ANNOTATED BIBLIOGRAPHY OF MEASUREMENTS OFSERUM COPPER IN MALIGNANT DISEASES

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VARIOUS NEOPLASMS

1. Keiderling, W. and Scharpf, H.: *Über die klinische Bedeutung der Serumkupfer- und Serum Eisenbestimmung bei neoplastischen Krankheitszuständen.* *Minsch. Med. Wschr.* 95:437-439, 1953.

Serum Cu was measured in 60 healthy subjects and 163 patients with various malignant tumors. The results in major categories are summarized in the following table:

Category	No. of Subjects	Serum Cu ($\mu\text{g}/100\text{ ml}$)	
		Mean $\pm$ S.D.	
Controls	60	105 $\pm$ 17	
Chronic Leukemia	16	156 $\pm$ 40	
Acute Leukemia	8	198 $\pm$ 45	
Plasmacytoma	9	144 $\pm$ 41	
Lymphoma	16	205 $\pm$ 41	
Pulmonary Ca	15	178 $\pm$ 26	
Gastro-Intestinal Ca	24	157 $\pm$ 31	
Liver-Gall Bladder Ca	34	209 $\pm$ 37	
Endocrine Tumors	14	164 $\pm$ 44	
Mesenchymal Tumors	10	192 $\pm$ 24	

LYMPHOMAS AND LEUKEMIAS**MASTER**

2. Lahey, M. E., Gubler, C. J., Cartwright, G. E., and Wintrobe, M. M.: *Studies on copper metabolism. VII. Blood copper in pregnancy and various pathologic states.* *J. Clin. Invest.* 32:329-339, 1953.

Plasma Cu was measured in healthy subjects and in patients with various clinical conditions. The results which are relevant to neoplastic diseases are summarized in the following table:

Category	No. of Subjects	Serum Cu ($\mu\text{g}/100\text{ ml}$)	
		Mean $\pm$ S.D.	
Normal Subjects	63	109 $\pm$ 17	
Acute Leukemia	21	236 $\pm$ 79	
Chronic Leukemia	22	148 $\pm$ 31	
Hodgkin's Disease	14	171 $\pm$ 58

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3. Koch, H. J., Smith, E. R., and McNeely, J.: *Analysis of trace elements in human tissues. II. The lymphomatous diseases. Cancer* 10:151-160, 1957.

Measurements of copper were performed upon plasma samples from normal subjects and from patients with various lymphomas and leukemias. The results which were obtained in major disease categories are as follows:

Category	No. of Subjects	Serum Cu ($\mu\text{g}/100\text{ ml}$)
		Mean $\pm$ S.D.
Normal Subjects	58	98 $\pm$ 12
Hodgkin's Disease	58	216 $\pm$ 68
Reticulum Cell Sarcoma	10	167 $\pm$ 32
Lymphosarcoma	14	199 $\pm$ 28
Chronic Lymphatic Leukemia	8	193 $\pm$ 50

4. Pagliardi, E. and Giangrandi, E.: *Clinical significance of the blood copper in Hodgkin's disease. Acta Haematol.* 24:201-212, 1960.

Serial measurements of serum Cu were made in 23 cases of Hodgkin's disease. The authors state that: "In Hodgkin's disease the serum copper level is constantly increased during relapse and its variations are intimately related with the course of the disease. A drop to normal always indicates an imminent remission, spontaneous or following treatment. This drop occurs early and precedes the normalization of the usual signs (sedimentation rate, temperature, white blood cell count). Likewise, persistent hypercupremia during or after treatment, or an increase of the serum copper level during a period of relative well-being are always a faithful sign of an imminent relapse."

5. Cherry, N. H., Kalas, J. P., and Zarafonetis, C. J. D.: *Study of plasma copper levels in patients with acute leukemia. J. Albert Einstein Med. Center* 9:24-32, 1961.

Serial analyses of serum Cu in 8 adult patients with acute leukemia. Serum Cu levels were correlated closely with leukocyte counts. "Periods of hypercupremia and normal cupremia were observed during the course of the disease with the periods of hypercupremia generally found during exacerbations of the disease and the periods of normal cupremia generally associated with periods of remission."

6. Jensen, K. B., Thorling, E. B., and Andersen, C. J.: *Serum copper in Hodgkin's disease. Scand. J. Haemat.* 1:63-74, 1964.

Analyses of serum Cu in 29 patients with Hodgkin's disease during chemotherapy and/or roentgen therapy. "A fall in serum Cu is often the first indication of a favorable therapeutic effect. The fall, which is often pronounced, will usually appear after a few days of treatment. In all cases such a fall was associated with an improvement. Lack of fall in serum Cu seems to indicate just as definitely that the therapy employed has no effect.... On termination of therapy, a renewed increase in serum Cu will often be the first sign of relapse, and sometimes the patient will feel well during the first period (weeks) after treatment, although serum Cu is increasing."

7. Hrgovic, M., Tessmer, C. F., Minckler, T. M., Mosier, B., and Taylor, G. H.: *Serum copper levels in lymphoma and leukemia. Cancer Res. 21:743-755, 1968.*

Serial analyses of serum Cu in 70 patients, including 28 patients with Hodgkin's disease, 23 patients with acute lymphocytic leukemia, and 9 patients with reticulum cell sarcoma. "Serum copper levels may anticipate clinical response to treatment in Hodgkin's disease. Serum copper levels are helpful in determining disease activity and response to therapy in other lymphomas but are of doubtful value in patients with reticulum cell sarcoma. Serum copper levels reflect bone marrow activity and response to treatment in previously untreated leukemic individuals."

8. Warren, R. L., Jelliffe, A. M., Watson, J. V., and Hobbs, C. B.: *Prolonged observations on variations in the serum copper in Hodgkin's disease.*

Serum Cu levels were measured in 64 patients with Hodgkin's disease for from 3 to 45 months. "There is close correlation between the fluctuation pattern and the prognosis. The persistence of a serum copper level of 150 $\mu\text{g}/100\text{ ml}$ or higher, strongly suggests the presence of active Hodgkin's disease. The most common unrelated causes of a high serum copper are pregnancy, administration of oestrogens and oral contraceptives, and chronic inflammation." "There is a linear relationship between the serum copper and the caeruloplasmin concentrations."

9. Ilicin, G.: *Serum copper and magnesium levels in leukaemia and malignant lymphoma. Lancet 2:1036-1037, 1971.*

In 22 patients with leukemias, 15 patients with malignant lymphoma and 17 healthy controls, the results for serum copper ($\mu\text{g}/100\text{ ml}$) were as follows:

	<u>Leukemia</u>	<u>Lymphoma</u>	<u>Controls</u>
Before therapy	334 $\pm$ 21	298 $\pm$ 37	102 $\pm$ 5
During therapy	242 $\pm$ 41	168 $\pm$ 34	

"The fall in serum-copper levels during treatment was accompanied by clinical and laboratory evidence of improvement.... I believe that determination of serum-copper levels in leukaemia and malignant lymphoma is a valuable means of monitoring therapy."

10. Mortazavi, S. H., Bani-Hashemi, A., Mozafari, M., and Raffi, A.: *Value of serum copper measurement in lymphomas and several other malignancies. Cancer 29:1193-1198, 1972.*

Study of serum Cu in 42 patients with lymphomas (Hodgkin's disease, reticulum cell sarcoma and lymphosarcoma). Twenty-three of 24 patients with generalized lymphomas had increased serum Cu, compared to 6 of 18 patients with localized lymphomas. In all patients, the clinical response to treatment correlated with the alteration in serum copper. "These observations suggest that serum copper measurements can be used as prognostic and therapeutic index...."

11. Tessmer, C. F., Hrgovcic, M., Brown, B. W., Wilbur, J., and Thomas, F. B.: *Serum copper correlations with bone marrow. Cancer* 29:173-179, 1972.

"A study of 346 bone marrow samples and serum copper levels obtained on the same day from 112 patients with acute leukemia shows highly significant relationships between serum copper levels and cellular components of the bone marrow. Of these, the relationship between percentage of blast cells and serum copper is the most important, in view of the significance of blast cells as an index of disease activity and their role in management of leukemias." The following table relates the clinical blast cell categories (in percent) to the serum copper concentration in 81 adult patients.

Bone marrow Blast Cells (%)	Serum Copper ($\mu\text{g}/100\text{ ml}$)			
	<69	69-101	101-133	>133
0-5	0	64	40	0
5-25	0	31	23	30
25-100	0	5	37	70

12. Tessmer, C. F., Hrgovcic, M., Thomas, F. B., Wilbur, J., and Mumford, D. M.: *Long-term serum copper studies in acute leukemia in children. Cancer* 30:358-365, 1972.

Sequential observations of serum Cu levels and bone marrow blast cell percentages in 25 children with acute leukemia. "The serum copper values provide a general index of disease activity which, if properly evaluated, can be of substantial assistance in the management of the patient.... No other chemical index is available which has been so closely correlated with disease activity."

13. Tessmer, C. F., Hrgovcic, M., and Wilbur, J.: *Serum copper in Hodgkin's disease in children. Cancer* 31:303-315, 1973.

"A study of 37 cases of Hodgkin's disease in children, including 669 serum copper levels (SCL), has demonstrated a clinically useful relationship between SCL and the disease process. SCL are high in untreated Hodgkin's disease, falling to normal levels when the clinical findings change from recognized disease to unrecognized or absent disease. SCL rises to abnormal levels upon relapse, and provides an indication of relapse before clinical findings."

14. Hrgovcic, M., Tessmer, C. F., Brown, B. W., Wilbur, J. R., Mumford, D. M., Thomas, F. B., Shullenberger, C. C., and Taylor, G.: *Serum copper studies in the lymphomas and acute leukemias. Prog. Clin. Cancer* 5:121-153, 1973.

An extensive review article with illustrative case reports. This paper recapitulates data given in references 5, 9, 10 and 11.

15. Tessmer, C. F., Hrgovcic, M., Thomas, F. B., Fuller, L. M., and Castro, J. R.: *Serum copper as an index of tumor response to radiotherapy. Therapeutic Radiology* 106:635-639, 1973.

In 6 patients with Hodgkin's disease who developed complete remission during 4 weeks of radiotherapy, serum Cu concentrations returned to the normal range. In 5 patients with Hodgkin's disease who developed partial remission during 4 weeks of radiotherapy, serum Cu concentrations diminished but did not reach the normal range. In contrast, in 10 cases of prostatic carcinoma, the initial concentrations of serum Cu were all normal, and serum Cu levels did not change significantly during 8 weeks of radiotherapy.

PULMONARY CARCINOMAS

16. Pirrie R.: *Serum copper and its relationship to serum iron in patients with neoplastic disease.* *J. Clin. Path.* 5:190-193, 1952.

In 9 men with pulmonary cancer, the mean concentration of serum Cu was 236 $\mu\text{g}/100\text{ ml}$ (range = 151 to 326). In contrast, the mean concentration of serum Cu in 20 healthy men was 105 $\mu\text{g}/100\text{ ml}$ (range = 74 to 151). Elevated concentrations of serum Cu were found in 8 of the 9 patients with pulmonary cancer.

17. Bariéty, M. and Gajdos, A.: *Étude de la sidéremie et de la cuprémie au cours des cancers et particulièrement des cancers bronchiques.* *Press Med.* 72:3259-3261, 1964.

Increased concentrations of serum Cu were found in 21 of 23 patients with bronchogenic carcinoma. In contrast, hypercupremia was present in only 6 of 23 patients with active pulmonary tuberculosis.

18. Davies, I. J. F., Musa, M., and Dormandy, T. L.: *Measurements of plasma zinc. II. In malignant disease.* *J. Clin. Path.* 21:363-365, 1968.

The mean concentration of serum Cu in 39 patients with bronchogenic carcinoma was 155 $\mu\text{g}/100\text{ ml}$ (range = 100 to 240). The concentrations of serum Cu were increased above the normal range of values (80 to 160 $\mu\text{g}/100\text{ ml}$) in 14 of the 39 patients with bronchogenic carcinoma.

19. Tani, P. and Kokkola, K.: *Serum iron, copper and iron-binding capacity in bronchogenic pulmonary carcinoma.* *Scand. J. Resp. Dis., Suppl.* 80:121-128, 1972.

In 31 untreated patients with pulmonary carcinoma, the mean concentration of serum Cu was $111 \pm 20\text{ }\mu\text{g}/100\text{ ml}$, which did not differ significantly from the mean value of $122 \pm 20\text{ }\mu\text{g}/100\text{ ml}$ in 20 healthy controls. "However, an internal trend established in the series was a gradual increase in the serum copper in accordance with the size of the tumour concerned. A highly significant positive correlation was found between serum copper and the sedimentation rate...."

LARYNGEAL CARCINOMAS

20. De Jorge, F. B., Paiva, L., Mion, D., and Da Nova, R.: *Biochemical studies on serum copper, copper oxidase, magnesium, sulfur, calcium and phosphorus in cancer of the larynx.* *Acta Otolaryng.* 61:454-458, 1966.

In 10 patients with squamous cell carcinoma of the larynx the mean concentration of serum Cu was $274 \pm 37\text{ }\mu\text{g}/100\text{ ml}$ (range = 209-320). In contrast, in 20 healthy controls, the mean serum Cu was $108 \pm 10\text{ }\mu\text{g}/100\text{ ml}$ (range = 90-125). The copper content of larynx tissue with histopathological diagnosis of carcinoma was significantly higher than the copper content of normal larynx tissue. The authors did not find increased ceruloplasmin (copper oxidase) activity in serums from their patients with cancer of the larynx.

21. Zakrzewski, A., Durska-Zakrzewska, A., Skonieczny, Jr., Konczewska Z., and Lissowska, B.: The content of some trace elements in blood serum of patients with larynx cancer. *Acta Otolaryng.* 73:227-229, 1972.

In 67 patients with cancer of the larynx, serum Cu was within the normal range in 43 cases, was elevated in 10 cases and lowered in 14 cases.

UROGENITAL CANCERS

22. Stegmann, H., Foehlich, F., and Clotten, R.: Der Serumkupferspiegel bei Frauen mit Genitalcarcinom. *Klin. Wschr.* 40:1120-1123, 1962.

The results of serum Cu analyses in women with gynecological cancers are given in the following table:

<u>Category</u>	<u>No. of Subjects</u>	<u>Serum Cu ($\mu\text{g}/100\text{ ml}$)</u>
		<u>Mean $\pm$ S.D.</u>
Healthy Women	30	107 $\pm$ 17
Cervix Ca-in Situ	25	125 $\pm$ 21
Cervix Ca-Stage I	16	141 $\pm$ 33
Cervix Ca-Stage II	34	175 $\pm$ 41
Cervix Ca-Stage III	23	169 $\pm$ 41
Cervix Ca-Stage IV	4	175 $\pm$ 28
Uterine Corpus Ca.	15	150 $\pm$ 37
Vulva, Vaginal and Ovarian Ca	8	166 $\pm$ 21

"The elevation of serum Cu was proportional to the size and severity of the carcinomatous process."

23. O'Leary, J. A. and Feldman, M.: Serum copper alterations in genital cancer. *Surg. Forum* 21:411-412, 1970.

A control group of 15 healthy women had mean serum Cu level of 117 $\mu\text{g}/100\text{ ml}$ (78 to 147). In 96 women with untreated genital cancers, serum Cu ranged from 162 to 219 $\mu\text{g}/100\text{ ml}$. The mean pretreatment concentrations of serum Cu ($\mu\text{g}/100\text{ ml}$) in various categories of patients were: *Cervical Ca*: Stage I - 162, Stage II - 184, Stage III - 202, Stage IV - 219; *Ovarian Ca*: 162; *Endometrial Ca*: 171; *Vaginal Ca*: 178; *Vulvar Ca*: 172. Concentrations of serum Cu decreased following successful therapy.

24. Albert, L., Hienzsch, E., Arndt, J., and Kriester, A.: Bedeutung und Veränderungen des Serum-Kupferspiegels während und nach der Bestrahlung von Harnblasenkarzinomen. *Z. Urol.* 8:561-566, 1972.

Serial measurements of serum Cu were made in 56 patients with carcinoma of the bladder. The mean pretreatment levels of serum Cu were as follows: Stage I - 119 $\mu\text{g}/100\text{ ml}$; Stage II - 144 $\mu\text{g}/100\text{ ml}$; Stage III - 175 $\mu\text{g}/100\text{ ml}$ and Stage IV - 217 $\mu\text{g}/100\text{ ml}$. In patients who responded favorably to cobalt radiotherapy, the serum Cu levels declined towards the normal range. "From these observations it appears that serum copper analysis is a reliable prognostic sign of bladder tumors."

(For data on serum Cu in prostatic carcinoma, refer to Ref. No. 15.)

BREAST CANCER

25. De Jorge, F. B., Goes, J. S., Jr., Guedes, J. L., and De Ulhoa Cintra, A. B.: *Biochemical studies on copper, copper oxidase, magnesium, sulfur, calcium and phosphorus in cancer of the breast. Clin. Chim. Acta* 12:403-406, 1965.

In 23 women with carcinoma of the breast, the mean concentration of serum Cu was 229 ± 34 $\mu\text{g}/100$ ml (range = 173 to 295), compared to a mean concentration of 108 ± 10 $\mu\text{g}/100$ ml (range = 90 to 125) in serums from 20 control subjects. The copper content of neoplastic mammary tissue was significantly increased in comparison to non-neoplastic mammary tissue. The authors did not find increased ceruloplasmin (copper oxidase) activity in serums from patients with carcinoma of the breast.

TUMORS IN EXPERIMENTAL ANIMALS

26. Hano, K. and Akashi, A.: *Influences of anticancer agents on the metabolism of δ -aminolevulinic acid in normal and tumor-bearing mice. Gann* 55:25:25-40, 1964.

During the growth of Ehrlich acites carcinoma cells after intraperitoneal inoculation in mice, increased mean concentrations of serum copper developed by the third day. The mean concentration of serum copper was approximately 230 $\mu\text{g}/100$ ml on the 10th day after inoculation, compared to a mean concentration of approximately 145 $\mu\text{g}/100$ ml in control mice. Administration of alkylating agents and 8-azaguanine to control mice had no effect upon serum Cu concentrations. Administration of these agents to tumor-bearing mice produced reductions of serum Cu to the normal range, in parallel with the therapeutic effects of the drugs.

27. Enneking, W. F., Flynn, L., and Vogel, S.: *VX-2 carcinoma in bone. J. Bone Joint Surg.* 49A:795, 1967.

A transplantable rabbit carcinoma, "VX-2" was implanted in the medullary cavity of tibias of rabbits. By 21 days after implantation, there was consistent marked increase in serum ceruloplasmin concentrations. The rabbits died with pulmonary metastases between 35 and 52 days after implantation. Hyperceruloplasminemia was diminished in serum samples which were obtained when the rabbits were moribund. (These ceruloplasmin analyses were performed by F. W. S., Jr.)

28. Pienta, R. J., Tessmer, C. F., and Thomas, F. B.: *Effect of murine oncogenic viruses on serum copper levels. Proc. Amer. Assn. Cancer Res.* 10:69, 1969.

In mice infected with either Rauscher leukemia virus or Moloney murine rhabdomyosarcoma virus, increases of serum Cu concentrations preceded the appearance of tumors, and paralleled the progression or regression of the induced tumors. Additional data on the increased serum Cu concentrations in mice following infection with Moloney murine rhabdomyosarcoma virus are included in Ref. No. 14. by Hrgovcic *et al.*

29. Wayss, K., Volm, M., Wesch, H., and Zimmerer, J.: *Relation between the alteration of the copper level in plasma and the growth of Morris-hepatoma No. 3924. Z. Naturforsch (B)* 27:846-849, 1972.

During the growth of Morris-hepatoma No. 3924 after subcutaneous implantation in rats, the concentration of plasma Cu became increased from the 16th to 44th day. The increase in plasma Cu correlated with the incorporation of ^3H -thymidine in the tumors.