The diagnostic significance of a simultaneous increase in the activities in serum of alkaline phosphatase (ALP) and lactate dehydrogenase (LD) with normal serum bilirubin has been studied in 202 hospital patients. Of these cases, 28% were due to congestive heart failure or myocardial infarction, 25% to malignancy, and 16% to various hepatobiliary disorders. Fewer cases were due to bone fractures with large hematomas, pulmonary embolism, renal failure, or malabsorption syndrome. These biochemical changes in the patients with malignancies did not necessarily signify the presence of hepatic or bony metastases. Hypercalcemia occurred only in this group of patients, and was thus of considerable diagnostic importance. Neither the other tests performed with the SMA 12/60 or the ratios between LD and ALP gave diagnostically useful results.

Additional Keyphrases liver disease • heart failure • myocardial infarction • malignancy, biochemical effects • diagnostic aid • serum calcium

We commonly observe increases in the activities of both serum lactate dehydrogenase (LD; L-lactate: NAD oxidoreductase, EC 1.1.1.27) and alkaline phosphatase (ALP; orthophosphoric monoester phosphohydrolase,

1 Nonstandard abbreviations used: LD, lactate dehydrogenase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; and CHF, congestive heart failure.
EC 3.1.3.1) with normal serum bilirubin. This pattern occurs in 9.3% of the estimations performed with the Technicon SMA 12/60 in our laboratory and has caused diagnostic difficulty on many occasions. If serum bilirubin is also increased, interpretation is relatively easy: the liver is usually the site of the abnormality. But if bilirubin is normal, interpretation is not so easy; in these cases increased ALP activity usually signifies bone disease, but bone diseases do not cause elevations in LD. Similarly, if LD activity is increased, one thinks, in the first instance, of diseases of the heart and blood, but these do not usually cause increases in ALP. I decided to study the causes of this pattern after having been consulted several times by clinical colleagues seeking assistance in interpretation.

This is a study of 202 hospital patients who developed this pattern of results. In addition, the results of the remaining tests performed with the SMA 12/60 were analyzed for possible diagnostic significance.

Since it might be expected that some disorders would tend to give a greater increase in ALP, and other disorders a greater rise in LD, the ratios between these in individual patients were also studied.

Methods

All estimations were performed with the Technicon SMA 12/60, the methods being those described in Technicon Manual T-70-135. The bilirubin method is based on the reaction with diazotized sulfanilic acid in the presence of caffeine–sodium benzoate. In the ALP method p-nitrophenyl phosphate is used as substrate. For LD, the oxidation of L-lactate by NAD is coupled to the reduction of a tetrazolium dye (INT), with diaphorase as an intermediate electron carrier. The remaining tests comprised total protein, albumin, calcium, phosphorus, cholesterol, urea nitrogen, uric acid, creatinine, and aspartate aminotransferase (AST; L-aspartate:2-oxoglutarate aminotransferase, EC 2.6.1.1). The sera used in this study were separated from the clot as soon as possible after venipuncture—usually within one hour.

The study was done retrospectively on all the SMA 12/60 results that showed normal bilirubin, elevated ALP, and elevated LD. The upper limits of the normal range set were: bilirubin, 12 mg/liter; ALP, 85 U/liter; and LD, 290 U/liter. The study period was two months.

I obtained 356 examples of this pattern, from a total of 235 patients. Of these, the case histories of 202 were available for study. The age and sex of these patients were found to have no bearing on the conclusions.

Results

The diagnoses are shown in Table 1. The term "congestive heart failure" means right-sided failure, and 12 of the 46 cases were secondary to myocardial infarction; the remaining 34 were secondary to other disorders.

Carcinoma accounted for 41 and the myeloproliferative and lymphoproliferative conditions accounted for another 10 cases. Thus a total of 51 (25%) were due to malignancy.

Eleven patients with carcinoma were examined post-mortem; liver metastases were found in six. The liver was examined by radioisotope scanning in another two patients, with negative results. Three more were examined at laparotomy, and liver metastases were found in all. Therefore, in 16 patients in whom the liver was examined, metastases were found in only 56%.

Metastases to bone were found by x-rays or radioisotope scans in five of seven patients. In another patient, skeletal metastases were excluded by postmortem examination. This patient was one of the five in whom autopsy did not disclose hepatic metastases either.

Fourteen cases were due to a combination of a large hematoma and recent bone fracture; all except two were sustained more than 12 days previously. Included in these were two patients with intracranial hematomas, in whom the bone "fractures" were a result of surgical craniotomy and the drilling of burr holes respectively (both two weeks before). Another patient, with rheumatoid arthritis, had an arthrodesis performed 13 days previously.

The group labeled "miscellaneous" had either a recognized cause for an increase in the activity of one of the enzymes, or various acute illnesses—such as diabetic ketoacidosis or intestinal obstruction—which might have produced the changes.

Of the remaining nine tests performed with the SMA 12/60, only one, the serum calcium, was of use in distinguishing the diagnostic groups. Hypercalcemia was present in six carcinoma patients and in one patient with lymphatic leukemia. This was a distinguishing feature for the malignancy group, because none of the patients in the other diagnostic categories had high serum calcium concentrations. Hypercalcemia did not necessarily indicate the presence of bony metastases.

Table 1. Causes of Increased Serum Alkaline Phosphatase (ALP) and Lactate Dehydrogenase (LD) Activities with Normal Serum Bilirubin in 202 Patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
<th>%</th>
<th>ALP Mean</th>
<th>ALP Highest Value</th>
<th>LD Mean</th>
<th>LD Highest Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>46</td>
<td>22.8</td>
<td>132</td>
<td>310</td>
<td>450</td>
<td>1005</td>
</tr>
<tr>
<td>Myocardial infarction without CHF</td>
<td>10</td>
<td>4.9</td>
<td>160</td>
<td>385</td>
<td>442</td>
<td>925</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>41</td>
<td>20.3</td>
<td>219</td>
<td>715</td>
<td>456</td>
<td>1710</td>
</tr>
<tr>
<td>Myelo- and lymphoproliferative</td>
<td>10</td>
<td>4.9</td>
<td>148</td>
<td>245</td>
<td>455</td>
<td>775</td>
</tr>
<tr>
<td>disorders</td>
<td>33</td>
<td>16.3</td>
<td>150</td>
<td>590</td>
<td>379</td>
<td>565</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>14</td>
<td>6.9</td>
<td>143</td>
<td>330</td>
<td>462</td>
<td>1070</td>
</tr>
<tr>
<td>Fracture plus hemotoma</td>
<td>6</td>
<td>3.0</td>
<td>131</td>
<td>185</td>
<td>393</td>
<td>486</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>7</td>
<td>3.5</td>
<td>202</td>
<td>505</td>
<td>409</td>
<td>530</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2</td>
<td>1.0</td>
<td>242</td>
<td>390</td>
<td>330</td>
<td>375</td>
</tr>
<tr>
<td>Malabsorption syndrome</td>
<td>22</td>
<td>11.0</td>
<td>137</td>
<td>370</td>
<td>438</td>
<td>950</td>
</tr>
<tr>
<td>None found</td>
<td>11</td>
<td>5.5</td>
<td>136</td>
<td>210</td>
<td>375</td>
<td>440</td>
</tr>
<tr>
<td>All patients</td>
<td>160</td>
<td></td>
<td>160</td>
<td>715</td>
<td>431</td>
<td>1710</td>
</tr>
</tbody>
</table>
because these were absent on x-ray or bone scan in two cases, although negative results by these two procedures do not completely exclude metastases. In three patients there were proven bone metastases with normal calcium concentrations even after correction for hypoalbuminemia.

No diagnostic assistance was obtained from the ratios between the LD and ALP activities.

Discussion

Congestive heart failure (CHF) accounted for 23% of cases. We were surprised at this high prevalence because, although abnormalities in liver function in heart failure are well known (1–4), most accounts state that bilirubin is increased much more often than is ALP (1, 2). In our patients, the concentration of serum bilirubin was normal. One possible reason is that these patients might represent only a small percentage of those presenting at this hospital with heart failure. However, in a subsequent study of 100 consecutive patients with heart failure, we found increased serum ALP activity in 58 but an increased serum bilirubin concentration in only 33.

Most accounts of hepatic impairment in heart failure do not mention increased serum LD activity, but it was present in all the patients reported here. However, Calderon and Alexander (4) state that increases may occur, and that the levels tend to parallel those of AST. This is contrary to our experience; AST was increased in only 7 of 34 patients in whom CHF was not secondary to myocardial infarction, and there was no correlation between it and LD.

In ten patients the changes were due to myocardial infarction without clinical evidence of CHF. In these, there is an obvious source for the LD but not for the ALP. Nevertheless, the liver is probably the source of the ALP, since CHF is sometimes not detected in cases of myocardial infarction (5), and in one study (6) serum activities of LD-5 and ornithine carbamyl transferase (carbamoylphosphate:l-ornithine carbamoyltransferase, EC 2.1.3.3)—an enzyme found only in the liver—were increased in 10 of 12 patients.

We expected a greater number of malignant disorders since it has been stated that “if the ALP is high and likewise the LD, metastatic tumor of the liver looms large as a diagnostic possibility” (7). However, malignancy accounted for only 25% of our cases.

Elevations in ALP activity with normal bilirubin concentration have been reported in various liver diseases, such as cirrhosis, space-occupying lesions, infiltrative and granulomatous conditions, and stones in the common bile duct (8–10). Infiltration of the liver by lymphocytes or other cells, which may produce a preferential elevation in serum ALP, is one possible reason for this. A second possible reason is that, in the recovery phase of several liver diseases, including that of obstruction of the bile ducts, serum ALP may take longer to return to normal than does serum bilirubin (8, 11). Ten of our 33 patients with hepatobiliary disorders had increased serum bilirubin concentrations within the preceding two weeks. (In contrast, in another four patients, serum bilirubin increased in the ensuing two weeks.) Since increases in serum bilirubin concentration and ALP activity reflect different processes within the liver, it is not surprising that one may sometimes occur without the other.

It is well known that increases in serum LD occur in cases of pulmonary embolism and infarction (12–14), the source being the extravasated red blood cells. Rises in serum ALP have also been described (15), but the mechanism is not known. The obvious explanation is that it is due to congestion of the liver. This assumption has been queried by Dijkman and Kloppenborg (16), who suggest that the elevation is related to organization of the lesion by fibroblastic tissue. They support this suggestion with their findings that the highest ALP level occurs one to three weeks after infarction, and that there is increased ALP activity in the young fibroblasts and in the walls of sprouting capillaries. Similar increases in serum ALP may occur late in cases of lobar pneumonia (15, 16) and radiation pneumonitis (17) at a time when organization of the lesion would be taking place.

References