Serum Lactic Dehydrogenase and Serum Transaminase in Human Leukemia

By GORDON B. MAGILL, FELIX WROBLEWSKI and JOHN S. LaDUE

DURING the initial studies on serum lactic dehydrogenase (SLD) and serum transaminase (SGOT) in relation to myocardial infarction, high levels of SLD activity were noted in patients with acute stem cell leukemia and with chronic myelogenous leukemia as well as in patients with widespread metastatic carcinoma. A preliminary report by Hill and Levi also indicated a high incidence of elevated SLD in neoplastic disease. Subsequent reports have extended the observations on leukemia, both in man and in animals, and have postulated certain mechanisms that might explain the SLD changes. In order to evaluate these SLD alterations, both in terms of clinical significance as well as in terms of possible use as a biochemical parameter of neoplastic activity, serial measurements of SLD and SGOT were studied in a large series of cases. The purpose of this report is to present the observations in a group of 66 patients with leukemia. Similar observations in a group of patients with solid tumors will be the subject of a separate report.

MATERIALS AND METHODS

Patients.—Included in the present report of 66 patients with leukemia are 56 adults and 10 children (table 1). Diagnoses were based on complete histories, physical examinations, peripheral hemograms and bone marrow aspirations.

Laboratory procedures.—Estimations of SLD and SGOT were performed by means of technics previously reported. Daily blood counts and periodic estimations of certain liver function tests (i.e. bilirubin, Bromsulphalein retention, alkaline phosphatase, thymol turbidity, cephalin flocculation, cholesterol and esters and serum proteins) were performed by standard laboratory procedures. Serial bone marrow aspirations were performed as indicated by the clinical condition of the patient, with estimations of over-all cellularity as well as differential counting of the aspirated material.

From the divisions of Clinical Chemotherapy and Experimental Medicine, Sloan-Kettering Institute for Cancer Research, and the Chemotherapy Service, Department of Medicine, Memorial and James Ewing Hospitals, New York, N. Y.

Supported by grants (C1889 and C3215) from the National Cancer Institute, of the National Institutes of Health, Public Health Service; and grants from the American Cancer Society, Inc., the Damon Runyon Memorial Fund for Cancer Research, Inc., the Albert and Mary Lasker Foundation, Inc., and the Grant Foundation.

Presented at the Colorado Regional Meeting of the American College of Physicians and the Colorado Society of Internal Medicine, Colorado Springs, Colo., January 18, 1958.

The authors are indebted to Drs. R. R. Ellison, M. L. Murphy and C. T. Tan for their help in the selection and evaluation of the patients. The authors wish also to acknowledge the technical assistance of Martin Padgainy, Carol Ross and Joan Pasternak.

Submitted May 27, 1958; accepted for publication Jan. 6, 1959.

*In the initial studies on 161 normal adults, the mean SLD level was 470 units with a range of ±130 units.

870
RESULTS

Serum Lactic Dehydrogenase

Acute leukemia (adults).—Of 30 adult patients with acute (or subacute) leukemia, 27 were followed serially for 1 to 82 weeks (average, 21 weeks). As indicated in table 1, 23, or 77 per cent, of the 30 patients demonstrated elevated

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>No. of Patients</th>
<th>Acute (Yr.)</th>
<th>% w/ Elev. SLD</th>
<th>Range Max. SLD (Units)</th>
<th>Aver. Max. SLD (Units)</th>
<th>Range WBC (&lt;1000)</th>
<th>Aver. WBC (&lt;1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (Adults)*</td>
<td>30</td>
<td>15-75</td>
<td>23</td>
<td>77</td>
<td>158-4860</td>
<td>1464</td>
<td>5.2-366.0</td>
</tr>
<tr>
<td>Acute (Children)</td>
<td>10</td>
<td>2-13</td>
<td>7</td>
<td>70</td>
<td>360-8232</td>
<td>2168</td>
<td>0.9-117.0</td>
</tr>
<tr>
<td>Chronic Myelocytic</td>
<td>16</td>
<td>31-77</td>
<td>15</td>
<td>94</td>
<td>530-8640</td>
<td>2114</td>
<td>6.8-500.0</td>
</tr>
<tr>
<td>Chronic Lymphocytic</td>
<td>10</td>
<td>42-74</td>
<td>6</td>
<td>60</td>
<td>360-1800</td>
<td>979</td>
<td>106.0-800.0</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>2-77</td>
<td>51</td>
<td>77%</td>
<td>156-8640</td>
<td>1806</td>
<td>0.9-800.0</td>
</tr>
</tbody>
</table>

*Includes subacute leukemia.
| At time of SLD sampling.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (Adults)</td>
<td>21</td>
<td>4</td>
<td>19</td>
<td>3</td>
<td>14</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Acute (Children)</td>
<td>5</td>
<td>1</td>
<td>20</td>
<td>2</td>
<td>40</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Chronic Myelocytic</td>
<td>12</td>
<td>6</td>
<td>50</td>
<td>2</td>
<td>17</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Chronic Lymphocytic</td>
<td>5</td>
<td>1</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>12</td>
<td>28</td>
<td>6</td>
<td>14</td>
<td>14</td>
<td>33</td>
</tr>
</tbody>
</table>

*Number of patients with increased SLD and followed serially (see text).

Group A: Patients in whom SLD levels were nearly always proportional to the activity of the leukemic process as measured by bone marrow aspiration, hemograms and clinical condition. SLD levels changed with other parameters on all or on all but one occasion, in each patient.

Group B: Those in whom SLD levels were indicative of leukemic activity on occasion but not in a reliable manner.

Group C: Those in whom there was a tendency for the SLD to parallel leukemic activity but in a poorly defined manner.

Group D: Those in whom there was no apparent correlation between leukemic activity and SLD.

Group E: Those in whom SLD became elevated only during the terminal phase of the leukemic process.
SLD (greater than 600 units) at least once. Two patients with elevated SLD were not available for serial determinations. Pertinent to the present study were the 21 patients who demonstrated increased SLD and who were followed serially. In order to evaluate SLD as a possible parameter in the management and therapy of leukemia, patients were grouped according to the degree of correlation between serial enzyme levels and hematologic status. Four patients (19 per cent) showed a reasonably clear-cut correlation between SLD and activity of the leukemic process (Group A, table 2). The serial changes in 2 of these patients are shown in figures 1 and 2. In another 3 patients (14 per cent), there was apparent correlation only part of the time (Group B, fig. 3). A rather vague, poorly defined relationship was noted between SLD and hematologic status in 8 patients (38 per cent) (Group C, fig. 3). No correlation between SLD levels and leukemic activity was noted in the other 6 patients, of whom 3 had periodic SLD elevations (Group D) and 3 had increased SLD only during the terminal phases of their illnesses (Group E).

Acute leukemia (children).—Among the 10 children in the study, 7 were followed serially for 10 to 37 weeks (average, 21 weeks). Of the 7 who demonstrated increased levels of SLD (table 1), 5 were followed with serial

![Graph showing serial SLD levels in an adult male with acute leukemia.](image)

**Fig. 1.**—Serial SLD levels in an adult male with acute leukemia. Note the rapid drop in both SLD and WBC and the rapid improvement in marrow counts with the initial prednisone therapy. Subsequent exacerbations of disease were associated with elevated SLD except for the terminal aleukemic phase. Classified as good correlation (Group A).

6CP = 6 Chloro-purine.
SERUM LACTIC DEHYDROGENASE AND TRANSAMINASE IN LEUKEMIA

C.K. 39 yrs. ♀ SUB-AC MYELO LEUKEMIA

Fig. 2.—SLD changes in an adult female with subacute myelocytic leukemia. Dehydrogenase levels in general paralleled leukemic state and in one instance (*) reverted to normal before improvement was noted in WBC. On another occasion, however, SLD remained normal during apparent leukemic relapse (days 275 to 350). Classified as good correlation (Group A).

6MP = 6 Mercaptopurine.

determinations (table 2). According to the above classification, 2 showed some correlation (Groups A and B, fig. 5), whereas 3 demonstrated little if any correlation between leukemic activity and SLD. Since the data on the children are rather sparse, they are presented only as preliminary observations.

Chronic myelocytic leukemia.—Thirteen of the 16 patients with chronic myelocytic leukemia were studied serially for 2 to 70 weeks (average, 30 weeks). Fifteen had elevated SLD activity (table 1), and 12 of these were in the group observed serially (table 2). As noted in the table, correlation
Subacute myelocytic leukemia.—Of 70 year old female with subacute myelocytic leukemia. Note that initially and terminally there was inconstant SLD elevation at times when WBC was moderately to markedly elevated.

Chronic lymphocytic leukemia.—Of the 10 subjects in this group, 8 were followed serially for 6 to 70 weeks (average, 40 weeks). Six patients demonstrated elevated levels of SLD activity but at a much lower level than the chronic myelocytic group (the average maximal SLD of group was 979 units as compared to 2114 units for the chronic myelocytic group; table 1). Five of the patients with increased SLD were among those followed serially. As noted in table 2, only 1 demonstrated apparent correlation between SLD levels and disease activity. In this instance the patient had an associated acquired
Fig. 4.—Example of poor correlation (Group C) in a 15 year old male with acute leukemia. Note the terminal flare in WBC associated with high levels of SLD.

DON = 6 diazo-5 oxo-1-norleucine.

hemolytic anemia, and the improvement noted in hematologic status with therapy was paralleled by decreased levels of SLD (fig. 7). Little or no correlation was noted between SLD levels and disease activity in the other 4 patients, in one of whom elevated SLD occurred only during the terminal phase of illness (Group E).

Serum Transaminase

In contrast to the frequency of SLD elevations in these patients, increased SGOT activity was not common. As indicated in table 3, 7 of 29 adults with acute leukemia showed initial elevations, of whom only 3 had levels over 100 units. Another 3 patients developed SGOT levels over 100 units during subsequent serial observations. Of the 6 subjects with SGOT levels of over 100 units, 4 had associated hepatitis with jaundice, 1 had possible liver damage from drug administration and 1 had terminal septicemia with presumed secondary hepatitis. It is interesting to note that in 2 of these cases SLD levels were normal.
Fig. 5.—Serial SLD in an 11 year boy with acute leukemia. Although initial blood samples were not obtained, subsequent SLD levels showed a fair correlation with the leukemic state (Group B).

HN2 = Nitrogen mustard (Mustargen).
Ameth. = Amethopterin (Methotrexate).

In the small group of children studied, a slight elevation of SGOT was observed in only 1. In other leukemic children not included here, SGOT levels were high in conjunction with acute hepatitis.
SERUM LACTIC DEHYDROGENASE AND TRANSAMINASE IN LEUKEMIA

**Fig. 6.**—Example of good correlation (Group A) between SLD levels and leukemic activity in a 58 year old male with chronic myelocytic leukemia.

TEM = triethylene melamine.

Two patients with chronic myelocytic leukemia had slightly elevated initial SGOT levels, but none were over 100 units. Two subjects subsequently showed levels over 100 units, 1 in association with transient drug toxicity and the other in relation to apparent hepatitis.

Of the 8 subjects with chronic lymphocytic leukemia, 1 had a slight SGOT elevation initially but none showed levels over 100 units.

**DISCUSSION**

The high incidence of elevated serum lactic dehydrogenase in patients with leukemia noted in previous preliminary observations has been confirmed in the present series of 66 patients. That this alteration is not specific for a leukemic or even hematologic process, however, is suggested from the similarly abnormal levels observed with disseminated carcinomas, pregnancy, myocardial infarction and hepatitis.

The mechanism by which SLD is elevated in leukemia is not clear. Although it has been suggested that an increased rate of destruction of erythrocytes might account for this elevation,

there are indications in the present series that weigh against this as a significant mechanism. For example, the patient with a marked, active hemolytic process was one with chronic lymphatic
leukemia and only a modest elevation of SLD (fig. 7). On the other hand, other patients with relatively mild anemia had markedly elevated SLD.

In investigating other possible mechanisms of SLD elevation, one can find cases in the present series to suggest a correlation with total peripheral white cell count, peripheral immature forms, percentage of blast forms in marrow aspirate, etc. However, for each of these there can also be found a significant number of cases to rule against any absolute correlation. There was noted a definite difference between the chronic myelocytic leukemias on the one hand and the chronic lymphatic variety on the other, with the maximal and mean levels running more than twice as high in the former group. In the myelocytic group there appeared to be some relationship between the level of SLD and the absolute number of circulating immature granulocytes.

The most attractive thesis as to the source of elevated SLD in leukemia is that of more rapid leakage of enzyme from more fragile cells. The fact that the cells of both myelocytic and lymphocytic leukemia have a low content of lactic dehydrogenase could be invoked to support such a thesis. That these very same myelocytic cells are high in isomerase in association with elevated serum isomerase, on the other hand, would weigh against this theory. Also
against such a simple explanation is the finding of elevated levels of lactic dehydrogenase in the tissues, as well as the sera, of mice with transplantable leukemia. It is apparent that further investigation is needed to clarify the mechanism for such enzyme alterations.

In regard to the clinical usefulness of SLD determinations in leukemia, it is apparent from the present series that there is a disappointing lack of over-all correlation between serial SLD levels and established parameters of leukemic activity. A reasonable correlation was noted in cases of chronic myelocytic leukemia, although even here there was a fair amount of variation both as to degree and timing of correlation between SLD changes and alterations in other parameters. In the acute leukemias, a group in which another parameter would be particularly useful, fair to good correlation was noted in only 33 per cent of the adults and 40 per cent of the children (table 2). In this regard, it should be emphasized that although these two groups showed 77 per cent and 70 per cent elevated SLD, respectively, at some time in their disease (table 1), in the majority of such cases (17 of 26) such elevations were noted only sporadically or terminally (table 2). In chronic lymphatic leukemia, such a difference was even more marked, and serial SLD appeared to be of no practical value.

Studies by Vesell and Bean, using electrophoretic fractionation of serum, indicated a qualitative difference between the elevated SLD levels of myocardial infarction and those of leukemia. In addition, they noted a shift in the fractionation pattern even in 2 leukemic subjects with normal total SLD levels. If these observations are confirmed by more extensive study, both the clinical and laboratory usefulness of lactic dehydrogenase determinations in leukemia could be enhanced.

The infrequency of elevated transaminase in spite of the high incidence of abnormal dehydrogenase in these cases indicates a possibly useful differential point. Of the 8 patients who demonstrated SGOT levels over 100 units, 5 presumably had viral hepatitis, 2 apparently had hepatic toxicity from drugs, and 1 had terminal septicemia. On the other hand, 7 patients with evidence of other types of liver involvement showed normal or slightly elevated SGOT. Of these, 4 had jaundice—2 apparently related to cirrhosis and 2, to terminal liver failure. Even more striking were the other 3 patients, all of whom showed leukemic infiltration of the liver at autopsy (SGOT levels antemortem were 25, 51 and 77). If these differences are confirmed with further

<table>
<thead>
<tr>
<th>Type of Leukemia</th>
<th>Total No.</th>
<th>Normal (10-50 U.)</th>
<th>Slight Elevation (51-100 U.)</th>
<th>Definite Elevation (&gt;100 U.)</th>
<th>Subsequent Elevation (&gt;100 U.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (Adults)</td>
<td>29</td>
<td>22</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Acute (Children)</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic Myelocytic</td>
<td>16</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Lymphocytic</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>51</td>
<td>7</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
studies, a transaminase of over 100 units in a leukemic patient with jaundice would suggest either a viral or a toxic type hepatitis. The presence of a normal or slightly elevated transaminase in a leukemic patient with jaundice or other evidence of hepatic involvement would be compatible with leukemic involvement of the liver.

SUMMARY AND CONCLUSIONS

1. Serum lactic dehydrogenase (SLD) was measured in 66 patients with leukemia. Elevated levels were observed in 23 (77 per cent) of 30 adults with acute leukemia; in 7 (70 per cent) of 10 children with acute leukemia; in 15 (94 per cent) of 16 patients with chronic myelocytic leukemia, and in 6 (60 per cent) of 10 subjects with chronic lymphatic leukemia.

2. The degree of SLD elevation appeared to be significantly greater in the chronic myelocytic than in the chronic lymphatic group.

3. Serial determinations of SLD were performed for periods of from 1 to 82 weeks in 55 patients, of whom 43 had elevated levels at one time or another. Fair to good correlation between SLD and conventional parameters of leukemic activity was noted in 7 (33 per cent) of adult acute leukemias; in 2 (40 per cent) of child leukemias; in 8 (67 per cent) of chronic myelocytic leukemias; and in 1 (20 per cent) of the chronic lymphatic group.

4. Possible sources of enzymes are discussed. At the present time the mechanism of SLD elevation in leukemia remains an unsolved problem.

5. Serum transaminase (SGOT) levels were studied in 61 subjects. Levels greater than 100 units were seen in only 8 patients, of whom 7 had either viral or toxic hepatitis and 1 had terminal septicemia. Other types of liver impairment, including leukemic infiltration, were associated with normal or slightly elevated SGOT.

SUMARIO IN INTERLINGUA

1. Dishydrogenase lactic del sero (DLS) esesseva mesurate in 66 patientes con leucemia. Le nivello de DLS esesseva elevate in 23 ex 30 adultos con leucemia acute (77 pro cento), in 7 ex 10 juveniles con leucemia acute (70 pro cento), in 15 ex 16 patientes con chronic leucemia myelocytic (94 pro cento), e in 6 ex 10 patientes con chronic leucemia lymphatic (60 pro cento).

2. Le grado del elevation de DLS esesseva significativemente plus alte in le gruppo con chronic leucemia myelocytic que in le gruppo con chronic leucemia lymphatic.

3. Determinationes serial de DLS esesseva effectuate durante periodos de inter 1 e 82 septimanas in 55 patientes. Quaranta-tres de illes monstrava nivellos elevate a un tempore o un altere. Correlationes satis bon o bon inter DLS e parametros conventional de activitate leucemic esesseva notate in 7 (33 pro cento) de un gruppo de adultos con leucemia acute, in 2 (40 pro cento) de un gruppo de juveniles con leucemia, in 8 (67 pro cento) de un gruppo de patientes con chronic leucemia myelocytic, e in 1 (20 pro cento) de un gruppo de patientes con chronic leucemia lymphatic.

4. Le fontes possibile de enzymeas es discutite. Al tempore presente le
mechanismo del elevation de DLS in leucemia remane un problema non solvite.

5. Nivellos de transaminase glutamic oxalacetic del sero (TGOS) esseva studiate in 61 subjectos. Nivelos de plus que 100 unitates esseva constatate in solmente 8 casos. Septe de iste 8 patientes habeva hepatitis virusal o toxic; le octave habeva septicemia terminal. Altere typos de affection hepatic, incluse infiltration leucemic, esseva associate con nivellos normal o levemente elevate de TGOS.

REFERENCES

Serum Lactic Dehydrogenase and Serum Transaminase in Human Leukemia

GORDON B. MAGILL, FELIX WROBLEWSKI and JOHN S. LADUE