

The Nutritional Relationships of Copper

David L. Watts, D.C., Ph.D., F.A.C.E.P.¹

Introduction

The mineral copper was shown to be an essential nutrient for hemoglobin synthesis in animals in 1928.¹ The therapeutic use of copper and its requirements in humans was later reported by Mills and others.^{2 3} Copper has since been found to be a constituent of many important enzymes including cytochrome c oxidase, superoxide dismutase (cytoplasm), Ceruloplasmin, dopamine B-hydroxylase, lysyl oxidase, tyrosinase, and monoamine oxidase.

The copper content of a healthy adult has been reported to be approximately eighty milligrams.⁴ The highest level of copper is found in the liver and brain, followed by the heart, kidney, pancreas, spleen, lungs, bone, and muscle.

Copper Evaluation Through Tissue Mineral Analysis (TMA) of Human Hair

TMA of hair has proven to be a good method for assessing nutritional copper status. Recently Medeiros⁵ reported positive correlations of TMA copper levels in animals based upon three levels of dietary copper intake. This study supports the feasibility for the use of TMA in detecting changes in the diet of copper and other minerals. Medeiros' study also confirms the findings of earlier investigators, which also support the validity of using TMA in assessing copper status.^{6 7 8 9} Ikeda, et al¹⁰ found that the hair concentration of copper correlates with blood hemoglobin levels in children. Hair copper concentrations have been found to reflect liver copper concentration.¹¹ A study reporting the mineral content of maternal and neonate hair revealed an excellent correlation of metals including copper and establishes a basis for the use of TMA in monitoring the nutritional mineral status of both the mother and fetus.¹²

The ideal TMA level of copper established by Trace Elements, Inc. is 2.5

Trace Elements, Inc., P.O. Box 514, Addison, Texas 75001.

milligrams percent. When sampled properly, TMA can provide a good index of nutritional copper status^{13 14} and relationship to other synergistic and antagonistic trace elements.

Conditions Associated with Copper Imbalance

One of the earliest conditions found to be associated with copper deficiency is iron deficiency anemia, which could only be corrected with copper supplementation. Copper deficiency impairs iron absorption, reduces heme synthesis, and increases iron accumulation in storage tissues. These processes are dependent upon copper through the effects of the copper enzyme Ceruloplasmin.¹⁵ A chronic copper deficiency can result in hemosiderosis, a condition characterized by an increase in iron accumulation in body tissues due to an impairment in the reutilization of hemoglobin iron. Hemosiderosis is known to occur in malignancies, inflammatory disorders, and rheumatoid arthritis.¹⁶

Arthritis and Copper

Iron accumulation in the joints due to copper deficiency can be a major contributor to rheumatoid arthritis.¹⁷ Studies reported by Kishore et al illustrated the relationship of copper deficiency and arthritis in animal studies. Adjuvant arthritis was more severe in animals on a copper deficient diet, and the tissue iron levels were found to be over four hundred percent of normal.¹⁸ It has been stated that rheumatoid arthritis has become prevalent within the past century due to industrialization, i.e. the increased production and use of copper antagonists such as cadmium, zinc, lead, etc. Rainsford hypothesized that the low incidence of rheumatoid arthritis in Europe during pre-industrial times may have been due to the protection by copper commonly used in cooking and eating utensils of the period.¹⁹ TMA studies of patients with rheuma-

toid arthritis almost always reveal a low tissue copper level. The more chronic cases show high iron/copper ratios. An elevated tissue iron/copper ratio can also indicate a chronic bacterial infection. Rheumatoid arthritis can be secondary to and sometimes caused by an infectious agent resulting in copper depletion or a disturbance in copper balance. It is also well known that spontaneous remission of rheumatoid arthritis occurs in conditions associated with increased copper retention such as pregnancy and biliary obstruction.²⁰ An Australian study (Walker, et al) demonstrated improvement of symptoms of rheumatoid arthritis by absorption of copper through the skin from the wearing of copper bracelets.

TMA studies clearly show that individuals with some forms of rheumatoid arthritis, have increased copper requirements. However, TMA studies have revealed that tissue copper levels are above normal in patients with osteoarthritis. This can be explained by the calcium-copper-vitamin D relationship discussed later.

Infections — Bacterial

Infections are known to affect mineral metabolism and requirements.²¹ During a bacterial infection iron is sequestered into storage tissue (reticuloendothelial-bone-spleen-liver). This is a normal response since bacteria require iron in order to proliferate; therefore, the body removes this nutrient source from the serum.^{22 23} Secondly, serum copper rises due to its removal from storage tissues thereby improving the capability to mount an attack and overcome the invading organism. The opposite is seen in the tissue mineral concentrations. In chronic infectious states, the tissue iron increases while the tissue copper decreases. This tissue mineral pattern (elevated iron/copper ratio), is strongly indicative of a chronic infection. The most common source of chronic infections have been dental abscesses often present for years without the patient's knowledge.

Infections — Viral

Viral infections produce an anabolic response, while bacterial infections produce a catabolic response. Tissue copper deficiency is commonly seen with chronic bacterial infections,^{24 25 26 27}

while elevated tissue copper is found with chronic viral infections. Presently it is not clear whether infectious conditions cause the TMA copper abnormalities, but it is strongly suspected that copper status can predispose an individual to either a viral or bacterial infection. The indication that copper can be a causative factor in the incidence of viral or bacterial infections is reflected in studies by Luster and co-workers. They report that estrogen has an enhancing or suppressing effect upon the immune system.²⁸ Thus the relationship between copper and estrogen cannot be overlooked. It has also been reported that women have an increased susceptibility to viral infections prior to menstruation (at which time estrogen and copper levels are high) and an increased tendency toward bacterial infections directly following menstruation (at which time estrogen and copper levels fall). Generally speaking, we find that copper deficiency causes a disturbance in cellular immunity, while copper excess causes a disturbance in humoral immunity.

This information indicates that any factor that antagonizes copper retention can be considered as having anti-viral properties. Those that are synergistic such as vitamin D, B₁, B₁₂, and B₁₀, which enhance copper retention, can be considered as having anti-bacterial properties (see figure 1 and 2). As an example, vitamin A, which is considered to be an anti-infectious vitamin, can specifically be categorized as anti-viral. This is also true of vitamin C and zinc. However, zinc, vitamin C, and vitamin A are mutually antagonistic to copper; if taken in excessively high dosages by individuals with a copper deficiency, they can actually promote infectious processes — especially those of bacterial origin.

TMA studies have shown that chronic candidiasis is frequently associated with copper excess. Therefore, minerals and vitamins antagonistic to copper can be considered to have anti-fungal and anti-yeast properties (see figure 1 and 2).

Malignancies and Copper

Low TMA copper levels are also frequently found in some types of malignancies,

most of which are of the catabolic or highly metastatic type. High tissue iron/ copper may or may not be present depending upon the type of malignancy. There have been reports that tissue iron accumulation is found in tissues and lymph nodes with Hodgkins disease.²⁹ TMA research is revealing the increased requirements for copper in some malignancy conditions. The necessity for copper is obvious due to its role in respiratory enzyme systems and its participation in superoxide dismutase activity, which helps protect the cell from damage from oxygen toxicity. Cytochrome c oxidase, the terminal oxidase in the electron transport chain, is copper dependent. A reduction in cytochrome c oxidase activity results in the mitochondria becoming enlarged and deformed with advanced copper deficiency. Animal studies have confirmed the effects of some copper compounds as an anti-neoplastic agent. The addition of copper decreased tumor growth, decreased metastasis, and increased survival of animals with certain types of neoplasms.³⁰ Several reports indicate that serum copper levels rise with the severity of some malignancies and return to normal with remission.^{31 32}

Osteoporosis

One of the early signs of copper deficiency is osteoporosis.^{33 34} A number of enzymes involved in collagen synthesis and cross-linking of the organic matrix of bone require copper. Bone changes in copper deficiency include a loss of trabecular formation with thinning of the cortex. It is common to find low tissue levels of calcium in conjunction with low tissue levels of copper on TMA studies. Through TMA studies, osteoporosis has been linked with both copper deficiency and copper excess and has been categorized as type I or type II osteoporosis respectively.³⁵

Cardiovascular

The structure and integrity of the vascular system is intimately related to copper. An adequate amount of copper is required for the production of the enzyme lysyl oxidase, which is involved in the quality and quantity of elastin formation and collagen cross-linking. Therefore, copper deficiency is related to vascular defects such as aneurysms, heart enlargement, heart failure, and

infarcts. Klevay has reported that a relative copper deficiency may contribute to ischemic heart disease.³⁶ A deficiency of copper relative to zinc produces a decrease in HDL (high density lipoproteins) and an increase in LDL (low density lipoproteins).³⁷

Copper excess may also contribute to cardiovascular problems from hypercholesterolemia, which is associated with hypothyroidism. Copper in excess has adverse effects upon thyroid activity and zinc status.

Orthopedic Disturbances and Copper Imbalance

As mentioned previously, adequate copper is required for the normal production and integrity of elastin and collagen, which are components of ligaments and the nucleus pulposus of the intervertebral disc. Other minerals and vitamins are also involved in collagen and elastin synthesis. As an example, vitamin C is required for the hydroxylation of proline to hydroxyproline, which forms chains of tropo-collagen. Vitamin C, iron, and manganese are all involved in the conversion of lysine to hydroxylysine. Manganese is required for the activity of galactosyltransferase and glucosyltransferase, and zinc is involved in protein synthesis. Each of these nutrients is affected by copper (see figure 1 and 2).

Davies³⁸ reported studies of lathyrism, which apparently produces copper deficiency resulting in structural skeletal abnormalities including scoliosis, spondylosis, and kyphoscoliosis.

Excessive tissue copper is also associated with structural skeletal defects. Pratt and Phippen reported findings in which elevated hair copper occurred with idiopathic scoliosis.³⁹ Copper and estrogen probably act synergistically in contributing to scoliosis. During pregnancy, estrogen is known to produce relaxation of the pelvic ligaments at the sacroiliac joints and symphysis pubis⁴⁰ in preparation for the birthing process. The resulting elasticity allows less resistance for the fetus when passing through the birth canal. The effect of estrogen is, of course, not confined only to the pelvis. By antagonizing or producing

deficiencies of other nutrients (see figure 1 and 2), copper elevation also contributes to ligamentous laxity throughout the skeletal structure. Therefore, any factor that contributes to increased copper retention such as, oral contraceptive and IUD use, pregnancy, cholestasis, etc., can result in structural skeletal instability and ligamentous laxity.

Neurological

Copper deficiency is known to affect the central nervous system. Reports of animal studies have shown defects in myelination with copper deficiency.⁴¹ Observation of TMA studies has shown low tissue copper levels in multiple sclerosis patients. Douglas, et al, confirmed this finding in their report, in which they found significant differences in hair copper levels in forty multiple sclerosis patients compared to forty-two controls.⁴² Similar observations have been seen on TMA patterns of patients with Parkinson's disease. Information from animal studies strongly suggests that copper deficiency can be a factor in Parkinson's disease in humans, since dopamine levels were found low in both copper deficient animals and patients with Parkinson's.⁴³

Menkes disease, also known as Steely Hair disease is an inherited inborn error of copper metabolism in infants. Infants with this condition manifest most of the conditions described with copper deficiency. This condition is usually fatal with a life expectancy of about two years. Diagnosis is difficult since these children appear relatively normal after birth and may not manifest severe symptoms for several weeks or months.⁴⁴ This condition emphasizes the need for nutritional monitoring of the fetus through the mother. Baumslag has stated the practicality of using TMA for this purpose. Copper supplementation of the mother should provide this nutrient to the fetus since copper easily crosses the placenta.⁴⁵

Other conditions reported to be related to copper deficiency include suppression of immune response⁴⁶ (cellular), celiac disease, cystic fibrosis of the pancreas,⁴⁷ and loss of pigmentation of the hair and skin.⁴⁸ TMA studies have revealed other

conditions commonly seen with low tissue copper levels. These include gout, hypertension, antibiotic sensitivity, hyperactivity, hyperglycemia, emotional disturbances (manic disorders), type I insomnia, and increased sympathetic neuroendocrine activity.

Factors Contributing to Copper Deficiency

Minerals

Figure 1 shows the minerals that are antagonistic to copper.^{49 50} Prolonged high intake of these elements, singularly or in combination, can produce a copper deficiency, especially if the nutritional or tissue copper status is marginal. The nutritional minerals shown in figure 1 can be used in the treatment of copper toxicity. Copper supplementation, however, can aid in decreasing the toxic effects of some heavy metals as well as inhibiting their absorption. A report by Fields, et al, revealed that copper is adversely affected by the consumption of fructose. Copper deficiency was exacerbated in animals fed fructose, and contributed to fatty degeneration of the liver.

Vitamins

Vitamins that are considered antagonistic to copper are shown in figure 2. Excessive intake of any one or combination of these vitamins can contribute to or exacerbate an existing copper deficiency. The opposite may also occur: excess copper intake or retention may produce a deficiency of any one or combination of these vitamins or increase their requirements.

It is interesting to note a similarity of copper deficiency to vitamin C deficiency. Many changes as a result of copper deficiency can be described as "scurvy-like". Indeed many symptoms of copper and vitamin C deficiency are similar and can be difficult to distinguish. High vitamin C intake should be approached with caution until copper status is evaluated since vitamin C is known to affect copper antagonistically,^{51 52 53} and/or enzymes that require copper. The biochemical defects of copper deficiency can be described as a copper deficient scurvy (CDS). Although the mechanisms of the biochemical defects

Figure 1.

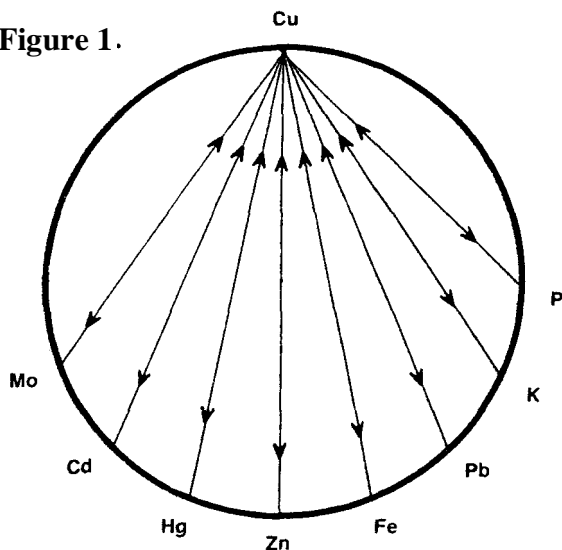
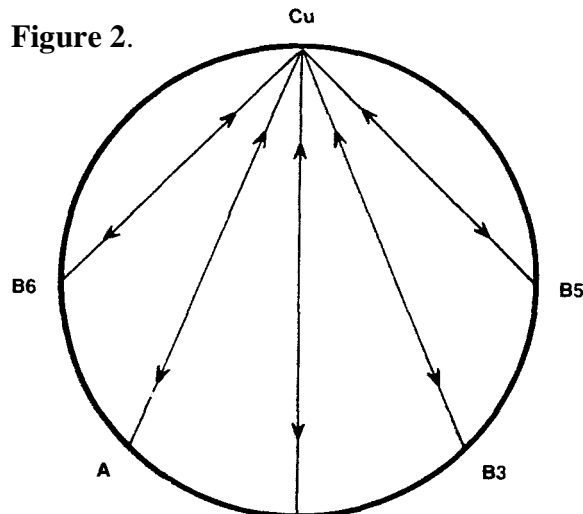


Figure 2.



of CDS are different from those caused by vitamin C deficient scurvy, CDS can be produced by excessive vitamin C intake. Conversely, vitamin C requirements are increased by excessive copper intake or tissue accumulation.

Endocrine Factors

Copper is normally excreted by the liver via adrenal stimulation. It has been demonstrated that copper excretion is increased by the administration of adrenal steroids.^{54 55} Increased activity of the sympathetic endocrines tend to increase the elimination of copper or increase its requirements due to increased metabolic demands. The sympathetic endocrines include the thyroid, adrenal cortex (glucocorticoids), adrenal medulla, and anterior pituitary.

Nutrients Synergistic to Copper

Rarely does a single nutrient deficiency develop exclusively. Other nutritional deficiencies and excess are always involved. Referring to figure 1 and 2, we can see the potential of vitamin and mineral toxicity that can develop in the presence of copper deficiency. As an example, the need for vitamin A, C, B₆, B₃, and B₅ is reduced in a copper-deficient state. Conversely, hyper-vitaminosis of most of these vitamins can be reduced by supplying adequate amounts of copper. We can see particularly that the adverse effects of hyper-vitaminosis A can be decreased by copper supplementation. Synergistic vitamins, those whose requirements are increased by copper

deficiency, include vitamin D, B₁, B₁₂, C, and folic acid (B₁₀). Supplementation of synergistic vitamins can aid in reducing the effects of copper deficiency and in restoring copper balance. As an example, increased adrenal corticosteroid production decreases copper retention⁵⁶ as well as antagonizes vitamin D metabolism.⁵⁷ Vitamin D can antagonize the effect of excessive corticosteroid production, thereby improving copper retention. This concept can be applied in helping to reduce the side effects of steroid therapy.

The synergistic minerals to copper include calcium, cobalt, selenium, sodium, and iron. The rickettsial bone changes that occur with copper deficiency are probably related to the copper-vitamin D-calcium relationship.

Some vitamins and minerals are both synergistic and antagonistic. This is due to their co-relationship with copper in metabolic functions such as the requirement for adequate amounts of iron and copper for hemoglobin production. But excessive iron intake antagonizes copper absorption on an intestinal level.

Copper Toxicity

Copper toxicity is common in the United States. TMA studies show that a large percent of the population has excessive tissue copper levels. This varies geographically due to high copper or low zinc soils and hard or soft water regions. The use of copper water pipes and dental prosthesis

have contributed greatly to increased copper intake. Copper also enters the food chain through the addition of copper to animal feeds and use of copper in spraying vegetables and grains for the prevention of fungus and algae growth.⁵⁸ Reports have shown that copper intake in the United States is approximately three to five milligrams per day. The copper intake in India is higher, averaging almost six milligrams per day and in some areas as much as thirteen milligrams.⁵⁹

We have learned that metabolic differences allow greater copper retention in some individuals than others, even with the same exposure. We have observed through TMA studies that vegetarians appear to have a greater tendency to retain copper than non-vegetarians. Henkin⁶⁰ reported that patients with adrenal insufficiency had higher serum copper levels, which improved with hormonal therapy. An increase in parasympathetic neuroendocrine activity would predispose an individual to an increased copper burden due to a decrease in copper excretion. The parasympathetic endocrines include the pancreas, parathyroid, and anabolic steroids. Copper is a sedative mineral, which when in excess, stimulates anabolic activity and increases parasympathetic activity.

TMA studies frequently reveal elevated tissue copper in women taking oral contraceptive agents which has been confirmed by others,^{61 62} as well in women with copper intrauterine devices. Since copper levels are noted to rise especially during the last trimester of pregnancy, it is not unusual to find multigravid women with excessive tissue copper accumulation, particularly if their pregnancies were not widely spaced. This will also contribute to inherited copper toxicity in children.

Copper toxicity can occur when there is a deficiency of the antagonistic nutrients shown in figure 1 and 2, especially vitamin B₆, B₃, B₅, A, and the minerals zinc and iron. The requirements for these nutrients are known to increase during pregnancy, with oral contraceptive use, and estrogen therapy.⁶³ Krishnamachari reported that in individuals suffering from pellagra (B₃ deficiency), copper absorption was increased.⁶⁴ Excessive intake of many of the

synergistic vitamins and minerals previously discussed can also contribute to copper toxicity. These factors should be explored in relation to Wilson's disease, an inborn error of metabolism resulting in toxic amounts of copper accumulation in the liver due to a lack of Ceruloplasmin. Elevated hair copper levels do not occur with Wilson's disease, but copper accumulation in tissues and organs other than the liver eventually develops. Excessive copper retention will often develop in the eye, producing the Kayser-Fleischer rings in the cornea which is a diagnostic sign of this disease. Increased copper accumulation has also been noted in individuals with sickle cell anemia.⁶⁵

A reduction or blockage in biliary excretion can increase copper accumulation, even if copper intake is not excessive. This type of copper accumulation may develop over prolonged periods involving several years. Excess estrogens are known to contribute to gall bladder stasis as well as cholesterol and calcium stone formation. The development of gallstones is found to have a higher incidence in women, especially those who have been pregnant.^{66 67} Elevation in estrogen levels during pregnancy⁶⁸ and oral contraceptive use have been reported to consistently produce defects in the excretory functions of the liver.⁶⁹ Increased copper retention can develop as a result of viral infections such as mononucleosis and hepatitis.⁷⁰ High tissue copper levels are frequently observed in individuals with a history of these conditions. Whether excess tissue copper causes viral manifestation or viral infections cause elevated tissue copper accumulation is speculative at this time, but one wonders if the anti-viral effects of zinc could be due to the antagonism of copper by zinc.

Medications That May Contribute to Copper Toxicity

The main excretory route for the removal of copper is through the intestinal tract; therefore, any factor that inhibits intrahepatic or extrahepatic excretion can potentially contribute to copper toxicity. There are many medications other than estrogens that can contribute to cholestasis. These include phenothiazine derivatives,

chlordiazepoxide, desipramine, imi-pramine, and meprobamate, which are contained in psychotropics, sedatives, and tranquilizers. Their common trade names are, Thorazine, Stelazine, Temaril, Norpramin, Tofranil, Librium, and Miltown; Trade names for chlorothiazide used in diuretics and anti-hypertensives are Diupres and Diuril; tolbutamide and chlorpropamide are used in anti-diabetic and oral hypoglycemic agents with trade names including Diabenese and Orinase; carbamazepine used for the control of convulsive disorders and severe neuralgias, trade name Tegretol; thiouracil and methi-mazole, trade name Tapazole, is used as an anti-thyroid preparation; indomethacine, trade name Indocin, used in analgesics and anti-inflammatory preparations; antifungal preparations which contain griseo-fulvin, trade names include Fulvicin-U/F and Grifulvin. This is only a partial list of commonly prescribed medications; for further information consult the *Physicians' Desk Reference*.

Thyroid Insufficiency and Copper

For several years it has been noted that elevated tissue copper is a common finding in conjunction with thyroid insufficiency. Copper's effect upon thyroid function involves multiple mechanisms. First, by the copper antagonistic effect upon iron. Dillman and co-workers have reported that iron deficiency results in thyroid insufficiency.⁷¹ Other investigators have concluded that iron status and thyroid function appears to have a reciprocal relationship in that iron deficiency can impair thyroid function, and iron stores can be reflective of thyroid function.⁷²

Copper can also affect thyroid function through an insulin effect. Insulin is known to antagonize thyroid function.⁷³ Through observations of TMA patterns, it has been noted that elevated tissue copper is associated with increased insulin secretion by the pancreas; it is conceivable that copper enhances insulin secretion. Studies that show an association of elevated estrogen with elevated insulin support this view. Plasma insulin levels are known to be elevated during pregnancy, being highest in the last trimester.⁷⁴ The same insulin effect is also observed during estrogen

therapy.^{75 76 77} While a direct effect of copper upon insulin has not been confirmed at this time, it has been confirmed that estrogen does not produce the insulin rise. An indirect effect of copper can be suspected due to the copper-calcium-vitamin D synergistic relationship. It is apparent from TMA studies that copper increases the tissue retention of calcium, and calcium is known to mediate the release of insulin.^{78 79} Vitamin D metabolites (1, 25(OH)₂ D₃) enhances the synthesis of insulin, and insulin enhances the synthesis of vitamin D metabolites.⁸⁰ Since zinc is required for the storage of insulin, it is possible that antagonism of zinc by copper could be responsible for the flooding of insulin into the plasma.

Other conditions commonly observed with excessive tissue copper accumulation via TMA studies include chronic E.B.V. and C.M.V. infections, emotional disturbances (depressive disorders), hypoglycemia, fatigue, fibroid tumors, low blood pressure, transient high blood pressure, anorexia, PMS, AIDS, dermatosis, endometriosis, infertility, hair loss, type II insomnia, and frontal headaches.

Generally it is often noted that adults who show elevated tissue copper accumulation have a tendency to be right brain dominant. They are usually emotionally oriented and artistically inclined. TMA tests of individuals whose occupation or hobby involves creativity such as artists, sculptors, musicians, and actors invariably have a tendency toward either a high tissue copper or a low zinc to copper ratio, whereas individuals with a low tissue copper or high zinc/copper ratio tend toward left brain dominance and often follow intellectual pursuits.

Conclusion

The importance of copper nutriture is obvious due to its requirement in enzyme systems. Often the adverse effects of copper toxicity are given more consideration than copper deficiency. However, copper balance is important particularly in relationship to other nutrients. Just as much consideration should be given to the possibility of copper deficiency as to copper toxicity.

References

1. Hart EB et al: Iron In Nutrition. VII. Copper as a Supplement to Iron for Heme-globin Building in the Rat. *J. Biol. Chem.* 77, 1928.
2. Mills ES: Idiopathic Hypochromemia. *Am. J. Med. Sci.*, 182, 1931.
3. Daniels AL, Wright OE: Iron and Copper Retentions in Young Children. *J. Nutr.* 8, 1934.
4. Cartwright GE, Wintrobe MM: Copper Metabolism in Normal Subjects. *J. Clin. Nutr.*, 14, 1964.
5. Medeiros DM et al. Copper and Sodium Concentration in Rat Hair as Related to Dietary Intake. *Nutr. Res.* 3, 1983.
6. Klevay LM: Hair as a Biopsy Material. II Assessment of Copper Nutrition. *Am. J. Clin. Nutr.* 23, 1970.
7. Deeming SB, Weber CW: Hair Analysis of Trace Minerals in Human Subjects as Influenced by Age, Sex and Oral Contraceptive Use. *Am. J. Clin. Nutr.*, 31, 1978.
8. Vir SC et al: Serum and Hair Concentrations of Copper During Pregnancy. *Am. J. Clin. Nutr.*, 34, 1981.
9. Laker M: On Determining Trace Element Levels in Man; The Uses of Blood and Hair. *Lancet*, 2, 1982.
10. Ikeda T, et al: Hair Copper and Zinc Concentrations in Handicapped Children with Anticonvulsants. *Dev. Pharmacol. Ther.*, 6, 1983.
11. Jacob RA et al: Hair as a Biopsy Material v. Hair Metal as an Index of Hepatic Metal in Rats; Copper and Zinc. *Am. J. Clin. Nutr.* 31, 1978.
12. Baumslag N, et al: Trace Metal Content of Maternal and Neonate Hair. *Arch. Environ. Hlth.* 29, 1974.
13. Hambidge KM: Increase in Hair Copper Concentration with Increasing Distance from the Scalp. *Am. J. Clin. Nutr.*, 26, 1973.
14. Hambidge KM: Hair Analysis. *Ped. Clin. N. Am.*, 27, 1980.
15. Osaki S, et al: The Mobilization of Iron from Perfused Mammalian Liver by a Serum Copper Enzyme, Ferroxidase I. *J. Biol. Chem.*, 246, 1971.
16. Fairbanks VF, et al: *Clinical Disorders of Iron Metabolism.* 2nd Ed. Grune and Stratton, N.Y., 1971.
17. Mowat AG, Hothersall TE: Nature of Anaemia in Rheumatoid Arthritis. VII. Iron Content of Synovial Tissue in Patients with Rheumatoid Arthritis and in Normal Individuals. *Ann. Rheum. Dis.*, 27, 1968.
18. Kishore V, et al: Effect of Nutritional Copper Deficiency on the Development of Adjuvant Arthritis in the Rat. *Trace Substances in Environmental Health XVI.* Hemphill, D.D., Ed. Univ. Mo. Columbia, 1982.
19. Rainsford KD: Environmental Metal Ion Perturbations, Especially as They Affect Copper Status, Are a Factor in the Etiology of Arthritic Conditions: An Hypothesis. *Inflammatory Diseases and Copper.* Sorenson, J.R.J., Ed. Humana Press, N.J., 1982.
20. Mason KE: A Conspectus of Research on Copper Metabolism and Requirements of Man. *J. Nutr.*, 109, 1979.
21. Chandra RH, Newberne AM: *Nutrition Immunity and Infection. Mechanism of Interactions.* Plenum Press, N.Y., 1977.
22. Weinberg ED: Iron and Susceptibility to Infectious Disease. *Bacterial Nutrition.* Lichstein H.C., Ed. Hutchinson Ross Publ., Co., Penn, 1983.
23. Beisel WR: The Effect of Infection on Host Nutritional Status. *Advances in Human Clinical Nutrition.* Vitale, J.J., Broitman, S.A., Eds. John Wright. PSG, Inc., Boston, 1982.
24. Collie WR et al: Hair in Menkes Disease: A Comprehensive Review. *Hair Trace Elements and Human Illness.* Brown, A.C., Crouse, R.G., Eds. Prager Pub., N.Y., 1980.
25. Graham GG, Cordano A: *John Hopkins Med. J.*, 124, 1969.
26. Al-Rashid RA, Spangler J: *N.E.J.M.*, 285, 1971.
27. Karpel JT, Peden VH: *J. Ped.*, 80, 1972.
28. Luster MI et al: Immunological Alterations in Mice Following Acute Exposure to Di-ethylstilbestrol. *Biological Relevance of Immune Suppression as Introduced by Genetic, Therapeutic and Environmental Factors.* Dean, J.H., Padarathsingh, M., Eds. Van Nosstrand Reinhold, Co., N.Y., 1981.
29. Dumont AE et al: Siderosis of Lymph Nodes in Patients with Hodgkin's Disease. *Cancer*, 38, 1976.
30. Sorenson RJ et al: Antineoplastic Activities of Some Copper Salicylates. *Trace Substances in Environmental Health XVI.* Hemphill, D.D., Ed. Univ. Mo. Columbia, 1982.
31. Dickerson JWT: Nutrition of the Cancer Patient. *Advances in Nutritional Research Vo. 5.* Draper, H.H., Ed. Plenum Pub., N.Y., 1983.
32. Aspin N, Sass-Kortsak A: Copper. *Disorders of Mineral Metabolism Vol.1. Trace Minerals.* Bronner, F., Coburn, J. Eds. Academic Press, N.Y., 1981.
33. Graham GC, Cordano A: Copper Deficiency in Human Subjects. *Trace Elements in Human Health and Disease.* Prasad, A.S., Ed. Academic Press, N.Y., 1976.
34. Underwood EJ: *Trace Elements in Human and Animal Nutrition 4th Ed.* Academic

- Press, N.Y., 1977.
35. Watts DL: Determining Osteoporotic Tendencies from Tissue Mineral Analysis of Human Hair, Type I and Type II. *Townsend Newsletter For Drs.* Aug./Sept., 1986.
 36. Klevay LM: Coronary Heart Disease: The Zinc/Copper Hypothesis. *Am. J. Clin. Nutr.*, 28, 1975.
 37. Klevay LM: The Role of Copper and Zinc in Cholesterol Metabolism. *Advances in Nutritional Research.* Draper, H.H., Ed. Plenum Pub., N.Y., 1971.
 38. Davies IJT: *The Clinical Significance of the Essential Biological Metals.* Charles Thomas, Pub., Ill, 1972.
 39. Pratt WB, Phippen WG: Elevated Hair Copper Level in Idiopathic Scoliosis, Preliminary Observations. *Spine* 5, 1980.
 40. Guyton AC: *Textbook of Medical Physiology, 4th Ed.* W.B. Saunders, Co., Phil., 1971.
 41. Underwood EJ: *Trace Elements in Human and Animal Nutrition, 4th Ed.* Academic Press, N.Y., 1971.
 42. Douglas et al: Trace Elements in Scalp-Hair of Persons with Multiple Sclerosis and of Normal Individuals. *Clin. Chem.* 24, 1978.
 43. O'Dell BL: Biochemistry of Copper. *The Medical Clinics of North America.* 60, 1976. W.B. Saunders, Co., Phil.
 44. Collie WR: Hair in Menkes Disease: A Comprehensive Review. *Hair Trace Elements and Human Illness.* Brown, Crouse, Eds. Prager Pub., N.Y., 1980.
 45. Scheinberg IH et al: The Concentration of Copper and Ceruloplasmin in Maternal and Infant Plasma at Delivery. *Clin. Invest.* 33, 1954.
 46. Prohaska JR, Lukaszewicz DA: Copper Deficiency Suppresses the Immune Response of Mice. *Science* 213, 1981.
 47. Mason KE: A Conspectus of Research on Copper Metabolism and Requirements of Man. *Nutr.*, 109, 1979.
 48. Aspin N, Sass-Kortsak A: Copper. *Disorders of Mineral Metabolism, Vol. I. Trace Minerals.* Bronner, F., Coburn, J., Eds. Academic Press, N.Y., 1981.
 49. Underwood EJ: *Trace Elements in Human and Animal Nutrition* 4th Ed. Academic Press, N.Y., 1977.
 50. Davies IJT: *The Clinical Significance of the Essential Biological Metals.* Charles Thomas, Pub., II., 1972.
 51. Finley EB, Cerklewski FL: Influences of Ascorbic Acid Supplementation on Copper Status in Young Adult Men. *Am. J. Clin. Nutr.*, 37, 1983.
 52. Carlton WW, Henderson W: Studies in Chickens Fed a Copper Deficient Diet Supplemented with Ascorbic Acid, Resperine and Diethylstilbestrol. *Nutr.*, 85, 1965.
 53. Hill CH, Starcher B: Effects of Reducing Agents on Copper Deficiency in the Chick. *Nutr.*, 85, 1965.
 54. Evans GW, Cornatzer WE: Biliary Copper Excretion in the Rat. *Proc. Soc. Exp. Biol. Med.* 136, 1971.
 55. Henkin RI: *Trace Element Metabolism in Animals Vol. II.* Hoekstra, W.G., et al, Eds. Univ. Park Press, Md., 1974.
 56. *Ibid.*
 57. Klim RG et al: Intestinal Calcium Absorption in Exogenous Hypercorticism. Role of 25(OH) D and Corticosteroid Dose. *Clin. Invest.*, 60, 1977.
 58. Scheinberg IH, Sternlieb I: Copper Toxicity and Wilson's Disease. *Trace Elements in Human Health and Disease, Vol. I.* Prasad, A.S., Ed. Academic Press, N.Y., 1976.
 59. Aspin N, Sass-Kortsak A: Copper. *Disorders of Mineral Metabolism, Vol. I.* Bronner, F., Coburn, J.W., Eds. Academic Press, N.Y., 1981.
 60. Henkin RI: *Trace Element Metabolism in Animals Vol II.* Hoekstra W.G. et al, Eds. Univ. Park Press, MD., 1974.
 61. Underwood EJ: *Trace Elements in Human and Animal Nutrition.* 4th Ed. Academic Press, N.Y., 1977.
 62. Watts DL: The Effects of Oral Contraceptive Agents on Nutritional Status. *Am. Chiro.* Mar. 1985.
 63. Altschule MD: *Nutritional Factors in General Medicine, Effects of Stress and Distorted Diets.* Charles Thomas, Pub. II., 1978.
 64. Kirshnamachari KAVR: Some Aspects of Copper Metabolism in Pellagra. *Am. J. Clin. Nutr.*, 27, 1967.
 65. Olatunbosun DA et al: Serum-Copper in Sickle-Cell Anemia. *Lancet* 1, 1975.
 66. Bennion LJ et al: Effects of Oral Contraceptives on the Gallbladder Bile of Normal Women. *N.E.J.M.*, 294, 1976.
 67. Ingelfinger FJ: Gallstones and Estrogens. *N.E.J.M.*, 290, 1974.
 68. Kranitt MJ et al: The Response to Challenge with the Synthetic Estrogen, Ethinyl Estradiol. *N.E.J.M.*, 277, 1967.
 69. Ockner RK, Davidson CS: Hepatic Effects of Oral Contraceptives. *N.E.J.M.*, 285, 1971.
 70. Altschule MD: *Nutritional Factors in General Medicine, Effects of Stress and Distorted Diets.* Charles Thomas, Pub. II., 1978.
 71. Dillman E et al: Hypothermia in Iron Deficiency Due to Altered Triiodothyronine Metabolism. *Am. J. Physiol.*, 1980.
 72. Tucker DM et al: Neuropsychological Effects of Iron Deficiency. *Neurobiology of the Trace Elements, Vol. I.* Dreosti, I.E., Smith, R.M., Eds. Humana Press, Clifton, NJ., 1983.
 73. Watts DL, Heise TL: *Balancing Body*

Chemistry. T.E.I. Sav. Ga. 1987.

74. Spellacy WN, Goetz FC: Plasma Insulin in Normal Late Pregnancy. *N.E.J.M.* 268,1963.

75. Gershberg H et al: Glucose Tolerance in Women Receiving an Ovulatory Suppressant. *Diabetes* 13, 1964.

76. Javier Z et al: Ovulatory Suppressants, Estrogen, and Carbohydrate Metabolism. *Metabolism* 17, 1968.

77. Flynn A: Estrogen Modulations of Blood Copper and Other Essential Metal Concentrations. *Inflammatory Disease and Copper*. Sorenson, R.J., Ed. Humana Press, Clifton, N.J., 1982.

78. Leclereq-Meyer V et al: Effect of Calcium and Magnesium on Glucagon Secretion. *Endocrinol.* 93, 1973.

79. Malaisse WJ et al: The Stimulus-Secretion Coupling of Glucose-Induced Insulin Release. *Lab. Clin. Med.* 76, 1970.

80. Cross HS, Peterlik M: Hormonal and Ionic Control of Phosphate Transport in the Differentiating Enterocyte. *Progress in Clinical and Biological Research, Vol. 168. Epithelial Calcium and Phosphate Transport Molecular and Cellular Aspects*. Bonner, F., Peterlik, M., Eds. Alan R. Liss, Inc., N.Y. 1984.