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The Relation Between Lymphosarcoma and Leukemia

J. W. IBBOTT, M.D., F.R.C.P.[C] and D. M. WHITELAW, M.D., F.R.C.P.[C], *Vancouver, B.C.*

ABSTRACT

Of 283 cases of lymphocytic disease, 81% fell within three distinct categories: lymphocytic and lymphoblastic lymphosarcoma and lymphocytic leukemia. The remaining 19% showed transitions from more mature to less mature cell types or from local to general anatomic distribution. The clinical course was related to the cell type and the extent of disease rather than to the presence of blood stream invasion. Survival of patients with lymphocytic leukemia and of those with lymphocytic lymphosarcoma was the same, while that of patients with lymphoblastic lymphosarcoma was much shorter. Survival curves are simple exponentials and do not suggest two populations, one with disease less malignant than the other.

SOMMAIRE

On a pu ranger dans trois catégories distinctes 81% des 283 cas de lymphocytose, soit lymphocytosarcome, lymphoblastosarcome et leucémie lymphoïde. Les cas restants, soit 19%, présentaient des signes de transition de formes de cellules plus ou moins jeunes ou des variations dans la distribution, locale ou générale. L'évolution clinique dépendait du type de cellule et du degré de la pathologie plutôt que de la présence de l'invasion dans le torrent circulatoire. La survie des malades souffrant de leucémie lymphoïde a été la même que celle de ceux atteints de lymphocytosarcome, mais celle des malades souffrant de lymphoblastosarcome a été beaucoup plus courte. Les courbes de survie sont de simples exponentielles et ne signifient pas qu'il s'agit de deux tranches distinctes de malades, l'une souffrant d'une affection d'une plus grand malignité que l'autre.

THE classification of lymphocytic diseases has been a matter of debate since Kundrat[1] first separated lymphosarcoma from the welter of soft-tissue sarcomas. As is usual among taxonomists, there has been a group who saw in the various clinical cases a series of distinct entities related by infrequent transitional forms and there has been an opposing group who saw one large species of disease manifesting itself by nosologically unimportant variations.

Kundrat himself distinguished lymphocytic lymphosarcoma from other lymphocytic disease by its disposition to penetrate the capsule and its tendency to remain localized to one or several anatomical sites. Sternberg[2] recognized a group of cases, which he dubbed "leukosarcoma", with large tumours in the mediastinum or other areas, associated with invasion of the blood stream by abnormal cells which did not become numerous enough to present the ordinary picture of lymphocytic leukemia. In a review of the literature[3] to 1925, 107 instances were found in which a locally invasive tumour was combined with lymphocytic leukemia, and retention of the classification of leukosarcoma was recommended to distinguish this group lying between lymphosarcoma and lymphocytic leukemia.

Based on the experience of the tumour registry of the American Association of Pathology and Bacteriology,[4] a classification of lymphocytic tumours was devised in which lymphocytic leukemia was defined as a condition in which more than 25,000 white blood cells/c.mm. were present with a predominant lymphocytosis. An aleukemic lymphocytoma was recognized which might be either diffuse

From the Department of Medicine, University of British Columbia, and the British Columbia Cancer Institute, Vancouver, B.C.

Address for reprints: Dr. D. M. Whitelaw, The British Columbia Cancer Institute, 2656 Heather Street, Vancouver 9, B.C.

or nodular and in which there were always abnormal lymphocytes circulating in the peripheral blood, and sometimes an actual increase in the number of lymphocytes. True lymphosarcoma might be aleukemic and show no abnormal forms in the blood unless irradiated, or it might be leukemic, in which case a considerable proportion of the circulating lymphocytes were abnormal young forms but the lymphosarcoma was recognized as being locally invasive. It was found that a leukemia might terminate in lymphosarcoma or might spontaneously become aleukemic.

The designation "lymphosarcoma cell leukemia" was applied[5] to patients who showed a palpably enlarged spleen, a fever accompanying the leukemic phase, frequent pulmonary involvement and a duration of life of two to 60 days following the appearance of the leukemia. It is doubtful whether this group of cases represented an intermediate form between lymphosarcoma and lymphocytic leukemia, since the very short duration following the development of the leukemic phase suggests a more acute form of the disease than would be compatible with either of the larger groups. No cases of lymphosarcoma cell leukemia were discovered among cases of lymphoma seen at the Mayo Clinic.[6]

The first effort to group these diseases was made in 1903 by Türk,[7] who proposed that lymphocytic leukemia and lymphosarcoma, chronic and acute, be regarded as manifestations of the same disease. The various lymphocytic diseases were also lumped together because of their similar response to radiation which distinguished them from Hodgkin's disease.[8] Warthin's[9] experience with 134 cases showed that there was no difference in the pathological appearance of lymph nodes from leukemic and non-leukemic cases, even though only nine instances showed an actual transformation from an isolated tumour to the leukemic state.

In the series reported by Gall and Mallory,[10] it was impossible to predict from the histological examination of excised lymph nodes whether or not the blood picture would prove to be leukemic. Occasionally the bone marrow might be normal even in the presence of leukemia, and, conversely, diffuse bone marrow changes might be present without any abnormality in the peripheral blood. There was no characteristic leukosarcoma cell. Lymphosarcoma was thought to represent a transient clinical phase of lymphocytic leukemia which might become generalized, although not necessarily leukemic, if the patient lived long enough. The average life expectancy was one year less in those with leukemia. Jackson and Parker[11] found that at the time of death most patients with lymphocytoma had developed either a leukemic blood picture or diffuse leukemic infiltration.

The association between lymphosarcoma and lymphocytic leukemia was found by Lumb[12] to be so close as to make it reasonable to assume that the two conditions represented different manifestations of a single disease entity. He felt that the leukemic changes which occur are nothing more than a blood stream transference of malignant cells.

As to the factors which determine the presence or absence of leukemia, there is a widespread opinion that the blood does not become leukemic until the marrow is involved. On the other hand, leukemia usually seems to follow soon after marrow invasion.[8]

Opinions as to the identity or non-identity of the various clinical types of disease have been based on clinical and pathological findings and examination of stained films of blood and bone marrow. By this means it is certainly possible to divide the patients into groups. Whether a grouping of this type has significance with respect to the natural history of the disease or to prognosis or therapy has not been finally decided. The study reported here was undertaken to determine, if possible, whether there were important prognostic advantages in making such a division.

MATERIAL AND METHODS

The records of patients admitted to The British Columbia Cancer Institute between January 1, 1948, and December 31, 1960, in whom a diagnosis of lymphocytic disease in some form or other had been made, were examined. There were 283 in whom the diagnosis of lymphocytic disease was firmly established by examinations of the peripheral blood and bone marrow or by histologic sections of lymph nodes taken at biopsy or autopsy. Many patients who were referred to the Institute had had biopsies performed before referral, but in all instances the microscopic sections of these biopsies had been obtained for review and had been examined and reported upon by the Department of Pathology at the Vancouver General Hospital. Examination of the peripheral blood had been carried out on all patients, usually at frequent intervals. In the majority of cases, marrow aspirations had been performed and all the peripheral blood specimens and the bone marrow films had been examined by the Department of Hematology of the Vancouver General Hospital. For the purposes of this review, as many as possible of the original peripheral blood and marrow films and the microscopic sections were reviewed again. The peripheral blood and marrow were examined with the assistance of Dr. J. W. Thomas and the available microscopic sections were reviewed by Dr. W. B. Leach. The extent to which material was reviewed is shown in Table I.

Where peripheral blood films were available, a differential count of 100 lymphocytes was made, using the following classification: (a) small mature lymphocyte, (b) large mature lymphocyte, (c) prolymphocyte, (d) lymphoblast, (e) lymphosarcoma cell, and (f) atypical lymphocyte.

TABLE I.—MATERIAL RE-EXAMINED

	Total cases	Material re-examined			
		PB	M	B	A
LL	122	109	93	58	23
LS	69	54	50	59	12
LBS	38	32	26	26	12
Mixed	54				
FL	6	5	4	5	0
FL→LS	16	15	14	14	3
FL→LS→LBS	5	5	4	5	3
FL→LS→LBL	2	2	2	1	0
LS→LL	6	6	6	5	3
LS→LBS	4	3	2	3	1
LS→LBL	1	1	1	1	0
LBS→LBL	6	6	6	6	3
Borderline LS—LL	8	7	6	6	3

Abbreviations:
LL = (Chronic) lymphocytic leukemia.
LS = Lymphocytic lymphosarcoma.
LBS = Lymphoblastic lymphosarcoma.
FL = (Giant) follicular lymphoma.
LBL = Lymphoblastic leukemia.
PB = Peripheral blood.
M = Bone marrow.
B = Biopsy.
A = Autopsy.

In order to establish the limits of absolute lymphocyte counts in individuals without leukemia, it was necessary to define the range of the absolute lymphocyte count in an adult population. For this purpose, records of 1205 consecutive admissions to the adult wards in the Vancouver General Hospital, in whom a total white count and differential count had been performed, were examined. A distribution was obtained approaching the normal but with a small tail extending to the right. The mean of this distribution is 2230 with a standard deviation of 1070. A figure of 5440 lymphocytes/c.mm., therefore, represents three standard deviations from the mean and was chosen as providing a satisfactory dividing line between leukemic and non-leukemic patients. We realize that this figure does not necessarily represent the distribution of the lymphocyte count in normal individuals, since the sample of persons surveyed was collected from a hospital population and was, perforce, chosen from those in whom white cell counts and differentials were performed. However, it is in general agreement with the findings of others.[13]

The cases were then divided into groups on the basis of: (a) the predominant cell in the histologic sections—whether small or large, i.e. whether lymphocytic or lymphoblastic; and (b) the total circulating lymphocyte count—whether less than 5440/c.mm. or 5440/c.mm. and over. Four homogeneous categories of patients were defined by these criteria as follows:

1. Lymphocytic lymphosarcoma: These patients had lymphocytic tumours when first seen and did not become leukemic, according to the above definition, during the period of observation.

2. Lymphoblastic lymphosarcoma: These patients had lymphoblastic tumours from the start and did not become leukemic during the period of observation.

3. Lymphocytic leukemia: These patients were leukemic when first seen. Only rarely did they develop large masses of tumour sufficient to cause local obstructive phenomena. No statement can be made as to whether all these patients would have remained leukemic during the course of their illness, since most of them were treated by means designed to reduce the lymphocyte count.

(4) Lymphoblastic leukemia: These patients were leukemic when first seen.

An additional mixed group was composed of those patients whose disease began as a localized tumour but subsequently became leukemic, and this is the group referred to by some as leukosarcoma. We shall include in it all those cases which appear to belong to the general group of lymphocytic disease but who do not clearly belong to one of the four preceding categories.

We excluded from further consideration cases in Category 4, that is, those with lymphoblastic leukemia. This is frequently a disease of childhood and is impossible to distinguish with certainty from myeloblastic leukemia; furthermore, disease appearing in this form at its inception seems at present to be somewhat different from lymphosarcoma and lymphocytic leukemia.

RESULTS

A. THE HOMOGENEOUS GROUPS

Distribution of Cases

There were 69 cases of lymphocytic lymphosarcoma, 38 cases of lymphoblastic lymphosarcoma and 122 cases of lymphocytic leukemia.

Sex

There were 195 males and 88 females, giving a male-to-female ratio for the whole group of 2.2. The ratio for lymphocytic leukemia was 3.8, whereas for lymphocytic lymphosarcoma it was 1.1. This

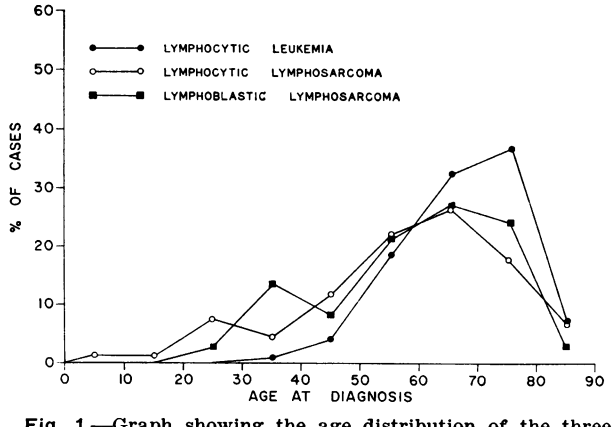

Fig. 1.—Graph showing the age distribution of the three main types of lymphocytic disease.

difference is significant at the 0.1% level. For lymphoblastic lymphosarcoma the ratio was 2.0 and for the mixed group it was 2.3.

Age

Age distribution in the three groups is illustrated in Fig. 1. It will be noted that the curves are similar but that the sarcomas appear at an earlier age and reach their peak about one decade earlier than lymphocytic leukemia. The age incidence is illustrated in Fig. 2, showing the continued rise to the seventh decade in all groups with decline in the ninth decade. The incidence of both types of lymphosarcoma reaches a peak slightly earlier than that of lymphocytic leukemia. The incidence for all lymphocytic disease reaches a peak about one decade earlier in females than in males.

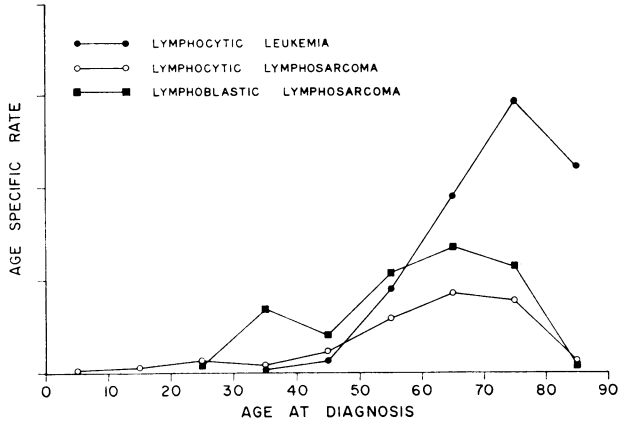

Fig. 2.—Graph showing the relative age specific incidence of the three main types of lymphocytic disease.

Race

In general, the distribution of cases among different racial and ethnic groups parallelled that of the population of British Columbia, but an exception occurred in respect of the oriental population. The series included one Chinese and one Japanese each with lymphosarcoma, giving a proportion of East Asians in the whole group of .007, whereas they comprise .021 of the population of British Columbia. The figures are too small to be significant but are in agreement with the generally observed phenomenon that lymphocytic disease is uncommon in East Asians and lymphocytic leukemia is rare.

Symptoms

Ninety-six of the patients with lymphocytic leukemia were discovered because they presented themselves with symptoms. In the remaining 26 the condition was discovered by examination of the blood in individuals who either had no symptoms or were being investigated for some unrelated reason. In those in whom the disease was discovered as a result of investigation of symptoms related to leukemia, the interval between the onset of symptoms and the diagnosis averaged eight months, although the median interval was five months. For lymphocytic lymphosarcoma the average interval from onset of symptoms to diagnosis was 7.7 months and the median was five months. The interval from diagnosis to beginning treatment in lymphocytic leukemia which was discovered because of symptoms was less than one month in 61 cases, and all but six of the remainder were treated within six months of the time of diagnosis. Six patients were never treated, either because they failed to co-operate or because they had concomitant disease which overshadowed the leukemia. Of the group discovered by accident, eight were treated within a month of discovery and seven were never treated. For the remainder, the interval between diagnosis and treatment extended to more than two years.

Four patients with lymphocytic lymphosarcoma were not treated, either because of concomitant disease or because of lack of co-operation. All of the remainder were treated within two months of the diagnosis. There was, therefore, a somewhat longer interval between the onset of symptoms and the first treatment in lymphocytic leukemia than in lymphocytic lymphosarcoma, reflecting the opinion held by the staff that many individuals with the early manifestations of lymphocytic leukemia do not require immediate treatment.

TABLE II.—FIRST SYMPTOMS

	LS	*LL*	*LBS*	*Mixed*
Discovered by accident	5	24	1	3
Fatigue, lack of energy, malaise	5	42	6	8
Enlarged lymph nodes	37	42	19	33
Weight loss	5	12	3	3
Repeated infections	0	9	0	0
Fever or sweating	0	6	5	2
Dyspnea	2	5	1	2
Enlarged or painful spleen	1	12	0	1
Abdominal swelling	5	0	0	2
Anorexia	1	6	2	2
Pain, various sites	11	22	8	7
Deafness	0	3	0	0
Exophthalmos	3	0	0	0

Other symptoms were mentioned less than three times.

The first symptoms noted by patients in the first three groups of cases are recorded in Table II. Since many of the patients initially complained of more than one symptom, the number of first symptoms for each group exceeds the number of cases. Individuals with lymphocytic or lymphoblastic lymphosarcoma or mixed disease complained principally of the mass of lymphoid tissue itself, either because of its presence and size or because of a secondary effect such as pain. A larger proportion of patients with lymphocytic leukemia complained of symptoms indicative of a generalized process and these included weight loss, repeated infections, fever and dyspnea, some of which was related to anemia.

Physical Signs

Table III shows the frequency with which one, two or multiple sites were involved in various groups. Only 13% of cases of lymphocytic leukemia showed palpable disease confined to one area, whereas about one-half of the patients in the other groups presented in this manner. While patients with lymphocytic leukemia occasionally showed no enlargement of lymph nodes, multiple sites were involved in 71%. Of the 122 cases of leukemia,

TABLE III.—PHYSICAL SIGNS WHEN FIRST SEEN

	LL	*LS*	*LBS*	*Mixed*
None	5	0	1	0
Palpable disease confined to one area	10	36	20	27
Palpable disease involving two areas	15	8	5	5
Palpable disease involving multiple sites	92	25	12	22
	122	69	38	54

six are recorded as having swelling of the legs, three had ascites (two chylous) and three had pleural effusion; otherwise there was no important lymphatic obstruction. Even in the cases mentioned there is no clear relationship between enlarged lymph nodes, lymphatic obstruction and edema of the legs, since in the six persons with this symptom, low plasma proteins, congestive failure, etc., were not entirely eliminated as causes of edema. Patients with lymphocytic lymphosarcoma showed obstructive phenomena somewhat more frequently. One had edema of one arm, three had obstruction of the superior vena cava with edema of head and arms, eight had edema of both legs, two had edema of both legs and the trunk, and two had ascites. In addition, two patients had ureteral obstruction. In the case of lymphoblastic lymphosarcoma, 10 patients showed edema of the legs; three had ascites; three had edema of the trunk; two had pleural effusion; and one had intestinal obstruction.

Eighty-two of the 122 patients with lymphocytic leukemia had died, and although not all of these had died of disease, 70 of them before death were noted to have enlargement of axillary, cervical and inguinal nodes; 71 had splenomegaly and 68 had hepatomegaly; and 11 had edema of the lower extremities. Even among the 40 who are still alive, 35 had involvement of all three major superficial lymph-node-bearing areas; 29 had hepatomegaly and 33 had splenomegaly.

Forty-two of the 69 patients with lymphocytic lymphosarcoma had died; 21 of these had shown involvement of cervical, axillary and inguinal areas; 13 had had hepatomegaly and eight had had splenomegaly. Among the 27 persons still alive with the disease, only two had hepatomegaly and three had splenomegaly.

TABLE IV.—BLOOD FINDINGS AT TIME OF DIAGNOSIS

	LL	*LS*	*LBS*
Hemoglobin values:			
12 g. and over	60	51	29
8 - 12 g.	52	18	7
Less than 8 g.	10	0	2
	122	69	38
Leukocyte counts:			
Below 10,000/c. mm.	0	62	30
10,000 to 30,000	41	7	8
30,000 to 100,000	41	0	0
100,000	40	0	0
	122	69	38
Absolute lymphocyte count:			
Less than 1000/c.mm.		7	9
1000 to 2000		36	14
2000 to 3000		19	11
3000 to 4000		5	2
4000 to 5440		2	1
5440 to 10,000	15	0	0
10,000 to 30,000	31	0	0
30,000 to 100,000	36	0	0
More than 100,000	39	0	0
	121*	69	37
Platelets:			
Less than 50,000/c.mm.	4	1	0
50,000 to 100,000	3	0	1
100,000 to 200,000	36	5	1
200,000 to 400,000	56	27	13
More than 400,000	18	24	15
	117	57	30
Erythrocyte sedimentation rate:			
0 - 14 mm. in 1 hr	44	22	5
15 - 49	35	27	16
More than 50	27	13	12
	106	62	33
Bone marrow lymphocytes:			
Less than 25%	3	45	27
25% - 50%	13	6	4
More than 50%	94	3	1
	110	54	32

*One patient had no initial differential count.

Bone marrow lymphocytes in lymphosarcoma: Of the three patients showing more than 50%, one had a hypoplastic marrow and the others had marrow lymphocytosis in each case ranging from 70% to 96% without either increase in numbers of circulating lymphocytes or appearance of abnormal forms.

Thirty-two patients of the 38 with localized lymphoblastic lymphosarcoma were dead; 17 of these had involvement of cervical, axillary and inguinal areas; 13 had enlargement of the liver and 11 had enlargement of the spleen; 10 ultimately developed edema of the legs; three developed ascites and three had edema of the trunk.

Hematologic Findings

The initial blood findings in the first three groups of diseases are shown in Table IV. Anemia was much more frequent in lymphocytic leukemia than in any of the localized diseases. The distribution of the white blood count, of course, is determined by our definition of the disease, so that the initial lymphocyte counts in lymphocytic and lymphoblastic sarcoma fell within the normal ranges and

only one patient in these groups approached the arbitrary dividing value of 5440/c.mm. Platelet counts were generally a little lower among the leukemic patients and a few showed significant thrombocytopenia. The sedimentation rate tended to be elevated above normal in the lymphoblastic sarcomas more often than in either leukemia or lymphocytic lymphosarcoma. The bone marrow was almost universally invaded by lymphocytes in lymphocytic leukemia, only five cases out of 93 showing less than 25% lymphocytes in the bone marrow. Only occasionally did patients with localized tumour show invasion of the marrow at the time of diagnosis, but 12 of these eventually showed lymphocytosis in the marrow of more than 25%. Of the three patients with lymphosarcoma who in the course of their disease showed more than 50% lymphocytes in the bone marrow, one had a definitely hypoplastic marrow, so that the high proportion of lymphocytes was only a reflection of diminution in the other elements. The other two had, on multiple aspirations, between 72% and 96% lymphocytes, although neither showed any increase in circulating lymphocytes.

In the patients with lymphosarcoma, attention was directed especially to the presence or absence of abnormal circulating cells, independent of any rise in the total circulating lymphocyte count. Specimens of the blood were available for re-examination in 54 cases and of bone marrow in 50. Only four of the 54 showed morphologically abnormal lymphocytes in concentration greater than 100/c.mm., and these showed 108, 146, 150 and 950, respectively. These were categorized as "atypical" lymphocytes.

Survival

Survival curves were calculated by the method of Berkson and Gage[14] for the whole group and for each of the three homogeneous groups, and these are shown in Figs. 3-6. These curves were constructed from information gathered to December 31, 1964, so that each patient had been followed up for at least four years, or until death.

B. THE MIXED GROUP

Fifty-four patients who could not be fitted into the four homogeneous classes were relegated to a "mixed group" and are considered under the following headings.

Follicular Lymphoma

Thirty-one patients were considered to show some evidence of the histologic pattern of follicular lymphoma in the first biopsy. Twenty-five of these were observed to undergo transition to another histologic type while under care and are considered below, leaving only six whose disease persisted as follicular lymphoma or disappeared with treatment and did not recur during the period of observation. There were five males and one female, and five of these were alive at the close of the study period; the other died of congestive heart failure, apparently unrelated to his lymphoma. Their ages were 23, 31, 46, 65, 71 and 76 and their duration of life since diagnosis has ranged from three to 10 years. None of these patients had abnormal circulating lymphocytes either in terms of type or numbers, and the four bone marrows that were examined showed no infiltration with lymphocytes.

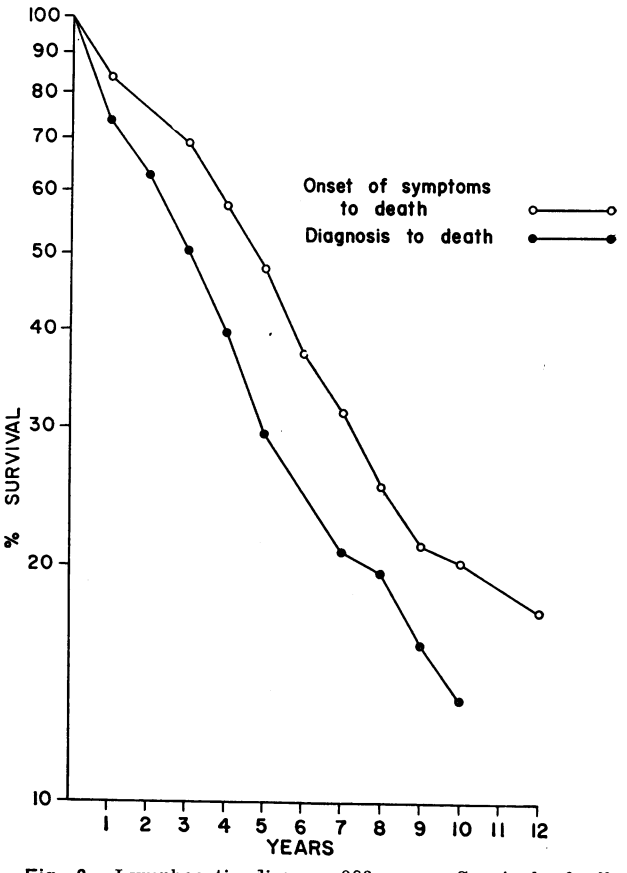

Fig. 3.—Lymphocytic disease, 283 cases. Survival of all cases, (a) from onset of symptoms, (b) from diagnosis to death, plotted as a logarithmic function of time. The curves are close to simple exponentials.

Follicular Lymphoma With Transition to Lymphocytic Lymphosarcoma

There were 16 patients in this group, six males and 10 females; eight are dead. The median age was 54 with a range from 23 to 68. The mean survival to date in this group, which includes the eight patients still living, is 49 months, so that the true mean survival will be considerably in excess of this figure. Only one of these patients showed even slight changes in the peripheral blood, and she showed only an occasional "atypical" lymphocyte. Bone marrow examinations were performed in 12 and were normal in 11. One showed abnormally large clumps of lymphocytes in squash preparations. These patients, therefore, have enjoyed a longer survival than would have been expected had they had lymphosarcoma from the start.

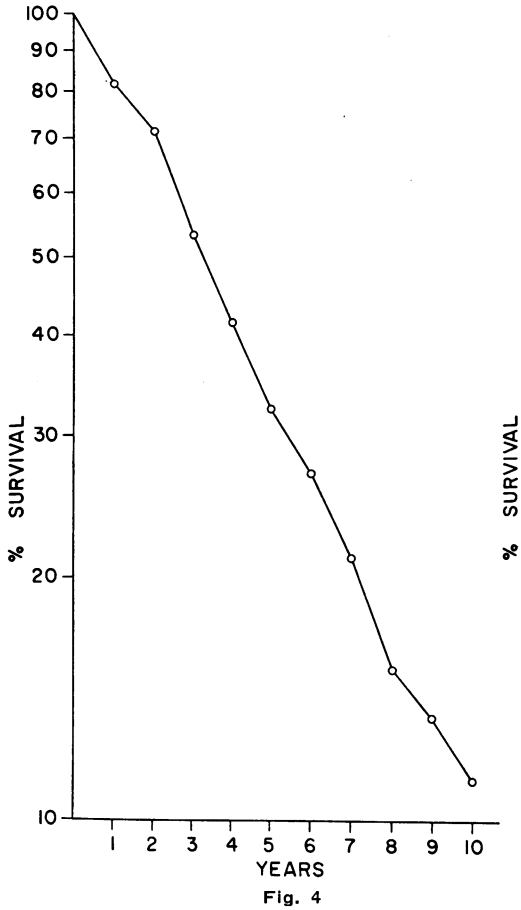

Fig. 4

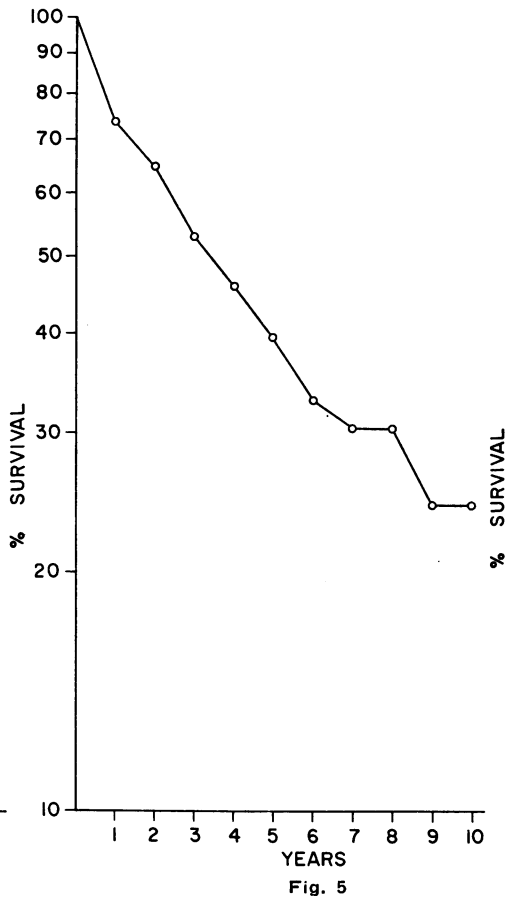

Fig. 5

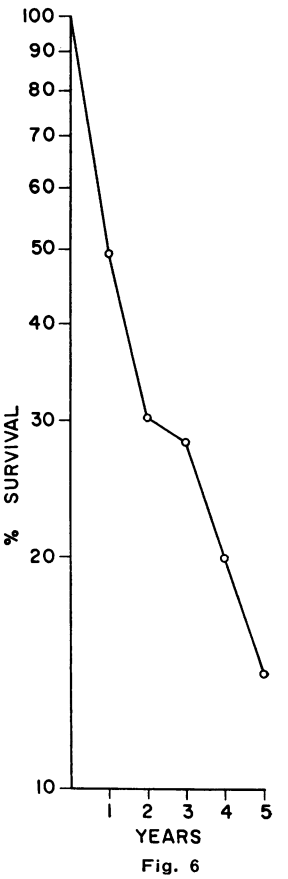

Fig. 6

Fig. 4.—Survival of 122 patients with lymphocytic leukemia. **Fig. 5.**—Survival of 68 patients with lymphocytic lymphosarcoma. **Fig. 6.**—Survival of 38 patients with lymphoblastic lymphosarcoma.

Follicular Lymphoma With Transition to Lymphocytic Lymphosarcoma and Then to Lymphoblastic Sarcoma

There were five such patients in this group, three males and two females, with an average age of 45 years; all are dead. Their mean survival was 57 months, which, again, is longer than the expected survival in either lymphocytic lymphosarcoma or lymphoblastic lymphosarcoma alone. In each of them the peripheral blood remained normal but in one of the four patients in whom bone marrow examination was performed there were 48% lymphocytes.

Follicular Lymphoma With Transition to Lymphocytic Lymphosarcoma and Then to Lymphoblastic Leukemia

There were two patients in this group, one male, aged 43, and one female, aged 64. The first died 31 months after diagnosis and the second 11 months after diagnosis. One of these patients had a few circulating abnormal blast cells at the time when the first biopsy showed follicular lymphoma, but in the other the peripheral blood was normal. Both died with a characteristic picture of blast-cell leukemia, but both lived longer than the average for adult acute leukemia.

Lymphocytic Lymphosarcoma With Transition to Lymphocytic Leukemia

Six patients fell into this group, all males, ranging in age from 36 to 78 years. The localized disease was recognized first in lymph nodes in the neck in three, in diffusely scattered areas in two and localized in the rectal mucosa in the other. In each case the total white count at the time of diagnosis was normal. In four of these six patients the absolute lymphocyte count was between 4000 and 5000/c.mm. but none of them displayed abnormal lymphocytes. Five of the six showed lymphocytosis in the bone marrow in excess of 25%. All, of course, went on to display lymphocytosis in excess of 5440/c.mm., reaching figures ranging from 7000 to 160,000 despite chemotherapy or radiation directed at the local lesions. All of these patients are dead, having survived six, 13, 24, 32, 58 and 64 months, respectively, from diagnosis.

On the basis of the sex distribution of the lymphosarcoma and lymphocytic leukemia groups, the probability that six successive patients from the first group would be males is 0.02, whereas the similar probability for the second group is 0.2. This suggests that this group of six cases may properly be categorized as leukemia rather than lymphosarcoma, a surmise that is consistent with the absence

of large masses and with the initial lymphocyte counts in blood and marrow.

Lymphocytic Lymphosarcoma With Transition to Lymphoblastic Lymphosarcoma

There were four patients in this group, three males and one female. The first patient, a 63-year-old man, had a 12-year history of enlarged lymph nodes in his groin which culminated in the development of edema of his thigh and a biopsy diagnosis of lymphosarcoma. Treatment was temporarily effective but rapidly progressive intra-abdominal disease developed which was unresponsive to therapy and he died 15 months after diagnosis. Blood and bone marrow were normal. The second patient was a 60-year-old woman who was proved to have a lymphosarcoma of cervical lymph nodes by biopsy and who received treatment to these lymph nodes and to the axillae and abdomen at that time. She remained well for 18 years, when a recurrence in the abdomen and mediastinum developed rapidly and, being unresponsive to treatment, caused her death within six months. The blood and bone marrow were persistently normal. The third patient was a 71-year-old man who, at laparotomy, had a retroperitoneal lymphosarcoma. Treatment kept the disease in check for nine years, after which large recurrences in the neck and mediastinum caused death in three months. No blood changes occurred. The fourth patient was a 54-year-old man who presented with a mass in the mediastinum. An inguinal lymph node biopsy showed lymphosarcoma. The chest mass disappeared with therapy, but lesions appeared in the bones and lymph nodes which did not respond to radiation and nitrogen mustard and he died nine months after the first intimation of disease. No blood changes were observed. These four cases illustrate the change in tempo of disease associated with a change in the histologic picture shown by repeat biopsy or autopsy.

Lymphocytic Lymphosarcoma With Transition to Lymphoblastic Leukemia

A 56-year-old man noted a lymph node in his neck which, on biopsy, was found to contain lymphocytic lymphosarcoma. The nodes responded to treatment and he remained well for 26 months when multiple rapidly growing skin infiltrates appeared and blast cells proliferated in his marrow and invaded his blood stream. Treatment had no effect and he died within two months.

Lymphoblastic Lymphosarcoma With Transition to Lymphoblastic Leukemia

Six patients, all males, are included in this category, their ages ranging from seven to 31. All died within five months of the diagnosis. Each patient presented with a localized tumour and three had normal peripheral blood and normal marrow. One, however, had 40% lymphocytes in his marrow and two had between 6000 and 7000 circulating, normal-appearing lymphocytes. In each case the change from normal hematologic findings to blast-cell proliferation came with explosive suddenness.

Borderline Cases

Eight cases could not be conveniently fitted into any of the foregoing categories and are briefly outlined here.

CASE 1

A 76-year-old man was shown to have a lymphocytic lymphosarcoma by biopsy. He followed a rapid course to death, unaffected by treatment, and died within four months after diagnosis. The first peripheral blood specimen showed 5130 circulating lymphocytes/c.mm. and his marrow contained 96% lymphocytes. The irradiation to which he was subjected resulted in a fall in his total lymphocyte count and may have interfered with the development of a full-blown picture of lymphocytic leukemia which he might have displayed had he been followed up without treatment.

CASE 2

A 55-year-old woman, on biopsy, showed lymphocytic lymphosarcoma. She remains alive and in good health following splenic irradiation. The first peripheral blood examined showed 5800 lymphocytes/c.mm. and 98% of the marrow cells were lymphocytes. By definition, then, this was an instance of lymphocytic leukemia but subsequent white blood counts and absolute lymphocyte counts have been normal. It seems likely that this patient will some day show the picture of chronic lymphocytic leukemia following relapse.

CASE 3

A 68-year-old man came to the hospital with symptoms of colonic obstruction. Lymphocytic lymphosarcoma of the sigmoid and adjacent mesenteric lymph nodes was discovered. He was treated with radiation and remains alive six years following diagnosis. The first peripheral blood showed a lymphocyte count of 6050/c.mm. and marrows on two occasions showed 23% and 26% lymphocytes, respectively. Although he has not been treated for five years, the patient has never again shown any increase in his peripheral lymphocytes.

CASE 4

A man aged 57 showed, on biopsy, a lymphocytic lymphosarcoma. He soon developed a severe hemolytic anemia which was temporarily relieved by splenectomy, but he died of anemia 12 months later. His first peripheral blood showed an absolute lymphocyte count of 5830/c.mm. and 50% of the marrow cells were lymphocytes. In the many subsequent examinations, however, he never again showed any increase in peripheral lymphocytes.

CASE 5

A 70-year-old woman presented herself with obvious intra-abdominal disease which was shown at operation to be due to lymphoblastic lymphosarcoma. She survived only two weeks and at autopsy had heavy in-

filtration of some of the skeletal structures with lymphoblastic lymphosarcoma. The initial peripheral blood showed 5450 circulating lymphocytes/c.mm. but no abnormal forms of blast cells.

CASE 6

A 62-year-old man was found, on biopsy of peripheral lymph nodes, to have a follicular lymphoma. He had widespread lymph node enlargement and, despite local radiation therapy and nitrogen mustard, went progressively downhill and died in 16 months. His initial lymphocyte count was 6780/c.mm. and the marrow contained 71% lymphocytes. None of the large number of subsequent examinations, however, showed any abnormality of the circulating cells either in type or in number.

CASE 7

A 75-year-old man became aware of multiple nodules in his skin. On biopsy these were found to be lymphoblastic lymphosarcoma. The disease spread rapidly to involve the lymph-node-bearing areas and, despite temporary improvement with therapy, he died seven months after diagnosis. The initial peripheral blood findings were normal, as was the marrow. Terminally, however, his white blood count rose to 28,900/c.mm. but the cells, surprisingly, were 80% mature lymphocytes, in contrast to the lymphoblastic nature of the tumour.

CASE 8

A 6-year-old boy was noted to have enlarged cervical nodes which proved to contain lymphocytic lymphosarcoma. He received radiation therapy to the neck, axilla and mediastinum. He remained well for five months but then abruptly became ill and died in three weeks. His blood counts were normal until just before death when a count of 55,000 white cells/c.mm. was recorded, with 95% lymphocytes. The slides were not available for review to determine whether these cells were actually lymphocytes or lymphoblasts.

DISCUSSION

It is obvious that the division of patients with lymphocytic disease into those with leukemia and those without it predetermines that the first group will display symptomatic and hematologic evidence of disseminated disease and the second group either will not show such evidence or will show it to a lesser degree. Many of the differences which have been discerned in this study between the well-defined lymphosarcomas and the well-defined leukemias are merely expressions of the extent of the disease. It might be expected that the symptoms complained of by those with leukemia would be of a generalized nature and this was, indeed, found to be so. When the tumour grew to a considerable size in one area, obstructive phenomena were encountered which were less frequent in those in whom the disease was more widely disseminated. Because the bone marrow was involved in the widespread form of the disease, anemia and thrombocytopenia were more frequently encountered in these instances.

It seems clear that we are not dealing with a disease complex which has any inevitable trend towards dissemination. Many of the cases are clearly widespread from the very beginning and many show no tendency whatever to become disseminated. While it is true that these latter patients received radiation therapy which might have suppressed lymphocytosis, other cases clearly showed that radiation is not capable of controlling lymphocytosis in all instances. Leukemia cannot be regarded only as the last phase in the evolution of lymphocytic disease. Rather, it would appear that in some instances the cells are unable to colonize the bone marrow or the spleen and remain confined to one place or to various lymph-node-bearing areas. Some of the cases of localized lymphosarcoma showed occasional abnormal circulating cells, indicating the possibility of spread through the blood stream, but leukemia rarely occurred in the absence of gross invasion of the marrow and it seems possible that the ability to colonize the marrow is a prerequisite for sustained levels of lymphocytes in the peripheral blood. It may be that local tissue factors in marrow and other tissues prevent the seeding and proliferation of these abnormal cells, which is essential to the development of leukemia.

Differences between lymphocytic leukemia and lymphosarcoma which cannot readily be explained are those related to age and sex. Lymphosarcoma is more frequent in young people than lymphocytic leukemia and, indeed, may affect children and young adults, a circumstance rarely observed with lymphocytic leukemia. In our series there is a striking sex difference between the localized tumour, in which the ratio of males to females was 1.1, and lymphocytic leukemia, in which it was 3.8. It may be that this reflects only the hormonal environment, which is known to have a significant effect on circulating lymphocytes and does not indicate any real difference in the tumour itself.

Contrary to our expectations, we found that patients with lymphocytic leukemia lived the same length of time as those with lymphocytic lymphosarcoma. On the one hand this would negate the hypothesis that lymphocytic leukemia is just the last step in the evolution of lymphocytic disease, for in that case the survival of the patient with lymphocytic leukemia should be less than that of the patient with lymphosarcoma. On the other hand it indicates that lymphocytic leukemia is no less malignant than the localized form.

The fact that many cases of lymphocytic leukemia are discovered by accident may mean no more than that a considerable number of neoplastic cells may be present without symptoms if they are distributed throughout the body, whereas a small number of cells concentrated in a strategically located tumour are soon revealed by the tumour's cosmetic or obstructive effects. Because of the frequency and ease with which peripheral blood may be examined, early discovery is more apt to be

made by this means than if a lesion requires biopsy for diagnosis.

The survival curve for lymphocytic leukemia when plotted on semi-log paper appears as a straight line, giving no evidence of more than one modality to suggest two populations of patients, one with disease more benign than the other.

There is a strong correlation between the type of cell forming the tumour and survival. Those cases showing large lymphoblastic cells had a much graver prognosis than those showing only small lymphocytes.

The mixed group, comprising 19% of the total, has been divided for purposes of description into eight classes, plus nine patients who did not conveniently fit into any category. This group includes all the possible combinations of the four initial categories taken two, three or four at a time. Transitions from mature to immature cell types and from localized to disseminated disease occurred. No changes from immature to mature forms were observed, and only rarely did a patient with essentially generalized disease display a significant local mass towards the end of his course.

Only six cases have shown the benign course described by Symmers[15] for follicular lymphoma in which the disease was controlled by one course of radiotherapy for periods exceeding three years. Sixteen patients evolved into typical lymphocytic lymphosarcoma and behaved, in every way, as though they were members of this group, except that their survival has been longer. It would appear that, in its giant follicular form, the disease progresses slowly and a long interval may pass before it evolves further into a lymphosarcoma, but, once having evolved in this way, it continues as a lymphosarcoma. There were five cases in which the evolution proceeded from follicular lymphoma through lymphocytic lymphosarcoma into a lymphoblastic process, and two of these showed a florid leukemia of acute type. In these cases the tempo of the disease increased as the morphological character of the cell altered toward immaturity.

Only six patients first presented with lymphocytic lymphosarcoma and then became frankly leukemic. Their mean survival was slightly less than for uncomplicated lymphocytic lymphosarcoma. A striking feature of this group was the fact that all were males. It is possible that this group would have been larger had the cases with lymphosarcoma not received any therapy, but we suspect that the number of cases that were prevented from showing this transition because of therapy alone must have been small. Five patients showed a transition from lymphocytic lymphosarcoma to a lymphoblastic process, and one of these showed a lymphoblastic leukemia. In all instances the change to a lymphoblastic process was marked by a striking acceleration in the tempo of the disease.

CONCLUSIONS

The picture presented by these 283 cases ranges from a "benign" course pursued by the six cases of follicular lymphoma to a highly malignant course pursued by six cases of lymphoblastic lymphosarcoma, proceeding to lymphoblastic leukemia. The majority of the cases (81%) fell into three distinct categories of lymphocytic lymphosarcoma, lymphoblastic lymphosarcoma and lymphocytic leukemia. They could readily be fitted into these groups when they first appeared and continued unaltered in this respect during their course. The remaining 19% showed transitions of two types: they proceeded from a more mature cellular type to a less mature with accompanying acceleration in the tempo of the disease, or they showed a change from localized to generalized anatomic distribution of lesions with or without invasion of the blood stream, or they showed both of these changes.

It was possible to relate the type of clinical course with the type of tumour cell: the more immature the cell, the more rapid the progression of the disease. There were differences in age distribution and age incidence between lymphocytic lymphosarcoma and lymphocytic leukemia, but these were slight. A more striking discrepancy was noted in the sex incidence in the two groups. This may possibly be related to differences in the hormonal environment rather than in the tumour itself.

In general the differences in symptoms were merely what one might have expected from the anatomic site of involvement. Those patients with generalized disease complained of weakness, fatigue and symptoms related to anemia, while those with localized disease complained of symptoms related to masses of tissue and obstructive phenomena. Hematologic changes reflected the extent of disease and the type of cell. No cases of "lymphosarcoma cell" leukemia were recognized as distinct from the whole group.

The median survival of patients with lymphocytic lymphosarcoma was the same as the survival for those with lymphocytic leukemia when measured from the date of diagnosis. The survival of patients with lymphoblastic lymphosarcoma was notably shorter. The curves for survival of the first two groups are simple exponentials and do not suggest the presence of two populations, one with disease less malignant than the other.

The mixed group is significantly large. Transitions from one clinical type of lymphocytic disease to another occur frequently as the cell type and its ability to colonize the marrow change with time.

Lymphocytic disease can be regarded as an entity which most frequently takes the form of lymphocytic leukemia, lymphocytic lymphosarcoma or lymphoblastic lymphosarcoma. But various combinations of clinical and hematologic characteristics occur more or less frequently. Prognosis depends not on the presence or absence of blood stream invasion but on the total bulk of tumour and the maturity of the cell.

SUMMARY

Two hundred and eighty-three cases of lymphocytic disease observed at the British Columbia Cancer Institute between 1948 and 1960 were reviewed. Eighty-one per cent fell into three distinct categories, namely lymphocytic lymphosarcoma, lymphoblastic lymphosarcoma and lymphocytic leukemia, in which they continued during their whole course. The remaining 19% showed transitions of two different sorts, i.e. alteration from mature to less mature cell types, and spread from localized to generalized distributions. The clinical course was related to the type of cell, and the symptomatic expression was related to the distribution of disease and not to the presence or absence of bloodstream invasion. The only notable exception was the male predominance seen in lymphocytic leukemia. The degree of anemia and thrombocytopenia were also in accord with the type of cell and the extent of disease.

The survival of patients with lymphocytic lymphosarcoma was the same as of those with lymphocytic leukemia when measured from the date of diagnosis. The survival of those with lymphoblastic lymphosarcoma was strikingly abbreviated. The curves for survival of the first two groups are simple exponentials and do not suggest the presence of two populations, one with disease less malignant than the other.

Lymphocytic disease can be regarded as an entity which most frequently takes the form of lymphocytic or lymphoblastic lymphosarcoma or lymphocytic leukemia but which sometimes displays features of two or three of these major groups or progresses from a more mature to a less mature cell type. Prognosis depends not on the presence or absence of blood stream invasion but on the total bulk of tumour and the maturity of the cell.

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