Zinc, copper, and iron content of pleural fluid in benign and neoplastic disease

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Zinc, copper, and iron were measured in the pleural fluid of 86 patients with benign conditions (including congestive heart failure, pulmonary embolus, collagen disease, pneumonitis, nonspecific pleuritis, and tuberculosis) and in 116 patients with malignant disease (including lymphoma, breast carcinoma, primary lung cancer, and metastatic lung cancer). Though a positive correlation was found between zinc and copper in the benign group and not in the malignant group, the test was not specific enough to differentiate benign from malignant disease, because of the wide scatter of results.

A positive regression for serum copper on pleural fluid copper was found in the benign, lymphoma, and malignant groups, but the differences between these three were not sufficient to help in the differential diagnosis.

These findings suggest that pleural fluid heavy metals do not have the specificity that has been reported for serum heavy metals in benign and malignant disease and in malignant lymphoma.

Earlier studies have shown that the serum copper is elevated in Hodgkin's lymphoma, tuberculosis, and neoplastic disease and that in the latter the serum iron is decreased.

The present study was designed to show whether the zinc, copper, and iron contents of pleural fluid could help to identify the cause of the effusion.

METHOD

Zinc, copper, and iron concentrations were measured by atomic absorption spectrometry. The solutions to be analysed were aspirated directly after eliminating the viscosity effect by dilution with glass-distilled water.

RESULTS

Two groups were studied—86 patients with benign disease and 116 patients with malignant disease.

The diagnoses in the benign group (Table I) included congestive heart failure (17), collagen disease (15), hypoalbuminaemia (13), pulmonary embolus (10), ‘pneumonitis’ (9), nonspecific

<table>
<thead>
<tr>
<th>No.</th>
<th>Subgroups</th>
<th>Cu</th>
<th>Zn</th>
<th>Fe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Min</td>
<td>Q1</td>
<td>Max</td>
</tr>
<tr>
<td>Benign</td>
<td>Congestive heart failure</td>
<td>26</td>
<td>67</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>80</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolus</td>
<td>30</td>
<td>85-5</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>Collagen disease</td>
<td>50</td>
<td>78</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
<td>29</td>
<td>70</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Nonspecific pleuritis</td>
<td>48</td>
<td>65</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Hypoalbuminaemia</td>
<td>13</td>
<td>48</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>Constrictive pericarditis</td>
<td>44</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>57</td>
<td>67</td>
<td>162</td>
</tr>
<tr>
<td>Malignant</td>
<td>Lymphoma</td>
<td>57</td>
<td>91</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma, metastatic</td>
<td>35</td>
<td>80</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>Lung carcinoma, primary</td>
<td>62</td>
<td>84-5</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>Metastatic tumours</td>
<td>41</td>
<td>83</td>
<td>148</td>
</tr>
</tbody>
</table>

*Median*
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'ventilitis' (9), tuberculosis (3), and constrictive pericarditis (3). In the remaining seven patients no definite diagnosis was made but one of these had pancreatitis with a pseudocyst and elevated amylase.

The diagnoses in the malignant group (Table I) included metastatic breast carcinoma (39), other metastatic tumours (30), primary bronchogenic carcinoma (28), and lymphoma (19).

A positive regression of serum copper on pleural fluid copper was found in the benign and malignant groups, with the highest slope in the lymphoma group, the next highest in the malignant group, and the lowest in the benign group (Figure; Table II).

In the benign group pleural fluid copper was positively and significantly correlated with pleural fluid protein, while zinc and iron each showed a weak relationship, of borderline significance, to protein. No such relationships were apparent in the malignant group. Copper and zinc were positively and significantly associated in the benign group, and again evidence for any such relationship in the malignant group was lacking (Table II).

**DISCUSSION**

Recently, there has been much interest in the concentrations of trace metals occurring in human and animal tissues and in the manner in which these concentrations may alter in malignant and other disease states (Parr and Taylor, 1964). Szmielinski and Litwin (1964) described decreased values of zinc in acute and chronic granulocytic leukaemia, Hodgkin’s disease, and plasma-cell leukaemia, and a decreased zinc content in blood granulocytes in other nonneoplastic disease states. Schrodt, Hall, and Whitmore (1964) have reported subnormal zinc concentrations in cancerous human prostatic tissues.

No such decrease was apparent in our study in which the pleural fluid mean zinc value in the malignant group was slightly higher than in the benign group.

Pirrie (1952) studied 19 patients who had neoplastic disease unaccompanied by haemorrhage, and found that serum copper levels were significantly higher and serum iron levels significantly lower in the neoplastic group than in normals. Nine of the 19 patients had carcinoma of the lung. Wiljasalo and Haikonen (1966) found that 35 patients with cancer of the lung had elevated plasma copper values (mean 192 ± 37 μg/100 ml) compared to 10 normals (mean 105 ± 15 μg/100 ml). Fifteen patients who had chronic pulmonary disease (tuberculosis, abscess, empyema, and bronchiectasis) also had elevated plasma copper values, with a mean of 147 ± 28 μg/100 ml. Jensen, Thorling, and Andersen (1964) found elevated serum copper levels in 29 patients with Hodgkin’s disease; the highest levels were observed in the sickest patients, and normal levels in those who were relatively symptom-free. Hypercupraemia has also been observed in chronic and

**TABLE II**

**CORRELATIONS OF PLEURAL FLUID VARIABLES WITH DISEASE STATE**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF protein, PF Cu</td>
<td>83</td>
<td>0.56*</td>
</tr>
<tr>
<td>PF protein, PF Zn</td>
<td>83</td>
<td>0.18</td>
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<tr>
<td>PF protein, PF Fe</td>
<td>82</td>
<td>0.11</td>
</tr>
<tr>
<td>PF Cu, PF Zn</td>
<td>85</td>
<td>0.37*</td>
</tr>
<tr>
<td>PF Cu, serum Cu</td>
<td>46</td>
<td>0.34*</td>
</tr>
</tbody>
</table>

*The n values differ as not all records included all measurements
*Significantly different from zero at the 1% level
*Significantly different from zero at the 5% level

**FIGURE.** Positive relationship between pleural fluid copper and serum copper in the benign and malignant groups.
acute infections, in blood diseases, in liver diseases, in collagen disease, and in hyperthyroidism (Nielsen, 1944; Van Ravesteyn, 1944). Serum copper (Holmberg and Laurell, 1947) is found in the $\alpha_2$-globulin fraction of the serum, and patients with neoplastic disease have been found to have an increase in $\alpha_2$-globulins in the serum. One other explanation for the observed hypercupraemia may lie in the reduced demand for copper, an essential catalyst in haemoglobin synthesis. There is no evidence, however, to indicate that hypercupraemia is related to alterations in erythropoiesis (Lahey et al., 1953).

In previous studies of copper metabolism normal subjects have provided material for control measurements. All pleural effusions are abnormal so no control values are possible. In our study a positive regression was found for serum copper on pleural fluid copper in the benign and malignant groups, with the highest slope in the lymphoma group, the next highest in the malignant group, and the lowest in the benign group. There were several relationships between pleural fluid variables in the benign group which were not present in the malignant group. This was true for the relationships between protein on the one hand and copper, zinc, and iron on the other, and it was also true for the relationship between copper and zinc.

REFERENCES
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