BONE MARROW IN RHEUMATOID ARTHRITIS

BY

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Various results have been reported from the study of the bone marrow in patients with rheumatoid arthritis. These include "hypocellularity" (Merlo and Tortori Donati, 1945), "general granulocytic hyperplasia" (Lucchesi, Lucchesi, and da Silva, 1946), reticulo-endothelial hyperactivity (Marmont, 1948), and a slight increase of metamyelocytes and decrease in the formation of buds of megacaryocytes (Jeffrey, 1952). The last, which also occurs in thrombocytopenic idiopathic purpura, could presumably be taken as an evidence of a slight degree of hypersplenism in patients with rheumatoid arthritis (Curtis and Pollard, 1940). This hypothesis seems to be substantiated by the fact that in some cases with leukopenia in the peripheral blood, the bone marrow was hyperplastic, which suggests a possible inhibitor factor. It is interesting to note that some published reports mention good results obtained in patients with rheumatoid arthritis following splenectomy (Bach and Jacobs, 1951).

In ten non-selected cases of rheumatoid arthritis, Hayhoe and Smith (1951) found 1.8 to 6.3 per cent. (normal 2 per cent.) of plasma cells by bone marrow biopsy, and a significant and constant increase in serum globulin, but it did not seem that either plasmocytosis or hyperglobulinaemia were due to the activity of the disease, as no parallelism was observed between them. This opinion was not shared by Jasiński and Staehelin (1951), who reported normal plasma cell counts in patients with the disease.

A study of 32 children with Still's disease, in its various stages, showed general bone marrow hyperplasia, especially affecting the granulocytic cells, which, in 29 cases, made up 60 per cent. or more of the total count. A shift to the left of the granulocytes was observed with pro-myelocyte rates of 20 and 30 per cent. myelocytes of the total bone marrow cells (Schlesinger and Cathie, 1951). An increase in the immature elements was reported

from other series as well as the presence of a great number of megacaryocytes.

Curtis and Pollard (1940) reported a relative decrease in immature erythroblastic cells in half of sixteen cases in which the peripheral red blood count revealed the presence of anaemia; this finding suggested the hypothesis of a disturbed formation of normoblasts as an explanation for the anaemia of rheumatoid arthritis.

The study of the bone marrow in 21 cases of rheumatoid arthritis by Marmont (1948) showed the presence of megaloblastic forms, hyperactivity of reticulum elements, and transition cells from primitive reticular cells and basophil erythroblasts. A decrease of haemocytoblasts, plasmocellular hyperplasia (Marmont, 1948), and eosinophilia was observed to occur simultaneously with the change found in the peripheral blood count (Volpicelli, 1951).

Present Investigations

We have recently had the opportunity of studying the bone marrow in twenty patients with rheumatoid arthritis.

The material analysed was obtained by biopsy-puncture, by aspiration of sternal bone marrow, and the preparations were coloured by the panoptic method of Pappenheim. In ten cases (1 to 10) 600 cells were counted, in three cases (11, 12, and 13) 400 cells, in two (14 and 15) 300 cells, and in the rest (16 to 20) only 200.

The twenty patients were classified according to the stage of the disease:*

- I. Initial, two cases;
- II. Moderately advanced, eleven cases;
- III. Advanced, seven cases;
- IV. Terminal, none.

* Steinbrocker and others (1949).

Case Nos.	1	2	3	4	5	6	7	8	9
Stage of Disease	II	III	II	II	II	III	III	II	II
Haemocytoblasts	0.3	0.3	0.2	0.5	0.3	—	0.2	—	0.2
Myeloblasts	2.8	0.3	1.2	3.0	1.3	3.0	3.0	1.0	2.6
Pro-myelocyte neutrophils ..	2.6	0.7	1.8	3.5	2.9	2.2	2.2	0.3	1.8
Myelocyte neutrophils ..	8.0	10.0	8.6	12.0	10.0	9.0	4.6	11.6	26.6
Metamyelocytes	12.3	6.6	21.2	14.5	11.6	7.0	9.6	10.3	16.8
Band-form neutrophils ..	16.5	15.0	15.0	9.5	16.3	15.6	0.8	14.0	11.2
Segmented forms	22.8	28.6	21.0	34.5	18.6	36.3	23.0	36.3	11.0
Pro-myelocyte eosinophils ..	0.5	1.7	1.0	0.5	—	1.3	1.8	—	0.6
Myelocyte eosinophils ..	—	—	—	—	—	—	1.8	—	—
Metamyelocyte eosinophils ..	—	—	—	—	—	—	1.8	—	—
Eosinophils	2.0	6.6	4.0	4.0	1.0	5.6	8.0	3.3	1.0
Myelocyte basophils	—	—	—	—	—	—	—	—	—
Basophils	0.5	—	—	—	—	0.3	0.2	0.6	0.2
Lymphocytes	7.3	4.3	6.2	4.5	6	10.3	3.4	8.3	1.8
Monocytes	0.3	0.3	—	0.5	—	0.3	—	1.0	—
Histiocytes	—	—	—	—	—	—	—	—	—
Plasmocytes	3.3	1.7	0.6	0.5	0.6	1.0	4.0	0.3	—
Pro-erythroblasts	0.8	0.3	1.8	—	0.3	—	—	0.3	0.2
Erythroblast basophils ..	1.6	1.7	4.0	2.0	2.3	4.3	5.4	0.6	4.2
Erythroblast polychromatophils	16.6	19.3	12.8	6.0	19.3	6.6	25.6	10.6	21.6
Erythroblast orthochromatics	2.0	1.3	1.0	0.5	6.6	2.0	1.8	0.6	0.2
Megacaryocytes	S	S	S	N	S	S	S	S	S
Leuco-erythroblastic ratio ..	3.5 : 1	3 : 1	4 : 1	9 : 1	2.3 : 1	5.8 : 1	3 : 1	6 : 1	2.8 : 1

N = normal.

Results

The results are presented in Table I.

Eosinophilia.—This was observed in seven cases (2, 6, 7, 13, 15, 16, 19; 35 per cent.). Comparing the bone marrow eosinophilia with that observed in peripheral blood counts (Table II), we observed similar counts in four cases. In another case the peripheral blood eosinophil count was normal. In the remaining two such a comparison was not possible.

TABLE II
COMPARISON OF BONE MARROW AND
PERIPHERAL BLOOD EOSINOPHILIA

Case Nos.	Relative Bone Marrow Eosinophilia	Relative Peripheral Eosinophilia
2	6.6	9
6	5.6	6
7	14.7	6
13	17	—
15	13.5	—
16	8	4
19	24	22

Plasma Cells.—The plasma cell counts were above normal in only five cases (1, 7, 11, 14, 18; 25 per cent.). The increase varied between 3 and 5.3 (Table I). The distribution of the plasmocytosis of the bone marrow, according to the stage of the disease was:

- I. two cases;
- II. two cases;
- III. three cases;
- IV. none.

We investigated the possibility of correlating bone marrow plasmocytosis with the blood protein

changes determined by the flocculation tests (cephalin-cholesterol, colloidal red, Gross-Jacobson, and cadmium sulphate). We selected a group of five "control" patients with rheumatoid arthritis at the same stage, in whom the bone marrow was normal, and compared the results of the flocculation tests with the five which showed plasmocytosis. Table III shows that the flocculation tests were generally positive whether or not there was plasmocytosis. Therefore we can conclude, allowing for objections due to the small number of cases studied, that there is no apparent correlation between bone marrow plasmocytosis and blood protein alterations measured by flocculation tests.

TABLE III
COMPARISON OF FLOCCULATION TEST IN PATIENTS
WITH PLASMOCYTOSIS AND CONTROLS

Flocculation Tests	Five Rheumatoid Patients with Bone-marrow Plasmocytosis					Five Rheumatoid Patients with Normal Plasmocytes in the Bone Marrow				
	1	7	11	14	18	F	G	H	J	K
Cephalin Cholesterol ..	4	3	3	—	3	2	3	3	2	3
Colloidal Red	3	4	3	—	4	3	3	0	3	3
Gross-Jacobson	1	0	0	—	—	2	3	0	2	2
Cadmium Sulphate	2	1	3	†	2	2	3	0	2	1
Evolutionary Stage of the Disease	II	III	II	III	III	II	III	II	III	III

Leuco-Erythroblastic Ratio.—This relation was normal in ten cases, depressed in five, and raised in five.

L.E. Cells.—The type of lesion found in patients with rheumatoid arthritis as well as its generalized distribution suggest that this condition should be

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LE I
MARROW BIOPSY

10	11	12	13	14	15	16	17	18	19	20	Normal Range
I	II	II	I	III	III	III	II	III	III	II	
—	—	0·205	—	0·5	1·0	—	0·3	1·0	—	N	0·1-0·3
0·6	5·0	0·705	0·5	1·0	1·0	—	—	1·0	—	N	1·2-2·5
0·6	2·5	0·705	0·5	1·0	0·5	1·0	1·0	0·6	1·0	N	2·3-5
9·6	2·5	6·000	12·0	12·0	10·0	5·0	11·5	1·0	6·0	N	11-17
11·3	8·5	15·000	14·0	10·0	14·5	13·5	20·0	29·1	9·0	N	8·5-12
24·0	12·5	15·500	16·5	16·0	12·5	17·5	16·5	16·6	19·5	N	8-18
20·0	25·0	19·205	15·5	22·0	8·0	26·5	5·0	17·3	21·5	N	22-31
0·6	2·5	—	—	—	—	—	—	—	—	N	2·4-4·7
—	—	2·500	4·0	—	3·5	1·0	0·5	—	4·0	N	1·5-2·5
—	—	0·705	—	—	1·5	1·0	—	1·6	1·0	N	1-2
1·6	3·5	11·500	13·0	4·5	8·5	6·0	4·5	—	19·0	N	0·5-4·7
—	—	0·000	—	1·0	—	—	—	—	—	N	—
0·3	1·0	0·205	0·5	1·0	0·5	0·5	—	—	—	N	0·2
4·6	5·5	1·500	0·5	—	—	1·0	—	1·3	1·5	N	2·7-2
1·0	1·5	0·500	—	—	—	0·5	—	0·3	—	N	0·5-6·6
—	—	—	—	—	1·0	0·5	—	1·6	1·0	N	0·5-3
1·0	3	1·000	1·5	4·5	1·0	1·0	—	5·3	0·5	N	0·5-2
—	2·5	—	—	0·5	1·5	—	1·0	0·3	0·5	N	0-1
0·6	1·5	0·705	—	—	2·0	—	1·3	0·3	0·6	N	2·5-4·2
3·6	9·0	9·500	8·5	13·0	14·0	8·0	29·5	3·6	3·5	N	9·2-14·2
13·3	2·5	13·250	13·0	12·5	15·0	16·0	9·5	9·6	10·5	N	8·5-11
N	S	0·205	0·5	0·5	1·0	0·5	0·5	0·6	0·5	N	0·03-0·4
3·5 : 1	5·3 : 1	3 : 1	3·6 : 1	2·6 : 1	2 : 1	3 : 1	1·5 : 1	4·6 : 1	5·3 : 1	—	2 : 1-4 : 1

S = present.

included in the group of collagen diseases; the main link between these conditions is the histo-pathological lesion, with all the restrictions inherent in such a broad concept.

In one form of collagenosis, lupus erythematosus disseminatus, a special type of cell described as the "L.E." cell (Hargraves, 1949) was initially found in the bone marrow and later in the peripheral blood (Haserick and Sundberg, 1948; Haserick, 1950; Haserick and Bortz, 1949; Morton, 1947; Sundberg and Lick, 1949). The L.E. cell is an adult neutrophil, with one phagocyte vacuole, which contains an amorphous homogeneous basophil mass, and stains purple by the method of Wright, and deep purple by the method of May-Grunwald-Giemsa. The neutrophil nucleus is compressed in the periphery of the cell and has a half-moon or bi-polar shape with two masses in the opposite extremities. The colouration by thymo-nucleic acid with Feulgen's reactive shows the nuclear origin of the inclusion. It is believed that it is formed by the phagocytosis of free nuclear material or by the autolysis of one or more neutrophil nuclei (Monteiro Marinho and others, 1952).

Some authors believe that the immunological phenomena represented by the formation of the L.E. cell is correlated to the increase of gamma globulin (Haserick, 1950) or one of its fractions, the so-called L.E. fraction. Other studies, however, have shown that the fraction in question was an immunological one, differing from gamma globulin (Haserick and Lewis, 1950).

Histo-chemical techniques suggest the possibility that L.E. cells probably originate from the depolymerization of nucleic acid (Gueft, 1950); the phago-

cited nuclear material would be formed by desoxy-ribonucleic acid, partially depolymerized, possibly with a glycoprotein or mucoprotein substratum.

It is believed that the L.E. cell is specific for lupus (Haserick and Sundberg, 1948; Morton, 1947), notwithstanding the fact that it has been described in patients with multiple myeloma and other diseases (Berman, Axelrod, Goodman, and McClaughry, 1950). The reported analysis of the bone marrow of patients with rheumatoid arthritis, dermatomyositis, scleroderma, or active rheumatic fever showed negative results (Lee, Michael, and Vural, 1951).

Because of the increase in the gamma-globulin fraction found in our patients with rheumatoid arthritis, and the presence of L.E. cell in other conditions, and because we also observed in two of our patients the "butterfly" cutaneous face lesions so common in patients with lupus erythematosus disseminatus, we decided to investigate the presence of L.E. cells in a group of fifteen patients.

The method employed was that of Hamburger (1950)* with slight modifications:

Withdrawal of 5 ml. venous blood in oxalated recipients, centrifugation, and separation from plasma. After puncture the collected bone marrow was placed in contact with plasma and stored at 37° C. The examination was done after 1, 2, and 3 hrs' incubation.

We selected representative cases of various stages of the disease: three in Stage I, three in Stage II, four in Stage III and one in Stage IV. The test was negative in all these fifteen patients, and also in another fifteen patients in various stages.

* We are indebted to Dr. Paul Wishart for his help in the use of Hamburger's technique.

Summary

The study of the bone marrow in twenty patients with rheumatoid arthritis revealed eosinophilia in seven cases, four of which presented concomitant eosinophilia in the peripheral blood. In five cases (20 per cent.) plasmocytosis was found; a comparison of bone marrow plasmocytosis with protein imbalance revealed by flocculation tests, showed no correlation between them. The leuco-erythroblastic ratio was normal in ten cases, depressed in five, and raised in five. L.E. cells were not found in fifteen patients who were investigated.

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Moelle osseuse dans l'arthrite rhumatoïdale Rapport sur vingt cas, y compris la recherche des cellules L.E.

RÉSUMÉ

L'étude de la moelle osseuse de vingt malades atteints d'arthrite rhumatoïdale révéla une éosinophilie dans sept cas, dont quatre présentèrent une éosinophilie concomitante dans le sang périphérique. Dans cinq cas (20 pour cent) on trouva de la plasmocytose; une comparaison de la plasmocytose de la moelle osseuse avec le déséquilibre protidique, trouvé par la réaction de flocculation, ne montra aucun rapport entre ces deux phénomènes. Le rapport leuco-érythroblastique fut normal dans dix cas, diminué dans cinq et augmenté dans cinq cas. On ne trouva pas de cellules L.E. chez les quinze malades étudiés de ce point de vue.

La médula ósea en la artritis reumatoide Informe sobre veinte casos, con investigación de la presencia de las células L.E.

SUMARIO

El estudio de la médula ósea en veinte enfermos con artritis reumatoide reveló una eosinofilia en siete casos, cuatro de los cuales presentaron una eosinofilia concomitante en la sangre periférica. En cinco casos (20 por ciento) se encontró una plasmocitosis; la comparación de la plasmocitosis medular con el desequilibrio protídico, revelado por la reacción de flocculación, no mostró relación alguna entre éstos. La razón leuco-eritroblástica fue normal en diez casos, disminuida en cinco y aumentada en cinco. No encontráronse células L.E. en los quince enfermos investigados.