Relation of Bone Marrow Findings to Serum Protein Changes in Lymphosarcoma, Chronic Lymphocytic Leukemia and Hodgkin’s Disease

By ALTAN ONAT AND TALBERT COOPER

ALTERATIONS in serum protein demonstrable by electrophoretic analysis have been noted fairly frequently in cases of lymphosarcoma, lymphocytic leukemia and Hodgkin’s disease. Abnormal proteins such as cryoglobulins and myeloma-type proteins also have been observed in the serum of an occasional patient with these conditions. In this study we attempted to determine whether disturbances in serum globulins are related to specific morphologic patterns in the bone marrow in cases of lymphosarcoma, chronic lymphocytic leukemia and Hodgkin’s disease. We studied especially (1) the concurrent plasma cell reaction or absence of plasma cells and (2) qualitative morphologic changes in lymphocytes in the sense of lymphoid atypia.

REVIEW OF THE LITERATURE

In lymphosarcoma and Hodgkin’s disease the changes in serum protein found by electrophoretic analysis in general have been nonspecific and greatly variable. In addition to decrease in albumin, the most consistent changes in serum proteins have been elevations in the alpha-1, alpha-2 and gamma globulin fractions,1-3 although deviation from normal in either direction in any of the globulin components may occur.

Chronic lymphatic leukemia, in some reported studies, has been characterized by relatively less marked alterations in serum proteins and more frequently by normal electrophoretic patterns.3,4 Except for a tendency toward elevation of the alpha and beta globulins, Jim5 found no characteristic changes in the serum globulins in 50 unselected cases of chronic lymphatic leukemia, but concentrations of gamma globulin in serum ranged from complete absence to moderate increases. Creyssel and associates6 and Wall7 emphasized the occurrence of hypogammaglobulinemia in almost 50 per cent of cases of chronic lymphatic leukemia observed.6,8

Agammaglobulinemia has been demonstrated only rarely in lymphocytic leukemia and malignant lymphoma. A review of the literature discloses three reports6,8,10 of four patients with chronic lymphocytic leukemia associated with agammaglobulinemia, presumably of the acquired type. In one of these cases Jim and Reinhard10 observed an absence of plasma cells in the bone

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marrow. Arends and co-workers also were unable to find plasma cells in bone marrow aspirate from a woman with malignant lymphoma and agammaglobulinemia. This is consistent with Good's findings in the bone marrow of patients with congenital agammaglobulinemia. He demonstrated a marked decrease or absence of plasma cells even after intense stimulation with antigen.

Abnormal serum proteins.—In a few instances of lymphosarcoma, Hodgkin's disease and lymphocytic leukemia, protein constituents, such as cryoglobulins, or proteins of myeloma type, which exhibit electrophoretically homogeneous characteristics (narrow base, sharp peak), have been observed.

Six reports of single cases of chronic lymphocytic leukemia have appeared in which cryoglobulins have been observed in the serum or serous fluids or both.

Barr and associates found traces of cryoglobulin in the blood serum in a case of Hodgkin's disease, and Shaw and Abrams and associates each noted cryoglobulin in a case of lymphosarcoma. The latter authors expressed the belief that this particular cryoglobulin was derived from the cells of the lymphosarcoma, since both serum and tissue extract contained large amounts. They presented arguments that the components of the tissue extract were not in part derived from the tissue lymph fluid or that containing blood.

Abnormal proteins other than cryoglobulins were found in three cases of chronic lymphocytic leukemia included in the survey of Remmele, and Jirgensons and Cooper isolated abnormal globulins from the sera of three patients with malignant lymphoma. Azar, Hill and Osserman recently reported a series of 13 patients, including one with Hodgkin's disease, with what they believed were malignant lymphoma and lymphatic leukemia. All had abnormal serum proteins characteristic of multiple myeloma, that is, an abnormal component or components on electrophoresis which had the mobility of a slow or fast gamma globulin or of both types of components. When the electrophoretic pattern was mentioned, the abnormal constituents were said to be electrophoretically homogeneous.

Bone marrow in lymphosarcoma, lymphatic leukemia and Hodgkin's disease.—The changes in the sternal marrow in Hodgkin's disease have been reviewed by Limarzi and Paul and Cooper and Watkins. Here we shall emphasize only that an increase has been observed in plasma cells in the sternal marrow in a considerable proportion of cases of Hodgkin's disease by various workers. A plasma cell reaction in other types of malignant lymphoma appears to be less frequent than in Hodgkin's disease. Plasma cytosis in bone marrow has been reported in a case of giant follicular lymphoma and in one of lymphosarcoma. A plasma cell reaction is rarely associated with chronic lymphocytic leukemia, and in this condition virtual absence of plasma cells in the bone marrow appears to be more frequent.

Potential factors affecting the serum proteins.—In lymphosarcoma, chronic lymphocytic leukemia and Hodgkin's disease, these seem to be: (1) the malnutrition which commonly accompanies these conditions, (2) the malignant process, (3) impaired hepatic function through involvement of the liver in the lymphomatous process or by anemia often associated with the blood dyscrasia and (4) disturbed function of the hematopoietic system in the formation of
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serum globulins, particularly reactive plasmacytosis. Finally, it is conceivable that abnormal lymphocytes of the malignant process may produce or contribute to the changes in serum proteins. This possibility has some support in the observations by Abrams and co-workers in the case of lymphosarcoma with cryoglobulinemia cited previously and in the experimental studies by Doggett and associates in which the evidence appears to indicate that transplanted nonmetastasizing lymphosarcoma in mice contained a high concentration of an immune globulin.

Other possible indirect factors affecting the composition of serum protein in these cases may be the presence of fever, concurrent infections and possibly the use of some therapeutic agents.

Correlative studies between the alterations in the serum globulins or abnormal serum proteins and the morphologic changes of the hematopoietic system in lymphosarcoma, Hodgkin’s disease and lymphocytic leukemia have been few. Azar, Hill and Osserman attempted to determine histologic features differentiating this group of cases from the usual variety of malignant lymphoma and lymphocytic leukemia. In 10 of their 13 cases in which abnormal serum proteins characteristic of myeloma were present, they found marked plasmacytosis or a large number of pyroninophilic reticulum cells and lymphoid cells in tissue sections from lymph nodes, bone marrow aspirates or both. Intermediate forms between reticulum cells and lymphocytes on the one hand, and plasma cells on the other, were seen frequently in the tissues studied. They suggested that, clinically and morphologically, transitional forms occur, with considerable overlapping between the various lymphatic tumors and the plasmacytomas.

The relationship of the cells of the lymphocytic series to the composition of serum protein is controversial. Some immunologic studies on animals have suggested concentration or formation of antibodies in lymphocytes, but others have failed to demonstrate this. Furthermore, the antibody titer in tissue cultures of the spleen from the immunized rabbit has been shown to be correlated to the number of plasma cells in the spleen. These observations, as well as the question as to the specific identity of the cells of the lymph nodes responsible for production of antibodies in the experiments suggesting this, have cast some doubt on the importance of the lymphocytes in this connection.

**Material and Methods**

The first group (cases 1 to 20) consists of 20 cases encountered at the Mayo Clinic during the years 1955 through 1957 in which a diagnosis of lymphosarcoma or Hodgkin’s disease was made on the basis of the microscopic appearance of tissue at biopsy or necropsy or both (table 1). Cases histologically classified as Hodgkin’s granuloma, Hodgkin’s disease, Hodgkin’s sarcoma, lymphosarcoma, lymphoblastic lymphoma, lymphocytic lymphoma, giant follicular lymphoma and reticulum cell sarcoma are included in this group.

The second group (cases 21 to 26) consists of six cases encountered in the same period in which a diagnosis of chronic lymphocytic leukemia was made by clinical examination or at necropsy or both (table 1).

In addition to the criterion of established diagnosis we selected only those cases in which the serum protein had been analyzed electrophoretically and a specimen of bone marrow had been examined during the same stage of the illness, that is, during the same
period of hospitalization or outpatient observation. Prior to the year 1955 these criteria were not fulfilled in any case.

Electrophoretic analysis of serum proteins was carried out by the paper electrophoresis method by a Durruni apparatus using a barbital (Veronal) buffer solution at pH 8.6, ionic strength 0.075 and a current of 5 ma. per eight strips of filter paper. The dye Amidoschwarz 10 B\(^*\) was used for staining the paper strips. The total amount of serum protein was determined in all cases by the Kingsley method. Normal values in grams per 100 ml. of serum in this laboratory for total protein and its various constituents are as follows: albumin, 3.6 to 4.1; alpha-1 globulin, 0.3 to 0.4; alpha-2 globulin, 0.6 to 0.7; beta globulin, 0.7 to 0.9; gamma globulin, 0.9 to 1.4; and total serum proteins, 6.4 to 7.8.

The smear specimens of bone marrow were fixed and stained with Wright's stain. Paraffin sections of isolated solid particles of marrow were prepared after fixation with 4 per cent formalin in saline solution. Serial sections were made from the paraffin blocks and were stained with hematoxylin and eosin.

A differential count of 500 nucleated cells was performed on each unconcentrated smear of bone marrow. Damaged cells encountered during the differential count were noted separately.

For the classification of lymphoid atypia, we used the four types of atypical lymphocytes originally described by Cooper and Watkins.\(^2\) The reader is referred to that article for a description of the individual types. The degree of the lymphoid atypia of the bone marrow was estimated as minimal when 0.2 to 2.0 per cent of the nucleated cells in the differential count of the bone marrow were atypical lymphocytes; mild when 2.2 to 5.0 per cent were; moderate when 5.2 to 15 per cent were; and marked when more than 15 per cent were atypical lymphocytes.

The normal range of plasma cells in per cent of the total nucleated cells of the bone marrow has been stated as 0 to 2.0 per cent\(^5\) and 0 to 1.5 per cent,\(^3\)\(^9\)\(^4\) with mean values of 0.4 per cent\(^3\)\(^9\) and 0.3 per cent,\(^4\)\(^0\) respectively. In our study the term "plasmacytosis" has been used whenever plasma cells constituted more than 2.0 per cent of the nucleated cells in a differential count of bone marrow.

**REPORT OF TWO CASES**

The two cases in which abnormal serum globulins were found will be presented briefly.

**Case 15 (table 1).—**In this case of Hodgkin's disease, the diagnosis having been established histologically at the time of splenectomy for pancytopenia, electrophoretic analysis showed minor qualitative abnormalities within the serum gamma globulin fraction (fig. 1). During laparotomy, that is, shortly after the demonstration of the presence of anomalous serum globulins, the liver appeared normal.

**Case 541 (table 1).—**A 68 year old woman gave a history of weakness during the previous year, bleeding from the gums and recent blurring of vision. Findings on physical examination included lymphadenopathy and splenomegaly, and, on funduscopic examination, huge, dilated retinal veins along with many scattered zones of retinal hemorrhage and exudates. Laboratory tests revealed normocytic normochromic anemia and hyperproteinemia with marked increase in gamma globulin. Ultracentrifugation disclosed that 40 per cent of the serum protein consisted of macroglobulins. Bence Jones proteinuria was present. Roentgenologic evidence of skeletal lesions and a history of bone pain were lacking and the concentration of blood urea was normal. Pronounced increase in mature plasma cells was found in some parts of the bone marrow smear (fig. 2a), whereas lymphocytes predominated in other areas. Fixed sections of marrow showed numerous large and small aggregates of lymphocytes and only a scattering of plasma cells. Findings were interpreted as being consistent with a diagnosis of malignant lymphoma. On biopsy of an axillary lymph node (fig. 2b), a diagnosis of lymphocytic lymphosarcoma with many plasmacytoid lymphocytes was made.

*Manufactured by the Bayerwerke, Leverkusen, Germany.*
RESULTS

No relationship was noted in this study between the values for serum protein and certain clinical findings, such as malnutrition, severity and degree of progression of the disease, except that in cases 4, 12 and 14, in which ascitic fluid was present, the concentrations of gamma globulin fraction in the serum were reduced.

The values for serum proteins as well as the differential counts of plasma cells and atypical lymphocytes in the bone marrow in 14 cases of lymphosarcoma, six cases of chronic lymphocytic leukemia and six cases of Hodgkin’s disease are given in table 1.

In the group of lymphosarcoma and Hodgkin’s disease the values for gamma globulin ranged from 5.51 to 0.44 Gm. per 100 ml. of serum. Two patients had moderate hypogammaglobulinemia (0.61 and 0.44 Gm. per 100 ml., respectively), and five others had slight reductions in gamma globulin. Hypergammaglobulinemia of moderate to marked degree (2.0 to 5.5 Gm. per 100 ml.) was noted in eight patients, one of whom also had an anomalous type of serum protein.

The values for serum gamma globulin were normal in three patients with chronic lymphatic leukemia and were remarkable by the pronounced reduction (0.60 to 0.38 Gm. per 100 ml.) in the remaining three.

Lymphoid atypia.—Atypical lymphocytes were found in the bone marrow of all patients studied. In general, these were encountered more frequently and constituted a considerably higher proportion of the total lymphoid cells in the marrow of the patients with lymphoma than of those with chronic
Fig. 2 (case 5).—(a) Bone marrow smear showing an area with an increase in the number of plasma cells (Wright's; × 675). (b) From excised lymph node (hematoxylin and eosin; × 250).

lymphocytic leukemia. Type 3 cells (fig. 3), as in Cooper and Watkins' study, were the most frequently encountered atypical lymphocytic form and the predominant atypical cell type in 20 cases.

Data have been summarized in table 2 regarding the relationship of lymphoid atypia and the plasma cell content of bone marrow to alterations in the concentration of serum gamma globulin. Since, except for gamma globulin, serum proteins when normal are almost wholly hepatic in origin, the attempt at correlation will be discussed only in regard to gamma globulin.

Atypical lymphocytic cells constituted 0.6 to 10.6 per cent of the total
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, yr. and sex</th>
<th>Tissue diagnosis</th>
<th>Serum proteins,* Gm. per 100 ml.</th>
<th>Per cent in differential count in bone marrow smear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Albumin</td>
<td>a1</td>
</tr>
<tr>
<td>1</td>
<td>55 F</td>
<td>Lymphocyt. lymphosar.</td>
<td>3.15</td>
<td>0.26</td>
</tr>
<tr>
<td>2</td>
<td>51 F</td>
<td>R. C. lymphosar.</td>
<td>3.12</td>
<td>0.36</td>
</tr>
<tr>
<td>3</td>
<td>73 M</td>
<td>Lymphosar.</td>
<td>2.60</td>
<td>0.55</td>
</tr>
<tr>
<td>4</td>
<td>40 F</td>
<td>G. folli. lymphosar.</td>
<td>2.07</td>
<td>0.49</td>
</tr>
<tr>
<td>5</td>
<td>68 F</td>
<td>Lymphocyt. lymphosar.</td>
<td>3.34</td>
<td>0.36</td>
</tr>
<tr>
<td>6</td>
<td>76 F</td>
<td>H. d.</td>
<td>2.24</td>
<td>0.39</td>
</tr>
<tr>
<td>7</td>
<td>46 M</td>
<td>Lymphosar.</td>
<td>2.71</td>
<td>0.37</td>
</tr>
<tr>
<td>8</td>
<td>67 M</td>
<td>H. d., granuloma type</td>
<td>2.76</td>
<td>0.40</td>
</tr>
<tr>
<td>9</td>
<td>74 F</td>
<td>R. C. lymphosar.</td>
<td>2.66</td>
<td>0.44</td>
</tr>
<tr>
<td>10</td>
<td>44 M</td>
<td>H. sar.</td>
<td>2.81</td>
<td>0.50</td>
</tr>
<tr>
<td>11</td>
<td>42 M</td>
<td>R. C. lymphosar.</td>
<td>2.53</td>
<td>0.43</td>
</tr>
<tr>
<td>12</td>
<td>51 M</td>
<td>Lymphocyt. lymphosar.</td>
<td>2.53</td>
<td>0.34</td>
</tr>
<tr>
<td>13</td>
<td>58 M</td>
<td>Lymphoblast. lymphosar.</td>
<td>2.30</td>
<td>0.37</td>
</tr>
<tr>
<td>14</td>
<td>49 F</td>
<td>H. d., granuloma type</td>
<td>2.27</td>
<td>0.39</td>
</tr>
<tr>
<td>15</td>
<td>60 F</td>
<td>H. d., granuloma type</td>
<td>3.02</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Table 1.—Clinical and Laboratory Data on Cases of Lymphosarcoma, Hodgkin's Disease and Chronic Lymphocytic Leukemia*
**Table: Bone Marrow-Serum Protein in Lymphomas and Leukemia**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Protein 1</th>
<th>Protein 2</th>
<th>Protein 3</th>
<th>Protein 4</th>
<th>Protein 5</th>
<th>Protein 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>60 M</td>
<td>Lymphosar.</td>
<td>3.33</td>
<td>0.60</td>
<td>1.29</td>
<td>1.49</td>
<td>1.20</td>
<td>7.91</td>
</tr>
<tr>
<td>17</td>
<td>47 F</td>
<td>R. C. lymphosar.</td>
<td>2.69</td>
<td>0.59</td>
<td>1.04</td>
<td>1.01</td>
<td>2.02</td>
<td>7.35</td>
</tr>
<tr>
<td>18</td>
<td>55 M</td>
<td>Lymphocyt. lymphosar.</td>
<td>1.83</td>
<td>0.41</td>
<td>1.11</td>
<td>1.27</td>
<td>1.58</td>
<td>6.20</td>
</tr>
<tr>
<td>19</td>
<td>42 M</td>
<td>R. C. lymphosar.</td>
<td>3.03</td>
<td>0.43</td>
<td>0.83</td>
<td>0.95</td>
<td>0.81</td>
<td>6.05</td>
</tr>
<tr>
<td>20</td>
<td>33 F</td>
<td>H. d.</td>
<td>1.87</td>
<td>0.48</td>
<td>0.93</td>
<td>0.96</td>
<td>2.04</td>
<td>6.28</td>
</tr>
<tr>
<td>21</td>
<td>62 M</td>
<td>Chron. lymphocyt. leuk.</td>
<td>2.26</td>
<td>0.46</td>
<td>1.04</td>
<td>0.84</td>
<td>0.51</td>
<td>5.11</td>
</tr>
<tr>
<td>22</td>
<td>70 M</td>
<td>Chron. lymphocyt. leuk.</td>
<td>3.19</td>
<td>0.28</td>
<td>0.60</td>
<td>0.70</td>
<td>1.11</td>
<td>5.88</td>
</tr>
<tr>
<td>23</td>
<td>68 M</td>
<td>Chron. lymphocyt. leuk.</td>
<td>2.78</td>
<td>0.43</td>
<td>0.63</td>
<td>0.68</td>
<td>0.43</td>
<td>4.95</td>
</tr>
<tr>
<td>24</td>
<td>58 M</td>
<td>Chron. lymphocyt. leuk.</td>
<td>3.18</td>
<td>0.40</td>
<td>0.69</td>
<td>0.63</td>
<td>0.38</td>
<td>5.28</td>
</tr>
<tr>
<td>25</td>
<td>53 M</td>
<td>Chron. lymphocyt. leuk.</td>
<td>3.42</td>
<td>0.38</td>
<td>0.62</td>
<td>0.88</td>
<td>1.12</td>
<td>6.42</td>
</tr>
<tr>
<td>26</td>
<td>75 M</td>
<td>Chron. lymphocyt. leuk.</td>
<td>3.53</td>
<td>0.38</td>
<td>0.77</td>
<td>0.83</td>
<td>1.10</td>
<td>6.61</td>
</tr>
</tbody>
</table>

*By paper electrophoresis.*
†By Kingsley method.
‡Macroglobulins constituted 40 per cent of total serum protein.
§After intramuscular administration of 3.3 Gm. of immune globulin.

| Abbreviations: lymphocyt., lymphocytic; lymphobl., lymphoblastic; R. C., reticulum cell; lymphosar., lymphosarcoma; H. d., Hodgkin's disease; leukemia, leukemia; chron., chronic; G. folli., giant follicular. |
FIG. 3.—Bone marrow smears illustrating atypical lymphocytes: (a) type 1 cell beside a mature lymphocyte. (b, case 23), two type 3 cells (Wright's; X 1000). (c, case 13), two type 2 and one type 1 atypical lymphocytic forms (Wright's; X 800).
Table 2.—Summary of Correlative Data from Cases of Lymphosarcoma, Hodgkin's Disease and Chronic Lymphocytic Leukemia (Arranged in Order of Decreasing Concentration of Serum Gamma Globulin)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Gamma globulin (Gm. per 100 ml.)</th>
<th>Lymphoid atypia*</th>
<th>Plasma cells in smear</th>
<th>Plasmacytosis in fixed section</th>
<th>Pertinent clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5.51</td>
<td>Moderate</td>
<td>Increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2.65</td>
<td>Minimal</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.44</td>
<td>Moderate</td>
<td>Normal</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.39</td>
<td>Minimal</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.24</td>
<td>Minimal</td>
<td>Increased</td>
<td>Present</td>
<td>Chronic suppuration</td>
</tr>
<tr>
<td>11</td>
<td>2.17</td>
<td>Mild</td>
<td>Normal</td>
<td>Present</td>
<td>26% BSP dye retention</td>
</tr>
<tr>
<td>20</td>
<td>2.04</td>
<td>Minimal</td>
<td>Increased</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>2.02</td>
<td>Mild</td>
<td>Increased</td>
<td>Present</td>
<td>Exfoliative dermatitis</td>
</tr>
<tr>
<td>18</td>
<td>1.58</td>
<td>Moderate</td>
<td>Normal</td>
<td>Present</td>
<td>Exfoliative dermatitis</td>
</tr>
<tr>
<td>10</td>
<td>1.49</td>
<td>Minimal</td>
<td>Normal</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.23</td>
<td>Mild</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.20</td>
<td>Moderate</td>
<td>Absent</td>
<td></td>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>7</td>
<td>1.13</td>
<td>Minimal</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1.12</td>
<td>Minimal</td>
<td>Absent</td>
<td>Retroauricular abscess</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1.11</td>
<td>Minimal</td>
<td>Normal</td>
<td>Hepatomegaly</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>1.10</td>
<td>Minimal</td>
<td>Normal</td>
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</tr>
<tr>
<td>15</td>
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<td>Absent</td>
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<td>0.81</td>
<td>Moderate</td>
<td>Normal</td>
<td>Present</td>
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<td>Normal</td>
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<td>13</td>
<td>0.72</td>
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<td>Normal</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>0.70</td>
<td>Minimal</td>
<td>Absent</td>
<td>Malnutrition, ascites</td>
<td>Lymphomatous liver involvement</td>
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<tr>
<td>14</td>
<td>0.61</td>
<td>Mild</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>0.60</td>
<td>Mild</td>
<td>Absent</td>
<td>Acute hepatitis</td>
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</tr>
<tr>
<td>21</td>
<td>0.48</td>
<td>Mild</td>
<td>Absent</td>
<td>Hepatomegaly</td>
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</tr>
<tr>
<td>12</td>
<td>0.44</td>
<td>Mild</td>
<td>Normal</td>
<td>Ascites</td>
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<tr>
<td>23</td>
<td>0.38</td>
<td>Minimal</td>
<td>Absent</td>
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</table>

*See page 117 for the estimate of the degree of lymphoid atypia.

Nucleated cells in the bone marrow, with an average of 3.7 per cent in the group of 10 patients who had elevated concentrations of gamma globulin. They ranged from 0.6 to 6.2 per cent, averaging 2.5 per cent in the six cases in which the concentration of gamma globulins were within normal limits, and from 0.8 to 51.8 per cent with a mean value of 8.0 per cent in the 10 patients who had decreased levels of gamma globulins. The overlapping in the degree of lymphoid atypia in the three groups is so great that determination of a numerical relationship between the degree of lymphoid atypia and the changes in serum gamma globulin is not possible. The lymphoid atypia in the two cases (cases 5 and 15) associated with abnormal serum proteins was moderate in degree.

A correlation appeared between the content of plasma cells in the bone marrow and the concentration of gamma globulin in the serum. In four of the 10 cases in which serum gamma globulins were elevated, plasmacytosis of 2.8,
and 12.8 per cent, respectively, was found in the bone marrow smear. Since a plasma cell reaction, in general, is predominantly of perivascular distribution, evidence of this may be absent on smear preparations in some cases. With this possibility in mind, findings in fixed sections of the marrow were included. In addition to the four cases demonstrating plasma cell reaction on the smear specimen, plasmacytosis was noted on examination of fixed sections of bone marrow in cases 2, 10, 11, 18 and 19. Thus, eight of 10 cases with hypergammaglobulinemia showed bone marrow plasmacytosis in the smear or fixed section or both (fig. 4). In the group of 16 cases having normal or decreased concentration of serum gamma globulin, in contrast, only one patient (case 19) demonstrated marrow plasmacytosis in the section, yet not in the smear specimen.

In five of the six cases of moderate or marked hypogammaglobulinemia (0.70 to 0.38 Gm. per 100 ml.) plasma cells were virtually absent in the bone marrow specimens, a finding parallel to that observed in agammaglobulinemia.

**COMMENT**

No plasma cells were found in bone marrow preparations from a patient (case 15) with Hodgkin’s granuloma in whom minor qualitative abnormalities of the low-normal gamma globulin fraction were observed.

Case 5 has been included on the basis of the diagnosis of lymphocytic
lymphosarcoma on tissue from lymph nodes supported by the findings of fixed sections of bone marrow. Association of macroglobulinemia and Bence Jones proteinuria, on the other hand, are certainly unusual features in malignant lymphoma. In addition to the syndrome of Waldenström’s macroglobulinemia and myeloma, macroglobulinemia has been reported to be associated occasionally with congenital syphilis, lupus erythematosus, Sjögren’s syndrome and carcinoma of the uterus. In view of this and the occasional association of cryoglobulin and the electrophoretically abnormal serum globulins of myeloma type with malignant lymphoma, it may be presumed that macroglobulins, too, may be encountered in the sera of some patients with this disease. Traces and small amounts of Bence Jones proteins have been found by immunochemical methods in the urine of patients suffering from a number of conditions other than myelomatosis, including reticulosarcoma, secondary bone neoplasms, and others. Although larger quantities of Bence Jones proteinuria also have been reported in isolated instances of metastatic cancer to bone, leukemia and sarcoma of bone, present opinion holds that excretion of larger amounts of Bence Jones protein in the urine is a unique characteristic of multiple myeloma.

Case 5 in this study has been reported elsewhere under the diagnosis of the syndrome of macroglobulinemia. The definite classification of this case with marked aberration in protein metabolism and pronounced increase in mature plasma cells in the bone marrow smear may be controversial; it is regarded as illustrating the possibly close relationship between lymphoma and myeloma.

In this connection, we should mention the report by Schaub of a case of macroglobulinemia and cryoglobulinemia, in which tissue from an excised lymph node permitted the diagnosis of reticulum cell sarcoma. At necropsy, after five months of illness, as well as preterminally, aspirates of bone marrow and lymph nodes were interpreted as showing reticulum cell sarcoma with transition to myeloma. This observation and case 5 in the present study tend to confirm the observation of Azar and associates that clinically and morphologically transitional forms occur with overlapping between the lymphatic tumors and the plasmacytomas.

**Summary and Conclusions**

In order to correlate the electrophoretic alterations in the serum proteins and the findings in the bone marrow, with particular reference to atypical lymphocytic forms and plasma cells, 14 cases of lymphosarcoma, six of chronic lymphocytic leukemia and six of Hodgkin’s disease were studied. No numerical relationship could be found between the degree of lymphoid atypia and the changes in serum globulin. A correlation, however, was apparent between the plasma cell concentration in the bone marrow and the changes in the serum gamma globulin, inasmuch as pronounced hypergammaglobulinemia occurred in all four cases of malignant lymphoma associated with bone marrow plasmacytosis (ranging from 2.8 to 12.8 per cent) and hypogammaglobulinemia of moderate to marked degree was present in five of the six cases of malignant lymphoma in which plasma cells were virtually absent in the bone marrow. When the findings of the fixed sections of the marrow are included, plasma-
cytosis was demonstrated in bone marrow in eight of 10 cases in which serum gamma globulins were elevated.

In two cases, serum globulins were qualitatively abnormal. In one, a case (case 15) of Hodgkin’s disease, a small fraction of electrophoretically homogeneous globulin was noted. In the other, case 5, in which the histologic diagnosis was lymphocytic lymphosarcoma, macroglobulins constituted 40 per cent of the serum proteins, and Bence Jones proteinuria was associated. Predominantly mature plasmacytosis of 12.8 per cent was present in the bone marrow. This case may be regarded as illustrative of the interrelationship between myeloma and lymphosarcoma and supports the view21 that, clinically and morphologically, transitional forms occur between lymphatic tumors and plasmacytomas.

On the basis of this material, it is suggested that in cases of lymphosarcoma, Hodgkin’s disease and chronic lymphocytic leukemia, alterations in the plasma content of the bone marrow, either as reactive plasmacytosis or as virtual absence of plasma cells, appear to be a major pathogenetic factor in the occurrence of hypergammaglobulinemia and hypogammaglobulinemia, respectively.

Hypogammaglobulinemia was observed in three of six cases of chronic lymphocytic leukemia; two of 14 cases of lymphosarcoma; and one of six classified as Hodgkin’s disease. Conversely, quantitative increases in the gamma globulin level occurred in none of the six cases of chronic lymphocytic leukemia; in six of 14 cases of lymphosarcoma (including two of three classified as lymphosarcoma, reticular cell type), and in three of the six cases of Hodgkin’s disease.

**Summario in Interlingua**

Pro correlationar le alterationes electrophoretic in le proteinas del sero con aspectos constatat in le medulla ossee—con referentia particular al atypic formas lymphocytic e al plasmocytos—14 casos de lymphosarcoma, sex de chronic leucemia lymphocytic, e sex de morbo de Hodgkin eseva studiate. Nulle correlation numeric poteva esser trovate inter le grado del atypia lymphoide e le alterationes del globulina seral. Tamen, un correation esseva apparente inter le concentration del plasmocytos in le medulla ossee e le alterationes in le globulina gamma del sero, i.e., un pronunciate hypergammaglobulinemia occurreva in omne le quatro casos de lymphoma maligne associate con plasmocytosis del medulla (inter 2,8 e 12,8 pro cento), e hypogammaglobulinemia de grados moderate o marcate esseva presente in cinque del sex casos de lymphoma maligne in le quilas plasmocytos esseva practicamente absente in le medulla ossee. Quando le constatationes in sectiones fixate de medulla es includite, plasmocytosis esseva demonstrate in le medulla ossee de octo inter 10 casos in que le nivellos del globulina gamma sera esseva elevate.

In duo casos, globulinas seral esseva qualitativamente anormal. In un, un caso de morbo de Hodgkin (caso 15), un micre fraction de globulina esseva notate que esseva electrophoreticamente homogenee. In le altere, in que le diagnose histologic eseva lymphosarcoma lymphocytic (caso 5), macroglobulinas constitueva 40 pro cento del proteina seral, e proteinuria de Bence Jones
esseva associate. Plasmocytosis predominantemente matur, amontante, a 12,8 pro cento, esseva presente in le medulla ossee. Iste caso pote esser reguardate como illustrative pro le relation inter myeloma e lymphosarcoma e supporta le these que formas transitional, tanto clinica- como etiam morphologicamente, occurre inter tumores lymphatic e plasmocytomas.

Super le base de iste constatationes il es suggerite que in casos de lymphosarcoma, de morbo de Hodgkin, e de chronic leukemia lymphocytic, alteraciones in le contento de plasma in le medulla ossee—resultante in plasmocytosis o in le absentia virtual de plasmocytos—pare esser un major factor pathogenetic in le occurrentia de hypergammaglobulinemia e hypogammaglobulinemia, respectivamente.

Hypogammaglobulinemia esseva observate in tres inter sex casos de chronic leukemia lymphocytic, in duo inter 14 casos de lymphosarcoma, e in un inter sex casos classificate como morbo de Hodgkin. Inversemente, augmentos quantitative del nivello de globulina gamma occurreva in nulle del sex casos de chronic leukemia lymphocytic, in sex del 14 casos de lymphosarcoma (incluso duo de tres classificate como lymphosarcoma del typo a cellulas reticular), e in tres de sex casos de morbo de Hodgkin.

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Relation of Bone Marrow Findings to Serum Protein Changes in Lymphosarcoma, Chronic Lymphocytic Leukemia and Hodgkin's Disease

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