Leukemic Reticuloendotheliosis

By Bertha A. Bouroncle, Bruce K. Wiseman and Charles A. Doan

The existence of leukemic reticuloendotheliosis as an independent entity and its relation to other types of leukemia have excited considerable interest among hematologists.

There have been scattered reports since 1923 in the medical literature of cases of leukemic reticuloendotheliosis, though designated by a variety of terms. The first report was by Ewald who described a case of leukemia characterized by hyperplasia of the reticulum tissue in the blood-forming organs with the appearance of reticuloendothelial cells in the blood stream. He termed this condition "leukämische reticuloendotheliose," as have other authors. "Histioeytic leukemia," "histioleukemia," "reticulosis," "malignant reticulosis," "malignant leukemic reticulo-histiocytosis," and "aleukemic reticulosis," are other synonyms.

The purpose of this paper is to present 26 cases of leukemic reticuloendotheliosis who have been seen and studied in the Hematology Department of the Ohio State University during the past eight years. The detailed follow-up of these cases supports the concept that leukemic reticuloendotheliosis is a definite hematologic and pathologic entity.

Materials and Methods

In the 26 patients the diagnosis was confirmed by the peripheral blood and bone marrow observations, using both supravital and Wright's stains. The bone marrow samples were obtained from sternum, iliac crest and/or spinous process by aspiration with a 16-gauge needle. In four patients the marrow specimen was obtained by a surgical biopsy and the material was observed under supravital, Wright's and hematoxylin-eosin stains. In five patients in whom splenectomy was performed, the diagnosis was confirmed by the observation of the tissue sections from spleen, liver and lymph nodes obtained at the time of the operation. The autopsy material from eight patients has been reviewed.

In two patients the survival time of transfused erythrocytes was determined employing the differential agglutination technic of Young et al.
Clinical Observations

Incidence: Leukemic reticuloendotheliosis is a rare disease. The average number of patients with leukemia admitted to our hospital per year, in the past eight years, is 140. The average number of patients with leukemic reticuloendotheliosis admitted per year is three. Its incidence, therefore, is approximately 2 per cent of all leukemias seen at this hospital per year.

Age and Sex: Among the 26 patients there were 21 males and 5 females. All were adults. Twelve patients were between 30 and 50, 10 patients were between 50 and 70, and 4 patients were over 70 years of age.

Presenting Symptoms: The onset of the disease was usually insidious. The most common symptoms, presenting in 12 of our patients, were weakness and easy fatigability; four patients had hemorrhagic diatheses manifested by the occurrence of spontaneous purpura, ecchymoses and/or repeated epistaxes; four patients sought medical advice because of marked pain in the left upper quadrant; the disease was discovered in three patients while they were being treated for pneumonia, and two others manifested low grade fever and respiratory symptoms at the onset of the disease. Infiltrative erythematous skin lesions were noted initially in one patient. None of these symptoms or signs are specific for leukemic reticuloendotheliosis.

Physical Findings: The most common physical finding was splenomegaly. It was present at the time of diagnosis in 25 or 96 per cent of our cases. In 14 or 54 per cent the spleen was moderately enlarged, in 11 or 42 per cent markedly enlarged, descending to the pelvis. In general, the size of the spleen fluctuated in the same patient during the exacerbations and remissions of the disease, whether spontaneous or possibly induced by therapy. In nine patients or 35 per cent, splenomegaly was the only abnormal finding. During the course of the disease painful episodes of splenic infarction and transitory perisplenitis were common.

Hepatomegaly was noted in 15 or 58 per cent of our cases.

Lymphadenopathy was present in only nine or 35 per cent of our series.

Infiltrative lesions of the skin were noted in three cases or 12 per cent.

Occurrence of Infection: Infection was a frequent complication during the course of this disease. Episodes of infection were manifested in 15 or 58 per cent of the patients during the course of their disease. Pneumonia was the most frequent; eight patients had one or two episodes of pneumonia; four patients had septicemia; two had urinary infection; two had thrombophlebitis and seven patients had other infections. The immediate cause of death in seven patients was due to secondary infection.

Hemorrhagic Manifestations: Hemorrhagic phenomena, such as epistaxes, purpura and ecchymoses, occurred in five or 20 per cent of our patients.

Survival Time and Follow-up: Of the 26 patients considered in this series we lost contact with only one. Nine of them are living at this time (July, 1957). The length of time from onset of symptoms to the present is: in two patients, less than one year; in four patients, from one to two years; in two patients, from two to five years; and in one patient, seven years.

Sixteen patients have died. The survival from the onset of their symptoms
to death was: in four patients, less than one year; in six patients, from one to two years; in four patients, from two to five years; in one patient, seven years; and in one, the longest survival, 15 years and 10 months.

HEMATOLOGIC OBSERVATIONS

Red Blood Cells and Hemoglobin: Initial observations made of red cell count and hemoglobin showed: severe anemia ranging from 1 to 2 million red cells per cu. mm. and 4 Gm. per cent of hemoglobin in one or 4 per cent of the cases; moderate anemia ranging from 2 to 3 million red cells per cu. mm. and 5 to 9 Gm. per cent of hemoglobin in nine or 35 per cent of the cases; mild degrees of anemia ranging from 3 to 4 million red cells per cu. mm. and 9 to 12 Gm. per cent of hemoglobin in 10 or 38 per cent of our cases; and normal red blood cell levels from 4 to 5 millions per cu. mm. and 13 to 15 Gm. per cent of hemoglobin in six or 23 per cent of the cases (fig. 1).

The anemia was most frequently normocytic, normochromic and was secondary to replacement of normal marrow elements by reticulum cells. In six patients the anemia was frankly hemolytic as evidenced by the increase in reticulocytes and/or increased fecal urobilinogen, elevated indirect reacting van den Bergh, positive Coomb's test and the increase in the osmotic fragility of the red blood cells. In two of these six patients the survival time of transfused erythrocytes was determined, and an increased destruction of red blood cells was demonstrated (fig. 2). Patient No. 13 was on steroid therapy while the survival time was being determined. In five of these six patients a splenectomy was performed: one of them, a 38-year-old male, died 13 days after surgery with an acute pneumonia. The second patient,

Fig. 1.—Initial peripheral blood counts (prior to therapy).
a 62-year-old female, had marked improvement of her anemia after splenectomy; she expired 20 months after surgery without any recurrence of hemolysis. The third patient, a 57-year-old male, showed no further evidence of the anemia and thrombocytopenia which were present before splenectomy; this patient expired six years later from an unassociated inoperable carcinoma of the colon. The fourth patient, a 31-year-old male, had panhematopenia and marked splenomegaly secondary to his leukemic reticuloendotheliosis; following splenectomy all three elements of the blood returned to normal levels. The patient is alive and in good health at present, one year and eleven months after splenectomy (fig. 10). The fifth patient, a 37-year-old male with panhematopenia died following removal of a 3,800 Gm. spleen, 6 days postoperatively, of massive retroperitoneal hemorrhage.

White Blood Cells: Leukopenia was the most frequent finding in patients with leukemic reticuloendotheliosis. The initial white count before any treatment was instituted was between 1,000 and 5,000 cells per cu. mm. in fifteen patients or 58 per cent; normal total leukocyte counts ranging between 6,000 and 10,000 cells per cu. mm. were found in five patients or 19 per cent; moderate leukocytoses between 12,000 and 23,000 per cu. mm. were found in five patients or 19 per cent; and in only one case was a marked leukocytosis of 134,000 cells per cu. mm. noted (fig. 1).

An absolute and relative neutropenia was present in 17 or 71 per cent of the patients.

The percentage of reticulum cells in the peripheral blood in the initial observation varied from 0 to 95 per cent (table 2). In general they fluctuated in the same patient corresponding with the remissions or exacerbations of the disease.

Platelets: A marked thrombocytopenia with levels under 100,000 platelets
per cu. mm. was noted in 12 or 46 per cent of the patients before any therapy was instituted; moderate thrombocytopenia, from 100,000 to 300,000 cells per cu. mm., was found in another nine, or 35 per cent of the patients; and mild thrombocytopenia with levels between 300,000 and 500,000 platelets per cu. mm. was noted in five or 19 per cent of the patients (fig. 1). (Normal platelet values in our laboratory are: 500,000 to 900,000 per cu. mm.)

Bone Marrow: Bone marrow aspirations were done in all 26 patients. In 20 or 77 per cent, the sample was aspirated with difficulty and no marrow fragments were obtained. As many as four or five attempts to aspirate bone marrow fragments from sternum, spinous process and/or iliac crest were made on each of these patients unsuccessfully. The microscopic observations of the aspirated samples showed that they were hypocellular and revealed from 30 to 94 per cent reticulum cells with scattered myeloid, erythroid and lymphoid elements and a rare megakaryocyte.

In six or 23 per cent of the patients, bone marrow fragments were obtained by aspiration. Microscopically they were of normal or increased cellularity and showed normal or diminished erythropoiesis, myelopoiesis and megakaryocytosis, with from 30 to 87 per cent reticulum cells present.

In patient No. 12, after failure to obtain bone marrow fragments by aspiration, a surgical marrow biopsy was obtained showing a cellular sample with a marked increase in reticulum cells and diminished erythro- and granulopoiesis.

Hematologic Diagnosis; the Reticulum cell: The diagnosis of leukemic reticuloendotheliosis was confirmed in all 26 patients by finding in films of the peripheral blood and bone marrow the characteristic cell—the free reticulum cell or histiocyte.

With supravital stains the differential morphologic characteristics of the reticulum cell were well preserved and distinctly emphasized, so that the cells could be readily identified. They were usually larger than the normal red and white blood cell series. In the living preparations, pseudopods protruded from the cytoplasm, constantly making a serrated border for the usually round, oval or polygonal cells. No amoeboid motility as such was apparent. The cytoplasm contained mitochondria which stained with Janus green and were seen as delicate dots and filaments throughout the cytoplasm, their diffuse distribution commonly following the shape of the cell. A few small individual neutral red vacuoles were present in the cytoplasm of most cells. Phagocytized particles were seen rarely. The nucleus was round or oval, about one-half the size of the cell and frequently eccentric in location. The nuclear membrane was sharp and distinct. The nuclear chromatin was spongy in appearance and nongranular. Sometimes single nucleolus was present. When the fresh preparations were observed under the phase contrast microscope the same characteristics already described were apparent. The “lacelike” outline of the membrane was present and the distinctive nuclear membrane and chromatin characteristics were accentuated (figs. 3, 4 and 5).

In fixed film with Wright's stain (fig. 6) the cytoplasm was irregular in
FIG. 3.—Microphotograph of a living reticulum cell from the circulating blood as seen with the supravital stains with the phase contrast microscope. The mitochondria are stained with Janus green and seen as delicate filaments. A few cytoplasmic vacuoles are present. The nuclear chromatin is spongy. A nucleolus is present. Magnification: approximately x 2,260.

FIG. 4.—Three reticulum cells observed in supravital films with the phase contrast microscope. The mitochondria and a few cytoplasmic vacuoles are present. The “lacelike” outline of the membrane is prominent. The nucleus is eccentric. Nucleoli are prominent. Magnification: approximately x 2,260.
Fig. 5.—Bone marrow observed in supravital film with the phase contrast microscope. The elongated cell in the left upper corner has the morphologic characteristics of an endothelial cell as seen in leukemic reticuloendotheliosis. The larger cell is a phagocytic clasmatoocyte. The others are reticulum cells. Magnification: approximately x 1,450.

Fig. 6.—Two reticulum cells as observed in Wright’s stain preparations showing the irregular outline of the cytoplasm which stains in sky-blue color. The nuclear chromatin is spongy in appearance. Magnification: approximately x 2,000.
outline; its color was sky-blue. The nuclear membrane was distinct and heavy and the chromatin was spongy in appearance.

When electron microscope pictures were observed (fig. 7) the "lacelike" outline of the membrane was very well delineated, and several long irregular pseudopods were noted. The cytoplasm contained mitochondria which were oval or round in shape and numerous small vesicles. The membrane of the nucleus was distinct. The nuclear chromatin was more dense in some areas, especially at the periphery. Some cells contained a large nucleolus.

Some of the cells observed were elongated, resembling closely the morphologic characteristics of the endothelial cells (fig. 5).

Histological Observations: Histologic observations were made on the sections of the spleen, liver and lymph nodes obtained at the time of splenectomy in five patients (cases 2, 5, 8, 12 and 26) and on autopsy material from eight patients (cases 2, 4, 5, 8, 13, 15, 25 and 26).

The spleen seemed to be the organ showing the most extensive involvement in all cases. The weight of the spleen ranged from 2,500 to 3,800 Gm., except for one patient in whom it weighed only 500 Gm. A gross diagnosis of

Fig. 7.—Electron micrograph of a reticulum cell. The "lacelike" outline of the membrane is well delineated and several long irregular pseudopods are noted. The mitochondria are oval or round in shape and distributed around the nucleus. Numerous small vesicles are present. The membrane of the nucleus is distinct. The nuclear chromatin is dense in some areas, especially at the periphery. Magnification: x 11,500.
splenic infarction was commonly made. The microscopic examination of preparations from the spleen showed an extensive proliferation and diffuse infiltration of reticulum cells. The infiltrating cells had proliferated to a considerable degree in the pulp, had in most cases replaced most of the Malpighian corpuscles, and were present in the sinusoids. The reticulum cells on hematoxylin-eosin stain 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 which were large, round or vesicular with small clumps of chromatin and frequently prominent nucleoli.

The weight of the liver varied from 1,100 to 4,000 Gm. On microscopic examination portal infiltration by reticulum cells was noted. The sinuses in many areas were slightly dilated and contained reticulum cells.

The lymph nodes showed complete loss of normal architecture with diffuse infiltration by reticulum cells of the same type as seen in the spleen. These cells usually infiltrated the capsule of the lymph node (figs. 8a and 8b).

The bone marrow from the autopsied cases showed a marked proliferation of reticulum cells. Some patients, in whom marrow fragments could not be aspirated by a needle biopsy during life, showed, on microscopic examination of the hematoxylin-eosin preparations at autopsy, normal to increased cellularity with a predominance and almost complete replacement of the normal elements of the marrow by reticulum cells.

Other organs in which increased reticulum cells were found were in order of frequency: the kidneys, lungs, pancreas, stomach, small intestines and the adrenal glands.

Other significant findings at autopsy were: pneumonia in four cases, a superimposed fungus infection in one, bilateral caseous tuberculosis of the adrenals in another, and a well differentiated adenocarcinoma of the rectum, previously noted at surgery, in one case (table 1).

The immediate cause of death as established by autopsy in these eight patients was: in two, terminal pneumonia; in the remaining six respectively, rupture of the spleen with massive hemoperitoneum, carcinoma of the colon with widespread abdominal metastases, acute adrenal insufficiency, sepsis, pulmonary edema and massive retroperitoneal hemorrhage.

Case Summaries

The hematologic and clinical findings, therapy and follow-up in 26 cases of leukemic reticuloendotheliosis reported in this study are summarized in table 2.

The case histories of three selected patients are given, illustrating the clinical, hematologic and pathologic findings and the typical course of the disease.

Case 10. H. J., a 68-year-old white male, was in good health until February 1953 when he experienced an episode of "flu" with fever. He became progressively weaker and a diagnosis of lymphatic leukemia was made by his family physician who treated him with vitamin B12 and iron. The patient had been a known diabetic since 1928 and was well controlled on 35 units of PZI insulin daily.

He was first seen at Ohio State University Hospital on February 17, 1954. On physical examination all vital signs were normal. No significant lymphadenopathy was noted. The
Fig. 8a. (top)—Section of mesenteric lymph node of case 2. There is a loss of normal architecture with diffuse replacement of the lymphoid tissue by reticulum cells. Hematoxylin and eosin stain. Magnification: x 150.

Fig. 8b.—A higher magnification of the same section of lymph node showing typical leukemic reticulum cell between the remnants of lymphoid tissue. Magnification: x 600.

spleen was palpable 3 cm. below the left costal margin, and the liver was normal. On auscultation of the heart a grade two aortic systolic murmur was heard. The rest of the physical examination was within normal limits. Peripheral blood studies showed: total
LEUKEMIC RETICULOENDOTHELIOSIS

Table 1.—Histologic Observations

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Bone marrow</th>
<th>Lymph node</th>
<th>Spleen</th>
<th>Liver</th>
<th>Other organs</th>
<th>Other findings at autopsy</th>
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<td>Pneumonia</td>
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<td></td>
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<td></td>
<td></td>
<td>Pancreas</td>
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</tr>
<tr>
<td>4</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>Kidneys</td>
<td>Rupture of Spleen</td>
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<td></td>
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<td>+</td>
<td>+</td>
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<td></td>
<td>Carcinoma of Rectum</td>
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<td></td>
<td></td>
<td>Acute and Chronic Pyelonephritis</td>
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<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Lungs</td>
<td>Bilateral Casous Tuberculous of Adrenals*</td>
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<tr>
<td>13</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Pneumonia</td>
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<td></td>
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<td>Hemorrhagic Appendicitis</td>
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<td>15</td>
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<td>+</td>
<td>+</td>
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<td>Interstitial Hemorrhage Involving Heart, Lungs, Serosal Surfaces, Intestinal Tract, Liver and Kidneys</td>
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<td>25</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td></td>
<td>Adrenals</td>
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<tr>
<td>26</td>
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<td>Adrenal</td>
<td>Massive Retroperitoneal Hemorrhage</td>
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<td></td>
<td></td>
<td></td>
<td>Accessory Spleen</td>
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*No other evidence of tuberculosis was found.

red blood cells, 2.70 million per cu.mm.; hemoglobin, 8.8 Gm. per cent; reticulocytes, 4.2 per cent; platelets, 183,000 per cu.mm.; and total white blood cells, 10,900 per cu. mm. with 8% neutrophils, 1% basophil, 18% lymphocytes and 72% reticulum cells. Attempts at bone marrow aspirations were made from the sternum, but no fragments were obtained. In the fluid marrow 56% of the cells were identified as reticulum cells.

The diagnosis of leukemic reticuloendotheliosis was made. He was started on February 17, 1954 on hydrocortisone 20 mg. t.i.d., this dose being decreased gradually and discontinued in March 1955. He was also given 5 mg. of T.E.M. two a week for three weeks and he continued on a maintenance dose of 2.5 mg. wk., until January 1955. The patient did well until May 1956, when he noticed the appearance of several raised non-tender skin lesions on the dorsum of both hands measuring 2–3 cm. in diameter. The T.E.M. was restarted and increased to 2.5 mg. daily for four consecutive days following which his skin cleared completely. He has continued on a maintenance dose of T.E.M. of 2.5 mg. once a week until the present time.

He did well until March 25, 1957 when he was admitted to the University Hospital with an acute pneumonia involving the right middle lobe. His temperature was 104 F. The peripheral blood at this time was: total red blood cells, 3.04 per cu.mm.; hemoglobin, 9.5 Gm. per cent; reticulocytes, 2 per cent; platelets, 370,880 per cu. mm.; and total white blood cells, 2,050 per cu. mm. with 44% neutrophils, 24% lymphocytes and 32% reticulum cells. A bone marrow containing a few small cellular fragments was aspirated from the sternum. There was a marked infiltration by reticulum cells which comprised 96% of the differential cell count. In some areas foci of erythroid elements were found, a marked reduction of myeloid elements was noted and a few megakaryocytes were seen. The patient was treated with chloromycetin, and received two units of blood. He became afebrile and was discharged on T.E.M. therapy 2.5 mg. once a week. He is still living and doing well 4 years and 6 months after the onset of his disease.

This patient illustrates the typical chronic course of leukemic reticuloendotheliosis. His chief clinical complaint has been tiredness, his chief physical finding has been splenomegaly,
### Table 2.—The Hematologic and Clinical Findings, Therapy and Follow-up in 26 Cases of Leukemic Reticuloendotheliosis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>W.B.C. (x 10,000/mm.)</th>
<th>R.B.C.</th>
<th>M.H.C.</th>
<th>Reticuloendotheliosis</th>
<th>Neutrophils</th>
<th>Lymph nodes</th>
<th>Skin infil.</th>
<th>Splenomegaly</th>
<th>Bone marrow aspiration</th>
<th>Known duration of disease or of illness to death</th>
<th>Treatment</th>
<th>Autopsy performed</th>
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<tr>
<td>1. G.B.</td>
<td>56</td>
<td>M</td>
<td>2.08</td>
<td>3.2</td>
<td>6.6</td>
<td>9.8</td>
<td>0</td>
<td>46</td>
<td>++</td>
<td>--</td>
<td>No fragments, 36% reti. cells</td>
<td>--</td>
<td>Pneumonia Septicemia</td>
<td>Steroids Blood transfusions</td>
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<tr>
<td>2. W.S.</td>
<td>38</td>
<td>M</td>
<td>2.52</td>
<td>19.0</td>
<td>9.8</td>
<td>7.4</td>
<td>100.8</td>
<td>94</td>
<td>2</td>
<td>++</td>
<td>Cellular fragments, 87% reti. cells</td>
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<td>Pneumonia Septicemia</td>
<td>Steroids T.E.M., x-ray over spleen Blood transfusion Splenectomy</td>
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<tr>
<td>3. T.F.</td>
<td>37</td>
<td>F</td>
<td>3.12</td>
<td>23.2</td>
<td>9.0</td>
<td>4.2</td>
<td>74.8</td>
<td>94</td>
<td>1</td>
<td>++</td>
<td>No fragments, 94% reti. cells</td>
<td>+++</td>
<td>None</td>
<td>HN, Blood transfusion</td>
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<td>4. H.K.</td>
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<td>M</td>
<td>2.58</td>
<td>3.5</td>
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<td>2.2</td>
<td>149.6</td>
<td>58</td>
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<td>10</td>
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<td>P02 Blood transfusion Splenectomy</td>
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<tr>
<td>6. J.L.</td>
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<td>F</td>
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<td>95</td>
<td>4</td>
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<td>Cellular fragments, 42% reti. cells</td>
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<td>x-ray over spleen Blood transfusions Splenectomy</td>
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Note: HN = hydroxyurea.
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<tr>
<th>No.</th>
<th>Name</th>
<th>A.G.</th>
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<th>11.7</th>
<th>7.4</th>
<th>442.1</th>
<th>10</th>
<th>50</th>
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<th>57% reti. cells</th>
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<td>56% reti. cells</td>
<td>++</td>
<td>—</td>
<td>—</td>
<td>Pneumonia</td>
<td>Steroids</td>
<td>T.E.M. Blood transfusions</td>
</tr>
<tr>
<td>11</td>
<td>W.S.</td>
<td>70</td>
<td>8.18</td>
<td>2.1</td>
<td>11.3</td>
<td>7.2</td>
<td>50.5</td>
<td>14</td>
<td>10</td>
<td>No fragments</td>
<td>69% reti. cells</td>
<td>++++</td>
<td>+++</td>
<td>—</td>
<td>Pneumonia</td>
<td>Steroids</td>
<td>Leukovorin (CB 1348) Blood transfusions</td>
</tr>
<tr>
<td>12</td>
<td>D.F.</td>
<td>31</td>
<td>5.57</td>
<td>1.4</td>
<td>10.2</td>
<td>6.4</td>
<td>35.7</td>
<td>0</td>
<td>16</td>
<td>No fragments</td>
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<td>—</td>
<td>—</td>
<td>None</td>
<td>Steroids</td>
<td>Blood transfusions</td>
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<tr>
<td>13</td>
<td>P.M.</td>
<td>50</td>
<td>5.68</td>
<td>4.6</td>
<td>12.2</td>
<td>5.0</td>
<td>412.1</td>
<td>16</td>
<td>46</td>
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<td>++</td>
<td>++</td>
<td>—</td>
<td>Pneumonia</td>
<td>Steroids</td>
<td>Appendicitis and Peritonitis Blood transfusions</td>
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<tr>
<td>14</td>
<td>W.F.</td>
<td>71</td>
<td>2.34</td>
<td>15.6</td>
<td>6.3</td>
<td>4.8</td>
<td>95.9</td>
<td>73</td>
<td>9</td>
<td>No fragments</td>
<td>80% reti. cells</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>None</td>
<td>HN: Blood transfusions</td>
<td>1 yr.</td>
</tr>
<tr>
<td>15</td>
<td>C.S.</td>
<td>33</td>
<td>5.64</td>
<td>5.9</td>
<td>10.6</td>
<td>4.0</td>
<td>36.4</td>
<td>80</td>
<td>8</td>
<td>No fragments</td>
<td>69% reti. cells</td>
<td>++++</td>
<td>++</td>
<td>+++</td>
<td>Thrombopelitis</td>
<td>HN: Blood transfusions</td>
<td>3 mos.</td>
</tr>
<tr>
<td>16</td>
<td>R.T.</td>
<td>36</td>
<td>2.02</td>
<td>1.0</td>
<td>5.2</td>
<td>1.4</td>
<td>12.1</td>
<td>9</td>
<td>8</td>
<td>No fragments</td>
<td>32% reti. cells</td>
<td>++++</td>
<td>—</td>
<td>—</td>
<td>None</td>
<td>HN: Blood transfusions</td>
<td>7 mos.</td>
</tr>
<tr>
<td>17</td>
<td>E.R.</td>
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<td>2.92</td>
<td>1.9</td>
<td>7.4</td>
<td>1.0</td>
<td>122.6</td>
<td>24</td>
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<td>Cellular fragments</td>
<td>41% reti. cells</td>
<td>++</td>
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<td>—</td>
<td>Pneumonia</td>
<td>Steroids</td>
<td>Blood transfusions</td>
</tr>
<tr>
<td>18</td>
<td>N.N.</td>
<td>57</td>
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<td>1.9</td>
<td>6.8</td>
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<td>362.5</td>
<td>26</td>
<td>34</td>
<td>No fragments</td>
<td>43% reti. cells</td>
<td>++</td>
<td>—</td>
<td>—</td>
<td>Intestinal infection</td>
<td>Steroids</td>
<td>Blood transfusions</td>
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<tr>
<td>19</td>
<td>E.E.</td>
<td>71</td>
<td>4.51</td>
<td>2.4</td>
<td>13.5</td>
<td>6.6</td>
<td>252.5</td>
<td>16</td>
<td>44</td>
<td>Cellular fragments</td>
<td>59% reti. cells</td>
<td>++</td>
<td>—</td>
<td>—</td>
<td>Urinary infection (2)</td>
<td>Steroids</td>
<td>HN: Blood transfusions</td>
</tr>
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Table 2 (Continued)

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex</th>
<th>Age yrs</th>
<th>H.B. %</th>
<th>W.B.C. x 10/mm.3</th>
<th>R.B.C. x 10/mm.3</th>
<th>Neutrophils %</th>
<th>Erythroblasts</th>
<th>Platelets x 10/mm.3</th>
<th>Retic. Cells</th>
<th>Bone Marrow Aspiration</th>
<th>Splenic</th>
<th>Liver</th>
<th>Lymph node</th>
<th>Skin Infiltration</th>
<th>Occurrence of</th>
<th>Treatment</th>
<th>Known duration of disease to death</th>
<th>Autopsy Performed</th>
<th>Diagnosis</th>
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</thead>
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<tr>
<td>20. F.B.</td>
<td>M</td>
<td>61</td>
<td>3.48</td>
<td>6.7</td>
<td>11.2</td>
<td>0.4</td>
<td>54.8</td>
<td>64</td>
<td>3</td>
<td>No fragments</td>
<td>95% reti. cells</td>
<td>++</td>
<td>—</td>
<td>++</td>
<td>Chronic sinusitis</td>
<td>HN: Blood transfusions</td>
<td>3 yrs</td>
<td>No</td>
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<tr>
<td>21. M.P.</td>
<td>F</td>
<td>59</td>
<td>4.09</td>
<td>1.2</td>
<td>12.6</td>
<td>0.8</td>
<td>245.4</td>
<td>4</td>
<td>32</td>
<td>No fragments</td>
<td>17% reti. cells</td>
<td>++++</td>
<td>++</td>
<td>—</td>
<td>None</td>
<td>Steroids: Blood transfusions</td>
<td>7 yrs - 2 mos</td>
<td>Alive</td>
<td></td>
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<tr>
<td>22. H.H.</td>
<td>M</td>
<td>40</td>
<td>3.59</td>
<td>10.0</td>
<td>11.6</td>
<td>3.8</td>
<td>351.8</td>
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<td>No fragments</td>
<td>33% reti. cells</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>Urinary infection</td>
<td>HN: Leukera: Blood transfusions</td>
<td>11 mos</td>
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<tr>
<td>23. J.L.</td>
<td>M</td>
<td>46</td>
<td>4.17</td>
<td>10.8</td>
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<td>4.0</td>
<td>336.8</td>
<td>88</td>
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<td>40% reti. cells</td>
<td>+++</td>
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<td>++</td>
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<td>Purinethol: x-ray over spleen: Steroids</td>
<td>5 mos</td>
<td>Alive</td>
<td></td>
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<tr>
<td>24. R.L.</td>
<td>M</td>
<td>76</td>
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<td>12.7</td>
<td>13.2</td>
<td>2.0</td>
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<td>56</td>
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<td>++++</td>
<td>—</td>
<td>—</td>
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<td>P12: x-ray over spleen</td>
<td>2 yrs - 8 mos</td>
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<td>25. L.M.</td>
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<td>42</td>
<td>2.51</td>
<td>1.1</td>
<td>7.6</td>
<td>1.5</td>
<td>15.0</td>
<td>80</td>
<td>5</td>
<td>No fragments</td>
<td>80% reti. cells</td>
<td>++++</td>
<td>—</td>
<td>++</td>
<td>Rectal abscess: Septicemia</td>
<td>P12: x-ray over spleen: Blood transfusions</td>
<td>2 yrs - 2 mos</td>
<td>Yes</td>
<td></td>
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<tr>
<td>26. E.L.</td>
<td>M</td>
<td>37</td>
<td>1.62</td>
<td>5.0</td>
<td>4.2</td>
<td>1.4</td>
<td>68.0</td>
<td>68</td>
<td>8</td>
<td>No fragments</td>
<td>80% reti. cells</td>
<td>+++</td>
<td>—</td>
<td>—</td>
<td>None</td>
<td>Steroids: Leukera: (CB 1348): Blood transfusions: Splenectomy</td>
<td>1 yrs - 6 mos</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>
his peripheral white count has fluctuated between 1,300 and 16,600 cells per cu. mm. with
4–88% reticulum cells, his hemoglobin between 8.8 and 14.3 Gm. per cent, his platelets
between 53,280 and 855,360 (fig. 9). Whether T.E.M. therapy has been a beneficial
influence in maintaining the continuing chronic equilibrium of the disease in this patient
is difficult to evaluate at this time.

Case 12. D. F., a 31-year-old white male, was well until September 1955 when he
developed progressive weakness, abdominal discomfort and "gas pains" following meals.
He was admitted to another hospital where the diagnosis of myelofibrosis was made. He
received four units of blood.

He was first seen at Ohio State University Hospital on May 26, 1956. On physical
examination he appeared pale. The spleen was greatly enlarged extending to the iliac
crest on the left and across the midline. No hepatomegaly or significant lymphadenopathy
were noted.

The initial peripheral blood count revealed: total red blood cells, 3.57 per cu. mm.;
hemoglobin, 10.2 Gm. per 100 ml.; reticulocytes, 4.8 per cent; platelets, 35,700 per cu.
mm.; total white blood cells, 1,400 per cu. mm. with 16% neutrophils, 2% eosinophils,
64% lymphocytes and 18% monocytes. Several attempts to aspirate bone marrow failed
to yield any fragments. The bone marrow obtained by surgical biopsy was interpreted under
supravital staining conditions. This material was cellular showing a marked proliferation
of reticulum cells. Erythropoiesis was active, however, at the normoblastic level. Myelopoiesis
though diminished was present. Megakaryocytes were normal morphologically and
functionally. The total serum Van den Bergh was 1.8 with an indirect of 1.2, and a 24-hr.
fecal urobilinogen excretion was 364 mg. per cent.

The patient was treated with steroids for 15 days without any improvement in the
hematologic picture.

In view of the peripheral pancytopenia with relatively active erythropoiesis and platelet
production by the bone marrow, plus the possibility of the spleen being the main organ

![Fig. 9.—Case 10, H. J., male, 68 years old.](image-url)
affected and the chief source of in situ production of reticulum cells, the patient accepted splenectomy on June 11, 1956. Immediately after the operation a remarkable and prompt return to normal circulating levels of all three cellular elements of the blood occurred and has persisted to date (July 1957).

The spleen weighed 3,200 Gm. and measured 25 x 18 x 10 cm. Microscopic examination of the spleen revealed increased fibrosis. The endothelial cells of the sinusoids were prominent and the sinusoids contained reticulum cells showing a comparatively large amount of pink-staining cytoplasm with atypical round or oval shaped nuclei. There were also numerous old and recent hemorrhagic infarctions.

The liver revealed partly distended sinusoids containing the same type of reticulum cells noted in the spleen.

The mesenteric lymph nodes showed a loss of normal architecture with marked infiltration by reticulum cells.

The patient was discharged from the hospital on no medication. He has been seen at periodic intervals as an out-patient, he is doing well, working full-time and his hematologic picture has remained excellent. His last blood count on July 3, 1957 showed a total red count of 5.23 cells per cu. mm.; hemoglobin, 16.5 Gm. per 100 ml.; reticulocytes, 0.6 per cent; platelets, 596,220 per cu. mm.; total white blood cells, 10,250 per cu. mm. with 46% neutrophils, 50% lymphocytes, 4% monocytes and no reticulum cells. A bone marrow specimen was aspirated from the sternum. No fragments were obtained but the sample was very cellular. Erythroid, myeloid elements and megakaryocytes were present in normal distribution, with reticulum cells comprising only 12% of the marrow differential.

This case illustrates a leukemic reticuloendotheliosis with an initial predominant splenic involvement, reflected by minimal reticulunu cells in the peripheral blood, diagnosed by the bone marrow findings, and complicated by a hypersplenic pancytopenic syndrome with excellent response to splenectomy (fig. 10).

Case 15. C. S., a 33-year-old white male, was first seen at University Hospital on April 28, 1952. He had been well until two months previously when he had an episode of pain in the left upper quadrant and at the same time he noticed a mass in that area "about the size of his fist." It grew rapidly, according to the patient, and in the next two weeks nearly filled the abdomen. He also noticed spontaneous ecchymoses appearing on the lower extremities. There was an 18 pound weight loss in two months time.

On physical examination this patient appeared chronically ill. His blood pressure was 130/80 mm. of mercury, his temperature was 100 F., pulse 90 per minute. Moderate generalized lymphadenopathy was found. The spleen reached the iliac crest on the left side and crossed the midline. The inferior margin of the liver extended 4 cm. below the right costal margin. A few petechiae were found on the buccal mucosa and a few ecchymoses on the lower extremities. The lungs were clear amid the heart was normal.

The initial peripheral blood count revealed: total red blood cells, 3.64 million per cu. mm.; hemoglobin, 10.6 Gm. per 100 ml.; reticulocytes, 4.0 per cent; platelets, 36,400 per cu. mm.; total white blood cells, 3,900 per cu. mm. with 8% neutrophils, 2% eosinophils, 14% lymphocytes, 2% monocytes and 80% reticulum cells. The hematocrit was 35 per cent. Several attempts to aspirate bone marrow from sternum, spinal process and iliac crest failed to yield any fragments. The cellularity of the specimens obtained was approximately 20,000 cells per cu. mm., with 69% reticulum cells present.

During his hospitalization the patient had a sudden onset of pain in the left upper quadrant probably due to splenic infarction. He received two units of blood. He was discharged under the care of his local physician with the recommendation for intravenous nitrogen mustard therapy. He received four intravenous injections of HN2 of 0.1 mg./Kg. each and several blood transfusions. However, the patient's condition continued to deteriorate. He ran an elevated temperature, developed an even more marked enlargement of the spleen and a marked enlargement of the cervical lymph nodes which encroached on the pharynx, making swallowing and breathing difficult. His last peripheral blood studies prior to death revealed total red blood cells of 4.50 per cu. mm.; hemoglobin, 11 Gm. per cent; platelets, 9,700 per cu. mm.; total white blood cells, 1,500 per cu. mm. with 94% reticulum cells. He expired on May 22, 1952 three months after the onset of the symptoms of leukemic reticulendotheliosis.
The most remarkable finding at autopsy was a spleen weighing 3,250 Gm. Gross examination was normal except for multiple areas of infarction. The microscopic examination revealed a loss of normal architecture as a result of infiltration and/or proliferation by reticulum cells.

The liver weighed 3,100 Gm. Gross examination was normal. The microscopic examination showed almost every sinusoid distended with reticulum cells. There was a diffuse hyperplasia of reticulum cells most marked in the portal areas.

The lymph nodes were large and numerous throughout the body and microscopically showed a complete loss of architecture as the result of diffuse proliferation and infiltration of reticulum cells with the same characteristics previously described. These cells were more pleomorphic and many of them appeared to function as macrophages.

The bone marrow was moderately depleted of cells and those that were present were chiefly reticulum cells. A moderate amount of adipose tissue still remained showing that the leukemic cells had not completely displaced the marrow.

On microscopic examination of the lungs several small foci of pneumonia were seen.

The final pathologic diagnoses were: leukemic reticuloendotheliosis with massive involvement of lymph nodes, spleen, liver and bone marrow; mild pulmonary edema; thrombophlebitis, left lower leg with edema.

This case illustrates a leukemic reticuloendotheliosis with marked generalized involve-
ment of spleen, liver, lymph nodes, bone marrow and peripheral blood, with a rapidly progressive course and a clinical picture quite similar to that of the other types of acute leukemias. Death occurred within three months after the onset of the first symptoms.

**DISCUSSION**

We have preferred the term leukemic reticuloendotheliosis, which was first used by Ewald in 1923, because it describes the diagnostic feature of the disease, namely the presence in the bone marrow and/or in the blood of a large number of primitive atypical free reticulum cells and endothelial cells. These cells are also found in the organs where the reticuloendothelial system predominates: the spleen, lymph nodes and liver. The differential morphologic features which characterize these cells under supravital, Wright's, and eosin-hematoxylin stains, as well as under phase contrast and electron microscopy, have been described and illustrated in this report (figs. 3–8).

Ewald's concept of the histopathologic correlations in this disease is based on his representation of the development of blood cells in the following diagram:

Level I Reticuloendothelial cells

Level II Lymphoblast Histiocyte Myeloblast

Level III Lymphocyte Monocyte Granulocyte Erythrocyte

His concept was that proliferation at level I resulted in the disease under discussion, at level II arose other types of leukemia and at level III proliferation occurred in response to infections. Our own earlier experimental studies followed by our later clinical experiences as reported in this paper, would suggest a modification of Ewald's concept as shown by figure 11.

Figure 11 suggests that unbridled proliferative influences at level I result in an aleukemic form of reticuloendotheliosis. Uncontrolled proliferative influences acting at level II primarily upon the primitive free reticulum cells result in the leukemic form of reticuloendotheliosis in which the large majority of abnormal circulating leukemic cells retain many of the morphologic characteristics of free reticulum cells (figs. 3–7): but there are some with elongated nuclei quite suggestive of endothelial cells (fig. 5) and some with a few features of very young monoblasts. Figure 11, levels III and IV, show that when differentiation has occurred toward the several definitive cell types, normal maturation may not occur and other mutant changes may result in one or other of the "acute" leukemias. Abnormal proliferation at the more mature stages leads to the more "chronic" forms of leukemia. Uncontrolled proliferative influences on the endothelial cells may result in a rare type of clasmatoctytic leukemia and if such influences involve the erythroid elements, so-

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*The use of the term "endothelial cell" in this paper is restricted to the endothelial cells of the reticuloendothelial system, as opposed to the conducting vascular and lymphatic endothelial cells.*
called erythremic myelosis (Di Guglielmo's disease22) may result. Controlled proliferative activity of the free reticulum cells and endothelial cells in which division and maturation are physiologically adjusted to the needs of the organisms and selective with regard to the type of cell needed give rise to the normal cells shown in levels III and IV. Under ordinary conditions megaloblasts arise only from the "specific endothelial" cells of the inter-sinusoidal capillaries of the bone marrow.24

It should be pointed out that the morphologic identification of leukemic reticuloendotheliosis, monocytic leukemia, and clasmatocytic leukemia, is best and most accurately made by the study of living cell preparations, preferably supravitally stained. Most of the cases of leukemic reticuloendotheliosis that we have seen in our clinic have been identified in hematologic laboratories elsewhere as either acute or chronic lymphatic leukemia. Part of this error is probably attributed to the fact that the phagocytic patterns of the cells in question are quite elusive in fixed stained preparations.

There is no pathognomonic clinical syndrome or definitive sign of leukemic reticuloendotheliosis and, clinically, it cannot be differentiated from other malignant lesions of the reticuloendothelial system or from progressive myelofibrosis, which it often closely simulates. In the majority of instances there is a marked splenomegaly early with or without moderate hepatomegaly; generalized peripheral lymphadenopathy is less commonly seen and suggestive infiltrative lesions of the skin occur only occasionally.

The clinical course is variable: 31 per cent of our cases had an acute and rapidly progressive course with a clinical picture quite similar to that of one of the untreated acute leukemias. This type is illustrated by case 15 of our series; 23 per cent had a subacute course and 46 per cent had a chronic course. In these latter cases the disease remained almost latent and extremely mild for prolonged periods of time, followed by exacerbations as described in case 10. Among this chronic group there are some cases which showed a predominant "splenic form" with marked initial splenomegaly but with mini-
mal invasion of the peripheral blood, bone marrow, lymph nodes and liver. Our case 12 is typical of this type.

Reticulum cells were present at some time in the peripheral blood in all of our cases, but in most of them a neutropenic leukopenia was noted necessitating a careful search for the diagnostic cells and their separate identification from lymphocytes and monocytes. A moderate or severe anemia secondary to myelophthisia was found in the more acute syndromes; however, a hemolytic or pancytopenic component was demonstrated in some of the more chronic types. Thrombocytopenia was common. The bone marrow was peculiarly difficult to aspirate, and in most instances no fragments could be obtained even after several attempts from different sites. With such a negative finding associated with peripheral blood pancytopenia and a steadily enlarging spleen, many of these patients are initially confused with chronic progressive myelofibrosis. The predominant cell, however, in the sparsely cellular bone marrow is the pathognomonic reticulum cell in these patients. The difficulty of aspirating marrow is due, in most cases, to the "packing" of the marrow cavity by reticulum cells, many of which are "fixed," since in marrow specimens obtained at post mortem or by surgical biopsy the marrow appeared cellular with a predominance of both fixed and free reticulum cells.

Concerning therapy, the acute and subacute forms of leukemic reticuloendotheliosis have thus far proven very resistant to all of the presently known therapeutic measures. Nitrogen mustard was given to 10 patients without obtaining any measurable response. The more chronic cases with splenomegaly seemed to respond favorably to x-ray therapy over the spleen. This therapy was usually followed by a reduction in the size of the spleen, a decrease of reticulum cells in the peripheral blood, and corresponding temporary clinical improvement. T.E.M. and P₃₂ have also seemed to produce some improvement in tissues and bone marrow, respectively. Steroids alone or in combination with T.E.M. have appeared to produce favorable results, especially in those cases showing a hemolytic component. Continuing maintenance therapy is indicated in some patients; in others the disease remains dormant without suppressive therapy. Splenectomy should be reserved for the chronic forms with predominance of splenic involvement and with a definite complicating secondary hypersplenism. Five of our patients were advised to have splenectomy. Cases 5 and 12 are the best examples of the excellent results that may be obtained in selected cases of chronic leukemic reticuloendotheliosis. Certainly the careful study and individualization of each patient is indicated from a review of this series of patients and the prognosis has varied so widely from patient to patient that caution is urged in any premature commitment in this respect.

SUMMARY

The clinical, hematologic, and pathologic findings in 26 cases of leukemic reticuloendotheliosis are presented.

A histopathologic correlation of the various forms of leukemia is suggested. Clinically the disease may follow an acute, subacute, or chronic course
There is no idiopathic clinical sign or symptom, but the hematologic picture is pathognomonic and is characterized by the presence of reticulum cells in the peripheral blood and bone marrow. These cells are also present in the organs where the reticuloendothelial system predominates: spleen, liver, and lymph nodes.

The study of these cases supports the concept that leukemic reticuloendotheliosis is an independent hematologic and pathologic entity.

**SUMMARIO IN INTERLINGUA**

Es presentate le constatationes clinic, hematologic, e pathologic in 26 casos de reticuloendotheliosis leucemic.

Es proponite un correlation histopathologic del varie formas de leucemia.

Le curso clinic del morbo pote esser acute, subacute, o chronic. Il existe nulle idiopathic signo o symptomo clinic, sed le tableau hematologic es pathognomonic e es characterisate per le presentia de cellulas reticular in le sanguine peripheric e in le medulla ossee. Tal cellulas es etiam presente in le organos a predominantia del sistema reticuloendothelial, i.e., le splen, le hepate, e le nodos lymphatic.

Le studio del presente casos supporta le conception que reticuloendotheliosis es un independente entitate hematologic e pathologic.

**REFERENCES**

Leukemic Reticuloendotheliosis

BERTHA A. BOURONCLE, BRUCE K. WISEMAN and CHARLES A. DOAN

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