoplasm stuffed with deep blue granules which are large, coarse, of variable size, and tend to obscure the nucleus. The highest percentage of them in this series (0.5%) is in a normal node. I have not seen any cells corresponding to eosinocytes.\textsuperscript{13, 21}

3. **Fibroblasts** have been described in lymph node smears\textsuperscript{3} but have not been seen in these nodes.

III. **Monoocyte Series**

The origin of these cells remains obscure. Forkner\textsuperscript{14} tabulated 19 suggested modes of origin none of which has been accepted. He demonstrated their origin in the lymph nodes of animals,\textsuperscript{15} but could find none in human nodes. Bloom\textsuperscript{16} found them rarely in lymph nodes and the majority of other reports do not mention them. The school of Tzank\textsuperscript{12} maintains their origin with histiocytes from a "blast cell common to both. Moeschlin\textsuperscript{15} described
lymphatic monoblasts and monocytes in lymph nodes; my own observations are in accord with this. Monocytes have many times been described in pathologic nodes.

1. The monoblast (figs. 1, 3 and 6) is the largest of the differentiated blast cells (diameter 18 microns). The cytoplasm is less abundant and less basophilic than that of the plasmoblast, and the nucleus is irregular in shape, often adherent to the cell membrane and placed across the long axis of the cell. The chromatin is pale and distributed in an open, even network in which are one to three poorly defined nucleoli which are always pale. Their average frequency in these normal nodes is 0.1 per cent compared with figures of 0.3 per cent\(^3\) and 0.12 per cent\(^3\) found by others.

2. The promonocyte (fig. 5) is smaller (diameter 15.5 microns), the cytoplasm is paler and may contain a few azure granules; irregularities in the nucleus are commoner and there are no nucleoli.

3. The monocyte is yet smaller (diameter 13.5 microns). The cells in the nodes show all the variations seen in the blood but oxidase positive monocytes are very rare.

   Cells of the monocyte series are consistently bigger than their lymphocytic counterparts; other points of distinction are the irregularity of their nuclei, their more abundant, clear cytoplasm which may contain azure granules, and their finer and more uniform chromatin. Similar points were made by Bloom\(^3\) and Tzank et al.\(^3\)

IV. Lymphocyte Series

Downey\(^10\) reserves the term lymphoblast for a cell peculiar to lymphatic leukemia. Some observers could find no lymphoblast in normal lymph nodes;\(^4\) others have described such
a cell\(^4\) and all recent reports on lymph node cytology refer to a lymphoblast. Perusal of these papers suggests that the difficulty is mainly one of terminology. There are no agreed criteria for assessing the maturity of lymphocytes. Wiseman's\(^4\) criteria of size, basophilia of cytoplasm and reaction to supravital dyes have been strongly refuted.\(^37\), \(^38\), \(^39\), \(^40\). Sundberg\(^32\) described a nucleolated “reticular lymphocyte” and she and Downey\(^32\) concluded that “Reticular cells assume lymphocytic characters through a series of transition forms which differ from each other so slightly that there is no object in describing any one of these cells as a typical stage.” With this statement I am in agreement but clinical medicine demands some means of assessing maturity, and nuclear structure seems to be the most reliable criterion.\(^41\), \(^42\)

1. **The lymphoblast** (figure 5) is the smallest nucleolated cell seen in lymph nodes (diameter 13 microns). The cytoplasm is scanty and moderately basophilic. The chromatin is distributed in fine, pale, closely-packed strands. One or two small pale nucleoli are always present.

2. **The prolymphocyte** contains more cytoplasm than other lymphocytic cells. The chromatin is pale, similar to that of the lymphoblast, but there are no nucleoli.

3. **Differentiated lymphocytes** are smaller than prolymphocytes and the nuclei are characterised by blocks of dense chromatin which may be separated by clear areas. The cytoplasm is pale blue and is often visible only as a thickening at one edge of the cell. They form the majority of the cells of normal nodes (average 83.5%).

The average for the whole series in these 15 normal nodes is 94.2 per cent (range 87-96%).
compared with 97.18 per cent\textsuperscript{25} and 97.8 per cent\textsuperscript{26} in other series. The percentage of lymphocytes is consistently reduced in disease of lymph nodes.

V. Plasma Cell Series

A blast cell in this series was described in lymph nodes by Moeschlin.\textsuperscript{17} Stuyt\textsuperscript{17} described a similar cell but was not convinced of the origin of plasma cells in lymph nodes.

1. The plasmoblast (figs. 1 and 3) is distinguished from other blast cells by its more abundant, deeply basophilic cytoplasm which often contains vacuoles and a clear area near the nucleus, but its fine rather darker chromatin, and by the presence of as many as six large, well-defined, blue nucleoli. They are rare; none was seen in six normal nodes and in only two nodes was one seen in the differential count.

2. The proplasma cell contains more cytoplasm than the plasmoblast, usually with a clear zone near the nucleus. The nucleus is smaller and there are no nucleoli.

3. Plasma cells vary greatly in size, depending on the amount of cytoplasm. The nucleus is small and eccentric (diameter 8.1 microns), and similar to that of the differentiated lymphocyte, either dense and pyknotic or containing blocks, sometimes arranged in the classical cartwheel manner.

The average frequency of the series in normal nodes is 2.3 per cent compared with 0.08 per cent\textsuperscript{25} and 0.02 per cent.\textsuperscript{18} The high figure in my series is largely a result of one case in which 5 per cent are present.
VI. Myeloid Cells

Polymorphonuclear leukocytes of all types are seen in normal nodes, presumably from the blood. De Renzi and Michelazzi\textsuperscript{25} found 0.96 per cent megakaryocytes but others have not described them in normal nodes. The percentage of polymorphs in disease depends mainly on blood contamination but all, especially eosinophils, may be present in excess in Hodgkin’s disease. Such increase is not constant and may occur in other disorders.

Mitoses are rare in normal nodes and most take place in cells intermediate between ‘blast cells and adult cells. ‘Blast cells are so rare that examination of inflamed nodes offers the only opportunity of observing transition forms. This gives constant results in different types of inflammation so is probably a true reflection of normal cytogenesis at an increased tempo. The few differential counts published suggest that the classification adopted can give results of a constancy comparable to that accepted in the bone marrow. It is worthy of comment that in those smears in which lymphocytes are relatively few, cells of both monocyte and plasma cell series are in excess; this suggests that such nodes are in fact the site of low grade inflammation, a suggestion which is supported by finding that they are of relatively large size, even within the maximum diameter of 0.5 cm.

Pathologic Lymph Nodes

Terminology. The leukoses and the frank blastomata have been kept separate in this description although modern opinion inclines to include them all under
the heading of neoplasm. The cytology of the lymph nodes in acute lymphatic leukemia differs from that in the lymphoblastic type of sarcoma (figs. 9 and 12); as the clinical picture, prognosis and response to treatment also differs, it seems best to keep them apart. In the same way, the course of the disease of those patients with chronic lymphatic leukemia proved consistently longer than of those with lymphosarcoma, irrespective of the predominant cell in the nodes; it therefore seems best to attempt to separate these groups although this is not always possible, either cytologically or histologically, as they merge imperceptibly. On the other hand, there was no difference in the course of the disease of those grouped as sarcoma, irrespective of the type of cell in the nodes. The term leukemia is retained because the presence of leukemia is of little consequence although it is clear that leukemia is much commoner in those cases with the most mature cells in the nodes.

I. Inflammation

Differential counts of 15 cases show similar features. There is an excess of hemocytoblasts (up to 6.5%), and of the monocyte (up to 11.3%) and plasma cell (up to 17.3%) series, at the expense of lymphocytes. Certain types of inflammation tend to show excess of monocytes (glandular fever and tuberculosis), of plasma cells (syphilis and glandular fever) or of histiocytes (erythroderrma), but it is rarely possible to distinguish them on these grounds. Some of the reticular cells are abnormal in size, shape or nucleoli when the reaction is intense; these resemble pre-Sternberg cells but none is greater than 30 microns in diameter.

1. The diagnoses of non-specific inflammation (3 cases) were made histologically. One case is of particular interest. The nodes, in the groin, were thought clinically to be "within normal limits" and remained so during a long follow-up. The smears obtained are not distinguishable from the other two (figure 5).

2. The excess of plasma cells (5.8%) in syphilis confirms previous reports. There is no difference between the two primary and the secondary cases.

3. Primitive cells in the lymph nodes in glandular fever were described by McLean. They have usually been described as lymphocytes. Excess of monoblasts and plasmoblasts has also been described, and my results confirm this; 0.9–1 per cent monoblasts and 2.2–2.5 per cent plasmoblasts were seen in my two cases. Cells have been described as specific for glandular fever but all the cells seen in my smears have been seen in normal nodes and much more frequently in inflamed nodes, although some of the monocytes show unusually marked clumping of nuclear chromatin (figure 6). The percentage of hemocytoblasts is outstandingly high (up to 6.5%). Smears from a single case of Herpes Zoster are indistinguishable from those of glandular fever.

4. The inflammatory reaction is particularly intense in erythroderrma (3 cases) which gives the best examples of the changes of inflammation. All three cases were of unknown etiology, section of the nodes showing the features of lipo-melanotic reticulosis. In addition to a marked excess of the monocyte (5.4–9.8%) and plasma cell (6.4–17.3%) series and of polymorphs (1.7–3.7%), there is a striking
excess of histiocytes (2.4–11.2%) stuffed with fat vacuoles or green pigment which I have seen in no other condition.

5. The earliest changes in tuberculous lymphadenitis are non-specific. The only means of making a definite diagnosis is demonstration of tubercle bacilli; they were found in 5 per cent and 10 per cent of cases, and in only one of my six cases. Epithelioid cells may be so rare as to be of little value in diagnosis or so common as to suggest neoplasm. Forteza Bover found 1.2–7.1 per cent epithelioid cells and 0–0.7 per cent Langhans' cells in 11 cases.

This type of inflammation is peculiar in showing excess of macrophages without excess of plasma cells or of any primitive cells. Epithelioid and Langhans' cells are present in three of my cases; pus only was aspirated from the other three. Epithelioid cells are also present in five of my cases of Hodgkin's disease and the case of sarcoid. The cytoplasm of epithelioid cells is abundant, of a peculiar thick, cloudy or stringy texture and merges imperceptibly with the background. The nucleus is characteristically lozenge-shaped and similar in all other respects to that of the histiocyte (fig. 7).

II. Reticulosis

1. The first reports of the cytology of Hodgkin's disease have been followed by more accounts of this disease than of any other. A detailed description of the
pleomorphic cytology was given by Guggenheim. As many as 26.5 per cent monocytes have been found in some cases, with up to 18 per cent eosinophils, 49 per cent neutrophils and predominant fibroblasts, plasma cells or histiocytes in others. The term pre-Sternberg cell has been introduced to describe the precursor of the multinucleated Sternberg cell.

The 17 cases examined show that there is a slight excess of the monocyte (up to 11.2%) and plasma cell (up to 5%) series and of polymorphs (up to 14.3%), but that blast cells are rare. Pre-Sternberg cells may be as much as 50 microns in diameter but may be recognizable when no bigger than monocytes. The cytoplasm is abundant. The nucleus is large and shows budding and lobulations with chromatin of variable thickness and staining, irregularly distributed and separated by clear spaces giving it a bloated edematous appearance. The nucleoli are their most characteristic feature, being very large or multiple, irregular in shape and staining a deep blue (fig. 8). Sternberg cells containing as many as 97 nuclei and nuclei as much as 150-200 microns in diameter have been described. They have been found in 20 per cent of cases, in all of 33 cases, and in 7 of 32 cases. Forteza Bover found 2.27-13.37 per cent in 8 cases. Pre-Sternberg cells are present in 13 of these 17 cases, Sternberg cells in 7, but in the differential counts
the figures are 7 and 2 respectively. In one case there are many bizarre cells as a result of recent radiotherapy, and in another there are 62.1 per cent pathologic monocytes and the precise histologic diagnosis is in doubt. Pre-Sternberg cells are easily distinguishable from epithelioid cells by their nucleoli, their size and the character of their chromatin.

2. Smears from single cases show: in lymphoid follicular reticulosis, masses of normal lymphocytes and occasional islands of reticular cells; in reticulum cell medullary reticulosis, 29 per cent bizarre-shaped reticular cells which resemble pre-Sternberg cells and cells seen in lymphosarcoma; in sarcoid, small numbers of both epithelioid and pre-Sternberg cells. Another case is included here because the patient had a generalized lymphadenopathy which progressed over the following three years and terminated as reticulosarcoma; although sections from two surgical biopsies show non-specific changes only, smears contain 27.2 per cent pathologic monocytes, suggesting a diagnosis of reticulosis.

3. Smears from a single case of acute lymphatic leukemia contain almost 100 per cent primitive 'blast cells which are quite different from any cells of normal nodes and any other in this series (fig. 9).

Fig. 9.—Acute Lymphatic Leukosis. A smear of cells of similar structure but marked individual variation. X750.
4. The monomorphism of the smears is a characteristic feature of chronic lymphatic leukemia. There are reports of cases showing mainly adult lymphocytes,¹⁶, ¹⁷ and others mainly primitive cells,⁶², ⁶³ or lymphoblasts.⁷² A characteristic "grumeele" cell has been described which contains 4–6 dark blocks of chromatin in the nucleus.¹⁵ An excellent description of the common abnormalities was given by Bessis.⁶¹

Smears from 29 aspirations of 19 cases contain over 99 per cent cells of the lymphocyte series (fig. 10). Eighteen of these cases were leukemic. The predominant cells are pathologic lymphoblasts in 2 cases, prolymphocytes in 3, grumeele cells in 7, and differentiated lymphocytes in 6. In any single smear cells vary greatly in maturity and nucleoli are often seen in nuclei of adult type. Mitoses are rare. Grumeele cells are present in every case but cells with equally discrete dark blocks of chromatin are seen in other disorders and even in normal nodes. The maturity of the cells has no relation to prognosis or duration of disease.

5. Nodes from a single case of acute monocytic leukemia contain 43.3 per cent bizarre pathologic monocytes and monoblasts identical to those in the blood and marrow (fig. 11).
6. In this series, 6.9 per cent primitive myeloid cells are present in one node. The marrow was infiltrated with "blast cells and the patient probably had myeloid leukemia, although the precise diagnosis was not established.

III. Neoplasm

1. Sarcoma (13 cases) of lymph nodes gives monomorphic smears of cells of lymphocytic or reticular type, usually with large blue nucleoli. Complex subdivisions based on the detailed cytology seem unnecessary; these seem to bear little relation to prognosis although Bessis maintains that the cells tend to become more primitive as the disease progresses.

More than 90 per cent of the cells are pathologic in 10 of these 13 cases. Cytopologically, two might be called pure lymphosarcoma, three pure reticulosarcoma (corresponding to the lymphoblastic and reticulum cell lymphoblastomatous of Berman), and three are mixed; two show some differentiation to monocytes and two to plasma cells, although these are more pleomorphic. This subdivision bears no relation to prognosis. Pus was aspirated from one case. The cells have all the features of immaturity and, in addition, show abnormalities in structure. Nucleoli

Fig. 11. Acute Monocytic Leukemia. Pathologic cells of the monocyte series with irregular nuclei, some of which contain nucleoli, adherent to the cell membrane and placed across the cell. X750.
are present in some nuclei in each smear and are large or multiple and stain blue. The cells are more primitive than those of leukemia and there is less variation from cell to cell, mitoses are much more frequent in sarcoma, nucleoli of sarcoma cells are bigger and stain blue, and granule cells are rarely seen (figs. 12 and 13); in spite of these differences, the two groups merge imperceptibly.

2. Smears from secondary carcinoma (8 cases) of lymph nodes are also monomorphic but there is marked variation from cell to cell in size, staining, and in relative areas of cytoplasm, nucleus and nucleoli. The chromatin is usually dark. Nucleoli are present in some nuclei of every smear and usually stain blue (figs. 14 and 15). Mitoses are less common than in sarcoma; none was seen in five cases. There is a striking tendency for the cells to adhere in nests; this was seen in every case except one but in no other condition except the salivary tumor. In 6 cases all the cells are pathologic, in the others 91 per cent and 64 per cent. The diagnosis of malignancy is thus much more certain than in exfoliative cytology. Surgical biopsy of one of these cases showed non-specific changes only, the diagnosis of malignancy being made post mortem.

3. Neither case of secondary melanoma contained much pigment. In one, almost all the cells are pathologic and there is little variation in structure. In the
other, 2 per cent of the cells are similar to those in the first case but are of monstrous size (up to 60 microns in diameter — figure 16), the remaining cells being lymphocytes. Both smears are striking for the size, number and blueness of the nucleoli, and both contain multinucleated cells. Some cells contain masses of small vacuoles at one side, giving them a foamy appearance not seen in any other smears. Individual cells closely resemble pre-Sternberg cells.

4. A case of salivary tumor is included in this series because it was thought, both clinically and at operation, to be a lymph node. Cell nests are present, but nucleoli are small, and occasional cells contain masses of black, red or green pigment such as have been seen in no other condition.

Discussion

Survey of this series suggests that the cytology of malignant disease and of some cases of reticulosarcoma is sufficiently characteristic for diagnosis. It remains to be seen whether any classification can be made from smears which would be of clinical value for diagnosis or prognosis, and whether it would throw any light on the nature of the underlying disease. The classification of Pavlovsky has achieved most popularity but I have found it of limited value. Strunge's classification...
Fig. 14.—Carcinoma. A group of malignant cells some of which contain blue nucleoli (primary in colon). X750.

Classification is too cumbersome for ordinary clinical practice. Stuyt's\textsuperscript{17} conclusions are more helpful, and my results confirm his statement that diagnosis is made on abnormal cells rather than on the relative frequency of normal cells. The time thus saved on differential counts is much better spent on a careful examination of smears under the one-sixth objective of the microscope; most abnormal cells are large and easily seen at this magnification. The following classification is of some assistance in diagnosis.

I. No abnormal cells are present

Most such lesions are inflammatory. The type of inflammation may be indicated by the type of cell present but precise diagnosis is rarely possible. Most observers found tuberculosis and Hodgkin's disease impossible to distinguish, although Weil et al.\textsuperscript{1} thought the pleomorphism of the latter diagnostic. Further information can be obtained only by repeated examination for abnormal cells or, more satisfactorily, by excision of a node. The proliferation of cells in inflammation depends on the activity of multipotent stem cells resulting in an increase in all types of primitive cell although one type of inflammation may cause differentiation to one series more than another. The evidence suggests that it is monocytes, rather than
lymphocytes, which proliferate in glandular fever; the changes are rarely sufficiently specific for diagnosis, although Morrison et al.21 were able to diagnose all their cases. It is clear that smears of this type do not rule out the presence of serious disease.

II. Abnormal cells are present

1. Large numbers of abnormal cells (more than 80%) of the same general type but showing some variation from cell to cell—this is diagnostic of neoplasm or leukosis, if the rare cases of tuberculosis containing very many epithelioid cells are excepted.21 14 27 Distinction of lymphatic leukosis from lymphosarcoma is often not possible even from sections. Distinction of the type of neoplasm may not be possible even on detailed examination of cells, but this is often of little clinical importance. Smears of neoplasm may contain fewer abnormal cells than this but inclusion of doubtful cases makes the method unreliable.

2. Small numbers of abnormal cells suggest tuberculosis or sarcoid if they are epithelioid type, Hodgkin's disease if of pre-Sternberg or Sternberg type. Tuberculosis or sarcoid cannot be distinguished unless tubercle bacilli are found.27 26
Epithelioid cells are not pathognomonic of these conditions and serve mainly to indicate careful search for tubercle bacilli. Sternberg cells are said to be pathognomonic of Hodgkin's disease but have been seen in lymphogranuloma inguinale and in mycosis fungoides. Similar cells are seen in lymphosarcoma and melanoma but the large numbers prevent confusion. Primitive myeloid cells are strongly suggestive of myeloid leukemia although they have been seen in inflammation and in Hodgkin's disease.

3. Moderate numbers of abnormal cells suggest some form of reticulosis, although the very cellular type of Hodgkin's disease and the less cellular types of neoplasm may be included.

4. Aspiration of necrotic tissue is often unhelpful in diagnosis, or even misleading. Bacteriologic examination may demonstrate suppurative infection or tuberculosis. Smears should always be made and examined for cells particularly at the ends. Epithelioid cells may be seen even in pus and in such circumstances are almost diagnostic. Nests of malignant cells can sometimes be seen, as in one of my cases.

5. Aspiration of non-lymphatic swellings is an occasional source of serious error. Stahel made a special study of this.
LYMPH NODE SMEARS IN DIAGNOSIS OF LYMPHADENOPATHY

The abnormalities of cells in the different reticuloses are so similar that it seems unlikely that study of smears will assist classification. Close study and follow-up of the cases in this series shows that neither the degree of abnormality nor the number of abnormal cells is any guide for prognosis.

In order to test the accuracy of the method, one smear from each of the 85 successful aspirations was numbered and placed at random by an assistant. Each smear was examined for an arbitrary period of 15 minutes. 52 cases (61%) were placed in the correct group (table 1). The only case placed in the wrong group was that of monocytic leukemia which was diagnosed reticulosarcoma. In the inflammatory group, only 8 cases were diagnosed and the correct type of inflammation was diagnosed in only one case each of tuberculosis, glandular fever and syphilis, and two cases of erythrodermia. Only 5 cases of Hodgkin's disease were correctly diagnosed; in this group particularly more diagnoses might have been made if more than one smear had been examined for a longer time. The cases of reticulum cell medullary reticulosis and the reticulosis of doubtful type were both diagnosed "reticulosis." Most of the leukoses were diagnosed and the method should be of value in aleukemic cases. It is in the neoplastic group that the method is of greatest clinical value. All except 3 of the cases were diagnosed as neoplastic, these three being impossible to distinguish from lymphatic leukemia. The correct type of neoplasm was diagnosed in 15 cases, including the salivary tumor; it was not possible to distinguish carcinoma from sarcoma in the remainder.

Morrison et al. diagnosed all of a series of cases of glandular fever, lymphatic leukemia and metastatic cancer, and 80 per cent of cases of inflammation, Hodgkin's disease and lymphosarcoma. Forkner diagnosed 21 of 25 nodes, Cathie 18 of 32 nodes, and Blinkenberg of 157 nodes. All these reports are in agreement with the conclusion of Martin and Ellis that the method is most valuable in diagnosis of malignancy. Reports of the success-rate in inflammation and particularly in Hodgkin's disease are much more variable and it seems that diagnostic criteria must be strict if accuracy is to be maintained.

SUMMARY AND CONCLUSIONS

1. A description of the cells of normal lymph nodes is presented, based on the examination and differential counts of smears from 15 nodes obtained at operation.
2. 95 per cent of the cells of normal nodes are lymphocytes. The most primitive cell is the multipotent hemohistioblast which gives rise to the histiocyte and the hemocytoblast the parent of three differentiated 'blast cells, the lymphoblast, monoblast and plasmoblast. 'Blast cells are rare in normal nodes but can be observed in inflammation.
3. The cytology of 85 pathologic nodes is described, the final diagnoses being confirmed histologically in most instances.
4. The features of inflammation are similar irrespective of the cause. Some types of inflammation result in excess of one series of cells more than another; it is rarely possible to distinguish them on these grounds, but the cytology may indicate those cases in which search for tubercle bacilli is likely to be rewarding.
5. Sternberg cells and their precursors are almost specific for Hodgkin's disease. Diagnosis is possible if they are present together with a pleomorphic cytology.
6. A diagnosis of leukemia or primary or secondary neoplasm can be made if 80 per cent of the cells are abnormal. Distinction of these three groups from smears depends on the type and distribution of cells. The degree of abnormality bears no relation to prognosis.

7. Diagnosis depends on finding abnormal cells; differential counts are of little value.

8. Analysis of the few cases of reticulosis examined suggest that cytologic classification is unlikely to be useful.

9. Examination of one smear from each of 85 nodes for 15 minutes without clinical information enabled a diagnosis to be in 52 cases; the only error was that monocytic leukemia was called reticulosarcoma.

10. On two occasions, one of secondary carcinoma and one of reticulosis, the correct diagnosis was made from smears at a time when histology showed non-specific changes only.

11. The method should find a useful place as a screening test in diagnosis of lymphadenopathy, excision of a node being carried out if aspiration fails or if the diagnosis cannot be made from smears.

**Summario e Conclusiones in Interlingua**

1. Es presentate un description del cellulas de normal nodos lymphatic, basate super le examine e contos differential de frottis ab 15 nodos obtenite in interventiones chirurgie.

2. In nodos normal, 95 pro cento del cellulas es lymphocytos. Le cellulas le plus primitive es le multipotente hemohistioblastos que es le forma original del histiocytes e etiam del hemocytoblastos que es le precursores de tres differentiate cellulas "blastic," i.e. del lympho-, mono-, e plasmoblastos. Cellulas "blastic" es rar in nodos normal sed pote esser incontrete in casos de inflammation.

3. Es describite le cytologia de 85 nodos pathologic. Le diagnose final esseva confirmate per medios histologic in le majoritate del casos.

4. Le caracteristicas del inflammation es simile, sin reguardo al causa responsabile pro illo. Certe typos de inflammation resulta in excessos de un serie de cellulas plus tosto que de un altere. Il es rarmente possibile distinguere le varie typos de inflammation super iste base, sed le cytologia pote a vices servir a identificar le casos in le quales le cerca pro baclilos tuberculotic es promittente.

5. Cellulas de Sternberg e lor precursores es quasi specific pro morbo de Hodgkin. Le diagnose deveni possibile si le cellulas de Sternberg occurre in le presentia de un cytologia pleomorphic.

6. Le diagnose de leucosis o neoplasma primari o secundari es permitite si 80 pro cento del cellulas es anormal. Le distinction de iste tres gruppos super le base de frottis depende del typo e del distribution del cellulas. Le grado de anormalitate observate non se monstra in correlation con le prognose.


8. Le examine del pauc numeroso in numero cases de reticulosis examinate pare indicar que un classification cytologic es probablemente sin utilitate.

9. Le examine de un frottis ab cata un de 85 nodos, arbitrarimente limitate a 15 minutas e non supplementate per informationes clinic, rendeva possibile un
diagnose in 52 cases. Le sol error esseva que leucosis monocytic esseva designate como reticulosarcoma.

10. In duo casos—un de carcinoma secundari, le altere de reticulosarcoma—le correcyte diagnose esseva facite super le base de frottis a un tempore quando studios histologic revelava solmente cambiamenti non-specific.

11. Le metodo merita esser utilizate como test de assortage preliminari in le diagnose de lymphadenopathia. Le excision de un nodo lymphatic essera necessari in casos in que le aspiration non succede o quando le diagnose non pote esser facite super le base de frottis.

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LYMPH NODE SMEARS IN DIAGNOSIS OF LYMPHADENOPATHY

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Lymph Node Smears in the Diagnosis of Lymphadenopathy: A Review

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