those associated with recto-urethral or recto-vesical fistulæ, a primary abdomino-perineal operation, or a transverse colon colostomy as a first-stage procedure, is advised.

If an external fistula was found to be of adequate size for decompression, definitive operation was delayed for a period of months or years, with considerable decrease in mortality rate.

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RÉSUMÉ

L'auteur présente une série de cent cas d'anus imperforé. On considère que ces malformations sont causées par un arrêt ou une déviation du cours habituel du développement. On les divise en 4 groupes déterminés d'après la période où l'arrêt s'est produit. Le groupe le plus commun, le type III, est aussi le plus difficile à traiter.

Environ 50% des cas sont accompagnés de fistules, lesquelles, selon leur position et leurs dimensions, facilitent ou compliquent le traitement.

La lésion est souvent accompagnée aussi d'anomalies congénitales simples ou multiples. Elles se présentent si fréquemment et sont d'une telle importance au point de vue clinique qu'on doit toujours en soupçonner l'existence.

Lorsque l'ampoule rectale se trouve près de l'extérieur, l'opération périnéale donne des résultats satisfaisants. Autrement, dans les cas d'ampoules plus hautes ou d'ampoules accompagnées de fistule recto-urétrale ou recto-vésicale, on conseille l'opération abdomino-périnéale primaire ou la colostomie du côlon transverse comme premier stage du traitement.

S'il existe une fistule externe suffisante pour assurer la décompression, l'opération définitive peut être retardée pendant des mois, même des années, avec comme résultat un taux de mortalité considérablement diminué.

M.R.D.

LEUKÆMIC RETICULOENDOTHELIOSIS*

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THE PROBLEM of reticulosis and reticuloendotheliosis abounds in controversy. The questions as to the existence of leukæmic reticuloendotheliosis and as to its relation to other types of leukæmia have excited much interest among hæmatologists, not merely because of the rarity of the condition, but also because of the bearing its demonstration might have on the controversy over the status of the reticuloendothelial cell. These are merely a phase of the larger problem of the origin of blood cells in general and the relation of mature leukocytes to the more primitive cells of the reticuloendothelial system.

The term "leukæmic reticuloendotheliosis" was first coined by Ewald[1] in 1923. Later Fieschi,[2] on the basis of morphological studies, distinguished the following forms: (1) reticuloendotheliosis with primitive cells; (2) reticuloendotheliosis with monocytoid cells, this last variant corresponding to the "Schilling type" of American authors; (3) reticuloendotheliosis with lymphoid cells.

In reviewing the literature on the subject, it is apparent that little agreement exists among authors concerning the nature and the limits of leukæmic reticuloendotheliosis. The term unfortunately has been and still is used as a synonym for monocytic leukæmia, especially among American authors. Most workers feel, and we concur, that reticuloendothelial cells are precursors of lymphocytes, and under certain special conditions and stimuli, there may be hyperplasia of the reticuloendothelial cells with passage of both precursors and end-products into the peripheral blood.

This study of 49 cases of leukæmic reticuloendotheliosis was undertaken in the hope of better delineating the clinical entity and perhaps clarifying some of the confusion that has existed in the literature.

MATERIAL AND METHODS

Data on 49 cases seen at the Mayo Clinic from 1944 through 1953 have been studied. All satis-

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factory smears of blood, bone marrow and splenic aspirates available to March 1954 were reviewed for cell types and indications of origin. Smears of bone marrow were available in the large majority of instances. In a few cases, fixed paraffin sections were also available and were reviewed. Differential counts of 500 nucleated cells on bone marrow smears, and of 200 white cells on peripheral blood, were recorded. Nucleated erythrocytes were noted per 100 leukocytes.

The members of the Hematology Laboratory of the Mayo Clinic aspirated the bone marrow and prepared the slides. The method of preparation of the aspirated marrow was similar to Schleicher's method, with slight modification.

CLINICAL ASPECT

The ubiquity of the reticuloendothelial cells makes leukæmic reticuloendotheliosis a very polymorphous clinical entity. Any organ of the body containing reticuloendothelial elements may be involved by the leukæmic process. However, in most cases the clinical manifestations result from disturbances or lesions in the spleen, liver, marrow and lymph nodes—those areas in which the reticuloendothelial system is most active. In rare cases, significant involvement may occur in the adventitia of vessels, in periglandular connective tissue, and so forth, giving rise therefore to a varied symptomatology.

The clinical picture will depend on the major sites of the hyperplasia, varying from primary, solitary involvement of one organ—for example, the spleen—to widespread infiltration of the entire reticuloendothelial system with systemic manifestations.

No specific or pathognomonic symptom, sign or clinical prototype exists. Each case has its own physiognomy. It must then be admitted that there are no clinical means to differentiate leukæmic reticuloendotheliosis from other malignant lesions of the reticulum, for example, lymphomas and leukæmias. Final differentiation is possible only by morphological evidence.

Leukæmic reticuloendotheliosis is a fatal disease with a course as irreversible as that of other leukæmias. The onset may be very insidious, and is often obscured by a history of some recent infection such as a common cold, influenza, otitis, tonsillitis, or gastrointestinal or even genitourinary infection. The presenting symptoms are quite variable: vague general symptoms like fatigability, "weakness", loss of weight, poor appetite, low-grade fever and, commonly, symptoms related to the anæmia (dyspnœa, palpitation, vertigo, and so forth). Evidence of a hæmorrhagic diathesis may often first be manifested by the occurrence of repeated attacks of epistaxis as well as by a generalized purpuric or petechial eruption. The main symptom may be an exfoliative dermatitis or another type of cutaneous involvement which we shall discuss later.

Physical examination may occasionally yield few striking changes. In most cases, however, the spleen, liver and skin are obviously involved.

TABLE I.

DEGREE OF CLINICAL INVOLVEMENT OF LIVER AND SPLEEN

Degree of involvement	*Liver*		*Spleen*	
	Cases	*%*	*Cases*	*%*
None	23	47	13	27
Slight	16	33	6	12
Moderate	9	18	13	27
Marked	1	2	17	34

Liver and spleen.—Splenomegaly is the most constant finding and the major clinical feature (73%) of our series. Degrees of enlargement are shown in Table I. This splenomegaly is usually progressive, although it may vary during remissions, spontaneous or therapeutic. In most cases it does not produce any secondary symptoms, except for a slight sensation of discomfort over the left upper quadrant of the abdomen. Occasionally, infarctions with varying degrees of perisplenitis will occur. In our cases there seemed to be no definite relationship between the degree of splenomegaly and the duration of the disease. Italian authors, however, have expressed the belief that the "pure splenic form" is the most frequent as well as the most benign.

Hepatomegaly is usually moderate. In only one of our cases was the inferior border of the liver below the umbilicus.

Lymph nodes.—Many authors claim that in 80 to 90% of cases there is marked involvement of the lymph nodes. Their patients presented themselves with enormous masses quite similar to those seen in Hodgkin's disease and involving both superficial and deep chains. The present survey is not in accord with these findings, as is shown in Table II.

In 10 of the 22 cases in which enlargement of lymph nodes was noted, there was marked in-

TABLE II.

DEGREE OF CLINICAL INVOLVEMENT OF LYMPH NODES

Degree of involvement	*Cases*	*%*
None	27	55
Slight	16	33
Moderate	6	12
Marked	0	0

volvement of the skin. We believe that the enlargement of these nodes was often due to a dermatopathic lymphadenitis (lipomelanotic reticulosis) as proved by biopsy in two cases. Lymph nodes were also biopsied in two other patients: one proved to be inflammatory while the other was reported as "malignant lymphoma."

TABLE III.

DEGREE OF CLINICAL INVOLVEMENT OF SKIN

Degree of involvement	*Cases*	*%*
None	35	72
Slight	2	4
Moderate	2	4
Marked	10	20

Skin (Table III).—Involvement of the skin is frequent in leukæmic reticuloendotheliosis, and many such cases have been reported. Cazal stated[3] that 20 to 25% of the patients present cutaneous manifestations. Bell[4] stated that "the skin is involved in about 10%. In the skin the infiltrations of leukæmic cells seem to begin around the dermal blood vessels, from which we may conclude that the undifferentiated mesenchyma is also involved in the leukæmic process."

Montgomery and Watkins[5] published data on four cases with exfoliative dermatitis as a manifestation of leukæmic reticuloendotheliosis. Case 1 belonged to the lymphocytic type, case 2 to the primitive cell type, cases 3 and 4 to the monocytic (Schilling's) type.

Epstein and MacEachern,[6] in an extensive study, have reviewed the dermatological manifestations of the lymphoblastoma-leukæmia group. Cazal[3] and de Graciansky and Paraf[7] have attempted to classify the cutaneous lesions found in leukæmic reticuloendotheliosis into two main groups: (1) non-specific cutaneous manifestations (pruritus, purpura, melanoderma, herpes zoster), and (2) so-called specific cutaneous lesions. The latter lesions have been said[3] to be a specific cellular infiltrate. "As one speaks of leukæmids in leukæmias, one could talk of reticulids in reticuloendotheliosis." Three types of lesions are most commonly encountered: (a) papular eruptions; (b) nodules, tumours, ulcerations; (c) erythroderma.[5]

From this series, one can conclude that no specific dermatological picture exists histologically or clinically and that lesions of the skin encountered in leukæmic reticuloendotheliosis are similar to those seen in any disease of the lymphoblastoma-leukæmia group.

HÆMATOLOGICAL ASPECT

The presence of an increased number of normal and abnormal reticular cells and reticular lymphocytes in the peripheral blood or in the bone-marrow aspirate should be considered as only one of the multiple localizations and manifestations of the disease.

Peripheral blood and reds cells (Fig. 1).—As a rule, marked anæmia is infrequent. When it occurs, it is a very serious prognostic sign. In this series, it was found only in the late stages of the disease. The anæmia is, in the majority of cases, normocytic and normochromic, although macrocytosis was found in 18 cases. This anæmia is progressive, and in none of the cases has its spontaneous or therapeutic reversion been noted during the course of the disease. No hæmolytic component was apparent in any of the cases. Rouleau formation of moderate degree was noted in 21 cases and the presence of normoblasts in five cases.

White cells (Fig. 1).—Leukopenia is a very important feature. It was observed in 28 cases (56%). The leukocyte count is usually around 2,000 to 3,000 per c.mm. of blood. It may reach critically low levels. In one case, agranulocytosis occurred and was rapidly followed by death. This situation, however, was most certainly secondary to administration of nitrogen mustard. Leukocytosis (more than 10,000) was present in 12 cases, the highest leukocyte count being 139,000. In 10 of these cases there were generalized cutaneous lesions with secondary infection. Differential counts have shown that neutropenia with distinct relative lymphocytosis is the rule. In rare cases, moderate eosinophilia (less than 10%) was encountered. The proportion of reticular cells and reticular lymphocytes was quite variable: from 1.5% to 89% with an average of 18%. One has, however, to bear in mind the relative accuracy of such counts because of the unavoidable listing of a certain pro-

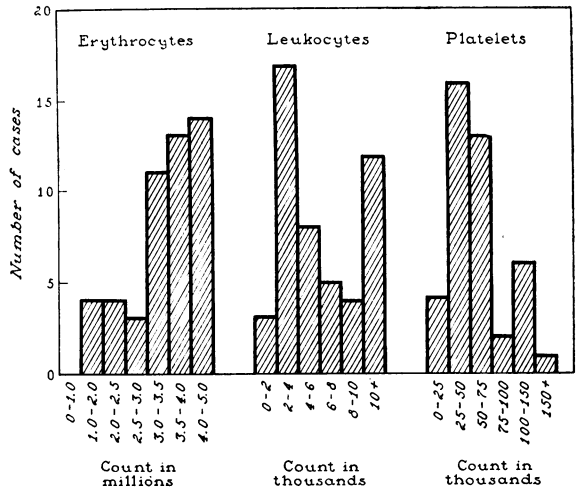

Fig. 1.—Frequency distributions of concentration of erythrocytes, leukocytes and platelets.

portion of reticular lymphocytes as mature lymphocytes.

Platelets (Fig. 1).—Thrombocytopenia (less than 100,000 platelets per c.mm. of blood) was observed in 35 of the 42 cases in which platelet counts were made. In only one case was the count above 150,000. Thrombocytopenia was manifest in the early stages and progressively increased during the course of the disease. Fourteen patients presented themselves with generalized petechiæ, and 28 had a history of bleeding (epistaxis, hæmoptysis, melæna, hæmatemesis, etc.).

Conclusions.—All in all, it may be stated that when the disease is in an advanced stage, one will find a pancytopenia or a reduction in the relative numbers of all formed elements of the peripheral blood, giving rise to the so-called myelophthisic type of picture due to extensive infiltration of marrow by reticular cells and reticular lymphocytes.

Bone marrow.—Smears or paraffin sections of bone marrow were available in 38 of our 49 patients. Those were carefully studied and differential counts of 500 cells were made.

Expressed as a percentage of the differential count, we considered the following as significant variations: red cell series, below 10%; myeloid series, below 35%; lymphocytes, above 10%; reticular cells, above 3%.

Our results were as follows: (1) erythropoiesis was depressed in 13 cases (34%); (2) myelopoiesis was depressed in 31 cases (82%); (3) lymphocytes were increased in 27 cases (71%); (4) reticular cells and reticular lymphocytes were increased in 37 cases (97%); (5) the myeloid-erythroid (M.E.) volume as determined by the hæmatocrit (normal = 4 to 8%) was less than 2% in 25 cases (66%); (6) the myeloid-erythroid ratio was around one or was reversed in 25 cases.

In six cases, only traces of normal myelopoietic and erythropoietic cells were present. The bulk of the specific tissue was replaced by dense accumulations of large polymorphous reticuloendothelial cells.

In contrast to van der Meer and Zeldenrust[8] and in agreement with Moeschlin,[9] Leitner[10] and Rohr and Hegglin,[11] we believe that marrow aspiration may be of great help in the diagnosis of leukæmic reticuloendotheliosis. Sundberg,[12] discussing leukæmic reticuloendotheliosis in her monograph on sternal aspiration, stated: "The M.E. volumes obtained are extremely variable, but section preparations generally show evidence of hyperplasia. Smears show a marked increase in the reticular cells with evidence of transformation of these cells to leukocytes (granulocytes or lymphocytes). Blast forms which show morphologic evidence of their derivation from reticular cells are prominent. Erythropoiesis and platelet formation are generally atypical and depressed." Our findings in the present series of cases substantiate Dr. Sundberg's statement.

A diagnosis of leukæmic reticuloendotheliosis is more likely to be made, *in vivo,* in films of blood, marrow, lymph nodes or spleen in which the characteristic cells may be found. There is no doubt that this method is less misleading than that of fixation, with the consequent shrinkage of cells.

Most of the publications that have appeared on this subject have been on a pathological and anatomical basis without examination of the marrow or the spleen. It is almost impossible by the anatomical method to distinguish a myeloblastic leukæmia from a small cell sarcoma or a reticuloendotheliosis. The only way to distinguish them is by films in which one can study the proliferating reticuloendothelial cells and the degree of their differentiation.

These cells (undifferentiated reticular cells, hæmatopoietic reticular cells, reticular lymphocytes and their transitional stages to lymphocytes) have been extensively described by Sundberg and Downey[13] and by Sundberg.[14]

The atypical reticuloendothelial cells and reticular lymphocytes when found in blood

smears have "a superficial resemblance to monocytes; they are monocytoid and lymphocytoid but not true monocytes or lymphocytes" (Sundberg and Downey[13]).

The recognition of these cells in blood smears is not a difficult matter for the experienced hæmatologist, but they are frequently misinterpreted by many laboratory workers as monocytes or lymphocytes and the condition is often diagnosed as either "subacute monocytic leukæmia" or "subacute lymphocytic leukæmia."

Whenever the possibility of leukæmic reticuloendotheliosis needs to be considered, blood smears should be repeatedly examined for lymphocytoid forms.

In summary, it is impossible to make the diagnosis of leukæmic reticuloendotheliosis clinically on the basis of history, symptomatology or physical findings, since these are not specific and are quite similar to those encountered in the lympholeukæmia group of diseases. However, clinically, these patients may present (1) a history of preceding respiratory infection or so-called flu syndrome, which may appear as the initial manifestation; (2) systemic, nondescript symptoms such as fatigability, loss of weight, low-grade fever, and night sweats; (3) a short history of splenomegaly and occasionally hepatomegaly; (4) a mild and variable generalized lymphadenopathy; (5) cutaneous manifestations such as generalized erythroderma, mycosis fungoides, and other non-specific lesions of the skin.

The diagnosis rests on the finding in the blood and marrow smears of reticuloendothelial cells, reticular lymphocytes, and transitional stages to the mature lymphocytes, a mild to moderate, usually normocytic, but often macrocytic anæmia, leukopenia with relative lymphocytosis, thrombocytopenia, and hypoplasia of the bone marrow.

COURSE AND PROGNOSIS

Leukæmic reticuloendotheliosis is inexorably and universally fatal, death being usually due to a complicating hæmorrhage or an intercurrent infection. It is an irreversible disease against which the human body does not react and in which treatment is only palliative. From this standpoint, it behaves exactly like other diseases characterized by abnormal cellular division such as neoplasms and leukæmias. Reports of many cases have been published without the mention of a fatal course. In most of these instances, however, authors have described only one phase of the disease, believing that a permanent cure had taken place, while in fact the patient was only in prolonged remission. The follow-up had not been long enough to permit evolution of the true course of the disease.

The course is extremely variable and the disease may be manifested in three main forms—acute, subacute and chronic.

1. The acute type is rapidly progressive, with a clinical picture quite similar to that of acute leukæmias. Death may occur in a few weeks, or the course may be as long as six months. This form is rarely seen in cases of the lymphocytic type (5 to 8%), while it is much more frequent in the monocytic and primitive cell types. Four cases of the present series belong to the acute type.

2. The subacute type is more frequently encountered (35 to 40%), and usually consists of two successive phases. The first phase, which is the longer, is characterized by the clinical involvement of one or many organs, quite frequently the skin, and by low-grade systemic manifestations. This period is almost benign in appearance and the disease remains slowly progressive until the onset of the second phase, which is an acute exacerbation with the clinical picture seen in the acute type. Death follows rapidly.

3. The chronic type accounts for 45% of the cases in the present series. In many of these, the disease remained almost latent and extremely mild for prolonged periods of time, so that little disability resulted. With this type, the diagnosis may be established during a routine examination in which the patient is found to have splenomegaly or leukopenia. Typical blood and marrow pictures are then discovered. A few patients had noted mild symptoms for several years before consulting a physician. The course in this type is very chronic and is characterized by prolonged spontaneous or therapeutic remissions with remarkable subjective improvement which may last for months. These latent stages are followed by exacerbation of weakness and fatigability, and by relapses of variable intensity and duration. In four cases, the patient was known to have lived for more than 10 years after the onset of symptoms.

Radiotherapy remains, at the present time, the treatment of choice in these chronic cases, and

frequently the initial lesions vanish surprisingly well. However, progressive radioresistance develops and, from then on, nothing seems to influence the course of the disease.

One should be very careful in attempting to predict the definite course of an individual case on the basis of clinical or hæmatological findings. There exists no definite correlation between the clinical course and the morphological picture although (1) cases in which there is a higher proportion of primitive reticuloendothelial cells have a definite tendency to behave like acute leukæmias, and (2) there is a direct relationship between the activity of the bone marrow and the course of the disease, patients with hypoplastic marrow having a shorter survival time. The degree of activity of the bone marrow should also be considered before treatment is instituted, since most of the methods now used in the treatment of "leukæmias and allied conditions" are potent depressors of the bone marrow.

FOLLOW-UP

Of 49 patients studied in this series, 45 have been traced. By March 1954, 16 were still alive, 28 had died from leukæmic reticuloendotheliosis, and one had died from an unrelated cause (Tables IV, V, and VI).

TABLE IV.

STATUS OF PATIENTS AS OF MARCH 1954

Status of patient	*Patients*	%
Untraced	4	8
Living	16	33
Died from leukæmic reticuloendotheliosis	28	57
Died from unrelated cause	1	2
Total	49	100

TABLE V.

DURATION OF SYMPTOMS OF 28 PATIENTS WHO HAD DIED FROM LEUKÆMIC RETICULOENDOTHELIOSIS

Duration of symptoms (years)	*Patients*
1	4
2	9
3	7
4	3
5	1
6	0
7	1
8	0
9	1
10 or more	2
Average survival time	3.5 years

TABLE VI.

DURATION OF SYMPTOMS OF PATIENTS LIVING (MARCH 1954)

Duration of symptoms (years)	*Patients*
1	1
2	2
3	3
4	1
5	3
6	3
7	0
8	0
9	0
10 or more	3

CONCLUSIONS

1. Leukæmic reticuloendotheliosis is a definite and distinct hæmatological entity which may be of three main types: the primitive cell type, the monocytic type (Schilling's monocytic leukæmia), and the lymphocytic type.

2. The present study was mainly concerned with the lymphocytic type of leukæmic reticuloendotheliosis; 49 cases were studied from the clinical and hæmatological standpoints.

3. Although the clinical aspects of this disease do not greatly differ from those of leukæmias, the hæmatological picture is pathognomonic and is characterized by the presence, in the smears of blood and bone marrow, of undifferentiated reticular cells, hæmatopoietic reticular cells, reticular lymphocytes and transitional stages to the mature lymphocytes.

4. The prognosis, as in leukæmias, is inexorably fatal.

5. The course of the disease parallels that of leukæmias, and in the chronic type, patients may survive for 10 to 15 years.

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