THE BLOOD AND BONE MARROW IN PATIENTS WITH CIRRHOSIS OF THE LIVER

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INTRODUCTION

A RELATIONSHIP between hematologic changes and cirrhosis of the liver has been shown experimentally and clinically. Many otherwise excellent studies are not completely satisfactory because the diagnoses of hepatic cirrhosis have not been verified by biopsy. The advantages of biopsy in the diagnosis of hepatic diseases have been emphasized and illustrated by Hofbauer, Evans and Watson, and others.

CASES AND METHODS

This study is based on a review of the literature and analysis of 25 cases with diagnoses of hepatic cirrhosis verified by biopsy of the liver. Complete blood studies with simultaneous aspiration biopsy of sternal marrow obtained within one-half to twenty-four hours before the liver specimen was removed were carried out on all patients. There were 19 males, and 6 females. The age range of the patients was 31 to 71 years; 76 per cent ranged between 43 and 68 years. The case histories, clinical and pathologic diagnoses are given in the appended case reports.

Peripheral blood studies, including determinations of volumetric data and corpuscular constants were carried out according to methods described by Wintrobe. Normal ranges for erythrocyte, leukocyte and platelet counts, mean corpuscular volume, and mean corpuscular hemoglobin referred to are those stated by Wintrobe and found to be in agreement with observations made in our laboratory. Differential counts of cells in the bone marrow were based on enumeration of a minimum of 2,000 cells. Serum protein levels were determined by the method described by Osgood.

The hematologic terminology used by us follows that in current use by Downey and Jones.

Liver specimens were obtained peritoneoscopically. The evaluation of the liver lesion was based chiefly on the degree of fibrosis and atrophy according to the following schedule: Grade I cirrhosis, traces of fibrosis; Grade II cirrhosis, definite fibrosis plus atrophy of hepatic cells; Grade III cirrhosis, fibrous tissue equal to hepatic parenchyma; Grade IV cirrhosis, fibrous tissue exceeds hepatic parenchyma. In addition, other factors such as fatty metamorphosis, lymphocytic infiltration, and atypical bile duct or hepatic cell regeneration were taken into consideration.

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The degree of hemosiderosis was determined by examination of sections stained for iron.

The sternal marrow was obtained and processed by the methods described by two of us (L. B. and A. R. A.). Estimations of megakaryocyte content of marrow samples were based on counts of megakaryocytes in serial sections of aspirated marrow particles. Fifty consecutive fields outlined by the Whipple eyepiece disc were examined at 100 micron intervals. The total numbers of megakaryocytes in the fifty fields were compared with similar counts on material from 10 healthy individuals.

All studies were made shortly after admission of the patients to the hospital, before various therapeutic measures were undertaken.

THE BLOOD PICTURE IN PATIENTS WITH CIRRHOSIS OF THE LIVER

Literature

Anemia. The common occurrence of anemia in patients with cirrhosis of the liver has been mentioned frequently. The presence of anemia is not considered to be dependent on bleeding. It has been stated that the anemia is usually either macrocytic or normocytic; it is not hypochromic unless hemorrhage is a complicating factor. Wintrobe noted that while macrocytic anemia is found in cases of liver disease of various types, and is most common in cirrhosis, the anemia is present only in instances of disease of long duration and wide extent. The reported frequencies of macrocytosis, macrocytic or hyperchromic anemia vary greatly. For example, Benhamou observed macrocytic anemia in only 11 per cent of 35 patients, whereas Rosenberg and Walters found that macrocytosis, almost invariably associated with anemia, was present in 89.7 per cent of 48 patients. Others have reported incidences from 43 to 93 per cent. Some of the inconsistency in the reports may be due to inadequacy of determining cell size without the use of data obtained with the hematocrit. The anemia of cirrhosis may also be normochromic or normocytic. In a group of patients reported by Fellingen and Klima, 31.5 per cent of 40 patients had normochromic anemia. Andersson and Strandell reported normochromic anemia in 48 per cent of 61 patients who did not have bleeding from the gastrointestinal tract. Although bleeding is not an essential factor in the pathogenesis of hyperchromic or normochromic anemia in patients with hepatic cirrhosis, it is usually a prominent cause for microcytic hypochromic anemia. A significant number of patients do not have appreciable anemia. When bleeding is carefully excluded, as has been done in the two reports by Fellingen and Klima, 34 per cent of patients in various stages of the disease are free of anemia. The dictum that anemia in cirrhosis is proportional to the duration and extent of the disease, as is true in experimental animals, does not seem to be substantiated by our review of the literature.

Qualitative Changes in Erythrocytes. With regard to qualitative changes in erythrocytes in the anemic patients, the literature presents conflicting views. According to Whitby and Britton there is a generalized macrocytosis without gross anisocytosis or poikilocytosis. Alessandri et al. described a characteristic isomacrocytosis, while others emphasized the prominence of increased anisocytosis. We have observed increased anisocytosis and poikilocytosis in some of our patients, but these features were neither present nor absent with sufficient regularity to be of value for distinguishing between the macrocytic anemia of cirrhosis and that of other conditions.

Leukocytes. There are few detailed reports of the leukocytic picture in patients with cirrhosis of the liver. Some authors were unable to find characteristic changes in the leukocytes; others have discussed the occurrence of leukopenia, especially in uncomplicated cases. It is generally recognized that some patients exhibit a normal leukocyte count, while others experience leukocytosis after paracentesis, surgical operations, or infections. Masina felt that the appearance of coarse azurophil granules in increased numbers in the majority of monocytes is a pathognomonic sign of cirrhosis of the liver. Saragea and Seicaresco stated that even in leukopenic cases there is a high
percentage of neutrophils. The latter statement implies that lymphopenia may be partly or largely responsible for the leukopenias.

Platelets. Occasional references to the platelet counts include few with particular emphasis on platelets. The counts were subnormal in a varying proportion of cases. Monges, Pointso and Fructus made a special study of platelets in 15 patients. In 12 there was thrombocytopenia of moderate degree. Morlock and Hall found thrombocytopenia in 17.5 per cent of 80 patients. A hemorrhagic tendency was present in many of their patients regardless of the presence or absence of low platelet counts, but it was relatively twice as frequent when thrombocytopenia was associated.

Results of the Present Study

Anemia. Our cases were analyzed for the presence or absence of anemia, and the characteristics of the anemia, when present. Twenty-one patients (84 per cent) had anemia. Sixteen of the anemic patients exhibited macrocytosis, 3 had normocytosis, and 2 had microcytosis. Approximately three-fourths of our patients had macrocytic anemia or macrocytosis on their initial studies. In 84 per cent of the cases with macrocytic anemia the mean corpuscular hemoglobin values were normal or elevated. Microcytic hypochromic anemia was associated with chronic and acute blood loss from the gastrointestinal tract in 1 of 2 patients with this type of anemia.

<table>
<thead>
<tr>
<th>Grade of cirrhosis</th>
<th>Number of cases</th>
<th>Range, RBC (per cu. mm.)</th>
<th>Average, RBC (per cu. mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>2,650,000-4,020,000</td>
<td>3,530,000</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>2,750,000-5,000,000</td>
<td>4,068,000</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2,790,000-3,870,000</td>
<td>3,393,000</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>2,590,000-4,950,000</td>
<td>3,700,600</td>
</tr>
</tbody>
</table>

There was no correlation between the severity of the anemia and the grade of cirrhosis (table 1).

Leukocytes. The total leukocyte counts ranged between 1,960 and 47,200 per cubic millimeter. Five patients had counts below 5,000, 10 had counts within the normal range (5,000 to 10,000), and 10 had leukocytosis. We did not observe a relationship between the total leukocyte counts and the presence or absence of ascites or bleeding, since leukopenia, leukocytosis and normal counts were present in both these categories. However, leukocytosis occurred with greater frequency among patients with fever or infection, or both. In other words, the presence of cirrhosis did not inhibit the leukocytic response to infection or toxemia. The severity of the liver lesion was not a factor affecting the total leukocyte counts.

In sixteen of the 25 patients (64 per cent) there was absolute lymphopenia (less than 1,500 lymphocytes per cubic millimeter). This was present regardless of whether the total counts were depressed, normal, or elevated (table 2). In fact, several of the lowest absolute counts of lymphocytes occurred in patients with leukocytosis. With the exception of 2 cases, one of which was that of a patient with both cirrhosis and chronic lymphatic leukemia, the absolute counts of lymphocytes were at low normal or lower than normal levels. Absolute lymphopenia was the most constant significant alteration in the leukocytic picture in patients with hepatic cirrhosis.
BLOOD AND BONE MARROW IN CIRRHOSIS

A special study was made of the peripheral blood smears in an effort to discover morphologic changes in the leukocytes of our patients. Except for occasional instances in which toxic changes of neutrophils and monocytes were seen, there were no significant alterations of the morphology of the cells.

Table 2.—Total leukocyte counts, absolute counts of lymphocytes, and types of leukocytic picture in 25 patients with cirrhosis of the liver

<table>
<thead>
<tr>
<th>Case</th>
<th>Total leukocytes (per cu. mm.)</th>
<th>Lymphocytes (per cu. mm.)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5,500</td>
<td>1,710</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>2</td>
<td>5,300</td>
<td>1,060</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>3</td>
<td>11,000</td>
<td>880</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>4</td>
<td>11,500</td>
<td>2,500</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>5</td>
<td>6,650</td>
<td>1,930</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>6</td>
<td>6,500</td>
<td>910</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>7</td>
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<td>1,360</td>
<td>Neutrophilia</td>
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<td>Lymphopenia</td>
</tr>
<tr>
<td>9</td>
<td>3,350</td>
<td>670</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>10</td>
<td>4,950</td>
<td>540</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>11</td>
<td>10,450</td>
<td>1,150</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>12</td>
<td>11,350</td>
<td>680</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>13</td>
<td>7,550</td>
<td>1,660</td>
<td>Neutrophilia</td>
</tr>
<tr>
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<td>23,300</td>
<td>930</td>
<td>Lymphopenia</td>
</tr>
<tr>
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<td>Lymphopenia</td>
</tr>
<tr>
<td>16</td>
<td>10,500</td>
<td>1,360</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>17</td>
<td>24,500</td>
<td>980</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>18</td>
<td>10,800</td>
<td>2,710</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>19</td>
<td>8,000</td>
<td>3,310</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>20</td>
<td>21,050</td>
<td>3,380</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>21</td>
<td>13,950</td>
<td>1,120</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>22</td>
<td>47,100</td>
<td>9,920</td>
<td>Lymphocytosis*</td>
</tr>
<tr>
<td>23</td>
<td>3,800</td>
<td>990</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>24</td>
<td>5,900</td>
<td>1,480</td>
<td>Lymphopenia</td>
</tr>
<tr>
<td>25</td>
<td>3,120</td>
<td>930</td>
<td>Neutropenia;</td>
</tr>
</tbody>
</table>

* Case 11 complicated by chronic lymphatic leukemia.

Table 3.—The platelet counts in 25 patients with cirrhosis of the liver

<table>
<thead>
<tr>
<th>Platelets (per cu. mm.)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50,000</td>
<td>2</td>
</tr>
<tr>
<td>50,000 to 100,000</td>
<td>3</td>
</tr>
<tr>
<td>100,000 to 150,000</td>
<td>8</td>
</tr>
<tr>
<td>150,000 to 300,000</td>
<td>11</td>
</tr>
<tr>
<td>300,000 to 400,000</td>
<td>1</td>
</tr>
</tbody>
</table>

Platelets. The platelet counts observed in our patients are shown in table 3. The counts were determined indirectly by comparing the number of erythrocytes with that of the platelets in stained blood smears. In our hands, the method yields
normal values ranging from 150,000 to 350,000 per cubic millimeter. The counts were in the low normal range or significantly lowered in 13 of 25 patients.

Discussion of the Peripheral Blood Findings

We may summarize the available information regarding the peripheral blood findings in patients with cirrhosis of the liver as follows:

1. Anemia, usually of macrocytic or normocytic type, is of common occurrence.
2. In the majority of instances of macrocytosis, the mean corpuscular hemoglobin values are normal or elevated.
3. Bleeding is not an essential factor in the production of macrocytic or normocytic anemia in cirrhosis.
4. Microcytic hypochromic anemia is suggestive of chronic bleeding when it occurs in patients with cirrhosis of the liver.
5. The severity of anemia is not proportional to the duration or extent of the liver lesion, although this appears to be true of experimental cirrhosis of the liver in rats.
6. There are no constant significant qualitative changes in the erythrocytes or leukocytes.
7. In uncomplicated cases, leukopenia is likely, but the presence of cirrhosis does not prevent the leukocytic response to infection or other complications.
8. Lymphopenia, regardless of the total leukocyte count, is the most constant significant change in the leukocytic picture in patients with cirrhosis. This point seems to have been overlooked. In Masina's data on 20 patients with the disease the total leukocyte counts ranged from 3,200 to 8,360 per cubic millimeter. The absolute counts of lymphocytes were less than 1,500 in 17 of his cases (85 per cent). Russo supplied data on 14 patients with total leukocyte counts from 3,000 to 16,000. In ten cases (71 per cent) the lymphocytes were below 1,500 per cubic millimeter and, in an additional case, the lymphocyte count was 1,564.
9. The platelet count is in the low normal range or significantly lowered in the majority of patients. Those with severe liver damage had lower counts, on the average, than was the case for patients with slight liver damage in our material. Hemorrhagic phenomena are approximately twice as frequent in patients with thrombocytopenia as compared with patients having normal platelet levels.

The pathogenesis of anemia in cirrhosis of the liver is obscure. While it is clear that microcytic hypochromic anemia can be attributed to chronic blood loss in nearly all instances, our material indicates that normocytic or macrocytic anemias are not dependent on bleeding, as has also been shown by others. It has been shown that some patients with cirrhosis of the liver have greatly increased plasma volumes. The importance of hemodilution as a factor resulting in depressed erythrocyte levels needs further evaluation.

Various theories concerning the cause of macrocytosis have been offered. Among them are: (1) Defective storage or metabolism of the anti-pernicious anemia principle (Wintrobe, Wintrobe and Shumacker); (2) Increased incidence of reticulocytes (which are larger than mature cells) (Rosenberg and Walters); (3) Swelling of erythrocytes as a result of direct action of retained bile derivatives in
the peripheral blood (Meulengracht7). None of these theories is satisfactory for the following reasons: (1) The hematopoietic factor has been demonstrated in the livers of patients dying of extensive hepatic disease;77 (2) Marked macrocytosis may be present without marked reticulocytosis (see our cases 5, 6 and 12); (3) The degree of icterus is not proportional to the degree of macrocytosis and, as Boros16 pointed out, not only is the cell volume increased but also the hemoglobin content and color index is elevated, which would not be the case if a plasma factor had caused simple swelling of the erythrocytes.

It cannot be denied, however, that increased hemolysis may play a role. This view is based on the observations of Watson99 who cited 8 patients with macrocytic hemolytic anemia and cirrhosis of the liver, and those of others1 who have utilized quantitative determinations of urobilinogen excretion in addition to complete blood studies.

It is of interest that both lymphopenia and hyperglobulinemia occurred in the majority of our patients. This combination recalls the work of Dougherty and White 22 who have demonstrated the relationship between pituitary-adrenal cortical secretion on the one hand, and lymphopenia and hyperglobulinemia on the other. It has also been shown that many kinds of stimuli can cause the adrenal cortical activation which results in this combination of phenomena. Among them are administration of large doses of estrogens. In view of the work of Glass, Edmonson and Soll22 which reveals increased excretion of free estrogens by patients with cirrhosis of the liver as a result of failure of the damaged liver to inactivate estrogens, the possibility exists that the lymphopenia and hyperglobulinemia so often seen in patients with cirrhosis, in part at least, have their origin in adrenal cortical activation.

**The Bone Marrow Picture in Patients with Cirrhosis of the Liver**

*Literature*

Reports of bone marrow can be divided into two groups: those based on autopsy material, and those based on aspiration of marrow from the living patient.

**Autopsy Material.** In most instances the marrow was studied by means of gross inspection, or by examination of sections prepared from various bones.12, 14, 22, 26-28, 30, 62, 72, 73, 80, 86, 97 The obvious advantage of autopsy material is that the diagnoses of hepatic cirrhosis can be accepted as verified. On the other hand, sectioned material obtained after death is less suitable for differentiation of marrow cells than is the case for marrow in the form of freshly prepared imprints or smears.41 Autolytic changes which develop rapidly after death preclude accurate identification of many of the cells of the marrow.70 However, the distribution of cellular marrow can be observed and, in fresh tissue, it is possible to distinguish the main varieties of leukocytoid and erythroid cells.

Various authors have described extension of hematopoietic marrow into the shafts of the femurs,14, 22, 26-28, 72. 89 transformation of yellow to red marrow in the long bones,12, 30, 72, 80, 97 and erythroid or normoblastic hyperplasia.25, 26, 72, 80, 89 In general, it has been stated that erythropoietic hyperplasia occurs in both the normal sites of hematopoiesis and in the sites representing replacement of yellow marrow by hemopoietically active marrow. There are, however, a few reports of "lymphocytic," "myelocytic," "myeloblastic" or fatty marrow.14, 62, 72, 85 Rossier, 75 who described an occasional "myeloblastic" reaction in addition to the usual erythropoietic reaction in his autopsy series, called attention to the fact that autopsy material is not satisfactory for identification of cells and that it was probable that the so-called myeloblasts represented erythropoietic elements. Fellinger and Klima77
studied a group of 48 patients with Laennec's cirrhosis. In each case occult and gross bleeding from the gastrointestinal tract had been carefully excluded. In the autopsied cases they found red marrow in the shafts of the femurs, even in the absence of bleeding.

**Biopsy Material.** The advantages of aspiration biopsy of the sternum are that the bone marrow can be examined during life before autolytic changes have occurred, the time of aspiration can be selected to coincide with the liver biopsy, the identification of cells can be made with relative ease and, in addition, that material for sectioning is obtainable for use in estimating the cellularity, fat content, and frequency of certain irregularly distributed cell types such as megakaryocytes.46, 47 In nearly all instances, investigations utilizing biopsy material have been based on the technic of sternal aspiration. The experimental work of Stasney and Higgins82 was based on fresh autopsy material from rats. Since these authors prepared dry films in addition to sections of bone marrow, their observations can be compared with those of others using similar preparations from patients.

Schulten73 was of the opinion that there are marrow changes in all cases of hepatic cirrhosis. Although Isaacs44 described both hypocellular and hypercellular marrows in 8 patients, the preponderance of reports implies a regular appearance of cellular or hypercellular bone marrow during life.1, 2, 3, 4, 5, 6, 7, 8, 9

**Fat Content of Marrow.** The relative fat content of aspirated marrow in cirrhosis has not been studied sufficiently. Klima47 stated that although the cellularity of the sternal marrow is markedly increased, the fat content may be considerable. In one patient in whom two simultaneous sternal aspirations were done, Pizzolato and Stasney66 found relative fat volumes of 1 and 3 per cent.

**Cell Content of Marrow.** The average myeloid-erythroid volume (ME volume), that is, the average relative volume occupied by nucleated cells in aspirated centrifuged sternal marrow, in 20 patients with hepatic cirrhosis was found to be 13 per cent by Limarzi et al.45 This was considered about twice the normal value. In an additional case reported by others46 the ME volumes were 5 and 10 per cent in material from two different sites in the sternum.

**Myeloid-erythroid Ratios.** A number of reports1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13 include data concerning the myeloid-erythroid ratios (ME ratios) which represent the relative frequencies of myeloid leukocytes and erythroblasts* in the aspirated specimens of marrow. In some cases we have calculated the ratios from the authors' data. The combined statistics from a total of 39 cases, yield ME ratios ranging from less than 1:1 to 6:1. The ME ratio was 1:1 or less in 14 cases, 2:1 to 3:1 in 23 cases, and over 4:1 in 2 cases. Benhamou and Nouchi1 mentioned a reversal of the ME ratio so that erythroblasts predominated, as was also observed by Limarzi and coworkers.51 A similar reversal of the ME ratio, indicating relative increase of erythropoiesis, has been noted in experimental cirrhosis of the liver in rats.80 The opinion that erythroblastic hyperplasia occurs frequently in patients with hepatic cirrhosis is upheld by additional observations on biopsy material.1, 2, 3, 4, 5, 6, 7, 10, 11, 12, 13 The presence of erythroblastic hyperplasia is not dependent on bleeding.73

**Differential Distribution of Erythroblasts.** A few studies have been concerned with the differential distribution of erythroblasts. It is difficult to interpret such material because of differences in terminology and lack of precise definition of the terms used. Tischendorf's material revealed erythroblastic hyperplasia with left shift of erythroblasts in all of his 11 patients.44 Predominance of basophilic forms was mentioned by several authors,20, 21, 22 According to Limarzi and co-workers the erythroblastic hyperplasia which occurred in their patients was due almost entirely to increase in the number of basophilic normoblasts, the pronormoblasts being significantly increased only rarely. Macronormoblasts were noted by Klima. Isaacs described the marrow in uncomplicated cirrhosis as resembling that of pernicious anemia, with megaloblasts present, but we have found no resemblance between the marrows of patients with pernicious anemia in relapse and cirrhosis of the liver. Our definition of the megaloblast has been given in detail elsewhere.51 Specific denials of the presence of megaloblasts in the bone marrows of patients with cirrhosis of the liver has been made by Klima,47 Limarzi et al.,45 Rossier,79 Benhamou,50 Loeper and Vignaliou,51 Isaacs and Wilkinson,61 and Fiessinger, Dupuy and Larur.29

**Granulocytes.** Granulocytic hypoplasia has been reported in patients with cirrhosis,1, 2, 3, 4, 5 as well as in rats with experimentally induced cirrhosis.92 When complications such as infection or carcinomatosis are present, or following laparotomy, the myelogram may show leukopoietic hyperplasia.65, 92

* Our term 'erythroblast' denotes any nucleated red cell, regardless of the state of maturation of either nucleus or cytoplasm.
Limarti et al. observed an average of 2.6.3 percent neutrophil myelocytes in the marrows of 20 patients. This represents an increase, as compared with our observations on normal persons. Eosinophil leukocytes are sometimes increased in number, even in the absence of eosinophilia in the peripheral blood. The majority of reports do not mention alterations in the differential distributions of myeloid leukocytes.

Lymphocytes. The earlier studies of postmortem material yielded a few reports of increases of lymphocytes. However, it is unlikely that all the cells designated as small and large lymphocytes could be differentiated from other elements of lymphoid character because sectioned material was used. Rossier described a decrease in the frequency of lymphoid nodules.

Plasma Cells. The frequency of plasma cells appears to be quite variable, some authors finding none and others noting increases. Leitner stated that in cirrhosis of the liver there is an increase of plasma cells, whereas the reverse is true of epidemic hepatitis.

Reticulum Cells. The evidence for or against reticulum cell hyperplasia is inconclusive. The usual aspiration technic is not satisfactory for determining the reticulum cell content of marrow, as these cells tend to be arranged in syncitial masses which are difficult to break up to form free cells in the aspirated fluid. Even so, Rohr and others found increased numbers of reticulum cells. Increased phagocytosis of pigment, usually hemosiderin, has been noted in many cases.

Qualitative Changes in Leukocytes. Among the reported morphologic changes in the leukocytes are increased anisocytosis of granular elements, and vacuolization of monocytes and granulopoietic cells. It has been pointed out that the marrow of cirrhosis shows none of the peculiar disturbances of myeloid tissue seen in pernicious anemia, but our material, as will be shown below, reveals that dysplasia of neutrophils, superficially resembling that seen in pernicious anemia, may occur.

Megakaryocytes. There are few recorded observations on megakaryocytogenesis in cirrhosis of the liver, and the various reports are conflicting. This may be expected as the methods for estimating megakaryocyte content of aspirated marrow now in use are generally unsatisfactory. Fiessinger, Dupuy and Laur found no megakaryocytes in the smears of sternal marrow from 10 patients, but Limarti et al. reported an increased number in all of their 20 patients. Others found normal or increased numbers and sometimes an increase of immature forms.

Results of the Present Study

There is no evidence to show variations in the bone marrow picture which could be ascribed to differences in age or sex of adult patients, type, duration or severity of the liver lesion, or the type of anemia present, except that erythropoiesis may be slightly more active in patients with microcytic hypochromic anemia.

Fat and Cell Content of Marrow and ME Ratios. Data concerning the relative volumes of fat and nucleated cells, as well as the differential distributions and ME ratios in our series of 25 patients are presented in table 4. The table also includes data from our control cases (19 normal individuals). The fat volumes showed a wide range, from 1 to 8 per cent, and a mean value of 1.8 per cent. The ME volumes ranged from 3 to 26.5 per cent, with a mean value of 13.9 per cent. Others have considered the sternal marrows of patients with hepatic cirrhosis to be about twice as cellular as normal because of the finding of a mean ME volume of 13 per cent. Although this value is in close agreement with our findings in cirrhosis, our normal controls also yielded a mean ME volume of approximately 13 per cent. It has been shown, however, that the volumetric method provides only a crude estimate of relative fat and cell content of aspirated marrow and that it is not reliable for detecting small variations. For these reasons, we made estimates of fat and cell content based on sectioned material, using the methods described by Berman and Axelrod.
The results of this analysis are shown in table 5. There does not appear to be any large difference between the average relative fat or cell content of sternal marrow from cirrhotic and normal individuals, but the marrows of normal persons

<table>
<thead>
<tr>
<th>Case</th>
<th>Fat %</th>
<th>ME volume</th>
<th>ME ratio</th>
<th>Erythroblasts</th>
<th>Basophilic normoblasts</th>
<th>Promegakaryocytes</th>
<th>Myeloblasts and monoblasts</th>
<th>Monocytoblasts</th>
<th>Myelocytes</th>
<th>Band form metamyelocytes</th>
<th>Neutrophil metamyelocytes</th>
<th>Neutrophil myelocytes</th>
<th>Band form metamyelocytes</th>
<th>Polymorphonuclear leucocytes</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Monocytes</th>
<th>Lymphocytes</th>
<th>Plasma cells</th>
<th>Reticuloendothelial cells</th>
<th>Macrophages</th>
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<tbody>
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<td>13.1</td>
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<td>3:10</td>
<td>86:1</td>
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<td>9</td>
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*Case 12 complicated by chronic lymphatic leukemia.

are more likely to have fat contents over 30 per cent than is the case for patients with cirrhosis. The corollary is that the sternal marrows of patients with cirrhosis are likely to be more cellular than normal (table 6).

We found no relationship between the degree of cellularity of the marrow and the severity of the anemia. Hyperplasia of the marrow in cirrhosis occurred in spite
of absence of severe anemia. Hypocellularity is an unusual finding in the marrow of patients with this disease. In all except one case (case 25) the marrow was either normal or increased in cellularity, in spite of absence of signs of accelerated erythropoiesis in the peripheral blood. The conclusion made by Limarzi and co-authors regarding the common occurrence of hypercellularity of the sternal marrow is substantiated by our findings in sectioned material.

Analysis of patients with cirrhosis and of normal individuals as separate groups, as we have done above, may mask variations within the groups. Accordingly, we studied our data in an effort to detect possible relationships between the following groups of factors: fat content of bone marrow and fat content of the liver; ME volume and degree of anemia or severity of the liver lesion; ME ratio and degree of anemia, severity of the liver lesion or presence or absence of hemorrhagic phenomena.

The observation by Moosnick, Schleicher and Peterson that choline therapy caused the fatty marrow and liver in a patient with refractory pernicious anemia to revert toward normal suggested a relationship between the fat content of these two organs. In our cirrhosis material there does not appear to be any quantitative relationship.

Low ME ratios were slightly, but not significantly, more frequent among patients with severe liver lesions. In general, patients who had experienced recent hemorrhages had lower ME ratios than the others. In one instance (case 15) a very low and reversed ratio of 0.4:1 occurred in a patient who had been bleeding from esophageal varices. Hence, recent blood loss increases the likelihood of a low ME ratio, which is expressive of receptively increased erythropoiesis, as would be expected, but hemorrhagic phenomena are not the sole contributing factors causing increased erythropoiesis in cirrhosis, as it was present also in patients without history or

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evidence of bleeding. We agree with Fellinger and Klima that increased erythropoiesis in cirrhosis may be independent of bleeding.

**Differential Distribution of Erythroblasts.** The differential distribution of erythroblasts in the marrow has been considered to be of diagnostic importance in hepatic cirrhosis. A review of the literature does not provide a clear picture of the type of differential pattern which may be expected. Morrison and Samwick proposed an "erythroblast-normoblast ratio" which indicates the relationship between the number of "early erythroblasts to the late erythroblasts (normoblasts)." According to them a high erythroblast-normoblast ratio is indicative of disturbed liver function, and is suggestive of liver disease even before the clinical manifestations are apparent. We were not able to confirm this view as regards cirrhosis of the liver. The distributions of erythroblasts in patients with cirrhosis were within the normal range in our material (table 7).

**Qualitative Changes in Erythroblasts.** Although no striking changes in the differential distributions of erythroblasts occurred, certain qualitative changes of diagnostic significance were found. One patient with microcytic hypochromic anemia (case 2) exhibited a micronormoblastic marrow. The majority of the erythroblasts were small, and in the polychromatophilic stages the nuclei were generally pyknotic. The cytoplasm was poorly hemoglobinized and the cell contours were ragged. This is the type of erythroblasts we expect to find in instances of chronic iron deficiency anemia, as has also been stated by Scott. In the remaining 24 patients, there were 11 (46 per cent) without evidence of qualitative change in the normoblasts, and 13 (54 per cent) with definite abnormalities.

The changes included increase of the diameters of normoblasts in all developmental stages, increase of nuclear diameters, and a disturbance of the nuclear-cytoplasmic ratios. The mean diameter of the large normoblasts was increased but the nuclear pattern, in most cases, was essentially that of normoblasts. The nuclear-cytoplasmic ratio was altered in favor of a relative increase of cytoplasm. The increase of cytoplasm was not as marked as seen in megaloblasts, and the large cells are of the type designated as macronormoblasts. In a few patients, the nuclear structure in the early basophilic stages resembled that of reticulum cells. The reticular characteristics of the nuclei of these macronormoblasts persist throughout all stages of development. Without careful inspection it is easy to confuse such cells with megaloblasts of pernicious anemia, especially in the proerythroblast.
stages. The differences between such abnormal large cells and megaloblasts of pernicious anemia have been emphasized by Jones and Downey. The frequency distributions and mean diameters of the polychromatophilic normoblasts in patients with cirrhosis and macronormoblastic marrows differ significantly from normal (fig. 1).

Theoretically, patients with cirrhosis of the liver might be expected to have megaloblastic marrow because of impaired storage of the antipernicious anemia principle, but no examples of such a change in erythropoiesis were seen in our series of 25 patients. Others have also stated that in the presence of cirrhosis of the liver the marrow is macronormoblastic in type. Furthermore, the macrocytic anemias of cirrhosis of the liver do not respond to folic acid therapy in the manner of the macrocytic-megaloblastic anemias of the pernicious type.

We noted correlation between the presence of macrocytosis in the blood and macronormoblastic erythropoiesis in the marrow. Twelve of 13 patients (92 per cent) with macrocytic anemia had macronormoblastic marrow, whereas 5 of 11 patients (22 per cent) with normoblastic marrow had normocytosis in the peripheral blood, the others having only slight macrocytosis. The change to macrocytosis in the blood originates in dysplasia in the bone marrow, and is not related to factors acting on the red cells after they have entered the circulation.

Granulocytes and Monocytes. The differential distributions of the granulopoietic and monocytic cells showed remarkable constancy (table 4). Except in 2 patients (cases 12 and 17), there were no significant deviations from normal. One patient had an elevated percentage of neutrophil promyelocytes (21 per cent). This individual had neutrophilic leukocytosis and evidence of chronic cholecystitis at the time of the marrow aspiration. In the second patient the neutrophil promyelocytes comprised 25 per cent of the myeloid leukocytes. This patient had a marked neutrophilic leukocytosis, fever, and residual drainage following a rib resection. eleven days previously, for empyema thoracis. The increases in promyelocytes were
compatible with the reactive change in myeloid leukopoiesis seen in some infections. Infection, as also observed by others, may provoke reactive changes in leukopoiesis in patients with cirrhosis, but the differential distributions of myeloid leukocytes appear approximately normal in most cases, regardless of the presence of complications such as jaundice, fever, ascites or bleeding, all of which were present to varying extents among our patients. Others have pointed out the constancy of the marrow pattern in cirrhosis. Fiessinger, Dupuy and Laur remarked that the myelogram was the same regardless of the appearance of icterus, oliguria, purpura, or the agonal state.

**Lymphocytes.** In spite of the fairly regular appearance of lymphopenia in the peripheral blood, the marrows contained normal incidences of lymphocytes, except in one patient with 45 per cent lymphocytes (case 22) who had chronic lymphatic leukemia in addition to cirrhosis of the liver.

**Plasma Cells.** The frequency of plasma cells is a point of special interest because of conflicting views in various reports. In our control material plasma cells comprise up to 2 per cent of the nucleated cells, exclusive of erythroblasts. A percentage of 4 per cent or more represents a significant increase. Six, or 30 per cent, of our patients had 4 per cent or more plasma cells in the sternal marrow smears. We are loth to accept Leitner’s view that the plasma cell content of marrow may be of importance in the differential diagnosis of cirrhosis and epidemic hepatitis.

**Reticulum Cells.** We do not regard the percentages of reticulum cells in smears of aspirated marrow as reliable indices of the reticulum cell content of sternal marrow. Such cells are best observed in imprints of marrow particles (Schleicher), as they tend to remain fixed in the marrow tissue. There was no regular increase or decrease in the incidence of reticulum cells in our material, as observed either in the smears made from the first drop of aspirated marrow or from the concentrates of marrow, or from the imprints of marrow particles.

**Qualitative Changes in Leukocytes and Reticulum Cells.** We were not able to confirm the previously reported prominence of vacuolization of granulocytes and monocytes in the marrows of patients with hepatic cirrhosis; such changes were of irregular appearance and never very marked. A few marrows revealed morphologic abnormalities of granulopoiesis. These included the appearance of giant band form neutrophils and giant polymorphonuclear neutrophils with hypersegmented nuclei. Such cells have a superficial resemblance to the large cells seen in pernicious anemia. However, there is no marked change in the type of granulation, nor is the chromatin pattern of the nuclei as fine as seen in the typical dysplastic cells associated with megaloblastic marrows. The significance of such changes is obscure. We have observed them occasionally in cases of iron deficiency anemia, in nonmegaloblastic nutritional macrocytic anemias not responsive to liver extract therapy, leukemias, and carcinomatosis. The peculiar giant neutrophils were seen in three cases in our series (cases 12, 14, 24), and they were not numerous. We have mentioned them only because of their possible confusion with the characteristic macropolycytes, (Cooke) or “pernicious-anemia neutrophils” (Jones) of megaloblastic anemias.

In the few cases in which reticulum cells were relatively numerous (over 4 per
The cells were of histiocytic rather than hematopoietic type. The nuclei were those of undifferentiated reticulum cells, and the cytoplasm was faintly acidophilic, abundant, and non-homogeneous, usually with some vacuolization and azurophil granulation, and often containing phagocytosed debris. We found no evidence of fat or lipoid storage, but in 4 cases in which the liver contained relatively large amounts of iron-containing pigment, and especially in one case of pigmentary cirrhosis (case 16), the free reticulum cells contained large amounts of iron-containing pigment. The presence of macrophages with phagocytosed hemosiderin would therefore appear to imply that the liver also contains pigment in relatively large amounts.

**Megakaryocytes.** We have experienced difficulty in estimating the megakaryocyte content of aspirated marrow. The inadequacy of methods in use at present have been noted by various authors. In our hands, the estimation of megakaryocytes based on their number in smears, as advocated by Limarzi et al., has not yielded consistent results. Krumbhaar and Custer have shown that reliable estimates can be based on enumeration of these cells in sectioned material. This is in accord with our experience. We have described our procedure for estimating

<table>
<thead>
<tr>
<th>Normal</th>
<th>10</th>
<th>14-60</th>
<th>35.7 ± 4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>18</td>
<td>13-84</td>
<td>43.4 ± 5.8</td>
</tr>
</tbody>
</table>

* Standard error of mean.

megakaryocyte content in sectioned particles of aspirated marrow above, under the heading, "Cases and Methods." The results in our series of patients are shown in table 8.

In the cirrhosis series, the megakaryocyte counts were slightly higher, on the average, than in the control series, but the difference was not statistically significant. The values obtained in cirrhosis were within normal limits or higher than normal. The point of chief interest is that, in spite of the common occurrence of peripheral thrombocytopenia, the megakaryocyte content of the marrow is normal or elevated in patients with cirrhosis of the liver. In this respect the findings are similar to those observed in instances of thrombocytopenia associated with hypersplenism. There were no important morphologic changes in the megakaryocytes nor changes in their differential distributions.

**Discussion of the Bone Marrow Findings**

The evidence from the literature and the information gained from the present study of the marrow in patients with cirrhosis of the liver may be summarized as follows:

1. Extension of red or functioning bone marrow into the shafts of the long bones is of regular occurrence in adults with cirrhosis of the liver.

2. The average relative fat content of the sternal marrow is not significantly
different from that of normal persons, but instances of high relative fat content are less likely to occur in patients with cirrhosis than is the case for normal individuals.

3. The cellularity of the bone marrow in both the normal sites of hematopoiesis and in the sites representing extension of active marrow is normal or increased in most instances.

4. Although hemorrhage tends to provoke marked relative increase of erythropoiesis, erythroblastic hyperplasia may be independent of bleeding in cirrhosis of the liver.

5. The differential distribution of erythroblasts of patients with cirrhosis is not significantly changed, but there is a high degree of correlation between macrocytosis in the peripheral blood and the appearance of macronormoblastic erythropoiesis in the bone marrow. Megaloblastic erythropoiesis is rare, if present at all, in patients with hepatic cirrhosis uncomplicated by pernicious anemia.

6. There are no significant changes in differential distributions of cells of the granulocytic, monocytic or lymphocytic series, but infection may result in a relative increase of immature granulocytes, especially promyelocytes. In occasional patients there is a disturbance of granulopoiesis indicated by the appearance of atypical giant neutrophils which are not identical with the characteristic macrocytes of "pernicious-anemia neutrophils" associated with megaloblastic marrows.

7. There are no constant quantitative changes in plasma cells or reticulum cells, although the finding of numerous reticulum cells containing hemosiderin implies hemosiderosis of the liver in patients with cirrhosis.

8. Megakaryocytes are of normal or increased infrequency in the sternal marrows of patients with hepatic cirrhosis, but no qualitative changes of importance occur.

It is clear that in patients with hepatic cirrhosis the marrow is of normal or increased cellularity, and that hypocellular marrows are unusual in spite of peripheral anemia which is often characterized by lack of signs of accelerated regeneration of red cells. Even in cases in which the sternal marrow is of normal cellularity, the fat in the shafts of the long bones is replaced by hematopoietically active tissue. With respect to cellularity, the most important change is extension of the marrow organ, since this appears to be more constant than hyperplasia at a given site, such as the sternum. In other words, the total active marrow in the body is increased in amount in cirrhosis of the liver.

The fact that normal or relatively increased erythropoiesis is the rule, not only in marrow which is normally cellular, but in marrow which is usually fatty, is of interest because it occurs in spite of careful exclusion of blood loss. It has been suggested that the explanation may be that the patients with cirrhosis suffer a partial deficiency of the antipernicious anemia principle due to deficiency of storage or metabolism in the diseased liver, but the considerations which refute this hypothesis as an explanation for the peripheral macrocytosis apply to the problem of the marrow changes.

Since it has been shown that patients with cirrhosis of the liver may excrete abnormally large quantities of urobilinogen,\textsuperscript{1-8} we are inclined to believe that
the factor of excessive destruction of erythrocytes may play a role. The erythro-
blastic hyperplasia and the appearance of macro- and reticulonormoblasts in the
marrow can be accounted for on the basis of hemolytic anemia, in which condition
such types of erythroblasts are known to appear.\textsuperscript{7, 8} The evaluation of the relative
importance of hemolysis in the pathogenesis of the anemia is a problem worthy
of further study.

The mechanism of hemolysis, if and when it occurs, must be regarded in the
light of the concept of hypersplenism.\textsuperscript{19, 20, 21} There are a number of peripheral
blood and marrow changes which are suggestive of hypersplenism. The peripheral
cytopenias (anemia and thrombocytopenia) occur in relation to normal or in-
creased formation of erythroblasts and megakaryocytes in the marrow. These
paradoxic phenomena are typical of hypersplenism which, in the case of cirrhosis,
should be considered as manifestations of secondary hypersplenism. The well
known involvement of the spleen in patients with hepatic cirrhosis is additional
evidence in favor of this view.

\textit{Diagnostic Significance of Hematologic Studies in Cirrhosis of the Liver}

Our hematologic studies, while controlled by observations on normal persons,
have not been extended to other diseases which may be characterized by findings
similar to those we have presented. Therefore we cannot consider any of the
changes in blood and marrow we have described as pathognomonic of cirrhosis,
even though they appear to be characteristic of the disease. This was emphasized
by Tischendorf\textsuperscript{84} who studied a group of patients with cirrhosis of the liver and
other diseases of the liver, gall bladder and biliary tract. He felt that the sternal
myelogram was not of value in the differential diagnosis of liver and gall bladder
diseases, as some of the findings in these conditions are similar. On the other hand,
it is not justifiable to consider complete blood and bone marrow studies as value-
less and without diagnostic importance in cirrhosis of the liver.

For example, in patients known to have the disease, the appearance of micro-
cytic hypochromic anemia or micronormoblastic marrow is indicative of chronic
blood loss. The presence of hypocellular marrow in patients with macrocytic
anemia suspected of having cirrhosis is unusual, and should point to other or
additional factors in the clinical picture. Furthermore, although normocytic or
macrocytic anemias are compatible with the diagnosis of cirrhosis, macrocytic
hypochromic anemia, as determined by the mean corpuscular volume and mean
corpuscular hemoglobin values, is not typical and should lead to further study of
the patient. The marrow examination may be of crucial importance in distin-
guishing between pernicious or other megaloblastic anemias and the macro-
cytic anemia of cirrhosis, as the peripheral blood study does not provide evidence
of the type of erythropoiesis in the marrow.\textsuperscript{11}

Some patients with cirrhosis of the liver do not present unequivocal clinical
signs of their disease. In such cases, we have found that the combined study of the
peripheral blood and sternal bone marrow may lead the clinician toward serious
consideration of cirrhosis of the liver. The combination of macrocytosis or macro-
cytic anemia without hypochromasia, plus lymphopenia and thrombocytopenia,
together with the presence of normal or increased marrow cellularity, and normal or increased erythrocytogenesis and megakaryocytogenesis, constitutes a group of hematological findings which point strongly to cirrhosis of the liver. Furthermore, when anemia is absent and the other findings are present the probability of cirrhosis is even greater. An example of the latter type of case is given in the following brief case report.

Case 25. A 53 year old female was admitted for repair of a large abdominal incisional hernia. Systemic review was noncontributory. There was no history of alcoholism. Appetite and food intake were adequate. The preoperative blood protein and prothrombin levels were within normal limits. Because the liver and spleen were palpable the patient was referred for hematological survey. Serum bilirubin and urinary urobilinogen concentrations were normal. The bromsulphthalein test gave normal results. There was no anemia and the erythrocytes were normocytic and normochromic, but lymphopenia (930 per cubic millimeter) and thrombocytopenia (57,000 per cubic millimeter) were present. The sternal marrow was hypercellular, with a relative increase of erythrocytogenesis and a normal megakaryocyte count. The hematologic findings indicated a diagnosis of cirrhosis of the liver. A biopsy specimen obtained from the liver at the time of repair of the hernia revealed grade 2 cirrhosis.

We have found the combined blood and sternal marrow study useful in establishing the diagnosis of cirrhosis of the liver in patients in whom other diseases have obscured its manifestations, or in whom historical evidence was absent so that the clinical diagnosis was difficult to make.

Summary

The peripheral blood and bone marrow findings in patients with cirrhosis of the liver have been analyzed on the basis of a review of the literature and the authors' study of 25 patients with diagnoses verified by biopsy of the liver.

The principal blood findings are macrocytic or normocytic anemia with normal or elevated mean corpuscular hemoglobin values, lymphopenia and thrombocytopenia in the majority of cases.

Anemia may be independent of bleeding, and the severity of anemia or macrocytosis does not appear to be related to the severity of the liver lesion.

The consistent change in the bone marrow is extension of the marrow organ so that active hematopoiesis is found in the shafts of the long bones.

Regardless of the presence or absence of bleeding or anemia, the marrow of the sternum is of normal or increased cellularity, with normal or increased erythrocytogenesis and megakaryocytogenesis in most cases.

Hypocellularity of the marrow is an unusual finding, even in patients with advanced liver lesions.

Macronormoblastic erythropoiesis is seen in patients with macrocytic anemia, but megaloblastic erythropoiesis does not result from cirrhosis of the liver.

The presence of peripheral cytopenias (anemia and thrombocytopenia) in spite of normal or increased formation of erythroblasts and megakaryocytes in the marrow is suggestive of hypersplenism in patients with hepatic cirrhosis.

In patients with chronic hemorrhage the blood and bone marrow pictures are those of iron deficiency anemia, although other changes such as lymphopenia and thrombocytopenia tend to persist.
The combined peripheral blood and sternal marrow examination is often of value in establishing the diagnosis of cirrhosis of the liver.

**APPENDIX**

**Case Reports**

**Case 1.** White male age 61 with history of diabetes; ascites two years. Examination: hepatosplenomegaly, edema of ankles, no hemorrhagic phenomena. RBC 1,790,000; Hb 7.8 grams; MCV 91; MCH 18; WBC 5,500; platelets 144,000. Clinical impression: hepatic cirrhosis; diabetes mellitus. Liver biopsy: cirrhosis, grade 3.

**Case 2.** White male age 55 with history of alcoholism; ascites three weeks. Examination: hepatomegaly, edema of ankles, spider angioma, loss of axillary and pubic hair, no hemorrhagic phenomena. RBC 3,720,000; Hb 9.3 grams; MCV 97; MCH 35; WBC 5,300; platelets 90,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 4.

**Case 3.** White male age 45 with history of alcoholism; ascites three weeks. Examination: hepatomegaly, ascites, spider angioma, no hemorrhagic phenomena. RBC 3,760,000; Hb 10.9 grams; MCV 90; MCH 34; WBC 12,500; platelets 200,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 4.

**Case 4.** White female age 31, hospitalized for meningitis from which uneventful recovery was made. No history of alcoholism. Examination: hepatosplenomegaly. RBC 1,970,000; Hb 10.1 grams; MCV 111; MCH 34; WBC 6,650; platelets 120,000. Clinical impression: probable hepatic cirrhosis but blood dyscrasia to be ruled out. Liver biopsy: cirrhosis, grade 2.

**Case 5.** White male age 52 with history of alcoholism; icterus, ascites, edema of ankles two weeks. Examination: hepatomegaly, ascites, edema of lower extremities, icterus, spider angioma, no hemorrhagic phenomena. RBC 3,070,000; Hb 10.7 grams; MCV 130; MCH 35; WBC 6,500; platelets 77,000. Clinical impression: acute hepatitis superimposed on hepatic cirrhosis. Liver biopsy: cirrhosis, grade 3.

**Case 6.** White male age 59 with history of alcoholism; icterus, ascites, edema of ankles three weeks. Examination: hepatomegaly, ascites, edema of legs, spider angioma, melena. RBC 3,840,000; Hb 11.3 grams; MCV 101; MCH 32; WBC 8,500; platelets 168,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 3.

**Case 7.** White male age 59 with history of alcoholism, hematemesis. Examination: hepatosplenomegaly, ascites, no hemorrhagic phenomena. RBC 3,790,000; Hb 12.8 grams; MCV 103; MCH 34; WBC 7,690; platelets 100,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 1.

**Case 8.** White male age 52 with history of alcoholism; ascites one year. Examination: hepatosplenomegaly, ascites, no hemorrhagic phenomena. RBC 3,700,000; Hb 11.5 grams; MCV 97; MCH 30; WBC 3,350; platelets 111,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 1.

**Case 9.** White male age 38 with history of alcoholism; icterus and weight loss five months. Examination: hepatosplenomegaly, ascites, icterus, melena. RBC 3,580,000; Hb 9.9 grams; MCV 94; MCH 18; WBC 4,950; platelets 150,000. Clinical impression: hepatic cirrhosis; bleeding hemorrhoids. Liver biopsy: cirrhosis, grade 4.

**Case 10.** White male age 59 with history of alcoholism; icterus and weight loss four weeks. Examination: hepatosplenomegaly, icterus, melena. RBC 4,200,000; Hb 11.6 grams; MCV 98; MCH 18; WBC 10,450; platelets 230,000. Clinical impression: acute hepatitis superimposed on hepatic cirrhosis; terminal uremia. Liver biopsy: cirrhosis, grade 2.

**Case 11.** White female age 49 with history of alcoholism; syphilis, icterus three weeks. Examination:
hepatomegaly, slight icterus, no hemorrhagic phenomena. RBC 4,910,000; Hb. 15.4 grams; MCH 31; WBC 7,550; platelets 280,000. Clinical impression: hepatic cirrhosis, hepatoma, or heplobatum. Liver biopsy: cirrhosis, grade 4; hepatoma.

Case 14. White male age 38 with history of alcoholism; weakness, nausea, vomiting, icterus, ascites two months. Examination: hepatosplenomegaly, ascites, edema of feet, icterus, spider angioma, melena. RBC 2,450,000; Hb. 8.0 grams; MCD 7.3 microns; MCH 33; WBC 13,300; platelets 45,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 1. Autopsy: cirrhosis, grade 1; acute suppurative pancreatitis.

Case 15. White male age 43; intermittent epistaxis, icterus, weight loss five years. Examination: hepatosplenomegaly, ascites, icterus, melena. RBC 3,870,000; Hb. 8.4 grams; MCV 72; MCH 22; WBC 4,850; platelets 94,000. Clinical impression: biliary cirrhosis. Liver biopsy: cirrhosis, grade 3.


Case 17. White male age 62 with history of alcoholism; diabetes mellitus seven years; cough, weight loss one year. Examination: hepatomegaly, spider angioma, fever, empyema thoracis, no hemorrhagic phenomena. RBC 4,350,000; Hb. 13.3 grams; MCV 95; MCH 31; WBC 14,500; platelets 143,000. Clinical impression: hepatic cirrhosis; empyema thoracis; diabetes mellitus. Liver biopsy: cirrhosis, grade 2.

Case 18. White male age 46, mentally incompetent since infancy; anorexia, vomiting, icterus one week. Examination: hepatomegaly, abdominal distension, icterus, no hemorrhagic phenomena. RBC 4,020,000; Hb. 12.0 grams; MCV 100; MCH 30; WBC 10,800; platelets 321,600. Clinical impression: infectious hepatitis. Liver biopsy: cirrhosis, grade 1.

Case 19. White male age 59 with history of alcoholism; hematemesis, melena two weeks. Examination: hepatomegaly, ascites, edema of ankles, loss of pubic hair, melena. RBC 3,610,000; Hb. 9.9 grams; MCV 94; MCH 27; WBC 8,000; platelets 100,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 4.

Case 20. White male age 68 with history of alcoholism; progressive weight loss, ascites of unknown duration. Examination: ascites, no hepatosplenomegaly, no hemorrhagic phenomena. RBC 4,730,000; Hb. 11.0 grams; MCV 97; MCH 25; WBC 12,050; platelets 288,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 3.

Case 21. Negro male age 43 with history of alcoholism; weight loss, peri-umbilical pain, nausea, three weeks. Examination: hepatosplenomegaly, slight ascites, icterus, no hemorrhagic phenomena. RBC 3,660,000; Hb. 10.4 grams; MCD 7.6 microns; MCH 29; WBC 13,950; platelets 400,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 2.

Case 22. White female age 65, known to have had hypertension many years; progressive dyspnea and dependent edema of unknown duration. Examination: hepatosplenomegaly, hypertensive retinopathy, left ventricular enlargement, left pleural effusion, no lymph node enlargement, no hemorrhagic phenomena. RBC 5,000,000; Hb. 14.7 grams; MCV 94; MCH 29; WBC 47,100; platelets 201,000. Clinical impression: hypertensive cardiovascular disease with decompensation; chronic lymphatic leukemia.

Liver biopsy: cirrhosis, grade 2; chronic lymphatic leukemia.

Case 23. White male age 71 with history of hematemesis; ascites three years. Examination: hepatosplenomegaly, esophageal varices, ascites. RBC 2,750,000; Hb. 7.0 grams; MCV 89; MCH 25; WBC 3,800; platelets 132,000. Clinical impression: hepatic cirrhosis. Liver biopsy: cirrhosis, grade 2.

Case 24. White male age 58 with history of alcoholism; progressive ascites, edema, weakness six years. Examination: hepatomegaly, ascites, spider angioma, no hemorrhagic phenomena, coarse tremor left hand. RBC 4,620,000; Hb. 11.6 grams; MCV 91; MCH 25; WBC 5,900; platelets 193,000. Clinical impression: hepatic cirrhosis; Parkinsonism. Liver biopsy: cirrhosis, grade 2.

Case 25. White female age 53 with history of diverticulitis followed by peritoneal abscesses, colostomy, and colostomy repair two years before present admission. Readmitted for repair of large incisional abdominal hernia. Examination: hepatosplenomegaly, large abdominal hernia, no hemorrhagic phenomena. RBC 4,330,000; Hb. 12.3 grams; MCV 88; MCH 28; WBC 3,200; platelets 57,000. Clinical impression: incisional hernia; mild diabetes mellitus; possible hepatic cirrhosis or blood dyscrasia. Liver biopsy: cirrhosis, grade 2.
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THE BLOOD AND BONE MARROW IN PATIENTS WITH CIRRHOSIS OF THE LIVER

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