Copper Antagonists Inhibit Angiogenesis

By Donald Yance

High serum levels of copper correlate with certain cancers and high copper appears to play a role in cancer promotion. (Senesse P, Meance S, Cottet V, Faivre J, Boutron-Ruault MC. High dietary iron and copper and risk of colorectal cancer: a case-control study in Burgundy, France. Nutr Cancer. 2004;49(1):66-71). The role of copper in cancer promotion through inflammation and angiogenesis is now well known. We are learning that copper status is critical to the function of many angiogenic growth factors. The concept of tumor growth driven by angiogenesis is well accepted, but what drives angiogenesis? Based on several lines of evidence, it is reasonable to hypothesize that angiogenesis is dependent on copper status. Copper is incorporated in the extra-cellular matrix that forms the very structure of blood vessels. Copper acts as a co-factor to molecules known as bFGF, VEGF, and angiogenin. Without it, they can not function, and growth of new blood vessels stop.

The angiogenic activity of bFGF, VEGF, TNF-alpha, and IL-1 were found to be copper dependent. Furthermore, copper repletion switches angiogenesis back "on" when a copper-sufficient diet is restored, providing evidence for a novel, physiologic, and metabolic control pathway of angiogenesis. Copper, but not other trace metals, stimulated the directional migration of endothelial cells. Using a low copper diet and penicillamine therapy, prostaglandin E-stimulated angiogenesis was suppressed. Diverse angiogenic molecules show high affinity for copper.

Copper metabolism is profoundly altered in neoplastic development in human cancer and in tumor-bearing animals. Serum copper levels correlate with tumor incidence, tumor burden, malignant progression, and recurrence in a variety of human cancers (Hodgkin's and non-Hodgkin’s lymphoma, sarcomas, leukemias, and cancer of the cervix, breast, liver, and lung as well as brain tumors).

(Steven, B. Lee, H., *Journal of the American Medical Association* dated 2/23/2000, regarding copper and cancer. "Angiogenesis in Cancer" *The Michigan Oncology Journal*, Spring, 1999, covering angiogenesis and its relationship to copper. “The Role of Copper in Angiogenesis.” Moffitt Cancer Center. "Angiogenesis and Cancer Control: From Concept to Therapeutic Trial")

Copper reduction, using specific supplements, can help to inhibit the angiogenic activity of four structurally diverse angiogenic factors and cytokines. The specific supplements used to lower copper include zinc, molybdenum, lipoic acid, sulphur, a low dose N-acetylcysteine, and selenium, A hypothetical scheme is one of a proposed "copper switch" that turns angiogenesis "on" (copper-sufficient) or "off" (copper deficient). Copper acts as an obligatory cofactor and is permissive to the angiogenic activator. Copper reduction blocks angiogenesis by "switching" endothelial cells into the apoptosis pathway.

Copper chelation for Glioblastoma Phase II trial

Penicillamine is an oral agent used to treat intracerebral copper overload in Wilson's disease. Copper is a known regulator of angiogenesis; copper reduction inhibits experimental glioma growth and invasiveness. This study examined the feasibility, safety, and efficacy of creating a copper deficiency in human glioblastoma multiforme. Forty eligible patients with newly diagnosed glioblastoma multiforme began radiation therapy (6000 cGy in 30 fractions) in conjunction with a low-copper diet and escalating doses of penicillamine. Serum copper was measured at baseline and monthly. The primary end point of this study was overall survival compared to historical controls within the NABTT CNS Consortium database. The 25 males and 15 females who were enrolled had a median age of 54 years and a median Karnofsky performance status of 90. Surgical resection was performed in 83% of these patients. Normal serum copper levels at baseline (median, 130 microg/dl; range, 50-227 microg/dl) fell to the target range of <50 microg/dl (median, 42 microg/dl; range, 12-118 microg/dl) after two months. Penicillamine-induced hypocupremia was well tolerated for months. Drug-related myelosuppression, elevated liver function tests, and skin rash rapidly reversed with copper repletion. Median survival was 11.3 months, and progression-free survival was 7.1 months.

(Brem S, Grossman SA, Carson KA, New P, Phuphanich S, Alavi JB, Mikkelsen T, Fisher JD; The New Approaches to Brain Tumor Therapy CNS Consortium. Phase 2 trial of copper depletion and penicillamine as antiangiogenesis therapy of glioblastoma. Neuro-oncol. 2005 Jul;7(3):246-53)

Copper stimulates the proliferation and migration of endothelial cells and is required for the secretion of several angiogenic factors by tumour cells. Copper chelation decreases the secretion of many of these factors. Serum copper levels are upregulated in many human tumors and correlate with tumor burden and prognosis. Copper chelators reduce tumor growth and microvascular density in animal models. New orally active copper chelators have enabled clinical trials to be undertaken, and there are several studies ongoing. A unifying mechanism of action by which copper chelation inhibits endothelial cell proliferation and tumor secretion of angiogenic factors remains to be elucidated, but possible targets include copper-dependent enzymes, chaperones, and transporters.

Lowndes SA, Harris AL. The role of copper in tumour angiogenesis. J Mammary Gland Biol Neoplasia. 2005 Oct;10(4):299-310

Copper deficiency induced by tetrathiomolybdate (TM) significantly impairs tumor growth and angiogenesis in two animal models of breast cancer: an inflammatory breast cancer xenograft in nude mice and Her2/neu cancer-prone transgenic mice. In vitro, TM decreases the production of five proangiogenic mediators: (a) vascular endothelial growth factor; (b) fibroblast growth factor 2/basic fibroblast growth factor; (c) interleukin (IL)-1alpha; (d) IL-6; and (e) IL-8. In addition, TM inhibits vessel network formation and suppresses nuclear factor (NF)kappaB levels and transcriptional activity. Our study suggests that a major mechanism of the antiangiogenic effect of copper deficiency induced by TM is suppression of NFkappaB, contributing to a global inhibition of NFkappaB-mediated transcription of proangiogenic factors.

Pan Q, Kleer CG, van Golen KL, Irani J, Bottema KM, Bias C, De Carvalho M, Mesri EA, Robins DM, Dick RD, Brewer GJ, Merajver SD. Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. Cancer Res. 2002 Sep 1;62(17):4854-9.

Tetrathiomolybdate blocks bFGF growth factor in cancer by reducing copper

Tetrathiomolybdate (TM) is a multi-hit antiangiogenic agent with actions against multiple angiogenic pathways. These inhibitory effects of TM are attributed to its potent copper level-reducing property. Copper is needed for activation of various angiogenic pathways at the transcriptional and protein levels. MATERIALS The direct effects of TM on angiogenesis of endothelial cells were examined using an in vitro sprout-forming system. RESULTS: It was shown that depletion of copper by TM selectively repressed bFGF-induced sprout formation (an early angiogenic step).

Mamou F, May KS, Schipper MJ, Gill N, Kariapper MS, Nair BM, Brewer G, Normolle D, Khan MK. Tetrathiomolybdate blocks bFGF- but not VEGF-induced incipient angiogenesis in vitro. Anticancer Res. 2006 May-Jun;26(3A):1753-8.

Copper deficiency induced by TM significantly impairs tumor growth and angiogenesis in two animal models of breast cancer: an inflammatory breast cancer xenograft in nude mice and Her2/neu cancer-prone transgenic mice.

Copper deficiency induced by lowering copper with a chelating agent, such as TM decreases the production of five proangiogenic mediators:
(a) vascular endothelial growth factor (VEGF);
(b) fibroblast growth factor 2(FGF-2)/basic fibroblast growth factor(bFGF);
(c) interleukin (IL)-1alpha;
(d) IL-6;
(e) IL-8;
(f) NF-kB levels and transcriptional activity.

A major mechanism of the antiangiogenic effect of copper deficiency is the suppression of NF-kB, contributing to a global inhibition of NF-kB-mediated transcription of proangiogenic factors.

Pan Q, Kleer CG, van Golen KL, Irani J, Bottema KM, Bias C, De Carvalho M, Mesri EA, Robins DM, Dick RD, Brewer GJ, Merajver SD. Copper deficiency induced by tetrathiomolybdate suppresses tumor growth and angiogenesis. Cancer Res. 2002 Sep 1;62(17):4854-9.

The underlying hypothesis of antiangiogenesis using copper-reduction therapy, is that the level of copper required for angiogenesis is higher than that required for essential copper-dependant cellular functions. The assumption is that there is a copper deficient level that impedes angiogenesis but does not interfere with other copper-dependant cellular functions. The optimal range for ceruloplasmin (the copper storage value) for someone with cancer is between 10-20% of the normal range, (20-25).

I have had a great deal of success using natural agents including molybdium, phenolic-rich companion adaptogens including green tea extract and grape seed extract, isothiocynates, NA-cysteine, cilantro and most importantly zinc.

Copper chelation with TM blocks angiogenesis in head & neck cancer

Angiogenesis is well recognized as an essential process that influences not only the growth of head and neck squamous cell carcinoma (HNSCC) but also promotes its invasive and metastatic behavior. The critical role of copper in multiple facets of angiogenesis makes it an important therapeutic target. Tetrathiomolybdate (TM) is a potent copper chelator, which has shown remarkable ability to suppress angiogenesis. Although this may involve multiple mechanisms, the effects on vascular endothelial growth factor (VEGF) are pivotal. Long-term TM treatment on the growth and metastatic progression in an animal model was recently tested. The results showed that TM treatment is able to maintain effective inhibition of angiogenesis. TM lowered copper and significant caused a reduction in the tumor size and vascularity TM-treated animals. These effects were highly correlated with suppression of human VEGF expressed in the developing tumors as well as the mouse VEGF levels detected in the plasma. TM treatment also drastically suppressed the development of lung metastases. Taken together, these results show that copper chemation can act long-term as a suppressor of vascularity and inhibit the growth of metastasis in this model of HNSCC.

Hassouneh B, Islam M, Nagel T, Pan Q, Merajver SD, Teknos TN. Tetrathiomolybdate promotes tumor necrosis and prevents distant metastases by suppressing angiogenesis in head and neck cancer. Mol Cancer Ther. 2007 Mar;6(3):1039-45.

Anti-copper therapy using TM against cancer also offers protection against DOX-induced heart damage

Tetrathiomolybdate (TM), presumably by lowering copper levels and availability, has shown excellent efficacy in animal models of cancer and models of injury that produce fibrotic or inflammatory damage in lung, heart, and liver. Trials in human patients are underway. If the efficacy of TM is indeed through lowering copper levels, other anticopper drugs should be equally efficacious. Zinc is an anticopper drug, with proven efficacy in Wilson's disease, a disease of copper toxicity. In this study, the efficacy of zinc is compared with TM on a mouse tumor model and on the doxorubicin model of heart damage, and it is hypothesized that when copper availability is lowered to an equivalent extent, the 2 drugs would show equivalent efficacy. No effect is found of zinc on inhibiting growth of a tumor that is markedly inhibited by TM, and zinc is found to be less effective than TM in inhibiting cardiac damage from doxorubicin. This study shows that TM's mechanism of action in protecting against doxorubicin toxicity is because of its anticopper effects, as copper supplementation eliminated the protective effect of TM. It is also hypothesized that the differences between TM and zinc may be caused by TM's mechanism of action in which it binds copper already in the body, whereas zinc does not.

Hou G, Dick R, Zeng C, Brewer GJ. Comparison of lowering copper levels with tetrathiomolybdate and

zinc on mouse tumor and doxorubicin models. Transl Res. 2006 Dec;148(6):309-14.

Copper lowering suppresses PC

Because copper often plays a role in the universal requirement for angiogenesis in solid tumor growth, the use of tetrathiomolybdate (TM) was tested for the efficacy of copper deficiency to retard tumor growth in the Dunning prostate cancer model. Significant reduction in size of the primary tumor was observed in mice rendered copper deficient. Improved survival, fewer metastatic lesions, and excellent tolerability were also observed.

van Golen KL, Bao L, Brewer GJ, Pienta KJ, Kamradt JM, Livant DL, Merajver SD. Suppression of tumor recurrence and metastasis by a combination of the PHSCN sequence and the antiangiogenic compound tetrathiomolybdate in prostate carcinoma. Neoplasia. 2002 Sep-Oct;4(5):373-9.

Serum ceruloplasmin as a marker in prostate cancer

Serum ceruloplasmin (Cp) increases in cancer patients; it may be a reliable marker for prostate cancer, but few data are available on specificity and sensitivity of Cp values. Serum prostate specific antigen (PSA) and Cp was determined in patients suffering from histologically proven prostate carcinoma or benign hyperplasia. The results were compared with those in controls matched for sex and age. In all studied subjects with a prostate cancer, serum Cp values were higher than age-matched healthy controls; they were also higher in cases with benign hyperplasia. No difference in serum Cp was noted among patients with earlier and advanced stages of the tumor. No difference in Cp was also found between benign hyperplasia and normal controls. There exists a significant difference in serum PSA between both prostate cancer and benign hyperplasia cases. There exists also a difference between benign hyperplasia cases and controls. It is suggested that serum Cp may complement the biochemical screening in prostate carcinoma, especially in cases where this cancer is not accompanied by elevation of serum PSA.

Fotiou K, Vaiopoulos G, Lilakos K, Giannopoulos A, Mandalenaki K, Marinos G, Koritsiadis G, Sourdis J, Konstantinidou E, Konstantopoulos K Serum ceruloplasmin as a marker in prostate cancer, Minerva Urol Nefrol. 2007 Dec;59(4):407-11.

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Copper-binding form active proteasome inhibition and cancer apoptosis

Several copper-binding compounds have been found to spontaneously complex with copper and form active proteasome inhibitors and apoptosis inducers. This review examines compounds in the quinoline and dithiocarbamate families and from the National Cancer Institute (NCI) Diversity Set that bind with copper and act as anticancer agents. In each case, it is shown that these compounds can bind with copper, inhibit the proteasome activity, and induce apoptosis in cancer cells. These activities are absent when copper is not present. Compounds alone, clioquinol and pyrrolidinedithiocarbamate as examples, are shown to have no effects in normal breast cells. Current research suggests that a possible therapeutic modality for cancer may be developed using the difference of high copper load in tumors versus low copper load in normal cells. This strategy would convert tumor cellular copper into a potent, specific proteasome inhibitor and apoptosis inducer. Thus, this approach could pave the way for the development of nontoxic anticancer therapy.

Daniel KG, Chen D, Yan B, Dou QP. Copper-binding compounds as proteasome inhibitors and apoptosis inducers in human cancer. Front Biosci. 2007 Jan 1;12:135-44.

Tetrathiomolybdate added to chemo-protocol for CRC adds anti-angiogenic effect

Tetrathiomolybdate (TM) is an oral copper chelator under development as an anti-angiogenic agent. We evaluated TM in combination with irinotecan, 5-fluorouracil, and leucovorin (IFL). Serum vascular endothelial growth factor (VEGF), basic fibroblast growth factor, interleukin 6 (IL-6), and IL-8 were measured to evaluate the anti-angiogenic effect. Twenty-four patients with metastatic colorectal cancer were treated. The combination with IFL was well tolerated and dose intensity of IFL was maintained during

combination therapy with TM. By intention to treat analysis, the overall response rate (RR) was 25% (95% CI 9.8-46.7) and the median time to progression (TTP) was 5.6 months (95% CI 2.7-7.7). VEGF levels were correlated with TTP, as were changes in VEGF, IL-8, and IL-6. TM can be safely added to IFL without compromising dose intensity or diminishing the expected RR. Changes in serum VEGF, IL-8, and IL-6 after treatment may directly reflect changes in CRC tissue angiogenesis.

Gartner EM, Griffith KA, Pan Q, Brewer GJ, Henja GF, Merajver SD, Zalupski MM. A pilot trial of the anti-angiogenic copper lowering agent tetrathiomolybdate in combination with irinotecan, 5-flurouracil, and leucovorin for metastatic colorectal cancer. Invest New Drugs. 2008 Aug 20

Where to get TM

Wayne Loveland's compounding pharmacy is the one Dr. McKee has used since 2001 (Rxcenter@charter.net <mailto:Rxcenter@charter.net> ,Rxcenter@gmail.com <mailto:Rxcenter@gmail.com>). College Pharmacy in Colorado Springs, and a number of other compounding pharmacies provide it as well. It can only be gotten from compounding pharmacies. Don't get more than 2 months at a time, as it slowly oxidizes. The pharmacies keep their stock under argon gas (if they know what they're doing).

Copper-binding drug, Disulfiram, induces apoptosis in breast cancer cells

Disulfiram (DSF), a member of the dithiocarbamate family capable of binding copper and an inhibitor of aldehyde dehydrogenase, is currently being used clinically for the treatment of alcoholism. Recent studies have suggested that DSF may have antitumor and chemosensitizing activities, although the detailed molecular mechanisms remain unclear. Copper has been shown to be essential for tumor angiogenesis processes. Consistently, high serum and tissue levels of copper have been found in many types of human cancers, including breast, prostate, and brain, supporting the idea that copper could be used as a potential tumor-specific target. Here we report that the DSF-copper complex potently inhibits the proteasomal activity in cultured breast cancer MDA-MB-231 and MCF10DCIS.com cells, but not normal, immortalized MCF-10A cells, before induction of apoptotic cancer cell death. Furthermore, MDA-MB-231 cells that contain copper at concentrations similar to those found in patients, when treated with just DSF, undergo proteasome inhibition and apoptosis. In addition, when administered to mice bearing MDA-MB-231 tumor xenografts, DSF significantly inhibited the tumor growth (by 74%), associated with in vivo proteasome inhibition (as measured by decreased levels of tumor tissue proteasome activity and accumulation of ubiquitinated proteins and natural proteasome substrates p27 and Bax) and apoptosis induction (as shown by caspase activation and apoptotic nuclei formation). Our study shows that inhibition of the proteasomal activity can be achieved by targeting tumor cellular copper with the nontoxic compound DSF, resulting in selective apoptosis induction within tumor cells.

Chen D, Cui QC, Yang H, Dou QP. Disulfiram, a clinically used anti-alcoholism drug and copper-binding agent, induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity. Cancer Res. 2006 Nov 1;66(21):10425-33.

Molybdenum and Zinc reduce copper levels

Molybdenum and zinc are the key supplements to implement into a protocol to target copper-chelation. Molybdenum is an essential trace mineral that is needed for the proper function of certain enzyme-dependant processes including the metabolism of iron. Unitary copper excretion will occur with daily molybdenum consumption of up to 10 or 15 mg. per day. In high doses molybdenum can increase uric acid levels, which can be helpful for people with low levels of uric acid. This is important to certain antioxidant functions. People with high levels need monitor uric acid and be careful of gout-like symptoms.

Zinc, which is deficient in up to 90% of the population, is a trace mineral needed for some 300 enzyme-systems used by the body. It is not a direct copper chelator but rather it acts by blocking dietary copper in the intestines preventing additional absorption of copper, and assisting the excretion in the stool. This means that any newly ingested copper does not reach the blood stream.

Some of Zinc's important roles in the body are:

- Zinc produces carbonic anhydrase, which conjugates CO2.
- Zinc is essential to the production of hydrochloric acid (HCL)
- Combined with copper in SOD, zinc acts as an antioxidant. This is why you do not want copper levels to fall below normal.
- Zinc provides nutritional support to the bones, teeth, nails, hair, skin, eyes, and prostate.
- Zinc is essential to the production of antibodies, WBC's, and thymus function
- Zinc is an essential co-factor in the production of seminal fluid.
- Zinc helps convert Linoleic Acid (LA) to Gamma Linoleic Acid (GLA).
- Zinc is involved with the metabolism of testes, pituitary, thyroid, and adrenals.
- Zinc is essential to normal fetal growth.

["Zinc," Body Wise, Independent Consultant, Karyl Kline (270) 852-4934]

The Mineral Zinc

Zinc is a trace metal needed for more than 300 enzymes used by the body. It is not a copper chelator, zinc acts to block dietary copper in the intestines by preventing additional absorption of copper. It induces cells of the intestinal tract to produce a metallothionein protein (MT) which has a very high affinity for copper and is excreted in the stool. This means that any newly ingested copper does not reach the blood circulation system.(Research Highlight Exploring Therapeutic Options for Wilson's Disease NCRR, Reporter September/October 1997, Wilson's disease) Zinc is an alternative to older copper chelating agents, and Wilson's disease patients frequently use it in their maintenance programs.

In 1997 Dr. Brewer sought and received FDA approval for a compound of zinc known as zinc acetate or Galzin® (32) to treat Wilson's disease. According to Dr. Brewer, Galzin® is made by a reputable company and measured in precise doses untainted with lead or other contaminants. Galzin® is expensive and requires a prescription. I feel as though the best form of zinc to use is either Albion lab Zinc, which is a fully reactive zinc chelate with the highest bioaviavability. I also use a liquid Zinc Sulfate as well.

Zinc Metabolism

Excessive supplemental zinc is not stored. The human body is extremely efficient in removing surplus zinc in fecal matter, urine, and sweat. Zinc supplementation can make some people nauseas so I recommend starting with low doses with meals and building up. Foods rich in Phytic acid, such as pasta and soy foods reduce the absorption of zinc so try and avoid taking zinc along with these foods. I typically have people take a good dosage with their smoothie.

High serum copper, sometimes combined with low serum zinc, is associated with increased mortality from all cardiovascular disease and higher risk of subsequent cancer diagnosis.

("Serum calcium, magnesium, copper and zinc and risk of cardiovascular death,", National Public Halth Institute, Helsinki, Finland, Eur J Clin Nutr (England), Jul 1996, 50 (7) p 431-7, PMID: 8862478. "High Serum Concentrations of Copper Associated with Cardiovascular Disease", Reuters Health, June 15, 2000.

"Cancer Risk in Relation to Serum Copper Levels", Cancer Research 49, Emory University, Atlanta Georgia, pp. 4353-4536, August 1, 1989.)

Zinc deficiency, low zinc serum levels below the normal range of 60 to 150 mcg/dL, is common in cancer and causes immune suppression since zinc is a key component of many enzyme systems necessary for T-cell function and regulation.

Studies such as Chrandra's (Ranjit Kumar Chandra, "Excessive Intake of Zinc Impairs Immune Responses" , JAMA, Sept 21, 1984, Vol 262, No. 11, PMID: 6471270) back in 1984 have claimed that zinc serum concentrations significantly above the optimal high-normal range of 140 to 160 mcg/dL can cause immune suppression. Other studies have concurred with Chrandra that the optimal zinc serum range of 140 to 160 mcg/dL is best for maximizing (doubling) T-cell function. (Duchateau J, Delespesse G, Vereecke P., "Influence of oral zinc supplementation on the lymphocyte response to mitogens of normal subjects", The American Journal of Clinical Nutrition, 1981;34:88-93. PMID: 7446464.
Duchateau J, Delespesse G, Vrijens R, et. al.,"Beneficial effects of oral zinc supplementation on the immune response of old people", The American Journal of Medicine, 1981;70:1001-1004. PMID: 6972165.
Golden MHN, Jackson AA, Golden BE, "Effect of zinc on thymus of recently malnourished children", The Lancet, Nov. 19,1977:1057-1059. PMID: 72960.)

Back in 1997, Dr. Brewer did his own study on the effects of high dose zinc on Wilson's disease patients. He found no compromise in T-cell / lymphocyte function and stated, "We have seen no indications of immune suppression or increased susceptibility to infections in our patients, who have now been treated with zinc for up to 15 years. We conclude that any side effects from compromised lymphocyte function caused by administration of zinc are not of concern to patients of Wilson's disease."("Treatment of Wilson's disease with zinc: XIV. Studies of the effect of zinc on lymphocyte function," J Lab Clin Med. 1997 Jun;129(6):649-52, PMID: 9178732)

Absorption and excretion rates of zinc are subject to individual variability. The copper reduction protocol developed in Wilson's disease is 50 mg zinc three times a day without food. A different formula is to take a sufficient amount of zinc to maintain optimal blood serum levels at the high normal range, between 140 and 160 mcg/dL. If 150 mg zinc per day does not increase zinc serum to this range, the dosage may be increased up to 1.5 mg per pound of body weight (or higher). For example, a 150 pound person could take as much as 150 multiplied by 1.5 mg or a total of 225 mg of zinc daily. The dosage may be adjusted to maintain zinc blood serum level between 140 to 160 mcg/dL, conservative enough to protect optimal immune function according to the Chrandra study while still producing copper-reduction effects.

Data indicates that as much as one-half of the world's population is at risk of zinc deficiency, but zinc toxicity is a rare phenomenon. High dose zinc supplementation has been used to treat patients with Wilson's disease to deplete copper for up to 15 years. Dr. Brewer saw no indications of immune suppression or increased susceptibility to infections in his patients.

There are over 1800 MedLine citations about "zinc deficiency" and only about 15 on "zinc toxicity." Zinc can stimulate the immune system to increase the number of circulating effector T-lymphocytes and natural killer (NK) cells which kill cancer. Zinc deficiency is related to immunosuppression, which allows cancer cells to grow freely.

History of Zinc Treatment in Cancer

In the early 1950s, discovery of abnormal zinc metabolism in chronic adult leukemia patients suggested use of zinc as a therapeutic drug in its treatment. Zinc may act by stimulating cell mediated immunity.

When in 1979 a child's acute T-cell lymphocytic leukemia (ALL) was put into permanent remission within two weeks of initiation of chemotherapy in conjunction with therapeutic doses of adult doses of vitamins and minerals, her oncologist questioned whether one of the supplements might have enhanced her therapy. It was the child's father, George Eby, who researched to identify zinc as the element saving his daughter's life. He found that raising zinc concentration in the serum to 140 mcg/dL resulted in numerous immunological and adjuvant to chemotherapy effects which had the effect of rapidly eliminating all detectable leukemic blasts in bone marrow and blood. The high normal zinc serum concentration was maintained according to blood test each two weeks during the three year chemotherapy program. The young woman remains without relapse to this date.

About a dozen other families with leukemic children and one with lymphoma followed Eby's protocol of zinc plus chemotherapy between 1985 and 1987. They were all successful in putting their child's cancer

into a very strong remission (zero blasts in bone marrow and blood) within about two weeks. When publicity ran out on the Eby case, no one followed up with human trials to supplement the diet with zinc in treating childhood leukemia.

George Eby changed his career to biomedical research and published years of research in one of the largest zinc sites on the Internet starting in 1996. He developed zinc cold lozenges which were proven effective in many trials, with the most recent clinical trial in 2000 led by an expert in zinc studies, Ananda S. Prasad, M.D., Ph.D., a well-known research oncologist at Wayne State University in Detroit, Michigan.

("Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial," Ananda S. Prasad, MD, Ph.D., et. al., Annals of Internal Medicine, 2000 August 15; Vol. 133, Number 4, pages 245-252, PMID: 10929163.)

The dosage of zinc used to lower copper is 30 to 150 mg. per day. Vitamin B-6 can assist with zinc in reducing copper, allicin-rich garlic tablets, the phenolic compounds in green tea, and many flavonoid-rich foods and herbs, all can be helpful at chelating out copper.

Coriandrum sativum (coriander)

Coriandrum sativum (coriander) has been documented as a traditional treatment of diabetes. Both coriander and cilantro (coriander leaf) are also an extremely effective chelator of toxic metals. Cilantro increases the elimination of copper, mercury, lead and other heavy metals. has Cilantro suppressive activity on lead deposition, probably resulting from the chelation of lead by some substances contained in cilantro. Coriander has antioxidant ability and improves glucose and insulin utilization. Recent research has demonstrated the presence of antihyperglycaemic, insulin-releasing and insulin-like activity in Coriandrum sativum.

[Preventive effect of Coriandrum sativum (Chinese parsley) on localized lead deposition in ICR mice. *J Ethnopharmacol* 2001 Oct;77(2-3):203-8 Aga M; Iwaki K; Ueda Y; Ushio S; Masaki N; Fukuda S; Kimoto T; Ikeda M. Kurimoto M Hayashibara Biochemical Laboratories, Inc., Fujisaki Institute, 675-1 Fujisaki, Okayama 702-8006, Japan.
Coriandrum sativum changes the levels of lipid peroxides and activity of antioxidant enzymes in experimental animals. *Indian J Biochem Biophys* 1999 Feb;36(1):59-61 Gray AM; Flatt PR School of Biomedical Sciences, University of Ulster, Coleraine, UK. Chithra V; Leelamma S Department of Biochemistry, University of Kerala, Kariavattom,
Insulin-releasing and insulin-like activity of the traditional anti-diabetic plant Coriandrum sativum (coriander*). Br J Nutr* 1999 Mar;81(3):203-9
Aga M, Iwaki K, Ueda Y, Ushio S, Masaki N, Fukuda S, Kimoto T, Ikeda M, Kurimoto M. Preventive effect of Coriandrum sativum (Chinese parsley) on localized lead deposition in ICR mice. J Ethnopharmacol. 2001 Oct;77(2-3):203-8.]

Copper Chelation Suppresses Experimental Liver Tumor Growth

Copper chelating agents inhibit carcinogenesis and angiogenesis in a mouse model of hepatocellular carcinoma (HCC), according to results published in the December 15th International Journal of Cancer.

Dr. Hitoshi Yoshiji from Nara Medical Center in Nara, Japan and colleagues explain that therapies that block angiogenesis have proven successful in experimental models of cancer treatment, and copper is known to play an important role in angiogenesis. The researchers examined the effect of two copper-chelating agents, trientine and penicillamine, on tumor development in mice.

Both copper-chelating agents significantly suppressed tumor development, the authors' report, with trientine demonstrating significantly more potent inhibition than penicillamine. Trientine or penicillamine, in combination with a copper-deficient diet, nearly abolished the development of HCC, the report indicates.

Trientine, at a dose corresponding to 3 to 4 times that used in clinical practice, also significantly inhibited neovascularization in HCC tumors, the researchers note, as well as increased the number of apoptotic cells.

In contrast, trientine had no effect on the in vitro proliferation of HCC cells, "suggesting that the inhibitory effect of trientine was not due to its cytotoxicity on the tumor cells."

"Since trientine is already used in clinical practice with minor side effects," the authors conclude, "it may be an effective new strategy for HCC therapy in the future."

Since antiangiogenic agents currently in development may not be available for some time, "this copper [chelation] modality would be an alternative idea to suppress the angiogenesis in HCC for the time being," Dr. Yoshiji commented.

He also pointed out that, apart from copper chelators, "we have found angiotensin-I converting enzyme inhibitor (ACE-I) significantly suppressed HCC growth and angiogenesis." It also inhibited the development of liver fibrosis, Dr. Yoshiji said, and "the combination of ACE-I and copper deficiency may be a good strategy for anti-cirrhosis and HCC."

[*Int J Cancer* 2001;94:768-773.]

Phase II Trial of Tetrathiomolybdate in Patients with Advanced Kidney Cancer 1
Bruce G. Redman 2,Peg Esper ,Quintin Pan ,Rodney L. Dunn ,Hero K. Hussain ,Thomas Chenevert ,George J. Brewer and Sofia D. Merajver

Division of Hematology and Oncology [B. G. R., P. E., Q. P., S. D. M.], Departments of Internal Medicine [G. J. B.], Radiology [H. K. H., T. C.], Human Genetics [G. J. B.], and University of Michigan Comprehensive Cancer Center [B. G. R., R. L. D., S. D. M.], University of Michigan, Ann Arbor, Michigan 48109-0948

Purpose: Tetrathiomolybdate (TM), a copper-lowering agent, has been shown in preclinical murine tumor models to be antiangiogenic. We evaluated the antitumor activity of TM in patients with advanced kidney cancer in a Phase II trial.

Experimental Design: Fifteen patients with advanced kidney cancer were eligible to participate in this trial. TM was initiated p.o. at 40 mg three times a day with meals and 60 mg at bedtime to deplete copper. A target serum ceruloplasmin (CP) level of 5–15 mg/dl was defined as copper depletion. Doses of TM were reduced for grade 3–4 toxicity and to maintain a CP level in the target range. Once copper depletion was attained, patients underwent baseline tumor measurements and then again every 12 weeks for response assessment. Patients not exhibiting progressive disease at 12 weeks after copper depletion continued on treatment. Serum levels of Interleukin (IL)-6, IL-8, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were assayed pretreatment and at various time points on treatment. Dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) was performed on selected patients in an attempt to assess changes in tumor vascularity.

Results: All of the patients rapidly became copper depleted. Thirteen patients were evaluable for response. No patient had a complete response or PR. Four patients (31%) had stable disease for at least 6 months during copper depletion (median, 34.5 weeks). TM was well tolerated, with dose reductions most commonly occurring for grade 3–4 granulocytopenia of short duration not associated with febrile episodes. Serum levels of IL-6, IL-8, VEGF, and bFGF did not correlate with clinical activity. Serial DCE-MRI was performed only in four patients, and a decrease in vascularity seemed to correlate with necrosis of a tumor mass associated with tumor growth.

Cancer therapy with tetrathiomolybdate: antiangiogenesis by lowering body copper-a review.

A new anticopper drug, tetrathiomolybdate (TM), developed for Wilson's disease, is a very promising antiangiogenic agent. Copper levels lowered into an antiangiogenic window by TM have shown efficacy against cancer in a variety of animal models as well as in patients. The only significant toxicity so far results from overtreatment and excessive bone marrow depletion of copper. The resulting anemia and/or

leukopenia is easily treatable by dose reduction or drug holiday. The underlying concept for TM efficacy as an anticancer agent is that when the body's copper status is in the window, cellular copper needs are met and toxicity is avoided. Copper status is relatively easily monitored by following serum ceruloplasmin, a copper-containing protein secreted by the liver at a rate dependent upon the amount of copper in the liver available to incorporate into the protein. The authors speculate that the copper level is a primitive angiogenesis and growth-signaling regulator that has been retained throughout evolution.

[Brewer GJ, Merajver SD. Cancer therapy with tetrathiomolybdate: antiangiogenesis by lowering body copper-a review. Integr Cancer Ther. 2002 Dec;1(4):327-37. Department of Human Genetics and Department of Internal Medicine, University of Michigan Medical School, 4009 Buhl Building, Ann Arbor, MI 48109-0618.]

Serum ceruloplasmin and the risk of cancer in Finland.
The relationship between serum ceruloplasmin level and cancer incidence was investigated in a case-control study nested within a longitudinal study of 39,268 Finns participating in the Social Insurance Institution's Mobile Clinic Health Examination Survey carried out in 1968-1972. During a median follow-up of 8 years, 766 cancer cases were identified. Ceruloplasmin levels were determined from stored serum samples collected at the baseline from these cancer cases and from two matched controls per case. The overall incidence of cancer was positively associated with serum ceruloplasmin level. The association was strongest for lung cancer and other cancers related to smoking and, consequently, in males. The smoking-adjusted relative risk of lung cancer among men was 4.3 (95% confidence interval (CI) = 1.8-10.6) in the highest quintile of serum ceruloplasmin as compared with that in the lowest quintile. The corresponding relative risks for cancers related to smoking combined, and for cancers not related to smoking were 3.9 (CI = 1.9-8.4) and 0.9 (CI = 0.6-1.5), respectively. The elevated risk of lung cancer at high concentrations of serum ceruloplasmin persisted after further adjustment for several potential confounding factors such as serum levels of vitamins A and E and selenium. The risk was stronger during the first 6 years of follow-up than later, and strongest during the first 2 years. The most likely explanation of the present results thus is that high serum ceruloplasmin levels in lung cancer are mainly due to occult cancer.

[**Knekt P, Aromaa A, Maatela J, Rissanen A, Hakama M, Aaran RK, Nikkari T, Hakulinen T, Peto R, Teppo L. Serum ceruloplasmin and the risk of cancer in Finland.** Br J Cancer. 1992 Feb;65(2):292-6.Social Insurance Institution, Helsinki, Finland.]

Conclusions: TM is well tolerated and consistently depletes copper as measured by the serum CP level. Clinical activity was limited to stable disease for a median of 34.5 weeks in this Phase II trial in patients with advanced kidney cancer. Serum levels of proangiogenic factors IL-6, IL-8, VEGF, and bFGF may correlate with copper depletion but not with disease stability in this small cohort. TM may have a role in the treatment of kidney cancer in combination with other antiangiogenic therapies.

The formation of new blood vessels is the initial step in progressive tumour development and metastasis. The first stage in tumour angiogenesis is the activation of endothelial cells. Copper ions stimulate proliferation and migration of endothelial cells. It has been shown that serum copper concentration increases as the cancer disease progresses and correlates with tumour incidence and burden. Copper ions also activate several proangiogenic factors, e.g., vascular endothelial growth factor, basic fibroblast growth factor, tumour necrosis factor alpha and interleukin 1.
(Nasulewicz A, Mazur A, Opolski A. Role of copper in tumour angiogenesis--clinical implications. J Trace Elem Med Biol. 2004;18(1):1-8)

TM inhibits angiogenesis by reducing copper

PURPOSE: To determine the effects of tetrathiomolybdate (TM), a copper-chelating agent, on retinal angiogenesis and vascular endothelial growth factor (VEGF) in a mouse model of retinal neovascularization. METHODS: Postnatal day (P)7 C57BL/6N mice were exposed to 75% +/- 2% oxygen for 5 days (P7-P11) and then returned to room air for 5 days (P12-P17) to induce retinal neovascularization.

Beginning on P10 or P12, mice received daily intraperitoneal injections of TM or phosphate-buffered saline (PBS; control) through P17. Retinal neovascularization was examined by fluorescein dextran angiography after 5 days in room air and was quantitated histologically by counting the neovascular endothelial cell nuclei anterior to the inner limiting membrane. TM's effects on VEGF expression were measured by ELISA. RESULTS: TM-treated and control animals demonstrated comparable regions of retinal nonperfusion. Retinas from control mice at P17 contained neovascular tufts at the junction between perfused and nonperfused retina. The tufts contained numerous neovascular nuclei. Retinas from mice treated with TM beginning on P10 (2 days before returning to room air), but not P12, demonstrated a 41% reduction in neovascular cell nuclei compared with control mice ($P < 0.01$). The P10-treated mice also demonstrated a 24% reduction of VEGF compared with control animals ($P = 0.01$). CONCLUSIONS: TM significantly inhibits retinal neovascularization and VEGF production in a mouse model of retinal neovascularization.

(Elner SG, Elner VM, Yoshida A, Dick RD, Brewer GJ. Effects of tetrathiomolybdate in a mouse model of retinal neovascularization. Invest Ophthalmol Vis Sci. 2005 Jan;46(1):299-303)

Zinc levels linked to prostate cancer spread

09/06/2005 - **Cancerous cells in the prostate appear to be less able to absorb zinc, suggest preliminary findings by the US Agricultural Research Service, and this may lead to the cancer's spread.**

Scientists have known for decades that zinc may play an important part in the health of the prostate, a walnut-sized gland in males, that secretes a zinc-containing liquid in seminal fluid.

They already have evidence that cancerous prostate cells contain less zinc than healthy prostate cells and the new findings may explain why. However they still need to test whether an increase of zinc in cancerous prostate cells may help prevent their proliferation.

Prostate cancer is the second most common cancer in men after lung cancer. It was the most common form of cancer diagnosed among men in the European Union during 2004, representing 15 per cent of male cancers and 238,000 new cases, according to the International Agency for Research on Cancer (IARC).

This high prevalence is pushing researchers to investigate nutritional invervention that could help prevent the disease.

ARS research geneticist Liping Huang compared the amounts of zinc taken up by the prostate's epithelial cells. She used noncancerous and cancerous human cells that had the same genetic source, or genotype. (Genes can influence the take-up and use of nutrients in food, including zinc.)

Cultured cells were exposed to zinc sulphate for two days.

"The cancerous cells accumulated about one-third less zinc than did the noncancerous cells," Huang reports.

The team also looked for significant differences in levels of zinc transporter proteins. These specialized proteins ferry zinc throughout the body, such as from storage in the liver, kidney, or bone to other sites. The amount of one such zinc transporter protein—ZIP1—was reduced in the cancerous cells. As a result, those cells had low ability to take in zinc.

In addition, analyses showed that even though a second zinc transporter protein, ZIP3, was present in the cancerous cells, it was not in its correct location.

"This error may have blunted any of ZIP3's potential protective effects," explained Huang.

She added that the study *"provides the first direct comparison of zinc-transporter-protein levels in noncancerous and cancerous prostate epithelial cells with the same genetic background and the first evidence of significant differences in the levels and localizations of the proteins."*

"Though these results are preliminary, they suggest that reduced levels of one transporter protein and mislocation of another may play a role in cancer's progression in the prostate."

To learn more, the team developed another experiment with ZIP1, artificially stepping up its manufacture in the cancerous cells by overexpressing the genes that cue production of this protein.

"Overexpressing ZIP1 significantly suppressed growth and spread of the cancerous cells," Huang reported. *"We don't yet have enough evidence to say with certainty that zinc in our foods acts as a chemopreventive. But zinc's natural abundance in the prostate of healthy men, and its performance in our tests, suggest it may be an important natural defense."*

The research is described in the June 2005 issue of Agricultural Research magazine.

Basic Copper Reduction Protocol

Molybdenum caps (Thorne)	**2-4 caps bid**
Lipoic acid (high grade)	**300-600 mg. bid or tid**
Zinc (Albion Lab, zinc sulfate, or New Chapter zinc)	**30-60 mg. bid or tid**
NAC (Cysteine)	**900 mg. bid or tid**
Undenatured Whey Protein Concentrate	**10-20 grams**
B-6	**25-100 mg. daily**
Botanical Treasures	**4-10 grams in powder or capsules**

Cilantro (as food 1/4 – 1/2 cup chopped daily, fresh juice 1/4 cup, or extract 30 drops bid)

Monitor serum levels of Ceruloplasmin, Copper and Zinc every 8-12 weeks.

Dietary Recommendations:

1. Eat a diet rich in fruits, vegetables and whole grains. Good sources of zinc include pumpkin seeds, almonds, cashews, pecans, beans, and chick peas. Shellfish, oysters in particular are great sources of zinc, but are also rich in copper. Avoid organ meats and limit shellfish.
2. All drinking water should be tested for copper. If water is high in copper than distilling or using reverse osmosis is advised.
3. Avoid using copper cookware.