

## FOLLICULAR LYMPHOMA: A SURVEY of 75 CASES WITH SPECIAL REFERENCE TO THE SYNDROME RESEMBLING CHRONIC LYMPHOCYTIC LEUKAEMIA

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**Summary.**—In a series of 75 cases of follicular lymphoma collected between 1950 and 1971 the following features were singled out as characteristic of, or specially frequent in, follicular lymphoma: (1) the high incidence in females; (2) the long history of symptomless lymph node enlargement; (3) the frequent presence of extensive symptomless disease at presentation, especially in patients below 40 years of age; (4) the syndrome resembling and often confused with chronic lymphocytic leukaemia, in which the notched nucleus cell, when present, is diagnostic; (5) the responsiveness of extensive disease to radiotherapy and alkylating agents at low dosage; (6) the long overall survival and the long survival after relapse; (7) the occurrence of abrupt change in the character of the disease in which, during a period of apparent quiescence, malignant transformation supervenes proving rapidly fatal. In the transformed stage the disease behaves as an invasive metastasizing sarcoma or as a blast cell leukaemia; in both cases the transformation is associated with the appearance of a new cell type, undifferentiated and distinct from that present before the onset of transformation, which may however persist. The syndrome resembling chronic lymphocytic leukaemia occurs only in follicular lymphoma.

IN THE Rappaport classification of the malignant lymphomata (Rappaport, Winter and Hicks, 1956), the status of "follicular lymphoma" was changed. The diversity of appearance of the cells within the "follicles" in different cases was emphasized and the uncertainty of the relationship of the "follicles" to germinal centres was indicated by the substitution of the adjective "nodular" for "follicular". Follicular lymphoma lost its former status as an entity and was now split among the malignant lymphomata as a number of "nodular" variants of the corresponding "diffuse" types classified according to the predominant cell type and its degree of differentiation. The classification has the advantage that the "nodular" variants may be compared with one another and with their diffuse counterparts in respect of any desired feature. The disadvantage is that attention is diverted from consideration of the possibility that the "nodular" variants of the malignant

lymphomata constitute a biological entity, as was implied in older classifications.

Lennert considers the nodular lymphomata as true tumours of germinal centre origin, arising from the germinoblast, a component of the germinal centre, and designates them "germinoblastoma" without further subdivision. Lukes also regards the nodular lymphomata as germinal centre tumours and his classification provides for the observed cytological diversity and for the extent of preservation of the follicular pattern. Both Lennert and Lukes recognize that cells of germinal centre origin may give rise to tumours lacking a nodular or follicular architecture, a concept not considered in the purely descriptive classification of Rappaport. Thus, follicular lymphoma might represent only one part of a larger biological entity, the definition of which awaits clarification.

We believe, from observations over a 25-year period, that several clinical features are, in the aggregate, characteristic

of "follicular lymphoma" though probably only the chronic lymphocytic leukaemia-like syndrome is exclusive to it. We will illustrate these features from a series of 75 of our patients at the Hammer-smith and the Royal Marsden Hospitals seen between 1950 and 1971 in the hope that they may be included among those studied in prospective surveys. The features discussed are: (1) the sex ratio; (2) history; (3) physical signs; (4) the chronic lymphocytic leukaemia-like syndrome and the significance of the notched nucleus cell; (5) response to treatment; and (6) malignant transformation including sarcoma of focal origin with metastases or terminal blast cell leukaemia.

All the histological material was reviewed during 1972\* by Dr I. M. E. Hamlin who classified each case according to Rappaport's nomenclature. The only basis for the selection of these 75 cases was that the blocks of the tissues on which the diagnosis was based could be assembled for reassessment by Professor Lennert, who made in each case a diagnosis of germinoblastoma.

Table I shows the distribution of the cases according to the Rappaport classification (2 cases of "mixed" type have been included with the "poorly differentiated lymphocytic" and "histiocytic" types according to the predominant cell) and the clinical stage. The staging was accomplished in more than half the cases without lymphography, bone marrow biopsy or liver biopsy. Of the patients

studied, 72% were already in Stage III or IV when the diagnosis was established, and the proportion would probably have been higher if current staging procedures had been used in the 21 Stage I and II cases. The 2 cases in which the disease at presentation was apparently confined to the lachrymal and the parotid glands are included in Stage I.

Table II shows the presenting sites of the disease in the 14 Stage I cases. The high proportion of "head-and-neck" presentations reflects the practice of Dr M. Lederman, to whom these patients were originally referred.

### 1. Age and sex

There were 35 males and 40 females. The high proportion of females is characteristic of follicular lymphoma, in contrast to the diffuse lymphomata in which there is an excess of males.

Table III shows the age distribution; 19% of the patients were below age 40 and 52% were between 40 and 59 years.

### 2. History

Four types of development seemed characteristic of follicular lymphoma and in our experience are rarely observed among the diffuse lymphomata: (1) presence of enlarged lymph nodes known to the patient for many years; medical advice sought when additional enlarged nodes appeared; (2) generalized recurrent lymph node enlargement since childhood.

TABLE I.—75 Cases of Follicular Lymphoma:  
Distribution according to Histological Type and Clinical Stage

| Histological type                 | Clinical Stage |    |     |    | All stages |
|-----------------------------------|----------------|----|-----|----|------------|
|                                   | I              | II | III | IV |            |
| Lymphocytic { Well differentiated | 7              | 3  | 5   | 12 | 27         |
| { Poorly differentiated           | 5              | 2  | 11  | 16 | 34         |
| Histiocytic                       | 2              | 2  | 6   | 4  | 14         |
| All histological types            | 14             | 7  | 22  | 32 | 75         |
| 72%                               |                |    |     |    |            |

\* Following a meeting of pathologists arranged by Dr. H. Rappaport in May 1973 in Chicago, these cases would be classified differently.

TABLE II.—14 Cases of Follicular Lymphoma Clinical Stage I

| Site                | Histological Type   |                       |             | All histological types |
|---------------------|---------------------|-----------------------|-------------|------------------------|
|                     | Lymphocytic         |                       | Histiocytic |                        |
|                     | Well differentiated | Poorly differentiated |             |                        |
| Inguinal node       | 2                   | 1                     | 2           | 5                      |
| Tonsil              | 4                   | 0                     | 0           | 4                      |
| Axillary node       | 1                   | 0                     | 0           | 1                      |
| Cervical node       | 0                   | 1                     | 0           | 1                      |
| Post-auricular node | 0                   | 1                     | 0           | 1                      |
| Parotid gland       | 0                   | 1                     | 0           | 1                      |
| Lachrymal gland     | 0                   | 1                     | 0           | 1                      |
| All Stage I         | 7                   | 5                     | 2           | 14                     |
| % of all Stages     | 26                  | 15                    | 14          | 19                     |

TABLE III.—75 Cases of Follicular Lymphoma, Age Distribution

| Age distribution |
|------------------|
| 0-19 : 0         |
| 20-29 : 4        |
| 30-39 : 10       |
| 40-49 : 17       |
| 50-59 : 22       |
| 60-69 : 16       |
| 70+ : 6          |
| Total : 75       |

Advice sought when enlargement seemed permanent and progressive (one case only); (3) recurrent nodes at one site (usually the groin) with repeated excisions for biopsy over several years: the diagnosis made following the first biopsy was reactive follicular hyperplasia; in some cases the possibility of follicular lymphoma was raised. (When, after the final excision, the diagnosis of follicular lymphoma was established, review of the initial biopsy material suggested either that the condition was follicular lymphoma or that there was no reason to change the original diagnosis of reactive follicular hyperplasia); (4) some clinical indication for laparotomy was present: numerous discrete large nodes were found in the mesentery, omentum or both.

### 3. Physical signs

The most characteristic finding, especially in patients below the age of 40, was the presence of extensive, often massive, discrete lymph node enlargement in otherwise symptomless patients, with in-

volvement of sites rarely involved in the diffuse lymphomata as part of generalized disease, namely, pre-auricular, mastoid, occipital, epitrochlear (and along the neurovascular bundle from the elbow to the axilla), infraclavicular, supra and infrascapular, and along the medial border of the scapula. Massive symmetrical involvement of the pelvic and para-aortic nodes was found by lymphography. In elderly symptomless patients, the presence of numerous large discrete mesenteric and omental nodes gave to the abdomen, on palpation, the feeling of a sack of potatoes.

In addition to the extensive lymph node involvement, some patients had extranodal involvement which, in cases of diffuse lymphoma, would have been of sinister import but proved to be readily controllable in follicular lymphoma. The lesions included cutaneous and subcutaneous infiltrates, extension of growth beyond the confines of individual lymph nodes with tethering of one node to another, thickening of the overlying soft tissue, restriction of mobility, oedema and sometimes reddening of the overlying skin, compression of veins, limb oedema and serous effusions.

### 4. The chronic lymphocytic leukaemia-like syndrome

Several patients were referred as cases of chronic lymphocytic leukaemia (CLL) and the diagnosis would have been accepted if lymph node excision for biopsy

had not been carried out. The diagnosis of CLL had been made originally because lymphocytosis and heavy lymphocytic infiltration of the bone marrow had been found. Lymph node biopsy is especially important in patients below age 40, when CLL is uncommon. We suspect that a high proportion of patients below this age diagnosed as having CLL would be found to have follicular lymphoma if lymph node biopsy were made.

In 17 cases the lymphocyte count at presentation was 5000/ $\mu$ l or more, the highest being 30,000/ $\mu$ l. In 8 other cases, in which the peripheral lymphocyte count was below 5000/ $\mu$ l, films of bone marrow aspirates showed lymphocytic infiltration (lymphocytes more than 25% of the nucleated cells).

*Notched nucleus lymphocytes.*—A characteristic form of lymphocyte, the “notched nucleus cell” of Anday and Schmitz (1952), or the “haematogone” of Rosenthal *et al.* (1952) was found in the peripheral blood in 8 of the 17 cases with lymphocytosis and accounted for the majority of lymphocytes in the cases in which the lymphocyte counts were considerably elevated, but the proportion was variable in those with only moderate lymphocytosis. In addition, notched nucleus cells were found in the blood films of some patients whose lymphocyte counts were below 5000/ $\mu$ l, but many films are no longer available for review and the proportion of cases in which notched nucleus cells were present cannot be

given. In 3 cases of lymphocytosis, notched nucleus cells were not present in the blood films. Table IV shows the histological diagnosis made in the 17 cases of lymphocytosis. It should be noted that notched nucleus cells were present in the blood films of 2 cases of “histiocytic” nodular lymphoma. We have also seen them as the main cell constituent in lymph node aspirates from cases of “histiocytic” nodular lymphoma and we believe that the pale cells with irregular reniform or cleft nuclei, accepted in histological sections as histiocytes, are in fact notched nucleus cells.

The morphological characteristics of these cells in May-Grünwald-Giemsa stained films of blood, bone marrow or aspirated lymph node juice suggests that they are lymphocytes, but we have not yet had the opportunity to examine these cells for specific surface markers, by cytochemical methods or by electron microscopy. In May-Grünwald-Giemsa stained films (Fig. 1), notched nucleus cells are on average slightly larger than small lymphocytes and they have very scanty pale blue cytoplasm, often seemingly confined to one-third to two-thirds of the cell circumference. The nucleus is highly characteristic. The most striking feature is the presence of one or 2 clefts, varying in depth from a shallow indentation or notch to a straight, deep cleft that divides the nucleus into 2, or, when 2 clefts are present, into 3 parts. Nucleoli are not visible in the light microscope

TABLE IV.—*Follicular Lymphoma: Lymphocytosis at Presentation (5000–30000/ $\mu$ l)*

| Histology                        |                | Lymphocytic         |                       | “Histiocytic” | All histological types |
|----------------------------------|----------------|---------------------|-----------------------|---------------|------------------------|
|                                  |                | Well differentiated | Poorly differentiated |               |                        |
| Notched nucleus cells            | Present        | 0                   | 6                     | 2             | 8                      |
|                                  | Not present    | 0                   | 3                     | 0             | 3                      |
|                                  | Films reviewed | 1                   | 4                     | 1             | 6                      |
|                                  | not reviewed   | 1                   | 13                    | 3             | 17                     |
| All cases of lymphocytosis       |                | 26                  | 21                    | 11            | 58                     |
| Lymphocyte count < 5000/ $\mu$ l |                |                     |                       |               |                        |

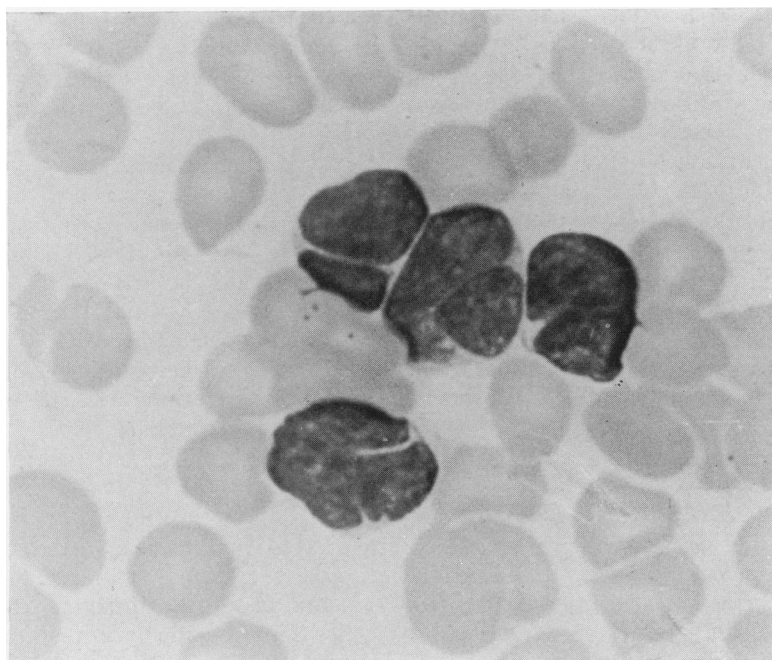


FIG. 1.—Four notched nucleus cells in peripheral blood film. May-Grünwald-Giemsa  $\times 1600$ .

Although the presence of nuclear clefts is the most striking feature of the notched nucleus cell, it may not be the most important defining character: the chromatin pattern is more homogeneous than that of the small lymphocyte and lacks the coarse blocks of densely stained chromatin separated by narrow, paler areas that characterize the chromatin pattern of the latter. Cells with scanty cytoplasm and barely perceptible nuclear notches may be recognized as notched nucleus cells by their homogeneous nuclear chromatin. Apart from the notches, the nuclei are not round like those of lymphocytes; the perimeter has one or more nearly straight edges making obtuse angles with the adjacent nuclear membrane. Cells lacking even the smallest notch may still be recognized as "notched nucleus" cells by the homogeneity of the chromatin, the angular outline to the nucleus and the scanty cytoplasm. The term "notched nucleus cell" is therefore not satisfactory but we have retained it because of long

usage. We prefer not to use the term "small cleaved cell" until Dr R. J. Lukes identifies our notched nucleus cell as such.

The association of lymphocytosis and lymphocytic infiltration of the bone marrow with "poorly differentiated lymphocytic" or "histiocytic" morphology in the lymph node sections is in marked contrast to the common finding in classic lymphocytic leukaemia, in which the predominant cell in the histological sections is almost always the "well differentiated" small lymphocyte.

*Patterns of lymphocytosis.*—Four patterns of lymphocyte count trends were observed among the 17 patients whose lymphocyte counts were raised at presentation, and among 10 others whose lymphocyte counts rose during the course of the disease: (1) The lymphocyte count, raised at presentation, declined spontaneously and remained within normal limits thereafter. In one case the count fell over a period of 2 years to normal

levels and did not rise again in the ensuing 10 years; no treatment other than blood transfusion had been administered during the first 2 years. The histological diagnosis was "poorly differentiated lymphocytic nodular lymphoma"; notched nucleus cells were not present. (2) The lymphocyte count, raised at presentation, declined as a result of treatment and remained within normal limits thereafter. In one case the count fell in a 6-month period of chlorambucil therapy and remained normal without further treatment for 16 years. (3) The lymphocyte count, raised at presentation, fell during treatment and increased during relapse. In one case the count subsequently fell spontaneously. (4) The lymphocyte count, normal at presentation and for several years thereafter, rose during a period of up to 6 months to between 20,000 and 30,000/ $\mu$ l when the first of several courses of chlorambucil was administered; during each course the counts fell to normal levels, and in the intervals between courses rose at the same rate as before the first course (Fig. 2). In one case in which the initial histological diagnosis was "nodular histiocytic lymphoma", a second lymph node was

excised 11 years later when the lymphocyte count had increased to 20,000/ $\mu$ l (Fig. 3). The lymphocytes were notched nucleus cells; in the sections of the second lymph node, the nodular pattern was lost and the appearance was that of "histiocytic diffuse lymphoma".

Thus, the presence of notched nucleus cells may indicate a diagnosis of follicular lymphoma even though the diagnosis cannot be made on histological grounds. The patient cited survived only 1 year after the second biopsy.

*Comment.*—Of the 4 patterns of lymphocytosis described, Pattern 3 is observed in CLL but Patterns 1, 2 and 4 are hardly ever observed in CLL or in the course of diffuse non-leukaemic lymphoma. They appear to be confined to follicular lymphoma. In our series, lymphocytosis (5000/ $\mu$ l or higher) at presentation or during the course of the disease was observed in 36% of the cases, but small numbers of notched nucleus cells appeared in the blood films in more cases and would probably be found more often if sought diligently. In 3 cases of lymphocytosis notched nucleus cells were not present, but the histological picture was the same (poorly differentiated lymphocytic nodu-

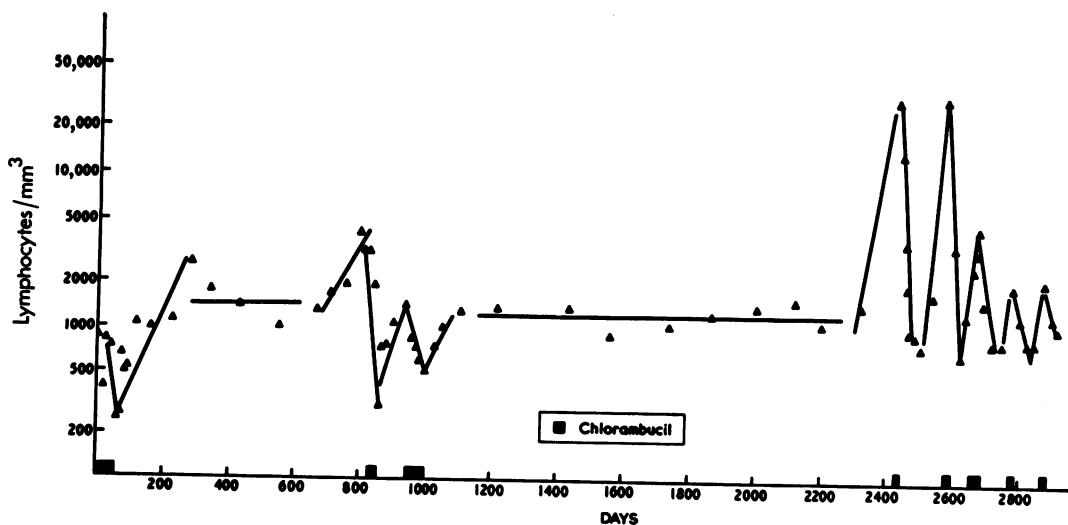


FIG. 2.—Lymphocyte counts during an 8-year period of a female aged 48 years at presentation when the histological diagnosis was poorly differentiated lymphocytic nodular lymphoma.

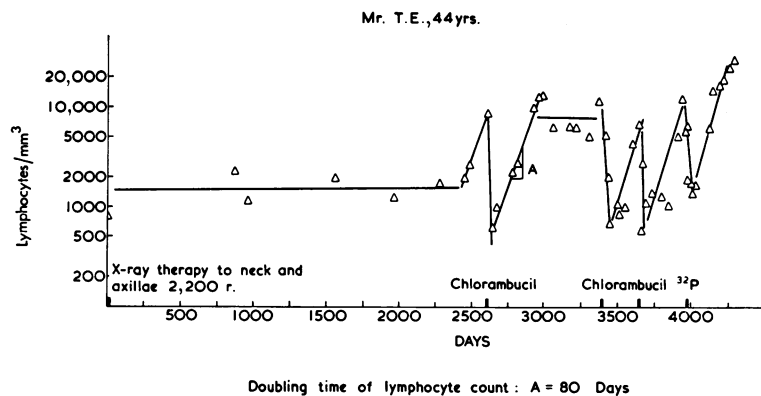


FIG. 3.—Lymphocyte counts during a 12-year period of a male aged 44 years at presentation when the histological diagnosis was nodular histiocytic lymphoma. Eleven years later, when the lymphocyte counts reached the order of 20,000/ $\mu$ l and the cells were typical notched nucleus cells, the histological diagnosis was diffuse histiocytic lymphoma.

lar) as in the majority of cases in which notched nucleus cells were present.

### 5. Treatment

In the 20-year period in which the patients attended, no consistent plan of treatment was followed except in the 4 Stage I patients who presented with tonsillar lesions. They were treated with radical radiotherapy by Dr M. Lederman. Two remain free of disease after 8 and 17½ years respectively and 2 relapsed after 5 and 9 years. In the remaining 10 Stage I cases, the initial treatment was by local radiotherapy. The pattern of relapse in the Stage I cases is shown in Table V. One patient with an inguinal node presentation who relapsed with generalized disease one month after treatment would have been placed in Stage III or IV by the current staging procedure. The survival of these patients is shown in Table VI. One is lost to follow-up, but 4 of the remainder (all with well differentiated lymphocytic disease) survived 10 years, and 5 survived from 5 to 10 years; 7 were living beyond 5 years at the close of the survey.

Treatment in the remaining cases was by the irradiation of locally involved sites

and by chemotherapy with chlorambucil, in a few cases with cyclophosphamide, or mustine, or with prednisone alone or in combination with chlorambucil or cyclophosphamide. Treatment was continued until the lesions had regressed or until no further improvement was evident or, rarely, until interruption was necessary because of bone marrow depression. Maintenance therapy was not given. Multiple drug therapy with intravenous vincristine, cyclophosphamide, procarbazine, prednisone and other agents was used after 1968 only for progressive disease resistant to conventional single agent therapy. Two patients were observed for 3 and 4½ years respectively before treatment was begun. In some cases local radiotherapy was used when single nodes or groups of nodes were resistant to chemotherapy after the remainder had regressed. In other cases of persistence of single nodes no further treatment was attempted; in some of these the residual nodes remained unchanged in size and reactivation occurred at other sites. In one case a large, central abdominal mass resistant to irradiation and to chlorambucil increased slowly in size without causing symptoms over a 12-year period, during which no further treatment was administered; the

TABLE V.—*Pattern of Recurrence and Relapse in 18 Cases of Stage I Follicular Lymphoma*

| Primary site                 | Relapse-free period (years) | Sites of relapse |           |                        | Extranodal                 | Total survival (years) |
|------------------------------|-----------------------------|------------------|-----------|------------------------|----------------------------|------------------------|
|                              |                             | Local recurrence | Distant   | Generalized (± spleen) |                            |                        |
| Tonsil                       | 5                           | +                |           | +                      | pharynx                    | 12½                    |
|                              | 8+                          |                  |           |                        |                            | 8+                     |
|                              | 9                           |                  |           |                        | nasopharynx                | 10+                    |
|                              | 17½+                        |                  |           |                        |                            | 17½+                   |
| Inguinal* nodes              | 2+                          |                  |           |                        |                            | 2+                     |
|                              | 5                           | +                |           | after 24 yr            |                            | 25                     |
|                              | 1 month                     | +                |           | +                      | bone deposits              | 2                      |
| Other nodes                  | 1                           |                  | op. groin |                        | chest wall mass            | 6½+                    |
|                              | 2                           |                  | abd. mass | +                      |                            | 7+                     |
|                              | 4†                          |                  |           |                        |                            | 4                      |
|                              | 1                           | +                |           |                        | breast after 4 yr          | 8+                     |
| Lachrymal and parotid glands | 2½                          |                  | abd. mass | +                      | chylothorax, skin deposits | 6½                     |
|                              | 3                           |                  | abd. mass |                        | serous effusions           | 4                      |

\* 1 patient lost to follow up.

† Road accident death.

TABLE VI.—*Follicular Lymphoma, Survival of 13 Stage I Patients*

| Histological type                 | Survival (years) |        |       |       |
|-----------------------------------|------------------|--------|-------|-------|
|                                   | < 1              | 1—     | 5—    | 10+   |
| Well differentiated lymphocytic   | 0                | 1*     | (2)   | 1+(3) |
| Poorly differentiated lymphocytic | 0                | 2      | 1+(2) | 0     |
| Histiocytic†                      | 0                | (1)    | 0     | 0     |
| All                               | 0                | 3+(1)* | 1+(4) | 1+(3) |

\* Road accident death 4 years: no sign of recurrence. Numbers in brackets: patients living 31.8.73.

† 1 lost to follow-up.

patient died following a cerebrovascular accident.

Seven of the 42 Stage III and IV patients who died were resistant to treatment with chlorambucil at higher dosage than was effective in the majority of cases; subsequent treatment with other drugs was equally ineffective: 2 of these patients had follicular tumours composed of large, poorly differentiated cells designated as "histiocytic", and their disease progressed in the manner of diffuse histiocytic lymphoma ("reticulum cell sarcoma"): the fulminating course in the remaining 5 could not have been predicted from any of the features recorded at presentation. Thirty-four of the remaining 35 patients responded to chemotherapy;

7 had no evidence of active disease when they died of intercurrent disease; in 16 cases successive relapses proved increasingly resistant to treatment; 11 patients responded well to treatment until their disease underwent a transformation in its character, as described below, and this was also observed in a twelfth patient whose disease progressed slowly in a 4½-year period during which no treatment was administered (Table VII).

*Comment.*—In spite of some variation in dosage and duration of chlorambucil treatment over the 20-year period, and the fact that in recent years other drugs were administered in the later stage of the disease, the series is essentially one in which single agent chemotherapy at low

TABLE VII.—*Follicular Lymphoma*  
Cause of Death in 42 Stage III and Stage IV Patients

| Cause of death                             | Lymphocytic         |                       | Histiocytic | All |
|--------------------------------------------|---------------------|-----------------------|-------------|-----|
|                                            | Well differentiated | Poorly differentiated |             |     |
| Sarcomatous transformation with metastases | 2                   | 4                     | 1           | 7   |
| Blast cell leukaemia                       | 3                   | 2                     | 0           | 5   |
| Progressive disease from presentation      | 1                   | 4                     | 2           | 7   |
| Progressive disease after "benign" course  | 5                   | 7                     | 4           | 16  |
| Intercurrent                               | 4                   | 3                     | 0           | 7   |
| All cases                                  | 15                  | 20                    | 7           | 42  |

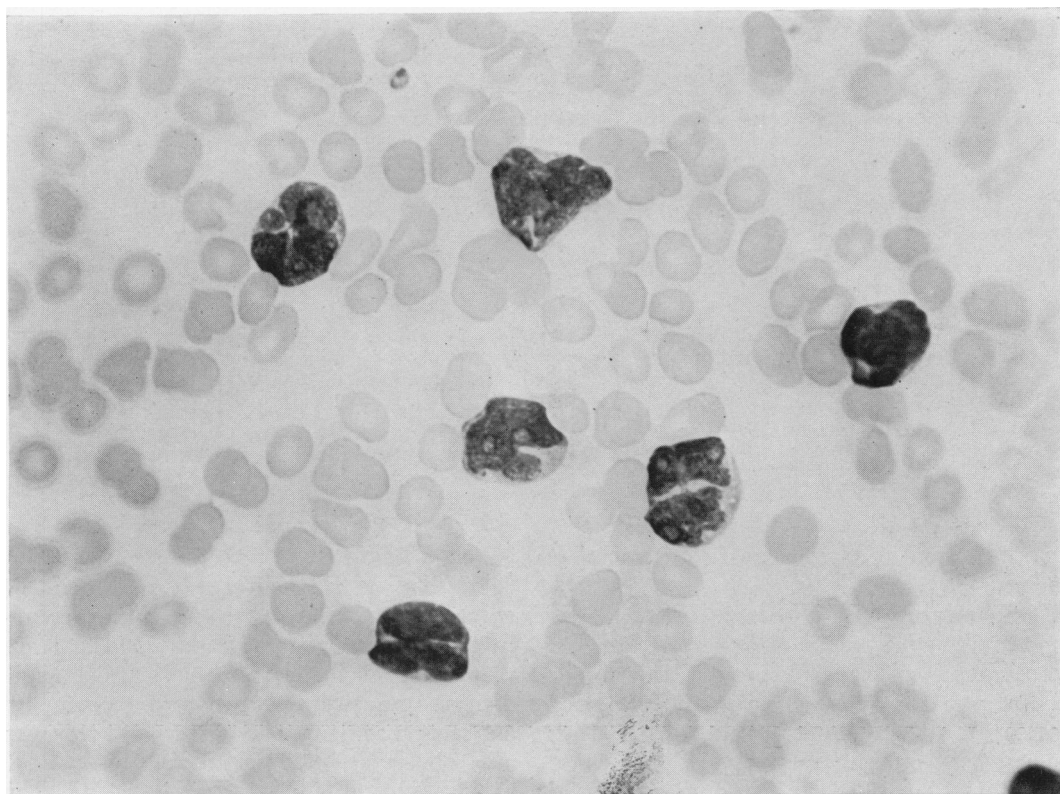


FIG. 4.—Bizarre large blast cells in peripheral blood (blast cell count 64,000/ $\mu$ l) one day before the death of a male aged 59 at presentation 4½ years previously. May-Grünwald-Giemsa  $\times 800$ . (See Fig. 5.)

dosage was used. The "success" of the treatment may be judged by the fact that hardly any changes were made during an era when growing dissatisfaction with the poor results of conventional treatment in

the diffuse lymphomata led to the trial of many new forms of treatment. There was indeed considerable reluctance to embark on more aggressive forms of treatment for follicular lymphoma in which dramatic

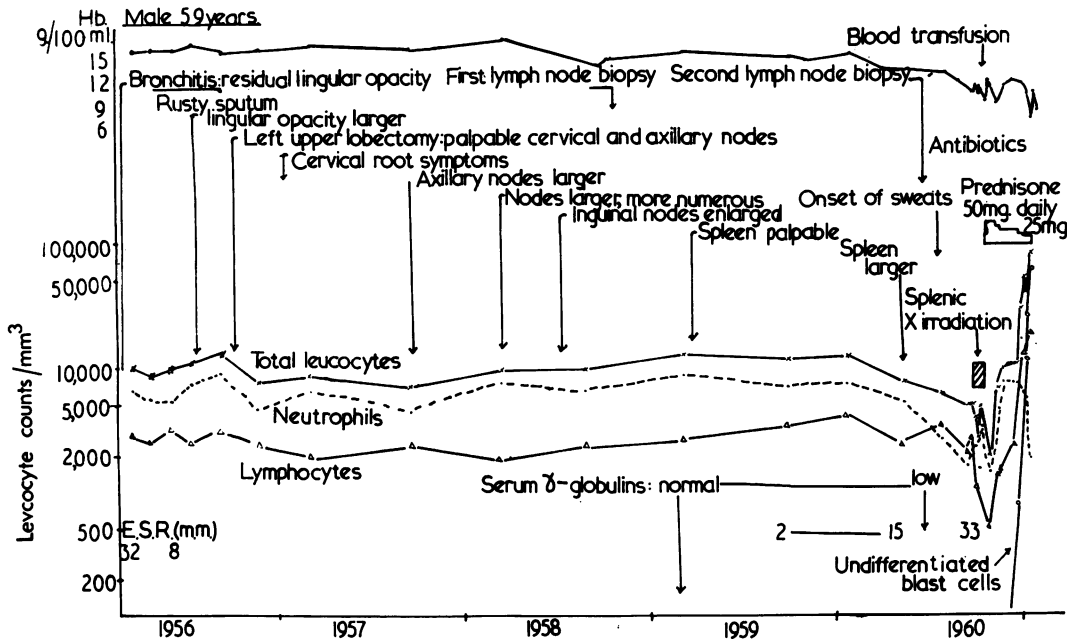


FIG. 5.—Course of illness (including haemoglobin concentration, total leucocyte, neutrophil, lymphocyte and blast cell counts) of male aged 59 years at presentation. Occasional notched nucleus cells were present in blood films during the course of the illness, but the bizarre blast cells shown in Fig. 4 were observed only during the acute terminal illness.

and long-lasting regression of extensive disease could usually be achieved so easily with little inconvenience and usually no discomfort to the patient. However, nearly one-half of the patients died within 5 years (see below) and most patients who survived beyond 10 years and were free of disease subsequently relapsed. Nevertheless, follicular lymphoma stands out as exceptionally responsive to single agent chemotherapy: in this series 64% of the patients had poorly differentiated lymphocytic or histiocytic disease. Among the diffuse lymphomata, only the well differentiated lymphocytic type would show comparable responsiveness.

#### *Malignant transformation*

At the end of the survey, 55 patients had died. In 12 cases (22%) death had resulted from a rapidly progressive malignant process that had intruded explosively during a period of apparent quiescence and proved fatal within 3 months. In 7

of these cases the terminal disease was sarcomatous in character, beginning in all but one case as an invasive local tumour resistant to radiotherapy or chemotherapy, which proved fatal because of its location (intraspinal or pelvic) or from which widespread metastases developed. In one case the first evidence of the terminal illness was an increase in the size and hardness of the left cervical and inguinal lymph nodes. In 5 cases the terminal disease was a fulminating blast cell leukaemia, in 2 cases accompanied by severe generalized bone pain. The morphology of the blast cells was that of "lymphosarcoma cell leukaemia" in 4 of these cases, insofar as lymphocytic differentiation was evident in the pleomorphic blast cell population. In the fifth case (Fig. 4), the blast cells were large undifferentiated cells with 2 or more broad lobes in the nuclei of Rieder cell type, each lobe often containing a nucleolus. The cytoplasm was variable in amount

and deeply basophilic. There was no evidence of differentiation. Terminally, the leucocyte count was 64,000/ $\mu$ l, consisting almost entirely of blast cells. Occasional notched nucleus lymphocytes were present in the blood films; during the preceding benign phase of the disease, which lasted for 4 years, the absolute lymphocyte count had been within normal limits, and the histology of two lymph nodes excised 20 months apart was that of well differentiated lymphocytic nodular lymphoma (Fig. 5). This was the only case of that histological type in which notched nucleus cells were known to have been present in the peripheral blood. Transitional forms between the undifferentiated blast cells and the notched nucleus cells were not seen.

The overall survival in the 12 cases was from 1 to 13½ years; in 6 the survival times were 6, 8½, 9½, 11½, 12 and 13½ years. The causes of death in the 42 Stage

III and IV patients who had died before 31 August 1973 are shown in Table VII.

*Comment.*—A remarkable feature of the terminal illness was that it appeared to develop independently of the pre-existing lymphoma, the manifestations of which did not change during its evolution. The phenomenon is comparable with the blast cell transformation of chronic granulocytic leukaemia and may be regarded as resulting from the emergence of a more malignant clone from the tumour cell population. The one-step transformation exemplified by these 12 cases is excessively rare in the diffuse lymphomata and in chronic lymphocytic leukaemia, and appears to be yet another feature characteristic of follicular lymphoma.

#### Survival

Table VIII shows the crude survival times according to age and stage. Survival was estimated from the time of discovery

TABLE VIII.—*Follicular Lymphoma, Survival according to Age and Clinical Stage*

| Age<br>(years) |                       | Stage    |            |            |
|----------------|-----------------------|----------|------------|------------|
|                |                       | I and II | III and IV | All stages |
| < 40           | No. of cases          | 4*       | 10†        | 14         |
|                | Range (years)         | 4–25     | 1½–16+     | 1½–25      |
|                | Median (years)        | 12½      | 4          | 4½         |
|                | 5-year survivors (%)  | 66       | 40         | 46         |
|                | 10-year survivors (%) | 66       | 10         | 23         |
|                | Alive 31.8.73         | 0        | 5          | 5          |
| 40–59          | No. of cases          | 14       | 24         | 38         |
|                | Range (years)         | 2½–17½   | 1½–14½     | 1½–17½     |
|                | Median (years)        | 7½       | 6½         | 7          |
|                | 5-year survivors (%)  | 71       | 66         | 68         |
|                | 10-year survivors (%) | 28       | 29         | 29         |
|                | Alive 31.8.73         | 5        | 5          | 10         |
| 60+            | No. of cases          | 3‡       | 20         | 23         |
|                | Range (years)         | 4–7      | 4–10       | 4–10       |
|                | Median                | 6½       | 3          | 4          |
|                | 5-year survivors (%)  | 66       | 30         | 35         |
|                | 10-year survivors (%) | 0        | 5          | 4          |
|                | Alive 31.8.43         | 2        | 2          | 4          |
| All ages       | No. of cases          | 21       | 54         | 75         |
|                | Range (years)         | 2½–25    | 4–16       | 1½–25      |
|                | Median (years)        | 6½       | 4½         | 5½         |
|                | 5-year survivors (%)  | 70       | 48         | 54         |
|                | 10-year survivors (%) | 30       | 17         | 20         |
|                | Alive 31.8.73         | 7        | 12         | 19         |

\* 1 lost to follow up.

† 16-year survivor lost to follow up after 1969.

‡ Of 52 possible 10-year survivors 15 did survive 10 years (29%).

‡ 1 road accident death in remission.

by the patient or doctor of the lesion which led to the diagnosis. For all 75 cases, the median survival was  $5\frac{1}{2}$  years, with 54% of the patients surviving 5 years or more and 20% surviving 10 years or more; 15 of the 52 patients who could have survived 10 years did so (29%).

The median duration of survival for the group of 38 patients aged 40–59 years was 7 years; 68% survived 5 years and 29% 10 years. Eleven were alive at the end of the survey (31.8.73), of whom 7 had already survived 5 years, and three 10 years. The median duration of survival for the 23 patients aged 60 years and more was 4 years; 35% survived 5 years but only 4% 10 years. Five were alive at the end of the survey, 4 of whom had survived 5 years. In all age groups the median duration of survival was longer in Stages I and II than in Stages III and IV. The group with the longest median survival (12 years 8 months) was that of the 4 Stage I and 11 patients below age 40, and that with the shortest median survival (3 years) was the group of 20 Stage III and IV patients aged 60 years or older. The 5- and 10-year survival was superior in the group of 27 poorly differentiated “lymphocytic” cases than in the group

of 17 “well-differentiated lymphocytic” cases, but the numbers are small.

Table IX shows the crude survival pattern of the 54 Stage III and IV patients according to histological type. There were no 10-year survivors among the 10 cases of histiocytic lymphoma.

Table X shows the survival of the 17 patients with lymphocytosis at the time of presentation. The median survival was  $6\frac{1}{2}$  years; 59% of the patients survived 5 years and 29% 10 years.

*Comment.*—The crude survival figures confirm the general experience that patients suffering from follicular lymphoma have a better chance of surviving 10 years than those suffering from diffuse lymphoma. The numbers in the various subgroups (according to age, histological type, clinical stage) and the high proportion of patients alive at the end of the survey are, however, too small for us to make statistically valid inferences. However, the long survival after local recurrence or generalized relapse in Stage I cases (Table V) contrasts markedly with the general experience of diffuse lymphoma.

We are indebted to Dr I. M. E. Hamlin

TABLE IX.—*Follicular Lymphoma*  
*Survival of 54 Stage III and IV Patients*

| Histological type                 | No. of cases | Range (years) | Median (years) | 5 years (%) | 10 years (%) |
|-----------------------------------|--------------|---------------|----------------|-------------|--------------|
| Well differentiated lymphocytic   | 17 (3)       | 0.5–13.5      | 4              | 40          | 12           |
| Poorly differentiated lymphocytic | 27 (6)       | 0.75–16       | 6              | 63          | 26           |
| Histiocytic                       | 10 (3)       | 0.3–7.25      | 4.5            | 40          | 0            |
| All                               | 54 (12)      | 0.3–16        | 4.75           | 48          | 17           |

Brackets: No. alive 31.8.73.

TABLE X.—*Survival of 17 Patients with Lymphocytosis at Presentation*

| Histological type                 |      | Survival (years) |       |       |       |
|-----------------------------------|------|------------------|-------|-------|-------|
|                                   |      | <1               | 1–    | 5–    | 10+   |
| Well differentiated lymphocytic   | (1)  |                  | (1)   |       |       |
| Poorly differentiated lymphocytic | (13) | 1                | 3+(1) | 3     | 4+(1) |
| Histiocytic                       | (3)  |                  | (1)   | 1+(1) |       |
| All                               |      | 1                | 3+(3) | 4+(1) | 4+(1) |

Numbers in brackets: patients living 31.12.72.

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