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, non-specific 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 I
PLEURAL FLUID METALS IN PATIENTS WITH BENIGN AND MALIGNANT DISEASE

No.	Subgroups	Cu			Zn			Fe		
		Min	Q ₁ ¹	Max	Min	Q ₁ ¹	Max	Min	Q ₁ ¹	Max
<i>Benign</i>										
17	Congestive heart failure	26	67	148	16	35	222	39	64	688
3	Tuberculosis	80	87	95	28	43	60	11	37	96
10	Pulmonary embolus	30	85.5	142	21	31.5	159	11	28	147
15	Collagen disease	50	78	124	22	60	225	11	57	250
9	Pneumonitis	29	70	130	13	44	97	27	48	97
9	Nonspecific pleuritis	48	65	100	3	49	79	56	89	350
13	Hypoalbuminaemia	13	48	123	5	24	130	9	28	120
3	Constrictive pericarditis	44	57	66	19	20	55	48	69	70
								n=6		
7	Other	57	67	162	17	66	235	15	80	720
<i>Malignant</i>										
19	Lymphoma	57	91	150	27	48	88	n=17		
								12	54	375
39	Breast carcinoma, metastatic	35	80	152	25	47	315	n=38		
								10	58	159
28	Lung carcinoma, primary	62	84.5	121	21	43	205	n=26		
30	Metastatic tumours	41	83	148	14	43	111	26	52	415
								8	51	225

¹Median

'pleuritis' (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). Szmigielski 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 neoplastic 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 $192 \pm 37 \mu\text{g}/100 \text{ ml}$) compared to 10 normals (mean $105 \pm 15 \mu\text{g}/100$

FIGURE. Positive relationship between pleural fluid copper and serum copper in the benign and malignant groups.

TABLE II
CORRELATIONS OF PLEURAL FLUID VARIABLES WITH DISEASE STATE

Variables	Correlation Coefficients			
	Benign		Malignant	
	n ¹	r	n	r
PF protein, PF Cu	83	0.56*	105	0.11
PF protein, PF Zn	83	0.18	105	-0.03
PF protein, PF Fe	82	0.11	103	0.20*
PF Cu, PF Zn	85	0.37*	116	0.07
PF Cu, serum Cu	46	0.34*	86	0.70* (all malignancies)
			14	0.83* (lymphoma)
			72	0.66* (other malignancies)

¹The 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

ml). Fifteen patients who had chronic pulmonary disease (tuberculosis, abscess, empyema, and bronchiectasis) also had elevated plasma copper values, with a mean of $147 \pm 28 \mu\text{g}/100 \text{ ml}$. 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

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 α_2 -globulin fraction of the serum, and patients with neoplastic disease have been found to have an increase in α_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

- Holmberg, C. G., and Laurell, C.-B. (1947). Investigations in serum copper. I. Nature of serum copper and its relation to the iron-binding protein in human serum. *Acta chem. scand.*, **1**, 944.
- Jensen, K. B., Thorling, E. B., and Andersen, C. J. (1964). Serum copper in Hodgkin's disease. *Scand. J. Haemat.*, **1**, 63.
- Lahey, M. E., Gubler, C. J., Brown, D. M., Smith, E. L., Jager, B. V., Cartwright, G. E., and Wintrobe, M. M. (1953). Studies on copper metabolism. VIII. The correlation between the serum copper level and various serum protein fractions. *J. Lab. clin. Med.*, **41**, 829.
- Nielsen, A. L. (1944). Serum copper. V. Thyrotoxicosis and myxoedema. *Acta med. scand.*, **118**, 431.
- Parr, R. M., and Taylor, D. M. (1964). The concentrations of cobalt, copper, iron and zinc in some normal human tissues as determined by neutron-activation analysis. *Biochem. J.* **91**, 424.
- Pirrie, R. (1952). Serum copper and its relationship to serum iron in patients with neoplastic diseases. *J. clin. Path.*, **5**, 190.
- Schrodt, G. R., Hall, T., and Whitmore, W. F., Jr. (1964). The concentration of zinc in diseased human prostate glands. *Cancer (Philad.)*, **17**, 1555.
- Szmigielski, S., and Litwin, J. (1964). The histochemical demonstration of zinc in blood granulocytes—the new test in diagnosis of neoplastic diseases. *Cancer (Philad.)*, **17**, 1381.
- Van Ravesteyn, A. H. (1944). Metabolism of copper in man. *Acta med. scand.*, **118**, 163.
- Wiljasalo, M. A., and Haikonen, M. (1966). Blood plasma copper in pulmonary cancer and in chronic pulmonary infections. *Ann. Med. intern. Fenn.*, **55**, 107.