The Low Cost of the Adenosine Deaminase Assay

To the Editor:

I read with interest the letter by Kent D. Miller (December 1995) who confirms the significant increase of adenosine deaminase (ADA) in effusions of a tuberculous origin. The author regrets the high cost-effectiveness rate of determining the activities of purified molecular forms of ADA.

Actually, as I described in my previous letters, this problem was easily bypassed through a substrate-specificity assay of ADA. Two forms of ADA, called ADA-1 and ADA-2, are present in biologic fluids. While having overlapping activity on adenosine, these forms can be differentiated by their activity on 2'/-deoxyadenosine. For this substrate, ADA-1 has higher activity than ADA-2. Thus, on the basis of the deamination rate of the two substrates, the nature of the prevailing isoenzyme can be discriminated at a very low cost.

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REFERENCES

To the Editor:

It is a pleasure to respond to Dr. Gakis' letter. Dr. Gakis' work was largely responsible for wide utilization of diagnostic adenosine deaminase (ADA) levels in Europe, including his extraordinary, early report, which correlated tuberculous meningitis with elevated spinal fluid ADA levels. We find the precision, accuracy, and sensitivity of the standard ADA assay, with adenosine as substrate, sufficient for detection of tuberculous (TB) and some other infectious processes, particularly among specimens drawn from anatomic sites of those processes (ie, spinal, pleural, ascites, and pericardial fluids). In my letter relating our experiences in pericardial fluid analyses, I stressed the low cost of the basic colorimetric test compared with measurements of other molecular forms of the enzyme. In his letter, Dr. Gakis points out that the differential measurement of ADA-1 and ADA-2, derived from separate assays using adenosine and 2'/-deoxyadenosine as substrates, is also cost effective, and I agree. We look forward to application of those differential assays, particularly on our markedly elevated ADA specimens. By that means, and according to Dr. Gakis, the high levels may be further differentiated: ADA-2 elevated in TB and some other infectious processes, and ADA-1 dominant in malignancies.

This correspondent believes the immediate objective in the United States should be the wide use of ADA analyses. In rational times, the tests would be available based on the current TB epidemic, on the sensitivity, relative specificity, and low cost of the procedure. Clearly the test is not widely available, and the reason is probably economic. Hospitals in the United States have come to depend on net laboratory incomes for support of other functions, a dependence that, unfortunately, can influence what is and is not done in the respective laboratories. On the other hand, it is well known that net income from laboratory operations strongly favors

Table 1—Number and Percentage of Pleural Effusions Misclassified by Each Parameter

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Transudates (n=40)</th>
<th>Exudates (n=153)</th>
<th>Total (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light's criteria (%)</td>
<td>10 (25)</td>
<td>3 (2)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>PF cholesterol ≥50 mg/dL (%)</td>
<td>3 (7)</td>
<td>14 (9)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>PF/S cholesterol ≥0.30 (%)</td>
<td>1 (2)</td>
<td>11 (7)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>PF LDH and/or cholesterol (%)</td>
<td>6 (15)</td>
<td>7 (5)</td>
<td>13 (7)</td>
</tr>
</tbody>
</table>

*PF=pleural fluid; S=serum.

dehydrogenase (LDH) distinguished exudates from transudates with higher specificity than the criteria by Light et al, with the advantages of not requiring a simultaneous blood sample and of a lower cost. A pleural effusion was considered an exudate when LDH was >200 IU/L and/or cholesterol >45 mg/dL in pleural fluid.

We have reproduced this analysis in our series of 193 patients diagnosed with pleurisy who were studied in our two hospitals (55 other patients were excluded: 45 had presumptive diagnosis or had more than 1 cause; 6 had empyema; 2 had hemothorax; and 2 had incomplete biochemical data). Forty were classified as having transudates (28 due to congestive heart failure, 7 liver disease, 4 nephrosis or hypoalbuminemia, and 1 urinorhoxis); and 153 were classified as having exudates (74 due to malignancy, 32 due to tuberculosis, 31 parapneumonic, and 16 other causes). We used a cutoff level of LDH greater than two thirds of the upper limit in the serum, as is proposed by Light, because the normal range was different in each hospital. The best results with the pleural fluid cholesterol level was for a cutoff point of ≥50 mg/dL. When we used an LDH level of >200 IU/L and/or a cholesterol level of >45 mg/dL, the results were poorer. Table 1 details the patients misclassified by each parameter. The combination of LDH and/or cholesterol was not superior to Light's criteria. We can argue that this combination has a lower cost, but also it was not significantly superior to the pleural fluid cholesterol level alone (McNemar's test).

In the study of Costa et al, 180 patients were analyzed, but there was a high number of excluded cases (371 and 108 of them because the diagnosis was considered presumptive or the patient had more than 1 disease). It is possible that this fact influenced the results by selecting the more obvious cases. Unfortunately, we have been unable to confirm in our patients the interesting results of Costa et al.

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