Differences in Inducing Activity for Human Bone Marrow Colonies in Normal Serum and Serum From Patients With Leukemia

By Uri Mintz and Leo Sachs

Normal serum and serums from patients with acute and chronic leukemia were assayed for granulocyte colony-inducing activity with human bone marrow cells. Serum from untreated acute leukemia, but not from the other patients, showed about normal inducing activity at low serum concentration and lower than normal activity at high concentration. This suggests that serum from patients with acute leukemia contained an inhibitor for colony formation. Serums from chronic myeloid leukemia were in about the same range as normal, whereas serums from chronic lymphocytic leukemia showed the highest colony-inducing activity.

We have shown that the differentiation of different types of hematopoietic cells can be studied in tissue culture and that various cells release a protein inducer for the formation of colonies in vitro with mature differentiated macrophages and granulocytes from single undifferentiated hematopoietic rodent cells.\(^1\)\(^{-15}\) Induction of colony formation with mature differentiated granulocytes has also been shown with human hematopoietic cells.\(^15\)\(^{-19}\) It has been reported that human serum does not have any inducing activity on bone marrow cells unless it is dialyzed or specially treated.\(^23\)

The present studies were undertaken to determine the inducing activity of human bone marrow cells of normal serum and serum from patients with leukemia. The results show that human serum contains inducing activity without dialysis or special treatment and that there are differences in the inducing activity in serums from normal people and patients with leukemia.

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MATERIALS AND METHODS

Collection of Serum

Samples of human venous blood were collected in glass tubes and were allowed to clot at room temperature for 1.5-2 hr. After centrifugation, the serums were removed, were passed through a 0.45 µm Millipore filter, and were stored at -20°C. Normal serums were obtained from volunteers within the Institute. Serums from various diseases (Tables 1 and 2) were obtained from patients hospitalized in the Beilinson Hospital, Tel-Aviv University Medical School. For a comparison of the activity of these serums, they were bioassayed for inducing activity with cells from the same bone marrow, unless otherwise stated.

Assay for Colony-inducing Activity

Unless otherwise stated, the cells used for cloning were obtained by aspiration from the sternum of a 47-yr-old woman with iron deficiency anemia who received no drug treatment. Differential counts of peripheral blood and bone marrow smears were within normal limits. After 1.5-hr sedimentation in a heparin (5000 U/ml) solution-containing glass tube, the bone marrow samples were centrifuged; the buffy coat was removed with a fine Pasteur pipette, and the cells were resuspended in serum-free Eagle's medium with a fourfold concentration of amino acids and vitamins. The cells were counted in Turk's solution, omitting metamyelocytes, stab forms, and mature granulocytes, since these were presumably no longer able to multiply. Nucleated cells, \(1 \times 10^5\), were seeded for cloning in a 0.85 ml soft agar layer (0.33%) on a 1.5 ml harder agar base (0.5%) in 35-mm Petri dishes (Falcon Co.). Both layers contained Eagle's medium and 20% fetal calf serum. To the lower agar layer was added 0.75 ml (50%), 0.375 ml (25%), and 0.187 ml (12.5%) of the tested human serum. Control assays were carried out without addition of human serum. After 10-12 days of incubation, colonies of at least 50 cells were counted with an inverted or dissecting microscope. Two to four Petri dishes were seeded per point; the results are given as the means of the number of colonies, and the number of colonies per Petri dish varied up to about 25% from the mean. Calculations of the number of cells per colony were based on counts of at least 30 pooled colonies. Single colonies, collected from the agar with a fine capillary tube, were examined after staining with May-Grünwald-Giemsa and aceto-orcein.\(^{15}\)

RESULTS

The clinical diagnosis and hematologic data on the patients examined are shown in Tables 1 and 2. Serum was tested from normal people and patients with acute myeloblastic and lymphoblastic leukemia, chronic myeloid and lymphocytic leukemia, Hodgkin's disease under treatment, and fever from various causes.

No colonies were obtained without the addition of human serum. The results with 25% human serum (Tables 1, 2 and Fig. 1) show that with this concentration the cloning efficiency with serum from the untreated acute leukemias was in about the same range as the normal controls, while it was higher in the treated acute leukemias (Table 2, patients No. 17 and 18). The cloning efficiency with serums from chronic myeloid leukemias was about the same or somewhat higher than with the normal serum, but a much higher average cloning efficiency was found in serums from patients with chronic lymphocytic leukemia and with Hodgkin's disease under treatment. The highest cloning efficiency was found in two of the patients with fever (Table 1, patients No. 13 and 14). In addition to fever in patients No. 11-14, fever was also found in patient no. 9 (38°C), 15 (37.4°C), 18 (38.5°C), 21 (37.3°C), and 26 (38°C). Of
### Table 1. Colony Formation With Serum From Normal People and Patients With Hodgkin’s Disease and Fever

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>First Diagnosed</th>
<th>Treatment</th>
<th>Time Under Treatment</th>
<th>Time Since Last Treatment</th>
<th>No. Leukocytes per cu mm</th>
<th>Differential Cell Counts (%)</th>
<th>No. Colonies With 25% Normal or Patient’s Serum†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>M</td>
<td>Normal</td>
<td></td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>7300</td>
<td>0 67 3 2 0 6 22 48</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>M</td>
<td>Normal</td>
<td></td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>8600</td>
<td>0 50 2 2 1 5 40 68</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>M</td>
<td>Normal</td>
<td></td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>9600</td>
<td>0 55 1 3 0 4 37 80</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>M</td>
<td>Normal</td>
<td></td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>6800</td>
<td>0 49 3 2 0 8 38 86</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>F</td>
<td>Hodgkin’s disease</td>
<td>1 yr</td>
<td>None</td>
<td>10 mo</td>
<td>—</td>
<td>5200</td>
<td>0 71 7 0 0 4 18 178</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>Hodgkin’s disease</td>
<td>10 mo</td>
<td>None</td>
<td>8 mo</td>
<td>—</td>
<td>4700</td>
<td>0 49 6 4 1 6 34 182</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>M</td>
<td>Hodgkin’s disease</td>
<td>5 yr Vinblastine</td>
<td>5 yr</td>
<td>1 wk</td>
<td>—</td>
<td>9600</td>
<td>0 67 7 2 0 6 18 264</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>F</td>
<td>Hodgkin’s disease</td>
<td>10 mo</td>
<td>None</td>
<td>8 mo</td>
<td>—</td>
<td>5000</td>
<td>0 48 3 3 0 4 42 288</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>F</td>
<td>Hodgkin’s disease</td>
<td>2 yr</td>
<td>None</td>
<td>20 mo</td>
<td>—</td>
<td>5000</td>
<td>0 63 4 2 1 4 26 296</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>M</td>
<td>Hodgkin’s disease</td>
<td>2 yr</td>
<td>None</td>
<td>22 mo</td>
<td>—</td>
<td>8100</td>
<td>0 54 4 2 0 7 32 318</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>F</td>
<td>Fever (38°C) cholecystitis</td>
<td>1 day</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>6850</td>
<td>0 61 7 3 0 4 25 162</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>26</td>
<td>F</td>
<td>Fever (38.5°C) urinary</td>
<td>1 wk</td>
<td>Ampicillin</td>
<td>1 wk</td>
<td>12 hr</td>
<td>5700</td>
<td>0 70 9 0 1 3 17 230</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>40</td>
<td>F</td>
<td>Fever (38°C) salmonellosis</td>
<td>3 days</td>
<td>Chloramphenicol</td>
<td>1 day</td>
<td>12 hr</td>
<td>7500</td>
<td>0 47 20 0 0 5 28 568</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>71</td>
<td>M</td>
<td>Fever (37.5°C) cause unknown</td>
<td>2 wk</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>7200</td>
<td>0 84 2 4 1 4 5 710</td>
<td></td>
</tr>
</tbody>
</table>

† B. blasts; N. neutrophils; S. stab forms; E. eosinophils; B. basophils; M. monocytes; L. lymphocytes.

I Patients were treated with irradiation right after diagnosis and, thereafter, were maintained with vinblastine once a week. The patients were in stages I or II A except patient no. 9 who was in II B. Patients nos. 5 and 9 had lymphocytic depletion; nos. 6, 7, and 10 had mixed cellularity, and no. 8 had nodular sclerosis.

† With a 25% concentration of the normal or patient’s serum seeded with 2 X 10⁵ nucleated normal human bone marrow cells; excluding metamyelocytes, stab forms, and mature granulocytes.
Table 2. Colony Formation With Serum From Acute and Chronic Leukemic Patients

| Patient No | Age | Sex | Diagnosis                          | First Diagnosed | Treatment | Time Under Treatment | Time Since Last Treatment | No. Leukocytes per mm³ | Differential cell counts (%) | No. of colonies with 25% patient's serum
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>25 F</td>
<td></td>
<td>Acute myeloblastic leukemia</td>
<td>2 hr</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>55000</td>
<td>95 2 1 0 0 0 2 32</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>33 F</td>
<td></td>
<td>Acute lymphoblastic leukemia</td>
<td>6 hr</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>19200</td>
<td>72 2 2 0 0 2 22 76</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>73 M</td>
<td></td>
<td>Acute myeloblastic leukemia</td>
<td>2 days</td>
<td>Cyt. Ar. I, 6 MP,† steroids</td>
<td>2 days 12 hr</td>
<td></td>
<td>3000</td>
<td>3 7 0 0 0 9 0 342</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>15 M</td>
<td></td>
<td>Acute myeloblastic leukemia</td>
<td>1 mo</td>
<td>Rubidomycin, steroids</td>
<td>1 mo 12 hr</td>
<td></td>
<td>1250</td>
<td>2 3 0 0 0 0 95 388</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>36 F</td>
<td></td>
<td>Chronic myeloid leukemia</td>
<td>9.5 yr</td>
<td>Busulfan</td>
<td>6 mo 9 yr</td>
<td>9900</td>
<td>0 60 3 1 0 6 30 82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>67 M</td>
<td></td>
<td>Chronic myeloid leukemia</td>
<td>6 yr</td>
<td>Busulfan</td>
<td>4 yr 4 mo</td>
<td>9600</td>
<td>0 48 6 6 2 6 32 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>68 F</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>7 yr</td>
<td>Busulfan</td>
<td>6.5 yr 3 mo</td>
<td>10150</td>
<td>0 60 26 2 7 2 3 86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>57 M</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>8 mo</td>
<td>Busulfan</td>
<td>7 mo 1 mo</td>
<td>8500</td>
<td>0 49 17 3 3 10 18 94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>49 F</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>15 yr</td>
<td>Busulfan</td>
<td>12 yr 3 yr</td>
<td>9300</td>
<td>0 60 8 0 2 30 146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>35 M</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>5 yr</td>
<td>Busulfan</td>
<td>3 yr 1 mo</td>
<td>8800</td>
<td>0 61 15 3 2 4 15 154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>57 F</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>3 yr</td>
<td>Chlorambucil</td>
<td>2.5 yr 3 mo</td>
<td>9400</td>
<td>0 20 6 2 0 6 66 174</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>50 M</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>4 yr</td>
<td>Chlorambucil</td>
<td>7 mo 3.5 yr</td>
<td>7800</td>
<td>0 34 3 0 3 60 192</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>59 F</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>5 yr</td>
<td>Chlorambucil</td>
<td>3.5 yr 1 mo</td>
<td>12000</td>
<td>0 31 1 1 1 2 64 208</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>64 M</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>13 yr</td>
<td>Chlorambucil</td>
<td>10 yr 1 day</td>
<td>32000</td>
<td>3 7 3 0 0 2 85 210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>65 F</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>4 yr</td>
<td>Chlorambucil, steroids</td>
<td>3.5 yr 2 wk</td>
<td>13900</td>
<td>0 3 0 0 0 1 96 226</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>54 M</td>
<td></td>
<td>Chronic lymphocytic leukemia</td>
<td>2 days</td>
<td>None</td>
<td>—</td>
<td>—</td>
<td>130000</td>
<td>2 2 1 0 0 0 95 306</td>
<td></td>
</tr>
</tbody>
</table>

* B. blasts; N. neutrophils; S. stab forms; E. eosinophils; Ba. basophils; M. monocytes; L. lymphocytes.
† With a 25% concentration of the patient's serum seeded with 2 X 10³ nucleated normal human bone marrow cells, excluding metamyelocytes, stab forms and mature granulocytes.
† Cyt. Ar. = Cytosine arabinoside. 6 MP = 6 – mercaptopurine.
these patients, the serums from Nos. 15 and 21 did not give a higher than normal cloning efficiency, despite the fever (Tables 1 and 2).

The average number of colonies at different concentrations of serum from the normals, chronic leukemias, and untreated acute leukemias is shown in Fig. 2. At high serum concentration (50%), a lower than normal cloning efficiency was seen with serum from the untreated acute leukemias but was not seen with serums from any of the other patients. The lowest average number of colonies from the three serum concentrations tested was found in the untreated acute myeloid leukemia. The data in Fig. 2 also show the high inducing activity of serums from chronic lymphocytic leukemia. The number of colonies with serum from the treated acute leukemias (Table 2, patients No. 17 and 18) with
Table 3. Colony Formation With Human Serum on Different Human Bone Marrows

<table>
<thead>
<tr>
<th>Serum from patient no.</th>
<th>Bone marrow no.</th>
<th>Concentration of Serum (%)</th>
<th>No. of colonies per $2 \times 10^5$ cells seeded</th>
<th>Serum from patient No.</th>
<th>Bone marrow no.</th>
<th>Concentration of Serum (%)</th>
<th>No. of colonies per $2 \times 10^5$ cells seeded</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>12.5 25 50</td>
<td>46 68 90</td>
<td>17</td>
<td>1</td>
<td>12.5 25 50</td>
<td>204 342 272</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>22 32 112</td>
<td>17</td>
<td>2</td>
<td></td>
<td>112 348 472</td>
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<td>1</td>
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<td>38 80 168</td>
<td>18</td>
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<td>248 388 350</td>
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<td>126 232 406</td>
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<td>4</td>
<td>1</td>
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<td>2</td>
<td></td>
<td>44 80 188</td>
<td>20</td>
<td>3</td>
<td></td>
<td>14 22 34</td>
</tr>
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<td>1</td>
<td></td>
<td>182 178 422</td>
<td>21</td>
<td>3</td>
<td></td>
<td>14 22 34</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>58 184 276</td>
<td>21</td>
<td>4</td>
<td></td>
<td>42 80 74</td>
</tr>
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<td>1</td>
<td></td>
<td>120 288 466</td>
<td>28</td>
<td>1</td>
<td></td>
<td>154 210 270</td>
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<td>2</td>
<td></td>
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<td>16</td>
<td>1</td>
<td></td>
<td>80 76 16</td>
<td></td>
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</tr>
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<td></td>
<td>2</td>
<td></td>
<td>NT 20 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bone marrow No. 1 was from the woman with iron deficiency anaemia whose bone marrow was used for the data on Tables 1 and 2 and Fig. 1 and 2; bone marrows Nos. 2, 3 and 4 were from adult men with polycythemia vera in remission.

† Nucleated cells excluding metamyelocytes, stab forms, and mature granulocytes.
Table 4. Colony Formation with Human Serum on Human and Rat Bone Marrow

<table>
<thead>
<tr>
<th>Serum From Patient No</th>
<th>Human Bone Marrow</th>
<th>Rat Bone Marrow</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration of Serum (%)</td>
<td>No of colonies per 2 X 10^6 cells seeded</td>
<td>No of colonies per 2 X 10^6 cells seeded</td>
</tr>
<tr>
<td>12.5</td>
<td>25</td>
<td>50</td>
<td>12.5</td>
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<td>46</td>
<td>68</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>108</td>
<td>162</td>
<td>208</td>
</tr>
<tr>
<td>12</td>
<td>120</td>
<td>230</td>
<td>328</td>
</tr>
<tr>
<td>30</td>
<td>212</td>
<td>306</td>
<td>426</td>
</tr>
</tbody>
</table>

* Human bone marrow was from bone marrow No. 1 (see Table 3) and rat bone marrow was obtained from 6–8 wk-old CR/RAR rats.

1. Nucleated cells excluding metamyelocytes, stab forms and mature granulocytes.

12.5%, 25%, and 50% concentration of serum were 204, 342, and 272 for patient No. 17 and 248, 388, and 350 for patient No. 18, respectively.

All the colonies in these experiments were granulocytic and contained cells in all stages of maturation to mature neutrophils. The number of cells per colony, calculated from colonies obtained with 50% human serum, ranged between 110 and 520, with no significant relationship to any disease.

The efficiency of colony formation with human serum can vary with cells from different bone marrows (Table 3). The comparison between sera in Tables 1 and 2 and Figs. 1 and 2 were, therefore, made with the same bone marrow cells. A comparison of the activity of human serum on human and rat bone marrow cells has indicated (Table 4) that although one of the normal human serums gave good colony formation with rat cells, three other active human serums tested gave poor colony formation with rat cells.

DISCUSSION

The present results have shown that human serum can induce colony formation with human bone marrow cells and that there is no need to dialyze or specially treat the serum, as has been reported when using rodent marrow cells. Our results show the importance of testing induction by human serum with human, and not with rodent, bone marrow cells. It has previously been reported that conditioned medium as a course of inducer can show species specificity. In all cases, all the colonies obtained from human bone marrow were granulocytic.

The results with 25% of human serum have shown that with this concentration sera from untreated acute leukemias and chronic myeloid leukemias had about the same average colony-inducing activity as normal sera. The treated acute leukemias had a higher activity than the untreated. Leukopenia can result in an increase in colony-inducing activity, and since leukopenia is induced by the antileukemia treatment, this may explain the higher activity in the treated patients. In the leukemias tested, sera from chronic lymphocytic leukemias showed the highest average inducing activity. The inducer can be produced by spleen and some lymphoid leukemic cells and these high levels may be due to the excess of lymphoid cells in these patients. The high activity in patients only with fever may also be due to hyperactivity of the
lymphoid system as a response to the fever. The serum from patients with Hodgkin’s disease tested; all had higher than normal inducing activity. However, since these patients were all under treatment, it will be of interest to extend these studies to untreated patients with Hodgkin’s disease. It will also be of interest to determine the role of external factors, such as infection and endotoxin, on the inducing activity of human serum.

The comparison of different concentrations of serum has shown that only in the untreated acute leukemias, but not in the other cases, was there a lower than normal activity at high serum concentration. This suggests that the serum of the untreated acute leukemias contained an inhibitor of colony formation. The lowest average number of colonies from the three serum concentrations tested was found in the untreated acute myeloid leukemia, and this suggests that there may also have been a deficiency of inducer. A deficiency of inducer in the bone marrow, and/or the presence of inhibitors, can help to explain the deficiency of mature cells in the acute leukemias. Since the highest concentration of serum tested was 50%, the 100% concentration that exists in the patients may show an even higher inhibition in vivo in these cases. There may also be a genetic deficiency in some myeloid leukemic cells in the ability to respond to the inducer,24 and the diagnosis of responding and nonresponding leukemic cells can be made by our in vitro assay.1415

The present results may be potentially of help in diagnosis. It would, of course, be of interest to extend these findings with human bone marrow to a similar analysis with other patients.

REFERENCES

Differences in Inducing Activity for Human Bone Marrow Colonies in Normal Serum and Serum From Patients With Leukemia

Uri Mintz and Leo Sachs