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RELATION BETWEEN EXTENSION OF NON-HODGKIN'S LYMPHOMA AND LYMPHOGRAPHIC FINDINGS

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The peripheral lymphocyte count often decreases with the clinical progression of a malignant non-Hodgkin's lymphoma (HANSEN & GOOD 1974, LAPES et coll. 1977, LUKES 1979, ANDERSON et coll. 1981). Extensive involvement of lymph nodes seems to alter the number of peripheral lymphocytes. The findings at lymphography were found to be reflected, to some extent, in the number of peripheral lymphocytes, including their subpopulations (MATSUBARA et coll. 1980). WONG et coll. (1975) reported a difference in the type of extension of non-Hodgkin's lymphoma between nodal and extra-nodal types of the disease. Therefore, in the present investigation, the relation between the lymphographic findings and the peripheral lymphocyte counts was analyzed with regard to anatomic type of disease (nodal, extra-nodal, and Waldeyer's ring) and histopathologic subtype (RAPPAPORT 1966).

Material and Methods

One hundred and five previously untreated patients with non-Hodgkin's lymphoma (61 males, 44 females, 6–86 years of age, mean 50.1 years) were analyzed between April 1973 and June 1982. The histologic diagnosis in these cases was retrospectively revised according to the RAPPAPORT classification and the correlation between findings at bipedal lymphography and absolute peripheral lymphocyte counts was analyzed. Cases with leukemic changes or cases complicated by diseases that might give rise to reactive lymphoid hyperplasia (PARKER et coll. 1974) were excluded. Patients who had been surgically explored or had received treatment for disease in the abdominal region before lymphography were also excluded.

The clinical stage of disease for each patient was defined according to the Ann Arbor classification (CARBONE et coll. 1971) by physical and laboratory examinations, lymphography, bone marrow aspiration, liver and ^{67}Ga-citrate scans. Lymphography was performed by the standard bipedal route and evaluated according to the criteria of TAKAHASHI & ABRAMS (1967). SCHELLINGER et coll. (1974) have shown characteristic lymph node patterns for different histologic subtypes (RAPPAPORT) of non-Hodgkin's lymphoma. In the present investigation, however, a simpler method of analysis was used. The lymph node chains were divided into 7 anatomic regions: right and left inguinal, right and left iliac, common iliac, and right and left lumbar chains. Foaminess or filling defects in the lymph nodes constituted the basis for the quantitative analysis. Filling defects, however, were used as an expression of lymph node involvement only when foaminess could not be evaluated.

The patients were classified into supra- and infradiaphragmatic groups, according to the site of the

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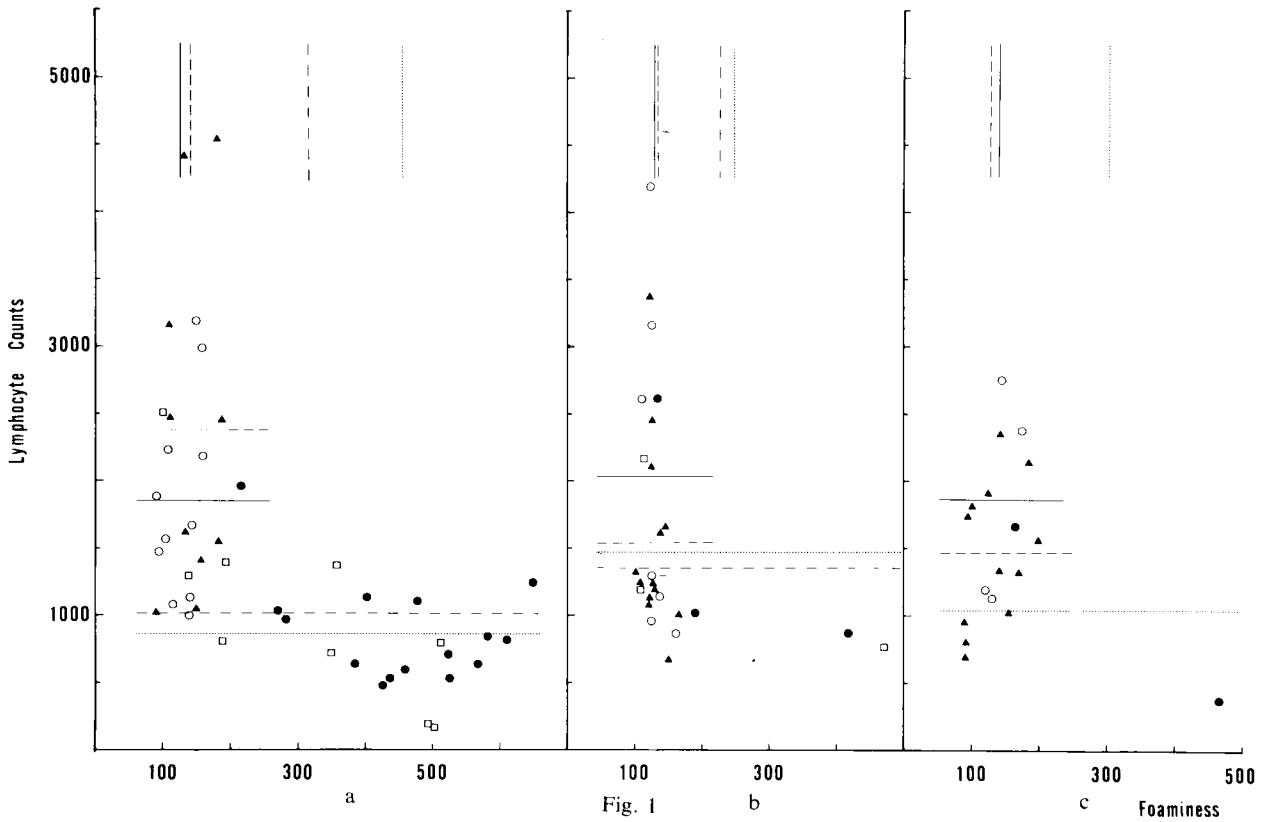
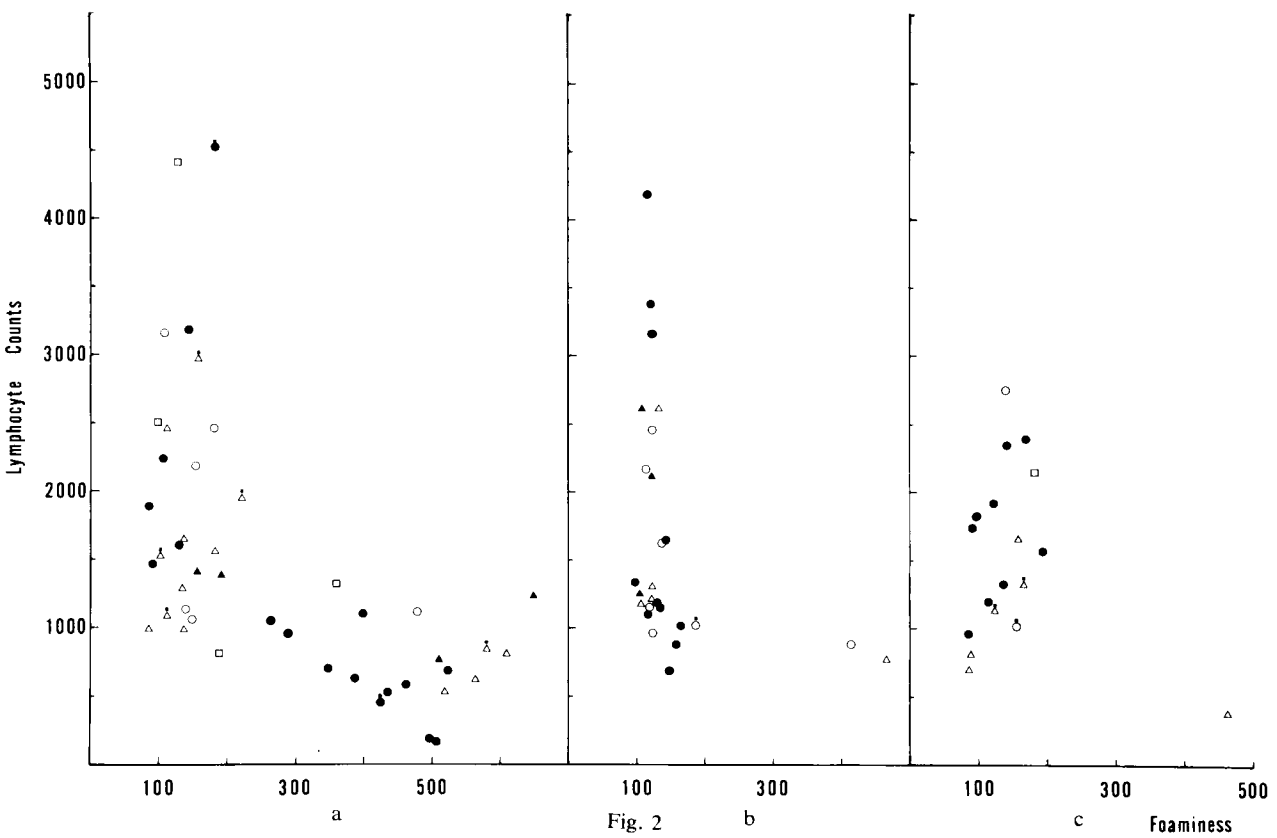

Lymphocyte Counts
5000
3000
1000
100
300
500
a
b
c
Foaminess

Fig. 1


Lymphocyte Counts
5000
4000
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Foaminess

Fig. 2

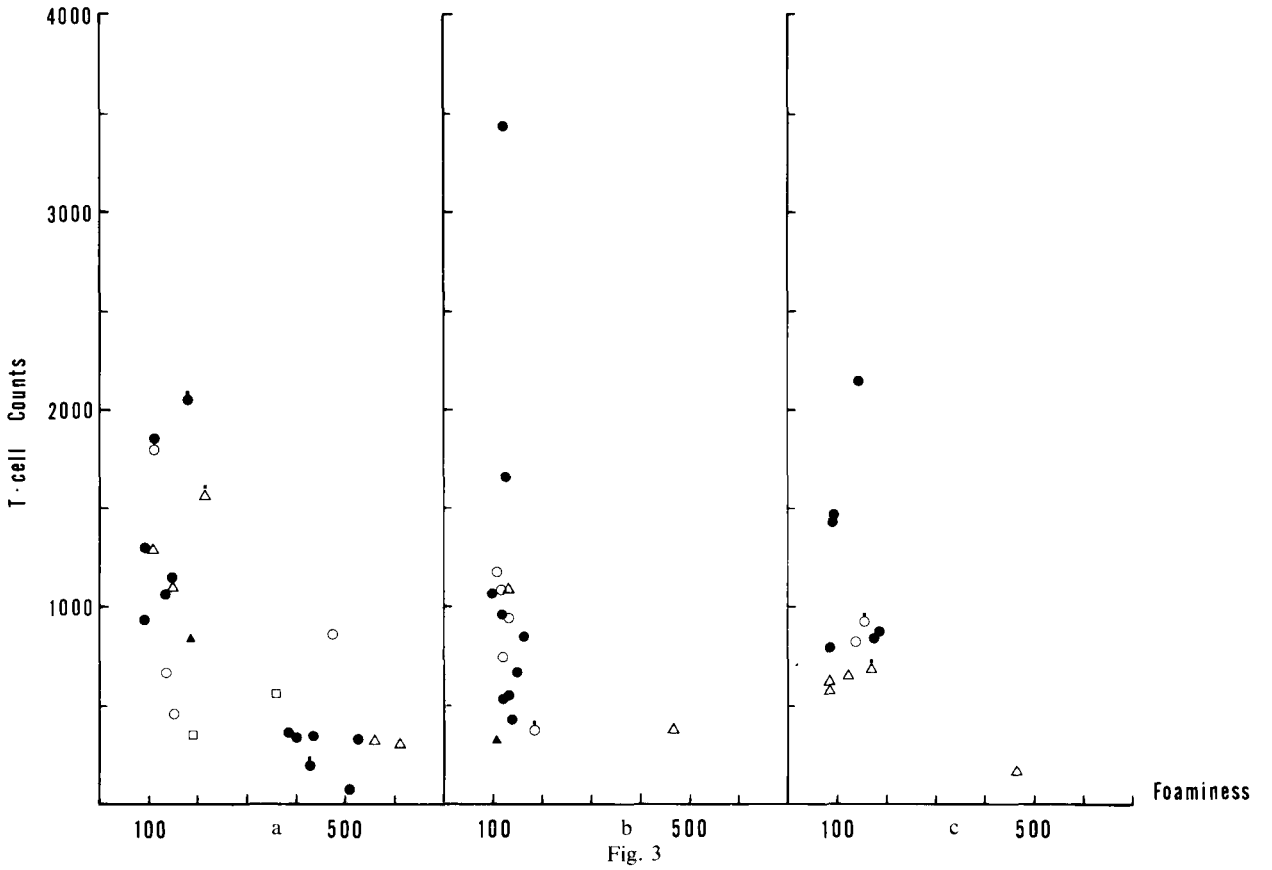

Fig. 3

Fig. 1. Peripheral lymphocyte counts plotted against total foaminess scores in patients classified according to the clinical stage of the disease. a) Nodal, b) extra-nodal, c) Waldeyer's ring. Stage I (—○—), stage II (--▲--), stage III (···●···), stage IV (—·—□—·—). Horizontal and vertical lines indicate mean values of lymphocyte counts and foaminess, respectively.

Fig. 2. Peripheral lymphocyte counts plotted against total foaminess scores in patients classified according to histologic subtypes (Rappaport). a) Nodal, b) extra-nodal, c) Waldeyer's ring. Lymphocytic, well differentiated (▲), lymphocytic, poorly differentiated (△), mixed, lymphocytic and histiocytic (○), histiocytic (●), Burkitt type (□), nodular lymphoma (·; lack of this mark indicates diffuse lymphoma).

Fig. 3. T-lymphocyte counts plotted against total foaminess scores in patients classified according to histologic subtypes (Rappaport). a) Nodal, b) extra-nodal, c) Waldeyer's ring. Symbols as in Fig. 2.

primary presentation, 89 and 16 patients, respectively, in the two groups. The former group was further divided into nodal and extra-nodal groups according to the initial site of involvement. Lymphomas originating in Waldeyer's ring were classified as a separate group. Clinical stages and histologic subtypes appear in Tables 1 and 2. For each group, the relation between pathologic findings in the lymphadenograms and the peripheral lymphocytes and their subpopulations was analyzed. The nodal supra-diaphragmatic group included cases with disease located in the cervical, supra-clavicu-

Table 1

Clinical stage and initial site of disease in the supra-diaphragmatic group

Site	Stage				Total
	I	II	III	IV	
Nodal	11	10	15	9	45
Extra-nodal	7	13	3	3	26
Waldeyer's ring	4	12	2	0	18
Total	22	35	20	12	89

Table 2

Histologic subtype and initial site of disease in the supra-diaphragmatic group

Site	LWD	LPD	M	H	B	Total
Nodal	4	14 (7)	6	17 (2)	4	45 (9)
Extra-nodal	3	5 (1)	7	11	0	26 (1)
Waldeyer's ring	0	6 (2)	2	9 (1)	1	18 (3)
Total	7	25 (10)	15	37 (3)	5	89 (13)

LWD: Lymphocytic, well differentiated. LPD: Lymphocytic, poorly differentiated. M: Mixed, lymphocytic and histiocytic. H: Histiocytic. B: Burkitt type. ( ): Histologically nodular in type, otherwise diffuse.

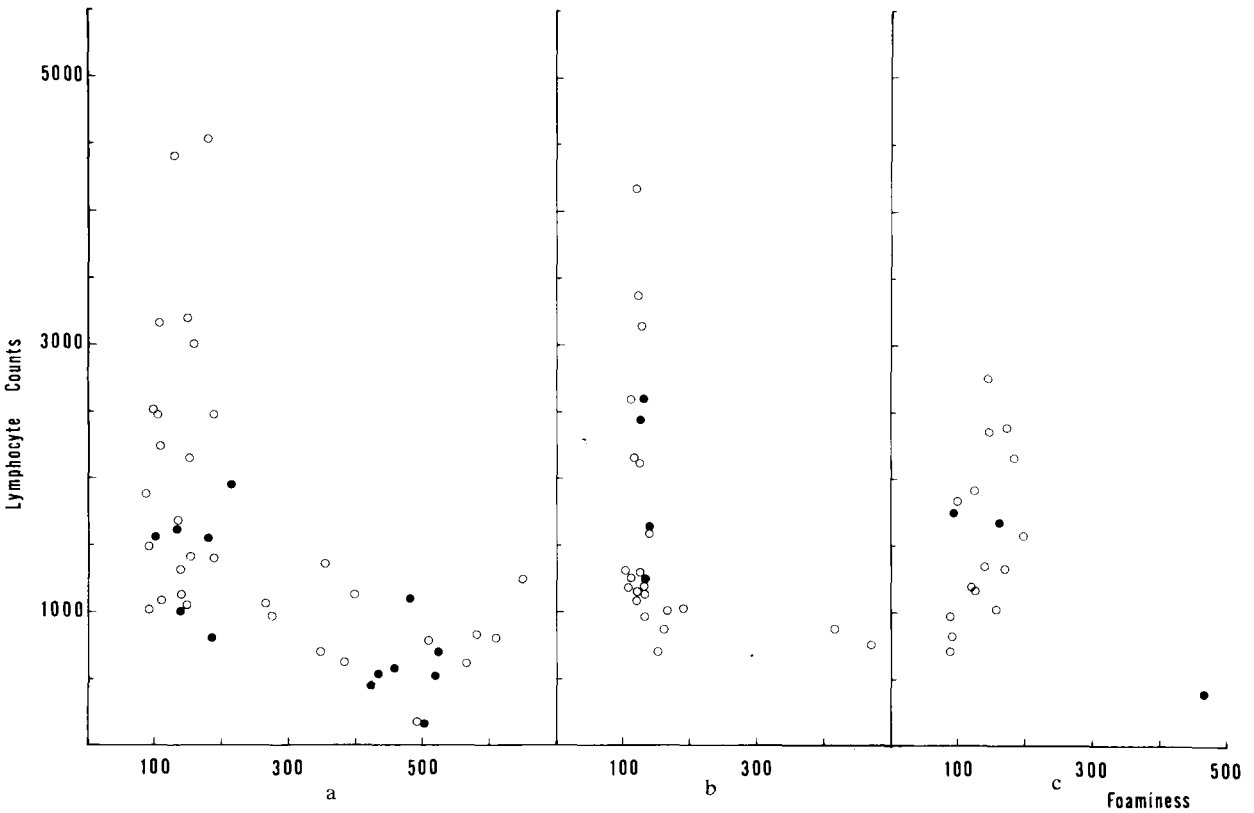

Fig. 4. Peripheral lymphocyte counts plotted against total foaminess scores in patients classified according to bulkiness of the disease. a) Nodal, b) extra-nodal, c) Waldeyer's ring. Patients without (○) and with (●) bulky mass.

lar, infra-clavicular, axillary, hilar and mediastinal nodes. The extra-nodal supra-diaphragmatic group comprised cases with lesions in the oral cavity, nasal cavity, mandibular bone and orbits. In the infra-diaphragmatic group, especially cases with abdominal disease, the lesions were so extensive that it was impossible to ascertain the exact location. Thus, these patients were simply classified into two major groups: 9 nodal and 7 extra-nodal cases. The former group included cases with inguinal and abdominal lymphomas (pelvic, intra-peritoneal and retro-peritoneal lymph nodes). The latter group comprised patients with primary involvement of abdominal viscera, skin of the lower extremity, and femoral bone. In each group, the relation between the lymphographic foaminess score and the peripheral lymphocyte count was analyzed according to clinical stage and histologic subtype. The T-lymphocyte counts were also assessed in 54 cases with supra-diaphragmatic presentation, of which 24, 17 and 13 cases belonged to the nodal, the extra-nodal and the Waldeyer's ring groups, respectively. Furthermore, the relation of a bulky mass of lymphoma (a major axis larger than 5 cm was regarded as a bulky mass) to the foaminess score and the lymphocyte count was noted.

The degree of foaminess or filling defects was classified as grade 0–3, according to TAKAHASHI & ABRAMS, and these grades were arbitrarily assigned scores: grade 0=10, grade 1=40, grade 2=70, and grade 3=100. With respect to the filling defects, grade 0 indicated no filling defect, grade 1 less than ⅓ replacement of the node, grade 2 ⅓ to ⅔ replacement, and grade 3 more than ⅔ replacement. The total score was obtained by adding the individual scores for the degree of foaminess or filling defects in all lymph nodes with a greater diameter than 5 mm in the 7 anatomic areas.

Absolute peripheral lymphocyte counts, calculated from white blood cell counts and differential counts on Giemsa-stained smears, were estimated within a week before lymphography. For the estimation of lymphocyte subpopulations, rosette formation in sheep red blood cells and identification of complement-receptor-carrying lymphocytes were used. Only the T-cell values were analyzed in the present series. The radiologist evaluating lymph node foaminess was not informed about histology or

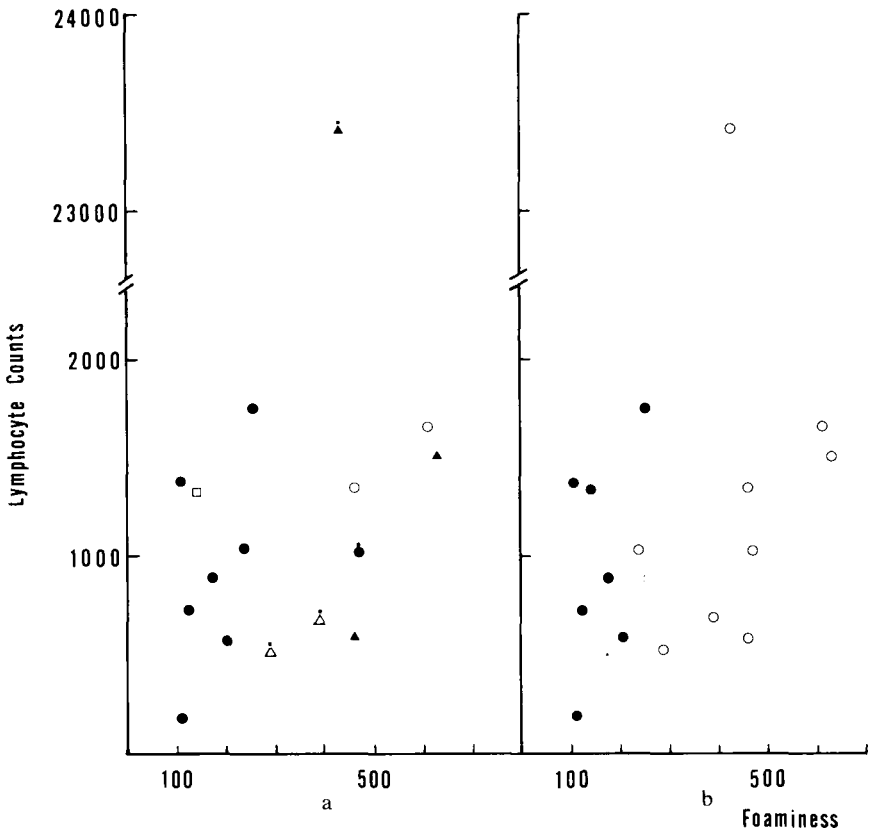

Fig. 5. Peripheral lymphocyte counts plotted against total foaminess scores in patients with infra-diaphragmatic initial disease. a) Histologic subtype. Lymphocytic, well differentiated (▲), lymphocytic, poorly differentiated (△), mixed, lymphocytic and histiocytic (○), histiocytic (●), nodular lymphoma (•; lack of this mark indicates diffuse lymphoma). b) Nodal (○) and extra-nodal (●) origin.

lymphocyte counts. Student's t-test was used in order to estimate the significance of a difference between two populations.

Results

In the nodal, extra-nodal and Waldeyer's ring groups the peripheral lymphocyte count showed a tendency to decrease when the foaminess score increased, although considerable variation was observed.

In the 89 supra-diaphragmatic cases a significant difference in lymphocyte counts between stages I or II and stages III or IV ($p<0.01$) was observed but not between stages I and II or stages III and IV ($p>0.05$). In the nodal group, the peripheral lymphocyte count was found to decrease rather exponentially with the increase of the foaminess score (Fig. 1 a). The foaminess scores in stages III and IV were markedly higher than in stages I and II ($p<0.01$). In addition, the foaminess score in stage III, in which lymph nodes were more extensively involved, was higher than in stage IV ($p<0.05$). In the extra-nodal group, however, the number of lymphocytes appeared to have decreased before any apparent increase of the foaminess score started, resulting in an L-shaped distribution on a linear scale, although very few cases had an increased foaminess score (Fig. 1 b). In the Waldeyer's ring group, the foaminess score and the lymphocyte count showed an essentially similar relationship as in the extra-nodal group, although there was a larger variation of the foaminess score up to 200 (Fig. 1 c).

In the nodal, extra-nodal and Waldeyer's ring groups, the histopathologic type according to RAPPAPORT was not significantly correlated with the foaminess score or the lymphocyte count (Fig. 2). Nodular lymphoma, although the number of cases was small, was seen more frequently in the lymphocytic poorly differentiated type, but did not show any specific type of distribution. The T-cell count seemed to have an essentially similar relation to the foaminess score as the whole peripheral lymphocyte count (Fig. 3). The cases with bulky disease in the

nodal group more often had a lymphocyte count less than 1 200/mm^3 ($p<0.05$; Fig. 4 a), but no such relation was noted in other groups (Fig. 4 b, c).

In the group with initial infra-diaphragmatic presentation, 2 patients of 7 with extra-nodal disease demonstrated a foaminess score of more than 200. All patients with nodal disease revealed foaminess scores above 200 ($p<0.05$). The lymphocyte counts were, however, not decreased in the cases with an increased foaminess score (Fig. 5). In the present series, the histologic subtype thus did not seem to influence the relation between foaminess score and lymphocyte count.

Discussion

In the nodal type of non-Hodgkin's lymphoma an increase of the foaminess score was associated with a decrease of the peripheral lymphocyte count (Fig. 1 a), which suggested a gradual replacement of lymphocytes with lymphoma cells within the lymph nodes during the progression of the disease. In the extra-nodal group, however, the relation between the foaminess score and the peripheral lymphocyte count was quite different and cases with increased lymph node foaminess were very few. This observation indicates that the extra-nodal type of disease rarely extends to lymph nodes demonstrated by bipedal lymphography and that the rarely seen tumor involvement of the nodes may be preceded by a marked reduction of the lymphocyte count. In most cases of this extra-nodal group, the extension of the disease appears to be exclusively directed towards extra-nodal tissues or organs, which is in good agreement with clinical observations (WONG et coll., HEIFETZ et coll. 1980). A similar relation between foaminess score and lymphocyte count was seen in the Waldeyer's ring group. According to the hypothesis that neoplastic cells mimic the behaviour of their normal counterparts, it should be possible to relate the clinico-pathologic course of various lymphocytic neoplasms to the behaviour of the corresponding normal variants of the lymphocytes (TAYLOR 1979). The frequent extension of Waldeyer's ring lymphoma to the gastro-intestinal tract has recently been related to the homing tendency of gut-associated lymphoid cells (ELVES 1972, DOUGLAS & WEETMAN 1975, REE et coll. 1980). The somewhat greater variation of the abdominal lymph node foaminess observed in Waldeyer's ring lymphoma might be an expression of the intestinal homing tendency. The present limited series does not, however, allow any definite conclusions.

The T-cell count had a similar relation to the foaminess score as the total lymphocyte count. Signs of immuno-deficiency have been reported to correlate to some degree with histology and clinical stage of the disease (ANDERSON et coll.). In the present analysis, however, no influence of the histopathology on the relation between foaminess score and lymphocyte count could be observed.

An effect of bulky disease upon the relation between foaminess score and peripheral lymphocyte count was found in the nodal group, but not in the extra-nodal or Waldeyer's ring group. The reason may be that the nodal lymphomas have a greater tendency to migrate into lymph node chains and thereby influence the peripheral lymphocyte counts.

In non-Hodgkin's lymphomas originating in the infra-diaphragmatic region (GILBERT et coll. 1973, WEINGRAD et coll. 1982), no consistent tendency was observed with the exception of the different distribution of foaminess scores in nodal and extra-nodal diseases. In the nodal disease of this group, no decrease of the lymphocyte count was evident in spite of an increased foaminess score. This discrepancy may have the following explanation. In the infra-diaphragmatic group the lymphoma cells may have a lesser tendency to migrate into the blood stream, due to a large volume or capacity of the abdominal lymph nodes.

SUMMARY

The relationship between the degree of lymph node foaminess observed in bipedal lymphadenograms and absolute peripheral lymphocyte counts in non-Hodgkin's lymphoma was analyzed with regard to the initial location, clinical stage, histologic subtype, and bulkiness of the disease. In the nodal type of disease with supra-diaphragmatic presentation, an inverse relation was often found between the peripheral lymphocyte count and the foaminess score. However, if the disease originated in the infra-diaphragmatic regions no such relation was found. The implications of these observations are discussed.

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