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Leukemic Reticuloendotheliosis (Hairy Cell Leukemia)

By Bertha A. Bouroncle

Leukemic reticuloendotheliosis (hairy cell leukemia) is a well-established independent clinical and pathologic entity. This study will report the clinical, hematologic, and histologic findings in 82 patients who have been followed for over 20 yr. The diagnosis must be confirmed by the finding in the peripheral blood and/or bone marrow of the pathognomonic mononuclear cell of leukemic reticuloendotheliosis, the so-called hairy cell, which is best characterized by the use of supravital stain, phase-contrast microscopy, slide-cultures, and electron microscopy. The most common physical finding is splenomegaly, which was present in 93 % of our patients. The course of the disease is, in general, chronic. The most frequent complication is

infection. Spontaneous remissions can occur in leukemic reticuloendotheliosis. Transition to other forms of leukemia or lymphoma has not been recorded. Splenic irradiation is usually followed by temporary improvement. Chemotherapy is not indicated initially. However, in patients who have life-threatening disease with a predominance of hairy cells in the peripheral blood, marked thrombocytopenia, neutropenia, and anemia due to extensive infiltration of the marrow by the malignant cells, aggressive chemotherapy should be initiated. Splenectomy is indicated in cases of frank hypersplenism, and the results, in the majority of patients, have been excellent and long-lasting.

IN 1958 we published a classic report¹ in which we described 26 patients with leukemic reticuloendotheliosis (LRE) and established the concept that it is an independent clinical and pathologic entity. Since then, more than 180 articles have been published concerning this rare type of chronic leukemia. Its incidence is approximately 2% of all the leukemias seen at our hospital each year.

The purpose of this study is to present our findings in 82 patients with LRE seen in the Division of Hematology and Oncology of The Ohio State University. Some of them have been followed for over 20 yr. We will discuss the clinical, hematologic, and pathologic findings, the criteria for diagnosis, and the results of treatment with chemotherapy, splenic irradiation, and splenectomy, with special emphasis on the indications for and results of splenectomy.

MATERIALS AND METHODS

This study is based on observations of 82 patients with LRE who have been seen and followed by the members of the Division of Hematology and Oncology at The Ohio State University. The 26 patients discussed in our original report are included.

All patients were studied by standard hematologic methods, including hemoglobin, platelet, and red

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and white cell counts, hematocrits, and reticulocyte counts. In each case the diagnosis was confirmed by peripheral blood and bone marrow observations under supravital² Wright stain and phase-contrast microscopy. The bone marrow biopsies were stained with hematoxylin-eosin, and in most cases reticulin staining was done. In selected cases electron microscopic studies were performed. Since 1966, observation of peripheral blood and bone marrow cells in Rose chamber cultures³ has been added to our routine diagnostic procedures. Tartrate-resistant acid phosphatase⁴ enzyme studies in peripheral blood and bone marrow slides were done in only 12 patients.

In 17 patients in whom splenectomy was performed the diagnosis was confirmed by examination of cells scraped from the spleen and observed by the use of supravital and Wright stains, slide cultures, phase-contrast microscopy, and in selected cases electron microscopy. Tissue sections from spleen, liver, and lymph nodes obtained at the time of operation were also examined routinely. The autopsy material from 26 patients has been reviewed.

CLINICAL OBSERVATIONS

Incidence

LRE is a rare disease. The average number of new patients admitted to our hospital each year is three. This is approximately 2% of all leukemias seen at our hospital. Our clinical observations are based on a total of 82 patients.

Age and Sex

There was male predominance: 67 males (82%) and 15 females (18%). The average age at the time of diagnosis was 54.4 yr, and the median age was 55 yr. The youngest patient at the time of diagnosis was a 22-yr-old female, and the oldest patient was a 76-yr-old male. The distribution of patients according to age and sex is presented in Fig. 1.

Presenting Symptoms

The onset of the disease is usually insidious. The most common presenting complaint in our patients was weakness and fatigue in 51% of patients. Hemorrhagic diathesis manifested by the occurrence of spontaneous ecchymosis, purpura, or epistaxis was present in 9%. Symptoms referred to splenomegaly, such as pain in the left upper quadrant, were the initial presentations in 14%. Infection was the initial presentation in 17%, and LRE was discovered as an incidental finding in 9% of patients. None of these symptoms is specific for LRE.

Physical Findings

There is no pathognomonic physical finding of LRE, but the most common physical finding at the time of initial diagnosis is splenomegaly, which was present

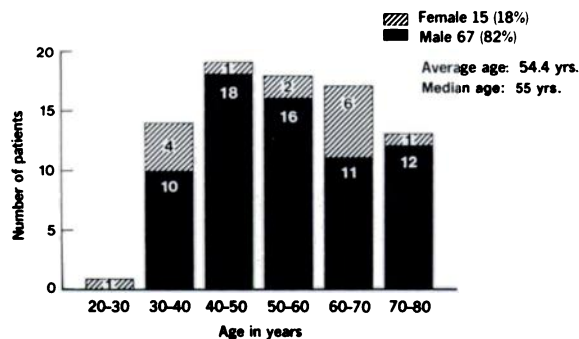


Fig. 1. LRE (hairy cell leukemia). Patient distribution according to age and sex.

Organ enlargement	Spleen	Liver	Lymph nodes	Skin infiltration
Normal	7%	60%	77%	94%
Slightly	7	21	12	5
Moderately	33	13	11	1
Markedly	26	6		
Tremendously	27			




Fig. 2. LRE (hairy cell leukemia). Sizes of spleen, liver, and lymph nodes and extent of skin infiltration at time of diagnosis.

in 93% of our patients. In 53% of patients the spleen was markedly enlarged and palpable below the umbilicus. In 7% of patients the spleen was not palpable. In general, the size of the spleen fluctuated in a given patient during the exacerbations and remissions of the disease, whether spontaneous or possibly induced by therapy (Fig. 2).

Hepatomegaly was present in 40% of patients and was of moderate degree. Lymphadenopathy was present in 23%, and it was, in general, discrete. Skin infiltrations were present in only 6% of patients.

Clinical Course and Occurrence of Infection

The course of the disease is, in general, chronic. It appears to vary from a clinical condition, with slow progression over periods of months or years, to a more steadily progressive illness complicated by bleeding due to low platelets, recurring anemia requiring blood transfusions, and repeated episodes of infection. However, nearly all of our patients were able to perform normally at their usual occupations throughout most of the illness.

Infection was the most frequent complication during the course of the disease. Sixty-four of our 82 patients developed from one to six febrile episodes related to infection during the course of the illness. The most common infections were pneumonia and septicemia, followed by urinary infection, cellulitis, and rectal or other abscesses. The most common organisms were bacterial. In order of frequency, the organisms isolated were *Pseudomonas*, *Escherichia coli*, coagulase-positive *Staphylococcus*, *Klebsiella*, *Proteus*, and *Salmonella*. One patient was found to have tuberculosis; the organism was cultured from sputum and was found in the spleen at the time of splenectomy; the patient was treated successfully. Two patients developed pulmonary *Mycobacterium kansasii* during the illness. Four of our patients developed fungal infections (two of them *Cryptococcus meningitidis* and two disseminated histoplasmosis) during the course of the illness. One patient developed *Pneumocystis carinii* pneumonia.

The causes of death of 63 patients in our series are presented in Table 1. The most common cause of death was infection, followed by massive bleeding. Two patients died from splenic rupture during the course of the illness. A case of spontaneous rupture of the spleen as the initial manifestation of LRE was reported by Rosier and Lefer.⁵

The average survival of all patients in our series is 5 yr 9 mo. Twelve patients have survived longer than 10 yr. The two longest survivors are still alive more than 22 and 27 yr from the time of diagnosis.

Table 1. Causes of Death of 63 Patients With LRE (Hairy Cell Leukemia)

	No. of Patients	Percentage
Bacterial pneumonia and/or sepsis	28	44.0
Systemic fungal infection	3	5.0
Bacterial plus fungal sepsis	2	3.1
Tuberculosis (adrenals)	1	1.6
Massive bleeding	8	13.0
Splenic rupture	2	3.1
Cardiovascular	3	5.0
Bowel carcinoma	2	3.1
Accidental	1	1.6
Suicide	1	1.6
Unknown	12	19.0

HEMATOLOGIC OBSERVATIONS

At the time of initial diagnosis, 69 patients had mild to moderate degrees of anemia, with hemoglobin levels fluctuating between 5 and 12 g/dl. Only 2 patients had frank anemia, with hemoglobin levels below 5 g/dl, and 13 patients had normal hemoglobin levels. The anemia was most frequently normocytic-normochromic and was secondary to replacement of normal marrow elements by leukemic cells. In some patients the anemia was frankly hemolytic.

Leukopenia was the most frequent finding. At the time of initial diagnosis, 41 patients had white blood cell counts below 3,000/cu mm, 38 patients had white blood cell counts between 3000 and 50,000/cu mm, and only 3 patients had white blood cell counts over 50,000/cu mm.

In 27 patients the platelet counts were between 20,000 and 50,000/cu mm at the time of initial diagnosis. In 31 patients the platelets were between 50,000 and 150,000/cu mm. Marked thrombocytopenia, with levels below 20,000/cu mm, was found in 8 patients, and 16 patients had normal platelet counts.

The abnormal mononuclear cell of LRE was seen in peripheral blood at the time of initial diagnosis in 80 patients. The leukemic cells varied from 1% to 80% in 69 patients and were over 80% in 11 patients (Fig. 3).

HEMATOLOGIC DIAGNOSIS

Morphology

The diagnosis of LRE must be confirmed by the finding in the peripheral blood and/or bone marrow of the pathognomonic mononuclear cell with its characteristic cytoplasmic projections. There are no differences in morphology of cells obtained from peripheral blood, bone marrow, spleen, liver, and lymph nodes. The morphologic characteristics of the LRE as revealed by the use of supravital stain and phase-contrast and electron microscopy were first described in our original report.¹

In fixed films with Wright stain (Fig. 4) the cytoplasm of the cells of LRE is usually poorly preserved; however, in a good slide the classic morphologic characteristics can be recognized. The cell border is irregular and serrated. Some nuclei are surrounded by very scant disrupted cytoplasm. The color of the cytoplasm is sky blue, and it has no granules. The nuclear membrane is distinct, and the chromatin is spongy in appearance.

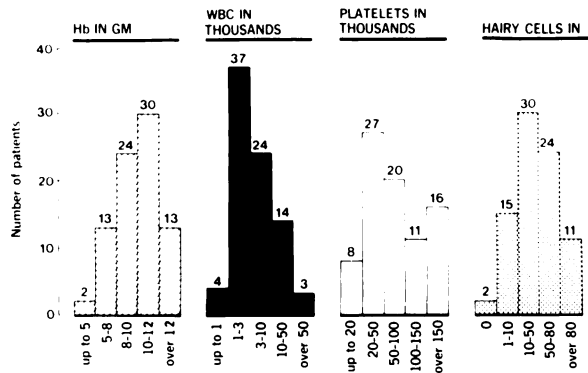


Fig. 3. Peripheral blood findings in 82 patients with LRE at time of initial diagnosis.

In supravital stain this abnormal mononuclear cell can be readily identified because the differential morphologic characteristics of the viable cells are well preserved. The cell has an irregular shape, usually round or polygonal, with a lacelike outline of the cell membrane giving it a serrated border. The cytoplasm contains mitochondria, which stain with Janus green, and its distribution commonly follows the shape of the cell. A few small neutral vacuoles are present in the cytoplasm. The nucleus is round or oval, about one-half the size of the cell, and is usually eccentric in location. The nuclear chromatin is sharp and distinct; it is spongy in appearance and nongranular. Sometimes single nucleoli are present.

When fresh preparations are observed under phase-contrast microscopy (Fig. 5) the same cell characteristics described in supravital stain are apparent. The morphology of the cell in well-spread slides is very distinctive, with numerous

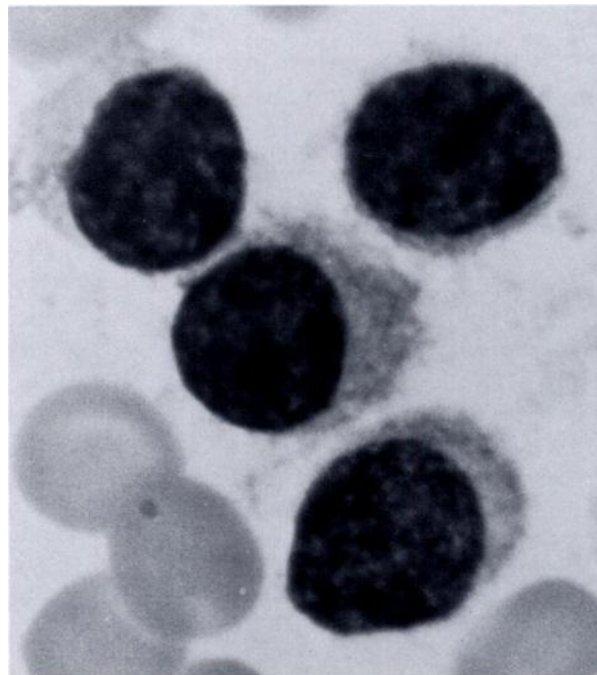


Fig. 4. Bone marrow smear of fixed preparation observed with Wright stain. The outline of the cytoplasm of the cell is irregular and stains sky blue without granules. The edges of the cytoplasm are frequently disrupted.

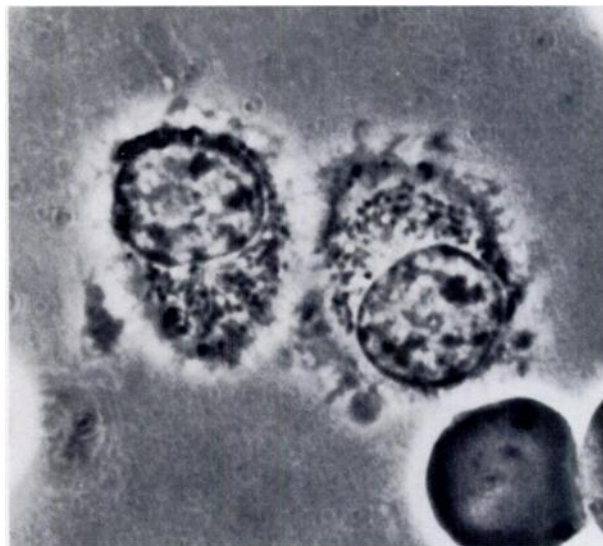


Fig. 5. Peripheral blood film of supravital preparation observed under phase-contrast microscopy. The mononuclear cells of LRE are typical, with numerous slender hairlike cytoplasmic projections that protrude constantly for the entire circumference of the cell.

slender hairlike cytoplasmic projections that protrude constantly from the cytoplasm of the cell. The value of phase-contrast microscopy for recognition of the hairy cell must be emphasized.

In 1966 Schreck and Donnelly⁶ described the morphologic appearance of these cells in blood and bone marrow of 2 patients with LRE in a culture suspension in slide chambers. Because of the numerous short villose projections from the surface of the cells, they gave these cells the descriptive name hairy cells. This has become a popular name because it does not imply any origin for the cell. Since then, LRE has also been reported as hairy cell leukemia (HCL). We use the names interchangeably in this report.

In our laboratory we use the Rose chamber³ for observation of cells in slide cultures. The hairy appearance of the mononuclear cell of LRE is characteristic of this disease (Fig. 6).

In electron microscopy (Fig. 7) the most characteristic finding is the presence of pseudopods and long cytoplasmic villi on the cell surface measuring up to $4\ \mu$ in length. Some of the microvilli of adjacent cells interdigitate. The cytoplasm contains abundant oval or round mitochondria with well-defined cristae, numerous vesicles, rough-surfaced endoplasmic reticulum, and few ribosomes. The Golgi complex appears to be of moderate size, generally consisting of three or four cisternae. Numerous fine fibrils surrounding the nucleus are present.

In addition to the cellular organelles previously described, cytoplasmic ribosome-lamella complexes are frequently seen in the hairy cells.

Bone Marrow

Frequently, bone marrow aspirations are unsuccessful (dry tap). When fragments are obtained there are several degrees of infiltration by the typical mononuclear hairy cells of LRE that are identical to those in the peripheral blood.

Bone marrow biopsies always reveal infiltration by mononuclear cells. In the early stages there is patchy infiltration, with preservation of normal marrow cells.

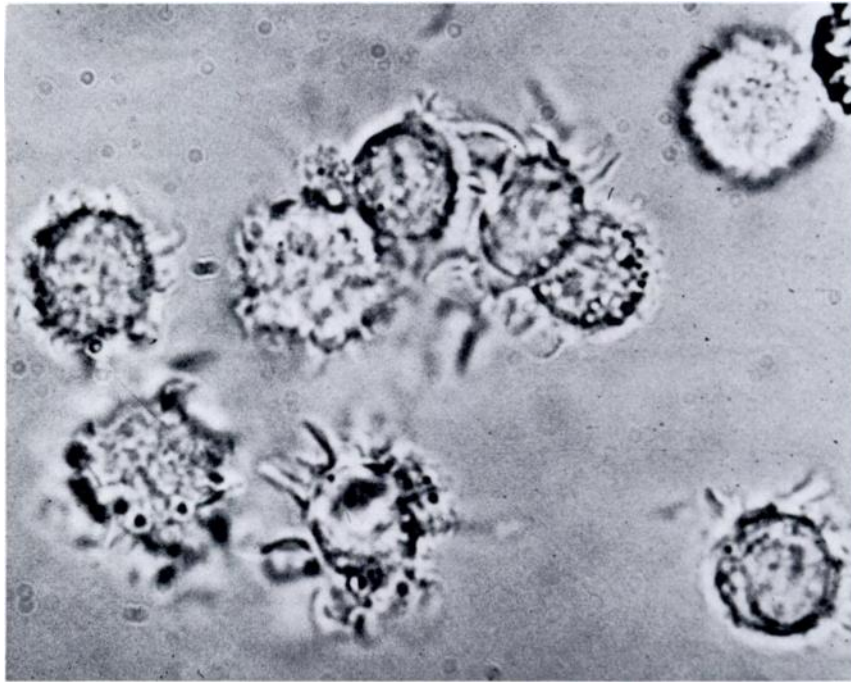


Fig. 6. Viable cells observed in Rose chamber slide cultures. Cells were obtained from bone marrow aspiration from patient 12. The typical hairy appearance of the cells is demonstrated, with prominent and retractile cytoplasmic projections extending from the entire circumference of the cells.

In the more advanced stages there is diffuse infiltration by uniform mononuclear cells. Even when the infiltration by hairy cells is very extensive the characteristic loose and spongy arrangement of these cells is preserved, and this permits differentiation from other kinds of neoplastic cells involving the bone marrow (Fig. 8).

Fibrosis of the bone marrow consisting of a feltlike network of thin reticulin fibers is present in the areas of LRE cell infiltration. This accounts for the difficulties encountered in obtaining adequate bone marrow aspirates.

According to a review of bone marrow findings in 24 patients with LRE, Vykoupil et al.⁷ consider bone marrow biopsy to be the most valuable method of achieving a correct diagnosis.

Cytochemical Studies

The tartrate-resistant acid phosphatase reaction has been used widely as a test for LRE. We examined blood smears of 12 of our patients, and all had positive tartrate-resistant acid phosphatase activity. In their original report, Yam et al.⁸ supported the belief that tartrate-resistant enzyme activity could be used as a marker enzyme to diagnose LRE.

Differential Diagnosis

LRE is sometimes diagnosed incorrectly, and in 10 of our patients (12.1%) the initial diagnosis was changed: in 6 patients, from chronic lymphatic leukemia; in 2

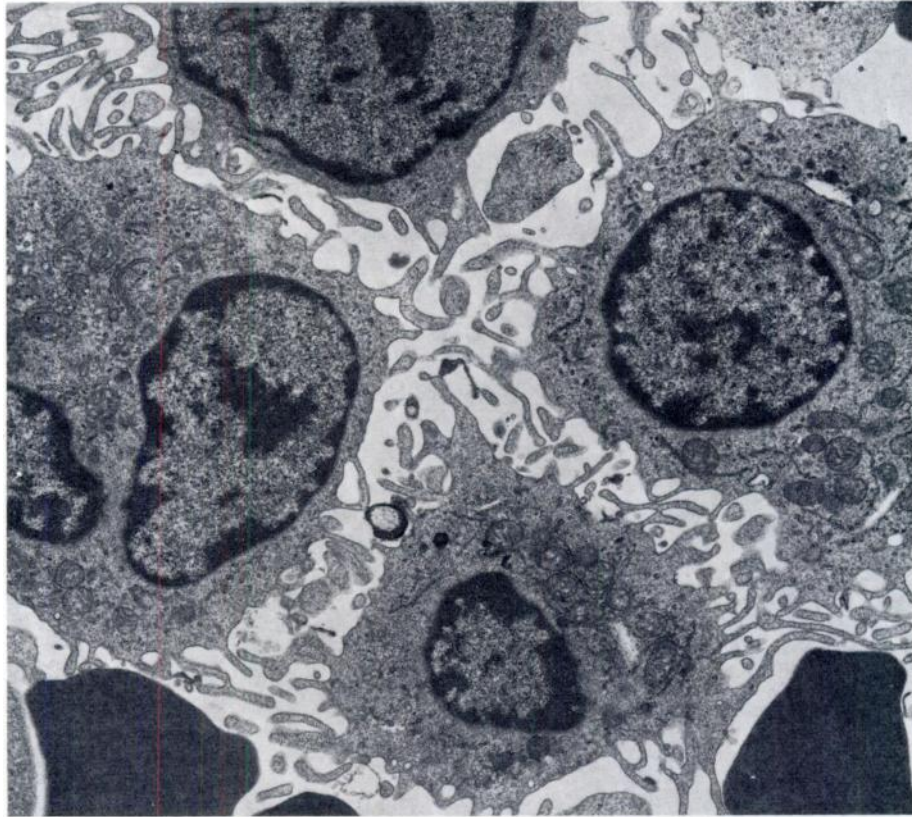


Fig. 7. Electron microscopy of a splenic cell suspension preparation from patient 19. The most characteristic finding is the presence of pseudopods and long cytoplasmic microvilli. Some of the microvilli of adjacent cells interdigitate. The cytoplasm contains a Golgi apparatus, lysosomelike bodies, and mitochondria.

patients, from myelofibrosis; in 1 patient, from malignant lymphoma; in 1 patient, from acute monoblastic leukemia. Accurate diagnosis rests on recognition of the pathognomic mononuclear cell.

HISTOLOGIC OBSERVATIONS

Spleen

Histologic observations regarding our patients were made on sections of spleens obtained at the time of splenectomy in 17 patients and on autopsy material from 18 patients. A total of 26 patients underwent complete autopsy.

The spleen seemed to be the organ showing the most extensive involvement, and like the bone marrow it was infiltrated by the abnormal mononuclear leukemic cells of LRE in all patients in whom it was observed. The weight of the spleen was over 350 g in all 17 patients at splenectomy. At autopsy, 3 of 18 patients had spleens that weighed less than 350 g (Table 2).

Grossly, the spleens were firm, and in 13 patients the gross diagnosis of splenic infarction was made. Microscopic examination of preparations from the spleens showed extensive proliferation and diffuse infiltration by the abnormal mononuclear cells. The cells infiltrated the red pulp and pulp cords. The sinuses were often

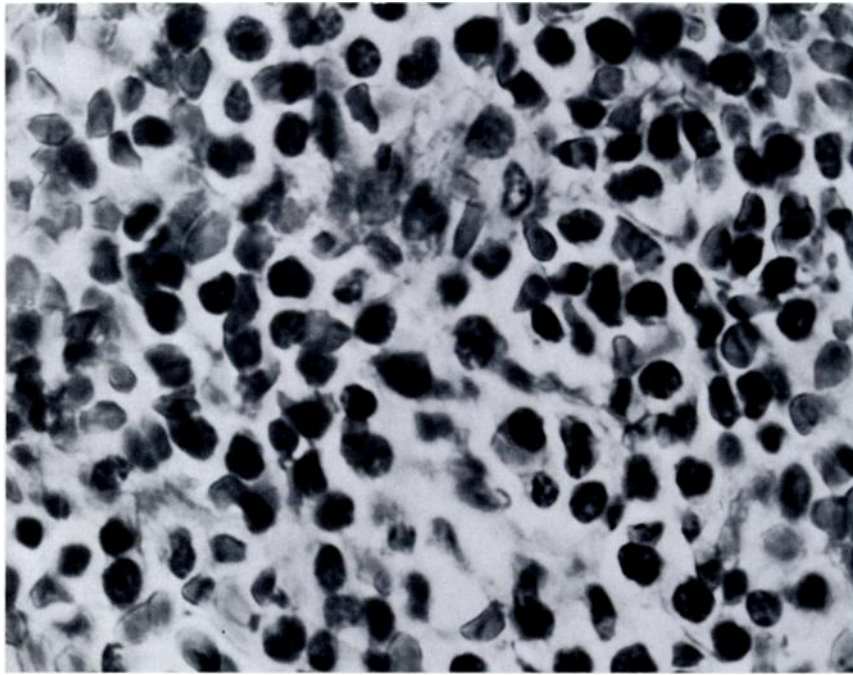


Fig. 8. Bone marrow biopsy from patient 4. There is marked infiltration by the LRE mononuclear cells. The characteristic loose and spongy arrangement of these cells is preserved.

engorged with the leukemic cells, and this resulted in partial or complete obliteration of red pulp architecture. The infiltration also encroached on the white pulp, and in most cases it tended to replace most of the malphigian corpuscles or reduce their diameter. The splenic capsule, the trabeculae, and the subendothelial regions of the trabecular veins were not affected by this infiltration. On hematoxylin-eosin stain the reticulum cells appeared to be of medium size, tending to be round or ovoid in shape, having a moderate amount of essentially clear or slightly translucent cytoplasm, with nuclei that were large and round or vesicular and with small clumps of chromatin and occasional nucleoli. No mitoses were observed (Fig. 9).

Suspensions of scrapings from the spleen were made in tissue culture medium (MEM). From this suspension supravital slides for observation under light and phase-contrast microscopy and for observation in Rose chambers were prepared, the cells had the same hairy appearance and morphologic characteristics as

Table 2. Weights of Spleens Available at Surgery or Autopsy From 35 Patients With LRE

Weight of Spleen (g)	Number of Patients	
	At Surgery	At Autopsy
Normal (< 350)	—	3
350-1000	9	6
1000-3000	5	9
3000-6000	2	—
> 6000	1	—

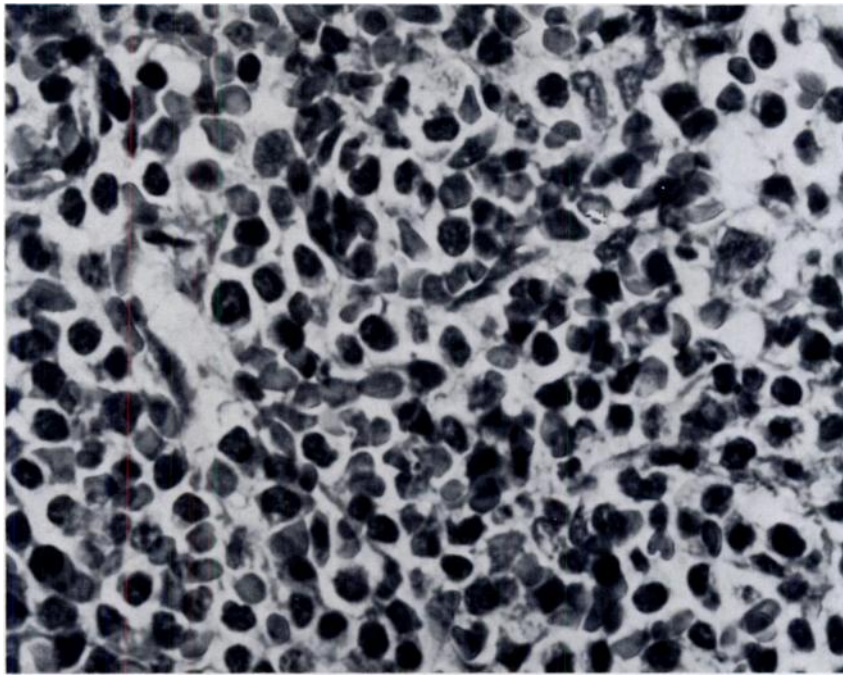


Fig. 9. Section of spleen from patient 4 showing the sinusoids containing red blood cells and the typical mononuclear cells of LRE. There is also diffuse infiltration of the pulp by the leukemic cells.

described previously in similar preparations from peripheral blood and bone marrow.

All our patients had confirmed diagnoses of LRE, before splenectomy or autopsy was performed, by examination of peripheral blood and bone marrow preparations. This is different from the situation described in the report of Burke et al.,⁹ where in 16 of their 21 patients the diagnosis of LRE was established following histologic study of spleen sections.

In some of our patients electron microscopic studies of the spleen were made. The morphologic characteristics of the hairy cells were the same as those described previously. The cytoplasmic projections interdigitated (Fig. 7).

Liver

The weights of livers varied from 1500 to 3000 g in 12 patients and from 3000 to 5000 g in 8 patients in our series. Under microscopic examination 5 of the 26 specimens obtained at autopsy did not show evidence of liver infiltration. The other 21 specimens showed diffuse infiltration throughout the hepatic sinuses, and many of them also showed portal infiltration by leukemic cells (Fig. 10). Of the 15 liver biopsies available for microscopic examination at the time of splenectomy, 14 showed infiltration by leukemic cells, and only one liver biopsy was negative.

Lymph Nodes

The lymph nodes of 24 of the 26 patients available at autopsy demonstrated diffuse infiltration by leukemic cells of the same type as seen in the spleen. Only 2

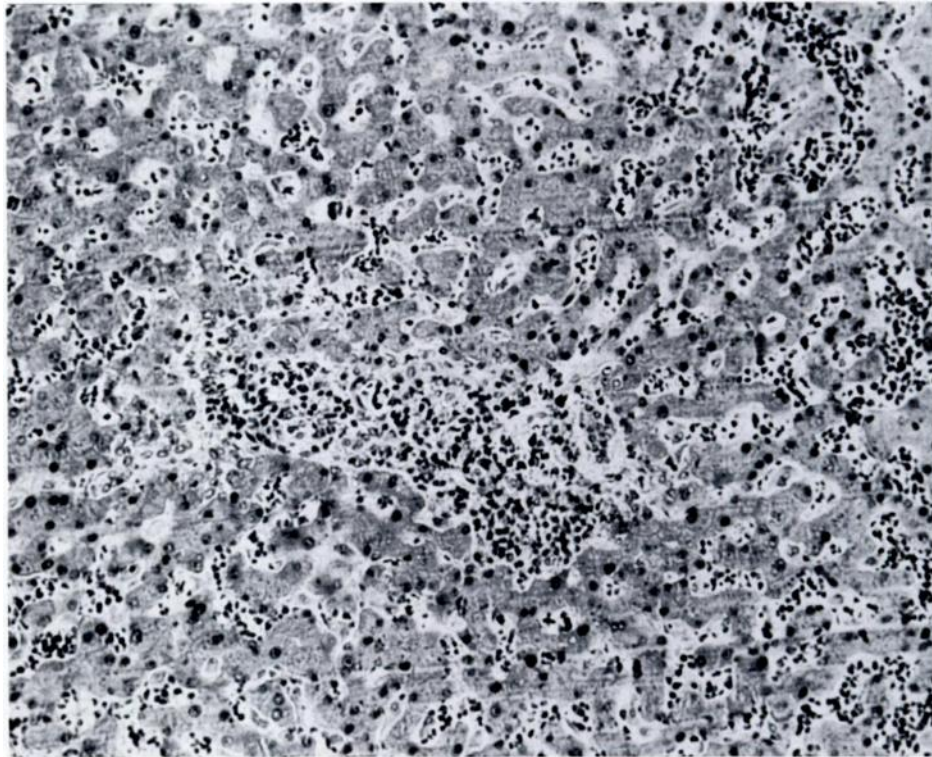


Fig. 10. Section of liver from patient 4 showing infiltration of the portal spaces with the typical mononuclear cells of LRE, as well as many sinusoids in the parenchyma, which is distended and packed with leukemic cells.

patients had negative lymph nodes at autopsy. In 11 patients lymph node biopsies were obtained at the time of splenectomy. Ten were positive and one negative for infiltration with leukemic cells.

Other organs in which increased infiltration by leukemic cells was found at autopsy were, in order of decreasing frequency; kidneys, lungs, pancreas, and adrenals (Table 3).

TREATMENT

It is difficult to evaluate the results of therapy in patients with LRE because of the extreme variability in the severity of the disease and because the course of the disease is, in general, chronic and is characterized by periods of exacerbation of symptoms followed by periods of objective improvement. Prompt recognition and diagnosis of infections and increased availability of more effective antibiotics are important in the management of patients with LRE, and they have definitely improved the prognosis.

Corticosteroids

Forty-six of our patients were treated with prednisone at some time during the period of observation. In only 5 patients was there some improvement in bone

Table 3. Histologic Observations in 26 Patients with LRE and Frequency of Leukemic Infiltration of Organs at Autopsy

Case	Bone Marrow	Spleen	Liver	Lymph Nodes	Kidney	Lungs	Adrenals	Pancreas	Other Organs
1	+	+	+	+		+			
2	+	+	+	+	+			+	
6	+	+	+	+	+	+		+	
8	+	+	+	+					
10	+	+	+	+			+		Accessory spleen
28	+	+	+						
29	+	+		+					
33	+	+	+		+		+		
34	+	+	+	+	+		+		
35	+	+		+					
36	+	+		+					
39	+	+	+	+				+	
41	+	+		+		+		+	
42	+	+	+	+	+	+			
45	+	+	+	+			+	+	
46	+	+	+	+					
47	+	+	+	+		+		+	Heart and aorta
48	+	+		+					Heart
51	+	+	+	+	+	+			
52	+	+	+	+					
54	+	+	+	+	+	+			
55	+	+	+	+					Stomach and small intestine
65	+	+	+	+	+			+	
70	+	+	+	+					
72	+	+	+	+					
77	+	+	+	+	+		+		

marrow function and reduction in spleen size. However, the effect was temporary, and the side effects of prolonged corticosteroid therapy must be considered.

Splenic Irradiation

Splenic irradiation was given to 24 of our patients; some patients had more than one course, with a maximum of five courses. The total amount of radiation for each course was usually from 400 to 900 rads.

Six patients showed no response. Sixteen patients had partial responses after splenic irradiation, with decreased spleen size and improvement in the hematologic picture that lasted 3–12 mo. Most frequently the response was delayed by weeks after completion of course of treatment. Beneficial results have also been reported by other authors.^{6, 10–12} Five of our patients who had partial responses to the first course of treatment failed to respond to subsequent courses.

One patient in our series, after 650 rads of splenic irradiation, went into complete remission, with a return to normal in the hematologic picture and disappearance of splenomegaly and hairy cells. His remission lasted 3 yr, at which time he died, at age 81 yr, from CVA, without evidence of leukemia.

One patient who received 1000 rads of splenic irradiation developed marked pancytopenia followed by overwhelming infection and death, probably precipitated by the treatment.

Chemotherapy

In our experience chemotherapy has not proved to be beneficial. In the early years of our study 12 patients were treated with nitrogen mustard, given as a course of 6–8 mg for 2–4 consecutive days. No beneficial effect was obtained, and 3 of the patients died from infection or bleeding possibly precipitated by the pancytopenia induced by the chemotherapy. Three patients received several doses of 2 mCi of radioactive phosphorus (^{32}P) without benefit.

Fifteen patients were treated with 6-mercaptopurine alone or in combination with Cytoxan or Leukeran for periods of 2–4 mo without improvement. Nine patients were treated with either Cytoxan or Leukeran alone without beneficial effect.

Of 5 patients treated with weekly injections of 2 mg of vincristine, only 1 patient showed temporary improvement and was continued on monthly injections for 6 mo.

In recent years 2 of our patients who had life-threatening disease with marked infiltration of the marrow by malignant cells were treated with aggressive combination chemotherapy consisting of cytosine arabinoside, cyclophosphamide, vincristine, and prednisone, but they showed no improvement.

Most investigators who have reported their observations in large numbers of patients agree on the ineffectiveness of chemotherapy.^{9,10,13,17} However, good temporary results have been described in single cases treated with vincristine by Lee et al.¹⁸ and James and Goodwin.¹² Complete hematologic remission of 2 yr duration induced by combination chemotherapy with cyclophosphamide and cytosine arabinoside has been reported by Davis et al.,¹⁹ and complete hematologic remission of 6 mo duration induced by combination chemotherapy with vincristine, endoxan, Natulan, and prednisone has been reported by Yoshikawa et al.²⁰

Spontaneous Remission

Among our 82 patients, 1 patient has gone into spontaneous remission (Fig. 11). This patient is a white female who was 39 yr old at the time of diagnosis in January 1958. The physical examination revealed a few ecchymoses and purpura and a large spleen palpable below the umbilicus. The liver was of normal size, and no lymph nodes were present. The peripheral blood had a white blood cell count of 5150/cu mm with 62% hairy cells. The hemoglobin was 10.2 g/dl; the platelets were 110,000/cu mm. The bone marrow fragments showed marked infiltration by hairy cells. The patient received two blood transfusions. We followed the patient periodically. In March 1959 she was hospitalized at her local hospital for influenza, and in January 1963 she had an episode of respiratory infection. As we followed this patient from 1958 to 1966, her spleen gradually decreased in size, and since 1966 it has no longer been palpable. The platelets, white blood cells, and hemoglobin have returned to normal levels. The white blood cell differential, since March 1968, is normal, showing no hairy cells present. In November 1977 we obtained a bone marrow aspiration and biopsy and also observed the marrow cells in Rose chamber cultures; all tests were normal. This is a remarkable case; the patient, after 8 yr without therapy, went into spontaneous remission, with a survival of 20 yr since diagnosis. It is not possible to determine if the respiratory infections had anything to do with this outcome, but it has been our observation, in some cases, that improvement has followed successfully treated overwhelming infection.

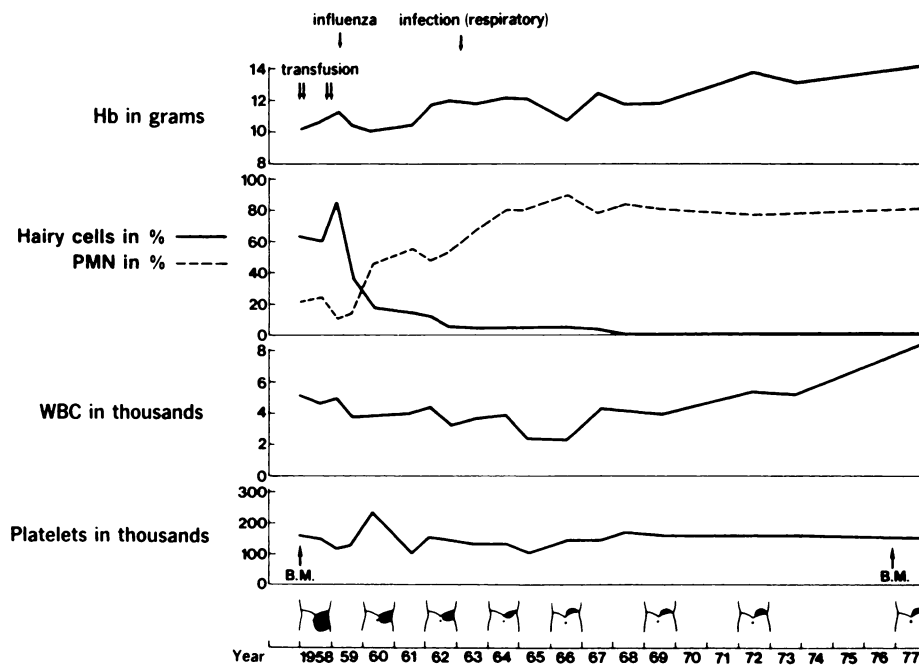


Fig. 11. Clinical course and hematologic findings for patient 27, age 39, female. This patient went into spontaneous remission 8 yr after diagnosis, with survival of 20 yr thereafter.

Splenectomy

In our opinion splenectomy is indicated only in patients who develop hypersplenism manifested either by marked anemia requiring frequent blood transfusions or by marked thrombocytopenia.

We consider that there is a partial response to splenectomy when there is some hematologic improvement, but the numbers of hairy cells continue at about the same levels as prior to splenectomy. A good response is achieved when there is hematologic improvement in all blood elements and the numbers of hairy cells are lower than they were prior to splenectomy. Complete remission is achieved when there is a return to normal hematologic values for all blood elements and disappearance of hairy cells from the peripheral blood and bone marrow.

Nineteen of our patients developed hypersplenism and underwent splenectomy. In this group of patients, 10 patients died, 3 within 14 days of splenectomy; 1 patient had a partial hematologic response of 3 mo duration, and 6 patients had good responses of from 1 to 7 yr. Nine patients are still alive; 3 have had partial hematologic responses for 3–10 yr, and the other 6 have had good responses that have lasted from 3 to 22 yr.

Only 1 of our patients has experienced complete remission after splenectomy. He is a white male who was 31 yr old at the time of diagnosis in May 1956 (Fig. 12). At that time, he had a huge spleen descending down to the iliac crest and across the midline; no hepatomegaly or lymphadenopathy was noted. The peripheral blood count revealed a hemoglobin of 10.2 g/dl, reticulocytes 4.8%, platelets 17,000/cu mm, and total white blood cell count 1400/cu mm, with 16% neutrophils and 14% hairy cells. The marrow aspiration yielded no fragments. The preparations made

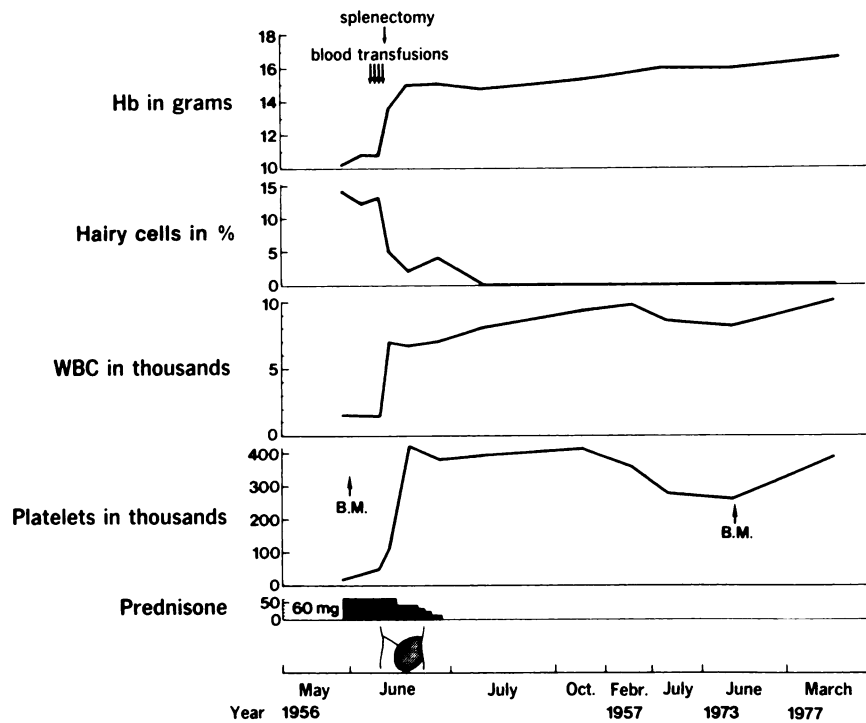


Fig. 12. Clinical course and hematologic findings for patient 11, age 31, male, illustrating the splenic form of LRE. This patient initially presented with marked splenomegaly and hypersplenism; there was complete remission after splenectomy.

from the aspirated sample and observed under Wright stain, supravital stain, and phase-contrast microscopy were interpreted as having marked infiltration with hairy cells, and this was confirmed by marrow biopsy. There were megakaryocytes present. The diagnosis of LRE with secondary hypersplenism was confirmed. The patient was treated with prednisone for 15 days without improvement. Splenectomy was performed on June 11, 1956. Immediately after surgery he had a remarkable and prompt return to normal circulating levels of all three cellular elements of the blood, and this has persisted to date. On his visit in March 1977 he had normal peripheral blood, bone marrow, and physical examinations. This patient illustrates the splenic form of LRE, with initial predominant splenic involvement and hypersplenism and with excellent response to splenectomy of 22 yr duration.

In the majority of patients hypersplenism develops later during the course of the illness. The average time between the diagnosis of LRE and the development of hypersplenism in our 19 patients was 34 mo, with a median of 9 mo. In 5 patients hypersplenism was present at the time of the original diagnosis or was manifested within 3 mo. In 6 patients frank hypersplenism developed between 18 to 156 mo from the time of diagnosis of LRE.

A more typical case of LRE is presented in Fig. 13. This 51-yr-old male was diagnosed as having chronic lymphatic leukemia in August 1964 and was found to have marked splenic enlargement. The patient was treated with chlorambucil without improvement. He was referred to our hospital, where the diagnosis of LRE

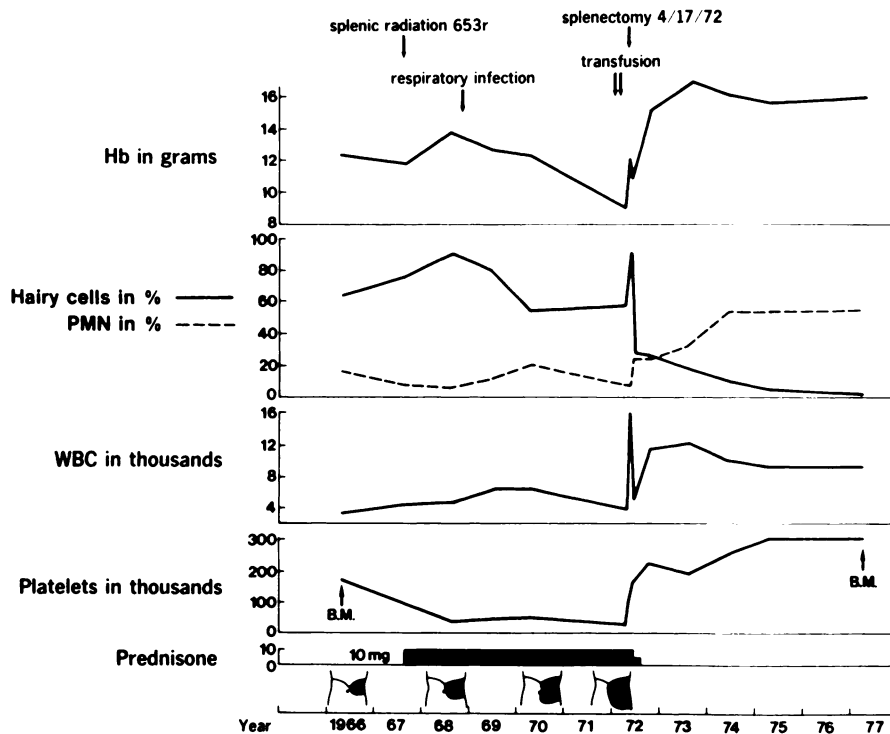


Fig. 13. Clinical course and hematologic findings for patient 12, age 51, male. The patient developed marked hypersplenism 6 yr after diagnosis and had an excellent response to splenectomy, with survival of 14 yr. The marked transitory leukocytosis and the increase in hairy cells immediately after splenectomy were due to manual squeezing of the spleen by the surgeon after ligation of the splenic artery. This manual procedure should be avoided in patients with LRE.

was confirmed. On his initial visit his white blood cell count was 3200/cu mm, with 16% neutrophils and 64% hairy cells; his hemoglobin was 12.3 g/dl, and platelets were 170,000/cu mm. The bone marrow examination confirmed the diagnosis of LRE. The patient was treated with splenic irradiation, with some decrease in the size of the spleen and temporary hematologic improvement. Subsequently he was placed on prednisone, with mild temporary improvement. In April 1972 he had marked exacerbation of symptoms: his spleen became tremendously enlarged, and he developed frank hypersplenism. The platelets decreased to 30,000/cu mm, and the patient had ecchymoses and purpura. The white blood cell count was 3500/cu mm, with 58% hairy cells, and the hemoglobin was 8.9 g/dl. Splenectomy was performed on April 17, 1972. The immediate post-operative blood count revealed increases in white blood cell count and hairy cells, but later he had an excellent hematologic remission that has persisted for the past 6 yr. On his last visit his bone marrow still had some infiltration by hairy cells, but the peripheral blood count was normal, with only 2% hairy cells, and he is leading a normal life. This patient had an excellent response to splenectomy after 6 yr from diagnosis, with a total survival of 14 yr.

In our opinion splenectomy is not indicated if the splenomegaly and pancytopenia are asymptomatic. Among 62 of our patients who did not have splenectomy, 25

Table 4. Length of Survival After Diagnosis for 81 Patients With LRE

Survival (yr)	Alive		Dead		Total Number of Patients
	With Splenectomy	Without Splenectomy	With Splenectomy	Without Splenectomy	
< 1			1	19	20
1-3	1	2	5	16	24
3-5	2	1		9	12
5-10	3	2	2	6	13
10-15	1	1		3	5
15-20	1	2	2		5
>20	1	1			2
Longest survivor	22 yr 2 mo	27 yr 4 mo	16 yr	11 yr 8 mo	81

have survived longer than 3 yr from diagnosis. In effect, the longest survivor of our series is an 86-yr-old white female who is alive with the disease for 27 yr 4 mo. Her last examination revealed marked splenomegaly. The hemoglobin was 12.8 g/dl, platelets 48,000/cu mm, and white blood cell count 3300/cu mm, with 56% PMN, 34% lymphocytes, 2% monocytes, and 8% hairy cells. She leads a normal and active life for her age. Splenectomy was not indicated in this patient because she had an adequate granulocyte count and an acceptable level of platelets.

On the basis of our data it is difficult to reach any definitive statistical conclusions regarding the influence of splenectomy on the length of survival. We have patients with and without splenectomy who have lived 16 and 11 yr, respectively, and patients with and without splenectomy who are still alive 22 and 27 yr after diagnosis (Table 4). However, the average survival of nonsplenectomized patients is 4.6 yr, and the average for splenectomized patients is 6.9 yr.

DISCUSSION

Since our first report in 1958, LRE has been well established as an independent clinical and pathologic entity. In recent years the disease has also been reported under the name of hairy cell leukemia.

There was a striking male predominance, and the population was mainly middle-aged or elderly, with a median age of 55 yr. The most frequent presenting complaints were weakness and fatigue, and hemorrhage being next in frequency. There is no pathognomonic physical finding, but at the time of initial diagnosis splenomegaly was present in 93% of patients, hepatomegaly in 40%, and lymphadenopathy in 23%. At the time of initial diagnosis the most common hematologic findings were leukopenia, a moderate degree of anemia, and thrombocytopenia.

The use of the tartrate-resistant acid phosphatase reaction as a diagnostic criterion has been extensively studied. In 1972 Yam et al.¹⁶ reported 6 patients in whom the LRE cells were characterized by having strong acid phosphatase activity with distinct resistance to inhibition by 1+ tartaric acid. This corresponds with the isoenzyme 5 demonstrated by disk acrylamide-gel electrophoresis. They concluded that from the practical point of view cytochemical study of acid phosphatase activity of blood smears may be the simplest and most useful method of identifying the reticuloendothelial cell and of diagnosing LRE. This was supported by the studies of Mover et al.,²¹ who examined blood smears of 22 patients with LRE and found cells with the strongest reactions for all 22 patients, whereas they could not

find such cells in blood smears from any of 238 patients with other disorders. However, this concept has not been supported in further studies. Negative reactions in patients with typical clinical and morphologic features of LRE have been reported.^{4,9,22-24}

The controversial results regarding the value of the tartrate-resistant acid phosphatase reaction in the diagnosis of LRE prompted Katayama and Yang²⁵ to reevaluate the diagnostic specificity of this test. They found that the tartrate-resistant acid phosphatase reactions were positive, intermediate, and negative for 76%, 21%, and 3% of 29 patients who had LRE, whereas the figures were 3%, 32%, and 65% for 37 patients who had chronic lymphatic leukemia or other hematologic disorders. Strong positive reactions for tartrate-resistant acid phosphatase have also been reported in patients with prolymphocytic leukemia²⁶ and in patients with Sézary syndrome.²⁷ From the studies mentioned we may conclude that the tartrate-resistant acid phosphatase reaction is helpful but not pathognomonic of LRE.

Electron microscopic studies indicating the high incidence of ribosome-lamella complex in LRE and its rarity in other neoplasms were first conducted by Katayama et al.,²⁸ who suggested a substantial relationship between this complex and LRE. In a later study, Katayama and Schneider²⁹ reported the presence of ribosome-lamella complexes in 10 of 23 LRE patients and in only 2 of 20 patients with other hematologic disorders. The same authors reviewed the literature and found that ribosome-lamella complexes were reported in 21 of 47 patients with LRE and in only 11 of 79 patients with other hematologic disorders. Consequently, they concluded that the ribosome-lamella complex is not specific but is more prevalent in patients with LRE and is seen in a higher percentage of leukemic cells in LRE than in other hematologic disorders. The presence of the ribosome-lamella complex in hairy cell leukemia has also been reported by other authors.^{10,30-33} The RNA nature of its ribosome component, as well as the demonstration that the lamellar component of this tubular structure is formed by an arithmetic coil, was proved by Daniel and Flandrin.³⁴ Ultrastructural observations of hairy cells by the freeze-etching technique have confirmed that the hairlike projections of the cells are not artifacts.³⁵ The Langerhans granulelike structures usually located at or near the cell membrane have been described by several authors.^{36,37} The phagocytic capacity of the hairy cells was demonstrated convincingly by Daniel and Flandrin³⁴ by the use of electron microscopy for latex particles and staphylococci *in vitro*. It has also been reported by other investigators.^{32,33} Histologic observations of bone marrow, spleen, and liver are quite characteristic, and it has been suggested that this may be helpful in making the correct diagnosis of hairy cell leukemia.^{7,9,38,39}

Burke et al.⁴⁰ have described the ultrastructure in seven spleens surgically removed from patients with hairy cell leukemia. From their observations they concluded that the evolution of a hypersplenic syndrome in LRE could be explained on the basis of the dense infiltration of hairy cells causing marked widening of the cords and retarding the passage of formed elements of the blood through the red pulp. Prolonged sojourn of these elements in a metabolically unfavorable environment results in cellular damage, increased exposure to cordal macrophages, and premature destruction, with the development of a hypersplenic syndrome. Diebold et al.⁴¹ have put forth similar conclusions in their report of 15 LRE spleens studied

with the usual techniques, as well as with immunofluorescence and electron microscopy.

Nanba et al.³⁸ have described the presence of a unique vascular lesion in spleens and livers from patients with hairy cell leukemia. These lesions consist of pseudosinuses in the spleen lined with hairy cells and lacking the endothelial cells and ring fibers of normal splenic sinuses. Similar observations have been reported by Kjeldsberg³⁹ in reviewing 15 spleens from patients with hairy cell leukemia. It has been suggested that since these pseudosinuses are not seen in other leukemias or lymphomas and appear to be unique to LRE, this may be a very helpful observation.

We believe that the only pathognomonic finding for confirmation of the diagnosis is recognition of the characteristic mononuclear cell of LRE in the peripheral blood, bone marrow, or spleen. If the smears are not properly stained, these cells may easily escape recognition under Wright stain. However, they are readily recognized in supravital stain, phase-contrast microscopy, slide chambers, and electron microscopy.

In our original paper¹ we used the name LRE to identify this type of leukemia as an independent clinical and pathologic entity. We preferred this term because it described the diagnostic feature of the disease, namely the presence in the blood, bone marrow, and organs of the reticuloendothelial system of the typical mononuclear cell, which we then described by the use of supravital stain, phase-contrast microscopy, Wright stain, and electron microscopy. The pathognomonic cell of LRE is frequently known as the hairy cell. It has unique morphologic features, quite unlike those of cells in any other type of leukemia or lymphoma; however, morphologically it most closely resembles reticulum cells or histiocytes.

Since that first study, newer techniques have been developed for the study and characterization of lymphocytes, monocytes, and histiocytes. The most commonly used techniques involve study of the phagocytic properties for latex particles or bacteria, sensitivity to exposure to radiation, ultrastructural studies by scanning electron microscopy, adherence to glass or nylon fibers, cell surface markers, metabolic studies, response to PHA and other mitogen stimulation, and cytochemical and enzyme determinations. There are more than 30 articles dealing with the problem of elucidating the precise nature and origin of the hairy cell. The investigators have applied the techniques mentioned, and the work has been done in reliable laboratories. In spite of this, the precise nature and origin of the hairy cell remain controversial.

The lymphocytic origin and its relationship to B lymphocytes have largely been based on demonstration of surface immunoglobulins and receptors on these cells, as well as on ultrastructure and cytochemical and enzymatic studies. This relationship has been supported by several investigators.⁴²⁻⁵² Others have demonstrated a relationship of hairy cells to T lymphocytes^{53,54} or both T and B lymphocytes.^{55,56}

A monocytic-histiocytic origin also has numerous supporters, with equally convincing evidence.^{22,33,57-60} In other reports authors have demonstrated that the cells of LRE are hybrid cells, since they share some immunologic characteristics of lymphocytes and some functional and phagocytic capabilities of monocytes or histiocytes.⁶¹⁻⁶⁵

Burns et al.⁶⁶ demonstrated a specific receptor for IgM by an EA_{IgM} rosette test in all 7 cases of LRE they studied. They presented evidence to suggest that the cells

of LRE are not related to either lymphocytes or the monocyte-histiocyte series. They proposed that LRE represents a leukemic proliferation of a newly identified population of EA_{IgM}-receptor-bearing mono-nuclear cells. However, a report describing EA_{IgM} receptor in 5 of 32 patients with Hodgkin disease supports the opinion that this test is not specific for LRE.⁶⁷ In a later report, Barker et al.⁶⁸ demonstrated that up to 4% of the mononuclear cells from normal peripheral blood also show EA_{IgM} receptors. These authors believe that these findings raise the possibility that the EA_{IgM} receptor represents a further phenotypic marker characterizing an unrecognized subset of mononuclear cells involved in the pathogenesis of LRE and in the hematologic reaction to Hodgkin's disease. Most recently, Braylan et al.⁶⁹ suggested that the hairy cells are structurally and functionally unique elements, different from any other normal or abnormal cell known at present.

We are unable to explain the divergent reports and discrepancies in the literature concerning the nature of the LRE cell. It is conceivable that the LRE may be the result of some aberration in maturation and proliferation of the reticulum cells in their differentiation from the stem cells. Thus, the various altered cell lines seen would represent different directions of differentiation arising from this cell. It is for this reason that the designation of LRE as hairy cell leukemia has become popular; this name does not imply an origin of the cell. Whatever may be the origin of the hairy cell of LRE, accurate diagnosis of this entity is essential for proper management of patients.

The course of the disease is, in general, chronic and is characterized by periods of exacerbation of symptoms followed by periods of objective improvement. Infection is the most frequent complication, with pneumonia and septicemia being most common. The organisms most frequently isolated were bacterial (*Pseudomonas*, *E. coli*, coagulase-positive *Staphylococcus*, *Klebsiella*, *Proteus*, and *Salmonella*), followed by fungi and *M. kansasii* and *P. carinii* pneumonia. The most common cause of death was infection followed by bleeding.

Infection complicating the course of LRE has been reported in all large series of patients.^{10,11,13-15,18} Marie et al.⁷⁰ reported 80% of deaths due to infection in a review of 131 patients. *M. tuberculosis* infection has been infrequently reported. Manes and Blair⁷¹ reported a case of disseminated *M. kansasii* infection complicating LRE; the organism was isolated from the spleen. A patient with LRE was reported to have died of mycobacterial infection.⁷² In the review of Marie et al.,⁷⁰ among 131 patients *M. tuberculosis* infection was confirmed in 7 cases (5.4%). This diagnosis should be considered in patients with LRE and chronic fever nonresponsive to other forms of antimicrobial therapy.

Humoral immunity studies in LRE have been reported as showing no significant humoral defect.⁷³ However, a recent report by Kjeldsberg⁷⁴ has shown a monocyte chemotactic factor inactivator in the sera of 5 patients with hairy cell leukemia. The cellular immune response has also been studied and has been reported as being normal.^{14,75}

The neutropenia is probably responsible for the majority of microbial infections. Bouza et al.⁷⁶ have reported a clear relationship between fungal disease and corticosteroid therapy in 20 patients with LRE. However, the occurrence of *M. tuberculosis* could be better explained on the basis of monocyte deficiency, since monocytes and macrophages are involved in the defense against *M. tuberculosis*.⁷⁷

Monocytopenia is frequently observed in patients with active LRE, and its role in the susceptibility to infection has been emphasized by Seshadri et al.⁷⁸ and Yam et al.⁷⁹

The results of therapy are difficult to evaluate because of the variability in severity of the disease and also because of the chronic course, with periods of exacerbation of symptoms followed by periods of objective improvement. We have documented 1 case of spontaneous remission after 8 yr of observation.

Some temporary improvement has been obtained in a few patients treated with prednisone. Improvement following the use of corticosteroids alone or in combination has been reported.^{10,61,80} Besa and Gardner⁸¹ reported a prolonged remission of 2 yr that followed 11 mo of treatment with etiocholanolone and prednisolone in a patient with LRE.

Splenic irradiation induced partial temporary responses in the majority of our patients treated. One patient went into complete remission that was documented for 3 yr; the patient died from CVA without evidence of leukemia.

Schreck and Donnelly⁶ have reported the relative radioresistance of hairy cells in vitro as compared with lymphocytes. Irradiation with 1000–2000 rads had practically no effect on the survival of hairy cells during 7 days of incubation, in contrast to the situation with lymphocyte suspensions, where all lymphocytes were killed. In spite of these in vitro results, they treated 1 patient with 548 rads over the spleen and obtained a partial response.

Leukapheresis as treatment for selected patients with LRE deserves further clinical trials. Rubin et al.⁶¹ and Berg and Brandt⁸² have reported that hairy cells from LRE have extremely low incorporation of tritiated thymidine, thus indicating a low proliferative capacity. The latter authors have suggested that the richness of hairy cells in blood, bone marrow, spleen, and liver is due to accumulation of cells with a low rate of proliferation. On the basis of that principle, Moore et al.⁸³ treated 1 patient (who had received no benefit from splenectomy) with intensive leukapheresis and obtained clinical remission of leukocytosis and skin, lymph node, and marrow infiltration, as well as improvement of anemia, granulocytopenia, and thrombocytopenia, that has lasted more than 6 mo.

In our experience chemotherapy with a single drug or combination has not proved to be beneficial and should not be used as the initial treatment. However, there are 2 cases reported in which complete remissions of 2 yr and 6 mo were obtained after combination chemotherapy.^{19,20} Consequently, in patients with life-threatening disease due to marked infiltration of the bone marrow by malignant cells, with marked neutropenia, thrombocytopenia, and/or anemia, it is suggested that aggressive chemotherapy be initiated. Facilities for provision of adequate supportive care are essential.

The value of splenectomy in the treatment of LRE has been supported by the majority of investigators. In our experience splenectomy is indicated only in patients who develop hypersplenism that is manifested by anemia requiring blood transfusions or by marked thrombocytopenia. Splenectomy is not indicated if the splenomegaly and pancytopenia are asymptomatic. One of our patients, who initially presented with marked hypersplenism, has experienced complete remission after splenectomy, documented for 22 yr. He had the splenic form of LRE. Usually patients develop hypersplenism later during the course of the illness. Among 19

patients who had splenectomy, 3 died within 14 days of surgery, 4 had partial responses, and 12 had good responses that have lasted from 1 to 22 yr.

In the patients in whom splenectomy was performed the quality of life was improved, and survival of the patients was definitely prolonged. From our studies it is more difficult to reach any definite conclusions regarding the influence of splenectomy on length of survival of patients with LRE on a statistical basis. However, the average survival of our splenectomized patients is 6.9 yr, and it is only 4.6 yr for the nonsplenectomized patients.

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