Serum Lactate Dehydrogenase Elevation in Ambulatory Cardiac Patients

Evidence for Chronic Hemolysis

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SUMMARY
Activity of total lactate dehydrogenase (LDH) and that of the heat-stable isozyme (LDH-1) was measured by the method of Strandjord and Clayson in the serum of 62 cardiac patients with congenital and valvular heart disease before and after cardiac catheterization and at follow-up examination after cardiac surgery. A universal elevation of both total and heat-stable LDH was found in patients with prosthetic heart valves of several types. Lesser degrees of abnormalities were seen in a number of the patients without prosthetic devices. Some patients had a small increase in serum enzyme activity the day after cardiac catheterization. The evidence presented implicates hemolysis in the production of these abnormalities. It is suggested that all patients with prosthetic valves and a significant percentage of patients with severe hemodynamic abnormalities have chronic, usually compensated, intravascular hemolysis secondary to mechanical damage to red blood cells. These findings must be kept in mind in interpreting serum LDH determinations in patients with valvular prostheses or congenital and valvular heart disease who present with complaints of chest pain.

Additional Indexing Words:
Isoenzymes Cardiac valve prosthesis Cardiac catheterization

Since 1954 it has been recognized that an elevation of serum lactate dehydrogenase (LDH) activity may reflect internal disease.1 This important enzyme is widely distributed in the body and raised serum levels may result from disease of the heart, liver, skeletal muscle, blood, kidneys, and lungs.2-7 In 1957, it was discovered that serum LDH is not a single protein,8 and it is now known that it usually consists of five isoenzymes or isozymes with varying physical and chemical properties.4,6,9 All human tissues studied except red blood cells contain all five isozymes but with differences in relative concentrations so that each organ tends to have a specific isoenzyme pattern.4,5 Vesell and Bearn8 in 1957 first suggested that separation of the serum activity into its five components might help to identify the tissue of origin when the total LDH activity in the blood is elevated and thus add a degree of diagnostic specificity to what is otherwise a relatively nonspecific examination. Wróblewski and associates10 in 1960 applied this principle to the diagnosis of myocardial infarction. Since then characteristic isozyme patterns have been identified in the conditions that produce elevated serum levels.3-7

Among the many different methods of separating or differentiating between the isozymes,9 electrophoresis has been the most widely employed.4-6,10-12 According to the convention which labels the most anodic components in the electrophoretic field as LDH-1 and the slowest component LDH-5, LDH-1 is the component most elevated in myocardial infarction and LDH-5 is the one most elevated.

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in hepatic parenchymal disease. Unfortunately, electrophoretic separation is too cumbersome for use by most routine clinical laboratories, so simpler methods have been sought. Hill\(^{11}\) appears to have been the first to study the varying heat lability of the different forms. In 1961 Strandjord and Clayson\(^{13}\) and Wróblewski and Gregory\(^{12}\) suggested that heat lability be used as a simple method of distinguishing between human LDH isozymes. Strandjord and associates\(^{14}\) showed that serum LDH activity may be separated into heat-stable (LDH-1) and heat-labile components on the basis of the activity which remains after incubation at 65 C for 30 minutes. They found determination of heat-stable LDH activity valuable in the diagnosis of myocardial infarction, especially in the presence of other conditions causing LDH elevation such as acute hepatocellular injury and during the postoperative period. Others have subsequently used this simple separative technique, primarily to distinguish isozymes of cardiac and hepatic origin.\(^{5,15-18}\)

We have experienced difficulty in interpreting elevated values of heat-stable and total LDH in several patients with cardiac disease but without evidence for myocardial infarction, particularly after cardiac catheterization or cardiac surgery. Therefore, we decided to survey a population of ambulatory cardiac patients in order to define further the usefulness of these determinations. It was found that all patients with valve prostheses and a number of those with heart disease associated with significant hemodynamic abnormalities but without prosthetic devices had elevated total and particularly heat-stable serum LDH activity. Red blood cells also contain large amounts of LDH-1, and it is our feeling that these elevations of serum enzyme activity reflect a low-grade intravascular hemolysis rather than myocardial damage. This factor of hemolysis should be recognized as a source of misinterpretation of the meaning of elevated serum LDH values.

A preliminary report of the findings has appeared elsewhere.\(^{19}\)

**Methods**

The population studied was divided into two groups of randomly selected patients. The patients in group I were those without prosthetic valves who were entering the hospital on an ambulatory basis for elective cardiac catheterization. The majority had congenital or rheumatic heart disease; some had arteriosclerosis, and one each had pericardial and primary pulmonary vessel disease (table 1). Fifteen patients who were returning for evaluation after previous cardiovascular surgery were entirely or nearly asymptomatic and had minimal or no demonstrable hemodynamic abnormality. Twenty-eight of the patients were being evaluated for possible cardiac surgery. These had symptoms of mild to severe cardiac decompensation and had varying degrees of hemodynamic abnormality. Four persons suspected of having heart disease were found to be normal by cardiac catheterization. There were 19 males and 28 females in this group and their ages ranged from 15 to 71 years with an average age of 33.

Group II was composed of patients with artificial heart valves of several designs 1 to 45 (average of 14) months after operation (tables 2 and 3). Most of these patients were in the hospital for elective, follow-up cardiac catheterization; some were in the outpatient clinic. Patient 62 had initially improved after insertion of a Bahnson type prosthesis for his diseased aortic valve, but at the time he was studied 40 months postoperatively, his condition was again deteriorating from "restenosis" of the prosthesis with some aortic insufficiency. Patients 63, 64, and 65 presented with evidence of a less than optimum surgical result as stated in the table. All of the others were considerably improved, although residual abnormalities were demonstrable in most. There were eight males and 16 females in group II, and their ages ranged from 26 to 66 years with an average age of 40.

None of the patients in either group gave a history suggestive of recent acute myocardial damage.

Blood was drawn for LDH determinations in the morning on the day of, but before, cardiac catheterization and on the following morning from all but four of the hospitalized patients, and at the time of follow-up clinic visit from the outpatients. Total and heat-stable activity was determined in the hospital's clinical chemistry laboratory by the automated method of Strandjord and Clayson\(^{20}\) which involves incubation at 65 C for 30 minutes. There was no visible evidence of hemolysis in the serum of any sample. Although trace amounts of LDH-2, 3, and 4 activity can be detected after incubation of serum at 65 C for 30 minutes, the heat-stable activity
so determined represents LDH-1 as determined electrophoretically, for all practical purposes.21

Normal values for this method have been established on a group of blood bank donors between the ages of 20 and 60 years with the upper limits of normal being given as 425 IU and 100 IU for total and heat-stable LDH, respectively.20 Standard techniques were used in the statistical analysis* of this group of normals. There was no significant variation of serum LDH with age. Although the data did not precisely fit a normal distribution, the fit was good enough and the size of the sample large enough so that an analysis based on the assumption of a normal distribution seemed appropriate. Mean values ± two standard deviations were 330 ± 124 IU and 68 ± 30 IU for total and heat-stable activity, respectively. Therefore, for the purposes of this study, the upper limits of normal were taken to be the convenient figures 450 and 100 IU, respectively. Reference to a table of the normal distribution reveals that the probability of a normal being above this level is 0.026 for the total and 0.017 for the heat-stable LDH. Replicate determinations on the same sample using this method are virtually identical (see fig. 7 of reference 20), and quality control studies performed on the same lyophilized sample over the course of several months yielded a coefficient of variation of 2.3%.20

Creatine phosphokinase (CPK) was determined in Dr. Yunis’ laboratory by the method of Tanzer and Bilvarg22 with the following modifications: (1) Ten microliters of 0.285 M aqueous solution of 2-mercaptoethanol (Eastman) was added to the blank, unknown, and control samples before the initiation of the reaction. (2) The optical density change per minute from 2 to 11 minutes of the enzyme reaction was used. (3) Recovery control samples consisted of the patient’s own serum to which was added 10 microliters of 0.05 M ammonium citrate containing 0.47 μg of purified creatine phosphokinase.† Mean values ± two standard deviations for the activity of this enzyme in the serum as determined by this method are 3 ± 2 units in females and 4.75 ± 3.75 units in males. Therefore, the upper limits of normal were taken to be 5 and 8.5 units, respectively, with the probability that a normal will be above this level being 0.023.

Hematological and other chemical procedures were carried out in the hospital’s routine clinical laboratories.

Results

Of the 43 patients in group I with hemodynamic abnormalities, 10, or 23%, had elevated total LDH and seven, or 16%, had elevated heat-stable LDH prior to cardiac catheterization (fig. 1). The serum enzyme values for this group were not normally distributed so a t-test could not be applied to compare this group to the normals, since this test assumes a normal distribution in both sample groups. Therefore, the Kolmogorov-Smirnov test23 was used. It was found that the probability was less than 0.01 that this patient group and the normals could be from the same population, both for total and heat-stable LDH.

Serum was obtained the day following hemodynamic studies in 39 of these patients. Fifteen, or 38%, showed abnormal total and nine, or 23%, abnormal heat-stable activities. Considering all 39 patients, the difference between pre-catheterization and post-catheterization values was significant at a probability level of 0.005 for the total LDH and 0.025 for the heat-stable LDH.

Patients 21 and 29 had rather striking elevations of serum enzyme activity the day following cardiac catheterization. Both had clinically obvious complications of the procedure which could account for these abnormalities. Patient 21 had fever, thrombophlebitis, and pulmonary emboli, and patient 29 had an arrhythmia with hypotension.

*The raw data for this analysis were supplied by Strandjord and Clayson.
†C.F. Boehringer and Sons, Mannheim, Germany.
Table 1
Serum LDH Activity in Patients without Prosthetic Valves (Group I)

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<td>P.O. closure of ostium primum atrial septal defect, with residual mitral insufficiency and third degree heart block</td>
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<td>M</td>
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<td>64</td>
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<td>F</td>
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<td>76</td>
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The four patients without demonstrable hemodynamic abnormalities had normal enzyme activities both before and after cardiac catheterization.

All of the 24 patients with prosthetic valves (Group II) had elevations of heat-stable LDH. All except patients 48 and 68 had elevated total LDH as well. In most of the patients the elevations were of a striking degree, particularly the heat-stable fraction. There was an increase of LDH regardless of the type of artificial valve used, the number of valves (one or two) replaced, or the valve or valves that were replaced. In most cases

**Table 1 (continued)**

<table>
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<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis or P.O. state</th>
<th>LDH before catheterization Total (I.U.)</th>
<th>LDH before catheterization Heat-stable (I.U.)</th>
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<th>LDH after catheterization Heat-stable (I.U.)</th>
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<td>F</td>
<td>Mitrall stenosis, aortic stenosis, and insufficiency</td>
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<td>455</td>
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**Table 2**

**Serum LDH Activity in Patients with Prosthetic Valves (Group II)**

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<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Valve type</th>
<th>Location</th>
<th>Time P.O. (mo)</th>
<th>LDH* Total (I.U.)</th>
<th>Heat-stable (I.U.)</th>
<th>HGB (%)</th>
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<td>Mitrall</td>
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<td>730</td>
<td>255</td>
<td>17.2</td>
</tr>
<tr>
<td>57</td>
<td>43</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Mitrall</td>
<td>13</td>
<td>761</td>
<td>204</td>
<td>16.9</td>
</tr>
<tr>
<td>58</td>
<td>36</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Mitrall</td>
<td>14</td>
<td>473</td>
<td>135</td>
<td>13.9</td>
</tr>
<tr>
<td>59</td>
<td>53</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Tricuspid</td>
<td>13</td>
<td>758</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>48</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Mitrall</td>
<td>15</td>
<td>614</td>
<td>183</td>
<td>15.9</td>
</tr>
<tr>
<td>61</td>
<td>38</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Tricuspid</td>
<td>27</td>
<td>506</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>44</td>
<td>M</td>
<td>Bahanson</td>
<td>Aortic</td>
<td>40</td>
<td>700</td>
<td>162</td>
<td></td>
</tr>
</tbody>
</table>

*All enzyme values reported are from blood drawn from outpatients or from inpatients prior to cardiac catheterization.
**Table 3**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Valve type</th>
<th>Location</th>
<th>Time P.O. (mo)</th>
<th>Clinical status</th>
<th>Hgb (g %)</th>
<th>Reticulocyte count (%)</th>
<th>Red cell indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>23</td>
<td>M</td>
<td>Gott-Daggett Magovern</td>
<td>Mitral, aortic</td>
<td>1½</td>
<td>Aortic insufficiency murmur developed 1½ mo P.O.</td>
<td>13.1</td>
<td>5.6</td>
<td>MCV76 α MCH25 γ γ MCC33 %</td>
</tr>
<tr>
<td>64</td>
<td>24</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Mitral</td>
<td>9</td>
<td>Mitral insufficiency murmur present since soon after surgery; symptomatic anemia</td>
<td>9.9</td>
<td>4.2</td>
<td>MCV84 MCH29 MCC33</td>
</tr>
<tr>
<td>65</td>
<td>36</td>
<td>M</td>
<td>Starr-Edwards</td>
<td>Aortic</td>
<td>11</td>
<td>Initially improved; then progressive congestive heart failure with onset of atrial fibrillation; significant mitral insufficiency and slight reflux around prosthesis</td>
<td>13.4</td>
<td>2.7</td>
<td>MCV81 MCH28 MCC35</td>
</tr>
<tr>
<td>66</td>
<td>42</td>
<td>F</td>
<td>Magovern</td>
<td>Aortic</td>
<td>10</td>
<td>Very good</td>
<td>14.6</td>
<td>2.6</td>
<td>MCV81 MCH28 MCC35</td>
</tr>
<tr>
<td>67†</td>
<td>53</td>
<td>M</td>
<td>Magovern</td>
<td>Aortic</td>
<td>12</td>
<td>Very good</td>
<td>17.6</td>
<td>2.3</td>
<td>MCV81 MCH28 MCC35</td>
</tr>
<tr>
<td>68</td>
<td>26</td>
<td>M</td>
<td>Starr-Edwards</td>
<td>Mitral</td>
<td>19</td>
<td>Excellent</td>
<td>15.6</td>
<td>1.3</td>
<td>MCV81 MCH28 MCC35</td>
</tr>
<tr>
<td>69</td>
<td>66</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Aortic</td>
<td>29</td>
<td>Excellent</td>
<td>13.3</td>
<td>2.1</td>
<td>MCV81 MCH28 MCC35</td>
</tr>
<tr>
<td>70</td>
<td>23</td>
<td>F</td>
<td>Starr-Edwards</td>
<td>Mitral</td>
<td>45</td>
<td>Very good</td>
<td>14.4</td>
<td>3.4</td>
<td>MCV81 MCH28 MCC35</td>
</tr>
</tbody>
</table>

*All enzyme values reported are from blood drawn from outpatients or from inpatients prior to cardiac catheterization.
†Nonspecific cold agglutinin present.
‡Fecal urobilinogen in patient 67 measured 362 Ehrlich units.

The elevation in total LDH activity was not entirely accounted for by the increased heat-stable fraction. The increased serum enzyme activity seen in this group is obviously significant; therefore, formal statistical analysis was not carried out.

Enzyme determinations were performed in 10 of these patients also on the day following cardiac catheterization. In only patient 57 was there a significant change. This patient had total LDH of 761 IU and heat-stable LDH of 204 IU the day before, and of 3,590 and 1,730, respectively, the day after the procedure. Although she was asymptomatic, she had definite electrocardiographic evidence of anterior myocardial damage. There was no evidence of myocardial damage, such as electrocardiographic changes, in any case except this one.

In eight patients hematopoietic studies were obtained (table 3). Pertinent data included a slight to significant anemia in many, a slight to significant elevation of the reticulocyte count in all even if hemoglobins were normal, abnormally low values for serum iron in two, complete absence of serum haptoglobin in all, a trace of methemalbumin detectable in only one patient, and no detectable hemoglobin or hemosiderin in the urine of any patient. All of our patients with prosthetic...
SERUM LACTATE DEHYDROGENASE

<table>
<thead>
<tr>
<th>Serum</th>
<th>Iron binding capacity (µg %)</th>
<th>Haptoglobin (µg %)</th>
<th>Methemalbumin (µg %)</th>
<th>Bilirubin (direct &amp; indir.)</th>
<th>Coombs' test</th>
<th>Urine</th>
<th>LDH*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Trace</td>
<td>0.4/1.4</td>
<td>Negative†</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>27</td>
<td>262</td>
<td>None</td>
<td>0.1/0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Trace</td>
<td>0.1/0.7</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>147</td>
<td>348</td>
<td>None</td>
<td>0.1/0.6</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>463</td>
<td>None</td>
<td>0.1/0.3</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>419</td>
<td>None</td>
<td>0.1/0.4</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>336</td>
<td>None</td>
<td>0.1/0.4</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>387</td>
<td>None</td>
<td>0.1/0.4</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Valves receive coumarin anticoagulants and patients 64 and 66 had had some menorrhagia and had been receiving oral iron therapy. Patient 64 was the only one with abnormal red cell indices. CPK levels were determined in six of these patients and were normal in all patients except patients 67 and 69 in whom the elevations were slight and proportionally much less than the LDH elevations in the same patients.

Preoperative and postoperative data were available in patient 33 only. Before surgery, values of both total and heat-stable LDH were well within normal limits. One month postoperatively there was a considerable elevation of both of these enzymes in the serum at 1,030 and 199 IU, respectively.

Discussion

The most striking finding in this study is the uniform elevation in both heat-stable and total LDH activities in the serum of all patients with prosthetic valves of several designs from 1 month to almost 5 years after surgery. Two possible explanations come to mind: (1) The presence of the valve causes continuing, low-grade myocardial damage, possibly by stresses imparted to the suture line in the case of the Starr-Edwards, Gott-Daggett, and Bahnson valves, or the metal points used for fixing the Magovern prosthesis which inserts into the myocardium. (2) The enzyme activity comes from a source other than myocardium.
Reports of fairly large series of patients having heart disease\textsuperscript{5,4} have shown that LDH-1 is elevated primarily in patients with definite myocardial infarction as evidenced by clinical and ECG data and usually not in patients with angina pectoris, coronary insufficiency, hypertension, or congestive heart failure. The latter can cause elevation in LDH-5 and hence total LDH by producing hepatic congestion. The amount of heat-stable enzyme activity found in some of our patients was equivalent to that found in patients with small myocardial infarctions. It is difficult to imagine myocardial damage continuing for this length of time, often years, without some deterioration in clinical status. However, all of our patients had shown great improvement after operation as evidenced by both clinical and laboratory data, and only a few had failed to maintain it. Therefore, a renewable source for this enzyme activity must be sought.

Although the primary interest in the determination of isozyme 1 (and 2) has been for the diagnosis of myocardial infarction,\textsuperscript{4, 10, 13, 14, 17, 18} other tissues have a relatively high concentration of these two isozymes, notably the renal cortex and red blood cells.\textsuperscript{1, 5, 9} Significant elevations of LDH-1 and LDH-2 have been noted in a variety of renal diseases and disease of red blood cells, particularly pernicious anemia and hemolytic anemias.\textsuperscript{3-5, 7, 24, 25} With regard to hemolytic anemias Wörner and his co-workers\textsuperscript{5, 24, 25} reported that electrophoretic separation of the isozymes allowed them to detect mild or completely compensated hemolysis and to demonstrate hemolysis not detectable with any other methods.\textsuperscript{25}

In 1961 reports began to appear of hemolytic anemias after surgery for endocardial cushion defects and at least seven cases have been reported after repair of both the incomplete (ostium primum type of atrial septal defect) and complete types.\textsuperscript{26-28} Since 1964 numerous instances have been reported of hemolysis in patients with ball-valve prostheses.\textsuperscript{29-33} Dacron-silicone rubber cusps,\textsuperscript{34} and Teflon leaflets\textsuperscript{35} inserted for aortic valve disease. These clinically significant anemias have been associated with mitral insufficiency with a regurgitant jet striking the Teflon patch in the case of the endocardial cushion defects, and development of aortic insufficiency in the case of the prosthetic valves. Laboratory studies in these patients have suggested intravascular hemolysis with fragmentation of red cells in the peripheral smear, elevated plasma hemoglobin, absence of serum haptoglobin with presence of methemalbumin, hemoglobinuria, hemosiderinuria, and iron deficiency resulting from loss of iron through the kidneys. Those patients who have come to autopsy have exhibited heavy renal deposition of hemosiderin without deposition of this pigment in other sites, a finding typical of intravascular hemolysis. In both types of cases turbulence in the regurgitant jet has been suggested most prominently as a causative factor. Fok and Schuboth\textsuperscript{36} stated that mechanical hemolysis is the result of trauma induced by turbulence, not a result of cells being trapped between opposing surfaces, and Sigler and co-workers reviewed other work implicating turbulence.\textsuperscript{27}

More recently Brodeur, and associates have studied red cell survival in patients with both aortic\textsuperscript{37} and mitral\textsuperscript{38} valve Starr-Edwards prostheses. They found that almost all of the subjects with aortic replacements had a decreased red cell half-life although anemia was present only if there was a complicating factor such as the development of aortic insufficiency. The patients with prosthetic mitral valves had a normal red cell half-life unless a complicating factor was present. In another series of patients with mitral valve replacement, mild intravascular hemolysis was suggested by the finding of markedly decreased serum haptoglobin in all but one of the 10 surviving patients and elevated reticulocyte counts in five.\textsuperscript{39}

With the possibility of subclinical to severe hemolytic anemia in patients with prosthetic valves of varying types so well documented,\textsuperscript{26-33, 37-39} and with the known sensitivity of LDH isozyme determination for detecting even the mildest hemolysis,\textsuperscript{5, 24, 25} it seems
reasonable that the consistent elevation of serum LDH levels in our patients with pro-
thetic valves is due to a universal, low-grade hemolysis. The data of table 3 support this
contention. All of the patients presented in table 3 had evidence of intravascular hemoly-
sis of a degree sufficient to cause saturation of the haptoglobin system but not enough to
produce methemalbuminemia, hemoglobinur-
ia, or hemosiderinuria.40 The three patients
with unsatisfactory complicated surgical re-
results had serum LDH levels approximately
twice those of the patients with satisfactory
surgical results. This suggests a relationship
between the success in correcting the hemo-
dynamic abnormalities and the degree of
hemolysis present and is in accord with the
results of others who found anemia only in
patients with significant residual postoperative
lesions (vide supra). The CPK determinations
are particularly helpful. The enzyme creatine
phosphokinase is very specific for disease or
injury to skeletal muscle and myocardium.41
In the presence of normal CPK levels it is
unlikely that the elevated levels of LDH de-
rive from myocardial necrosis. Serum CPK
levels are known to be completely normal in
the presence of hemolysis.41,42 We conclude
that all patients with prosthetic valves have
some degree of intravascular hemolysis.

While this manuscript was in preparation,
the paper of Andersen and associates48 ap-
peared. They demonstrated chronic hemolysis
of a significant degree in 10 patients with
mitral and eight patients with aortic prosth-
eses. Furthermore, they found an increase in
both total LDH and the two terminal LDH
electrophoretic fractions (presumably the two
most anodic components). Our work confirns
and extends their findings.

Hemolysis can also account for the increase
in total LDH seen in these patients beyond
that which is contributed by LDH-1 since
hemolysis commonly elevates LDH-2 even
more than LDH-1.24,25 Furthermore heating
inactivates some of the LDH-1 also so that
the heat-stable LDH does not represent all of
the LDH-1 in a given sample.

Significantly elevated LDH levels were
found in a number of the patients without ar-
tificial valves. These can also be attributed to
a low-grade, compensated, chronic hemolysis
since severe hemodynamic abnormalities caus-
ing turbulent flow may reasonably be ex-
pected to lead to mechanical damage of the
red cells. Brodeur’s group37,38 has demon-
strated that a certain proportion of subjects
with either aortic or mitral valve disease have
decreased red cell survival times even though
they are not anemic.

The reason for the increase in serum en-
zyme values after catheterization is not clear.
One can speculate that the minor trauma in-
volved in the procedure (cutdowns, arterial
punctures, hematomas) must certainly cause
some enzyme release from various types of
tissues, but we have no data to quantitate
this and determine whether it is enough to
induce the elevations observed. The increase
in total LDH was more significant than that
of heat-stable LDH supporting the hypothesis
of trauma to a variety of different tissues.

Concurrent low-grade myocardial damage
by the valve is admittedly not ruled out by
these studies. Although it seems unlikely to
be a significant contributor to the increased
serum enzyme activity seen, it could possibly
account for the small elevations of serum CPK
seen in two patients.

This chronic LDH elevation is a source
of potential confusion in interpreting values
for heat-stable and total LDH in patients pre-
senting with symptoms suggestive of acute
myocardial damage who have valvular pro-
theses or structural heart disease.

Addendum

Since submission of this manuscript for
publication, several papers (references 44-47)
have appeared presenting additional data and
concepts of mechanical hemolytic anemia in
patients without valvular prostheses.

Acknowledgment

The authors wish to express their appreciation to
Dr. Paul Strandjord for helpful suggestions through-
out the course of this work and for reviewing the
manuscript, to Dr. Jorge Yunis whose laboratory
performed the determinations of CPK, and to Miss
Joan Lariviere for help with the statistical analysis.
References

Circulation, Volume XXXV, January 1967

Meditations of an Aging Mystic

Surely a medical man, like every other human being, has the right to laugh at himself now and then to keep up his spirits, maybe even to laugh at his colleagues if he is willing to stand the risk. But he has no right to laugh at his patients. To shed tears with them is even worse, a whimpering doctor is a bad doctor. An old physician should, besides, think twice before sitting down in his arm-chair to write his memoirs. Better keep to himself what he has seen of Life and Death. Better write no memoirs at all, and leave the dead in peace and the living to their illusions.—Axel Munthe: The Story of San Michele. London, John Murray, 1936, p. xv.
Serum Lactate Dehydrogenase Elevation in Ambulatory Cardiac Patients: Evidence for Chronic Hemolysis
CHARLES R. JORGENSEN, THEODORE S. ZIMMERMAN and YANG WANG

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