Excess Copper as a Factor in Human Diseases

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Abstract

A review of hypercupremia is provided. Although hypocupremia is discussed, it is significantly less relevant in disease. Elevated copper levels are correlated to various mental and neurological illnesses including schizophrenia, depression, autism, tardive dyskinesia, and memory loss. Hepatic and renal dysfunctions may result from the specific accumulation of copper in these tissues. Copper excess may be the largest factor in the etiology of hypertension. A particularly strong correlation exists between high serum copper and hypertension in the dark-skinned populations. Elevated tissue copper levels have been observed in aging and most types of cancer. Positive correlations to estrogens, dialysis treatment, and blood type are discussed. While contaminated drinking water is the most common route of copper intoxication, multivitamin supplements and cigarette smoking also contribute. Nutritional therapy using zinc, manganese, vitamin C, and molybdenum supplements has the greatest potential for eliminating an excess burden of copper. Copper poisoning with zinc deficiency will explain the present dopamine theory of simplistic schizophrenia since this condition occurs only in one-half of the patients labelled schizophrenic. These findings also introduce elemental or atomic biology which is more basic than molecular biology.

Introduction

Although of paramount importance in normal homeostasis, especially with regard to hemoglobin, copper is necessary only in minute amounts in comparison with other minerals such as iron and zinc. Much research in rats has been reported by Klevay (1, 2, 3,4) focusing on the problems of hypocupremia. However, human adult difficulties of this nature are rare and hence, of limited importance. A report of the National Academy of Sciences (5) states that clinically apparent copper deficiency is extremely rare and difficult to achieve by dietary means. The utilization of copper by modern society implies the pervasive nature of this heavy metal pollutant. Twice the amount of copper is annually mined as compared to the more common heavy metal pollutant, lead (6). At the Princeton Brain Bio Center, where serum heavy metal concentrations are routinely assayed, only three cases of hypocupremia have been documented from over twenty-five thousand patients treated, and these were precipitated by excessive zinc ingestion. In contrast, 64% of all female patients and 37% of all male patients exhibited copper intoxication and subsequent zinc deficiency in 1982. From a clinical standpoint, it is these symptoms and signs with which the physician should be familiar.

Copper: The Physiology of of Oxidative Enzymes

The essential nature of copper in the human body results from its incorporation in many basic oxidative enzymes. Usually absorbed in the proximal intestinal tract, recent research claims copper's physical properties allow uptake as early as the stomach (7). If ingested, copper does reach the small intestine, and uptake is facilitated by the simultaneous absorption of amino acids. Additionally, Solomons (7) reports that diets high in calcium and phosphorus cause a greater fecal loss of copper, although the mechanism of this antagonism is undetermined. Zinc and vitamin C are copper antagonists inhibiting intestinal absorption of

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copper, while promoting its excretion. Molybdenum, although having no effect on intestinal absorption, promotes excretion. The excretion of copper occurs primarily through the bile, placing much of the burden upon the liver, although detectable copper is present in the urine (8).

Copper Transport

Once copper enters the gut circulation, it is bound to albumin, transcuprein, and low molecular weight ligands such as histidine in the plasma. Once transported to the liver, hepatic mechanisms incorporate copper into Ceruloplasmin, a serum protein (9). Seventy to eighty percent of all circulating copper is in the form of Ceruloplasmin and as such is responsible for one of copper's most important enzymatic activities, feroxidatively involved in the mobilization of iron and the regulation of hemoglobin. Ceruloplasmin and a second cupric enzyme, histaminase, are involved in the degradation of the chemical modulator histamine. Histamine is a neurotransmitter of the body and brain, a stimulator of gastric secretion in the gut, and responsible for anaphylaxis. Monoamine oxidase and dopamine B-hydroxylase are cupric enzymes responsible for an even more prominent neurotransmitter, norepinephrine. In addition to its roles in the brain, norepinephrine is noted for its involvement in the "fight or flight" reaction when secreted by the adrenal medulla.

Additional cupric enzymes include cytochrome C, the rate-limiting enzyme of oxidative phosphorylation, lysyl oxidase, involved in the cross-linking of elastin and collagen, and tyrosinase, involved in the production of melanin. Recent research has pointed to a role for copper in blood clotting, namely as a constituent of factor V (10).

Copper and Aging

Copper has also been implicated in many of the degenerative diseases of aging. Copper accumulates with age as zinc declines, resulting in a higher risk of intoxication in the elderly than any other age group. Dr. George Schambaugh, Jr. (11) noted an increase in mean serum copper from 1.12 ug/g in the age group 20-39 to 1.20 ug/g in the age group 70-79. Even more profound changes were noted in studies of human brain tissue by Isabelle Tipton (12). Copper in the brain, measured in micrograms per gram of tissue ash, rose from 200 in childhood to over 400 by age 60. Free unbound copper increases as the copper burden is elevated and is responsible for the formation of toxic oxygen radicals in the body. A growing number of "free radical diseases" are being identified and to date these include cancer, atherosclerosis, hypertension, senile dementia, and immune deficiency. Surprisingly, two cupric enzymes are responsible for the neutralization of such radicals, namely superoxide dismutase and Ceruloplasmin. If elevated, free copper overwhelms these natural defenses; however, the copper intoxication is treatable.

Hypocupremia

Sloane (13) describes three clinical situations wherein hypocupremia may be present. These include premature infants, patients receiving total parenteral nutrition, and severely malnourished children. Additionally, Pfeiffer (14) has described hypocupremia in conjunction with zinc intoxication (2300 mg/day). Manifestation of copper deficiency documented by Fields (15) include growth retardation, anemia, hypercholesterolemia, lesions of the myocardium, hypertriglyceridemia, hypertrophy of the heart, increased blood urea nitrogen and ammonia, decreased activity of copper enzymes, decreased ATP, impaired glucose tolerance, decreased insulin binding, decreased lipogenesis, decreased blood pressure, and neurological impairment.

Copper as A Nervous Stimulant

Despite the relative severity of copper deficiency, a much more clinically relevant problem and the focus of this article is hypercupremia. The most pertinent syndrome of copper poisoning regards its toxic disturbance of the nervous system. The stimulant effects of copper were first described by Uss-ing in 1949 (16) as he measured an increased electrical potential of the frog skin placed in a copper containing Ringer's solution. Tonnies and Ferreira (17) verified Ussing's original findings with copper concentrations as low as 10 uM, postulating that the increased electrical potential may be due to unrestricted sodium movement across the membrane. Pfeiffer and Goldstein (18) using the quantitative EEG demonstrated that five milligrams of copper given orally to male volunteers has

the same central nervous system stimulative effects as five milligrams of d-amphetamine. In sufficient quantities these inherent qualities of copper may yield profound effects upon the regulatory and behavioral functions of the nervous system.

Pfeiffer and his colleagues (19) reported on copper's role in mental illness as they defined histapenia, a schizophrenia-like disorder. They hypothesize that histamine, a neurotransmitter and chemical modulator of anaphylaxis, is regulated by the cupric proteins histaminase and Ceruloplasmin. Abnormally high levels of copper increase the activity of these two enzymes resulting in excessive degradation of histamine. This histamine deficit and copper intoxication have been found to represent fifty percent of those patients presently labelled schizophrenic (20).

Bowman and Lewis (21) studied elevated copper and lowered zinc of hair (40 patients) and the relation to dopamine homeostasis in an attempt to explain schizophrenia abnormalities. Copper is the rate-limiting component of the enzyme tyrosinase.

Thus elevated copper and elevated tyrosinase will siphon tyrosine from dopamine production and funnel it into the synthesis of melanin. The anabolic enzyme, dopa decarboxylase, which converts dopa to dopamine is severely inhibited by free copper. At the synapse dopamine is degraded by dopamine B-hydroxylase and monoamine oxidase, both cupric enzymes. The presence of elevated copper in neuronal tissue will not only inhibit dopamine production but accelerate the degradation and reuptake of the neurotransmitter, thus greatly depressing the activity of dopaminergic pathways.

Bowman and Lewis conclude that a subset of schizophrenic subjects suffer from a disorder of copper metabolism other than Wilson's Disease. In these patients the copper to zinc ratio is significantly increased, which amplifies the functional severity of copper intoxication. This may cause a neural hyperdopaminergic activity.

The neurotoxicity of copper may also result from an energy deficiency due to the inhibition of the body's basic pathways of metabolism. Lai and Blass (22) have found **high** copper concentrations in rat brains to inhibit hexokinase, pyruvate kinase and lactate dehydrogenase which are essential enzymes in the glycolytic pathway. Not only may neurotransmitter imbalances disrupt neuronal functioning, but the neurons may actually be starved for energy.

Regardless of the mechanisms involved, the correlation between hypercupremia and schizophrenia is well documented. Chugh et al. (23) found increased serum copper in East Indian schizophrenics, but attributed the intoxication to ascorbic acid deficiency. A subsequent study by Olatunbosun et al. (24) countered the "vitamin C theory" by again depicting the high copper/schizophrenia correlation in Nigerians, but failing to discover any evidence of ascorbic acid deficiency. Chitre and Punekar (25) demonstrated significantly elevated serum copper in diagnosed schizophrenics. The schizophrenics were divided into subtypes, with the greatest increase being apparent in the paranoid-hebephrenic group (199.5 plus or minus 30.6, normal = 98.4 plus or minus 10.6). These authors found copper to be even higher in Parkinson patients (219.1 plus or minus 45.5). In a relatively unnoted study, Kimura and Kumura (26) documented significantly decreased zinc content in the hippocampus, the frontal lobe, and the occipital lobe of the brains of schizophrenics as compared to normals and patients with other cerebral disorders. Although copper levels were not determined, the depressed zinc levels might be caused by elevated copper levels due to the antagonistic relationship between these two metals.

Adult Insomnia

Patients presenting themselves at the Brain Bio Center with a chief complaint of insomnia have hypercupremia. The so-called light sleep of the geriatric patient is probably induced by copper intoxication. These patients invariably get relief from their insomnia in 4 to 6 weeks as the zinc, manganese, molybdenum with vitamin C supplements reduce their copper burden. Other signs of copper intoxication are tinnitus, opaquely white nails, hypertension, abnormal loss of hair, depression, paranoia, stuttering, and tremor. These symptoms also subside with the decrease in serum and tissue copper.

Some patients may have increased symptoms as the copper is mobilized from the large tissues such as the skin, muscles, and

liver. In other words, serum copper may rise in the first few weeks of zinc (etc.) supplementation. D-penicillamine can be used to speed the elimination of copper in these patients.

Dogs Get Copper Excess

Bedlington terriers provide an excellent study of copper toxicity and also Wilson's disease as these animals seem to inherently accumulate copper. Many of the symptoms are apparent in these dogs including gross hepatic necrosis, hair loss, and increased pigmentation of the skin. Behavioral changes are noted in older animals, most likely due to the increased deposition of the heavy metal in the brain and subsequent autopsy has revealed elevated copper levels in the central nervous system (27). One should add that elevated copper, as in pregnancy or contraceptive pill use, results in hair loss and pigmentation of the skin.

Further insight into the neurotoxicity of copper was provided in a study of elemental blood levels by Ali, Peet, and Ward (28). Copper levels were significantly reduced in recovered depressive patients as compared to those currently suffering from depression. Pfeiffer's (19) research and clinical experience have linked other neurological syndromes to hypercupremia including stuttering, blepharospasm, autism, childhood hyperactivity, preeclampsia, premenstrual tension, tardive dyskinesia, psychiatric depression, hypertension, tinnitus, senility, and hypoglycemia.

As with other cerebral metal intoxications (lead, bismuth, mercury, aluminum) (29) continued high tissue levels of copper can cause loss of memory. This observation suggests caution and the use of the smallest dose of estrogen in post-menopausal females. We never use more than 0.6 mg oral daily dose of conjugated estrogens.

Wilson's Disease (Hepatolenticular degeneration)

This familial disease is rare as shown by an incidence of only 1 in 200,000 cases seen at the Mayo Clinic. The ability to make Ceruloplasmin is deficient and excess copper is absorbed from the intestines. The serum copper level is low but the tissue level by liver biopsy is very high. The presenting symptoms of Wilson's disease in the adult may be psychosis, which if not diagnosed, results in death, and diagnosis by "sibling autopsy" since the other children in the family may also have the defect.

Renal and Hepatic Effects

The alternative foci of copper's toxicity are the body's detoxifying systems, namely the liver and the kidney. In studying patients with Wilson's disease with their increased copper burden, it becomes obvious that fatalities result mainly from hepatic and renal failure rather than nervous disturbances. Gross hepatic necrosis and destruction of the proximal tubule of the nephron evolve as the body attempts to eliminate excess copper. Although most copper is excreted in the bile, formation of an ultrafiltrate in the proximal tubule leaves this tissue susceptible to damage.

Much speculation has surrounded the mechanism of this resultant necrosis, and Susan Haywood has been a leader in these studies. Initially, Haywood (30) suggested the rupturing of lysosomes and the subsequent release of destructive enzymes were responsible for cell death and necrosis. Studies of copper intoxication reveal an initial deposition of excess copper in hepatic lysosomes. The "rupture hypothesis" was a natural extension of this observation.

Further study revealed that lysosomal rupture could only explain necrosis in the liver, since no lysosomal accumulation was apparent in renal tissue. Haywood (31) modified her original hypothesis, describing a copper saturation of the nucleus following lysosomal loading. She proposed that copper destabilized the nucleus, resulting in the cessation of coordinated cellular metabolism. Single and double-standard DNA breaks have been associated with copper accumulation in the nucleus. Although this theory will explain both hepatic and renal necrosis, more studies are needed.

Hypertension

The most common manifestation of hypercupremia is hypertension. As early as 1974, the World Health Organization (32) warned that high copper levels in the tissues are positively correlated with cardiovascular diseases and hypertension. Medeiros and Lui (33, 34) have repeatedly demonstrated that rats placed on high copper diets have

significantly higher systolic blood pressures than those with low copper intakes. Ahmed and Sackner (35) documented a similar correlation with sheep receiving infusions of copper sulfate. Similarly, most hypertensive patients seen at the Princeton Brain Bio Center exhibit elevated serum copper as well as depressed serum zinc.

Melanin, the natural skin pigment, seems to be a factor in the etiology of some forms of hypertension, especially in the darker skinned populations. Larsson and Tjalve (36) reported the physical properties of melanin cause it to bind heavy metal cations. This osmotically inactive pool of heavy metals was substantiated by epidemiological data collected by Creason et al. (37) which documented significantly higher blood copper and lead levels in black military recruits as compared to white military recruits. Thus copper, through its strong correlations to hypertension and its ability to be sequestered by melanin, may well lie at the heart of the high incidence (25%) of hypertension in the black population. Additional studies have found positive correlations between the darkness of skin color (38) and the admixture of African heritage (39, 40) with the degree of hypertension, further emphasizing the possible role of melanin.

Copper and Cancer

Although its role has yet to be adequately explained, elevated copper is related to cancer, either as a possible cause or as a sign of malignancy. As early as 1954 (41), researchers detected a significant increase in serum copper in patients suffering from certain cancers. Since these initial studies, epidermoid cancers of the head and neck are the only documented malignancies in which serum copper concentrations did not exceed normal levels (42). Accenting the magnitude of the elevation, Margalioth et al. (43) reported in a study of one hundred patients that malignant tissue concentrations of copper averaged 46% higher than those of normal tissues. Of great diagnostic value to the physician is the positive correlation between Ceruloplasmin levels and the effect of therapy. Patients responding to therapy demonstrated a significant reduction in Ceruloplasmin, while those whose levels remained high or increased had increasing spread of cancer. Margalioth and his colleagues (43) suggested a causative role be assigned copper, noting that elevated copper levels enhance the biological damage of oxygen radicals leading to the loss of enzymatic activity, single or double standard breaks in DNA, and changes in protein properties.

Free radicals, whose production is catalyzed by free, unbound copper, have been linked to a number of the "diseases of aging." In addition to cancer, the cellular irritation generated by toxic radicals has been linked to atherosclerosis, senile dementia, and immune deficiency. Massie and Aiello (44) found that increased ingestion of copper in the form of gluconate reduced the survival time as much as 14.4% in male rats. Copper, thus may play an integral role in the degenerative processes of aging.

A causative role of copper in cancer still remains a controversy, despite extensive research in the field. Chakraborty et al. (45) reported a rise in Ceruloplasmin with viral and inflammatory diseases, implying that increases may occur as a result of any generalized insult to the body and not specifically cancer. Certainly more evidence is necessary to determine the exact role of copper, but its positive correlation to malignancies is irrefutable.

The Estrogen Link

As shown by a multitude of studies, Ceruloplasmin levels follow those of estrogens, fluctuating throughout the menstrual cycle and rising in the pregnant woman during gestation. These elevated copper burdens may well be the physiological factor responsible for premenstrual tension and postpartum or puerperal psychosis. Estrogenic steroids have been shown to increase plasma Ceruloplasmin in rodents (46), chickens (47), and women taking oral contraceptives (48). In pregnancy Henkin, Marshall, and Meret (49) reported the doubling of serum copper from conception to term, explaining frequent mood shifts and psychotic breaks. Often two to three months are required for copper levels to return to normal following delivery or cessation of the oral contraceptives.

In spite of these seemingly astronomical levels, Pfeiffer and Iliev (50) have documented cases where the potent estrogens in oral contraceptives resulted in copper levels exceeding those in the ninth month of

pregnancy (51). Female patients in complete remission from their schizophrenia have a prompt return of symptoms when they try to use oral contraceptives. Serum copper rises, and then the degree of Psychopathology as measured by the EWI rises.

Side effects of these elevated copper levels are common, with hypertension being the most frequent manifestation. Hunt et al. (52) found without preventive treatment 16% of the pregnant females he studied developed hypertension (systolic> 140 mm Hg, diastolic > 90 mm Hg). Additional research by Horwitt and his coworkers (53) revealed the rise in Ceruloplasmin and blood pressure exhibited by oral contraceptive users is directly related to the potency of the estrogen contained in the contraceptive. These data raise the question of safety in the long-term use of oral contraceptives and underscore the importance of careful monitoring in patients choosing this method of birth control.

Dementia Dialytica

In 1964 Peterson and Swanson (54) first described dementia dialytica, a heavy metal poisoning resulting from the use of tap water for a dialysis of kidney patients. Symptoms of this acute intoxication range from stuttering, aphasia, psychosis, and loss of reality to such fatal complications as cardiac failure and hemolytic anemia. Blomfield, McPher-son, and George (55) pointed to the active intake of copper by plasma and red blood cells as the causative factor in the syndrome. Later studies implicated magnesium (56), fluoride (57), zinc, and aluminum as other possible intoxicants. Thus, it appears that a number of metals may be involved. The strongest correlation for psychosis still remains with copper, and undoubtedly this metal is responsible for much of the pathogenicity in dementia dialytica. Fortunately, the use of de-ionized water in standard dialysis has greatly reduced the threat of heavy metal intoxication in such treatments.

A Correlation with Blood Type

In 1973, Wiener et al. (58, 59) discovered significant differences among the three blood types in sheep with respect to copper levels in whole blood and plasma. Type BB sheep had significantly higher circulating copper levels than type AB. Type AB was intermediate in copper levels. Since these data suggest a differing biochemical balance among blood types, Bonnett, Pfeiffer, and Aston (60) undertook a similar study on human schizophrenics. Previously, schizophrenic patients had been shown to present an unusually high copper burden. Results revealed that chronic schizophrenics have a high incidence of type A blood. It appears that those individuals with blood type A have a difficult time eliminating copper and require prolonged therapy to ameliorate their psychosis. Additional studies (61, 62, 63) have found the incidence of myocardial infarction to be significantly elevated in individuals with type A blood. As heart tissue is stimulated by copper, an increased copper burden could sensitize the tissue leading to a propensity for heart irregularities. Also, a woman with type A blood, especially one who smokes, should be wary of oral contraceptives due to their combined hypercupremic actions.

Intoxication

The most common route of copper intoxication appears to be through the ingestion of contaminated drinking water. The usual epidemic of mass copper poisoning occurs when copper sulfate is used to reduce algae growth in reservoirs. This technique involves pulling a large cloth bag filled with bluestone (copper sulfate) behind a boat until all the copper dissolves. The algae are killed; however, the population drinking the water is often intoxicated. Isolated cases of copper poisoning have increased with the replacement of galvanized steel plumbing with newer copper systems. The easily dissolved copper in combination with unusually soft or acidic water can lead to high concentrations of copper and cadmium in the water flowing from the tap. One of the better documentations was prepared by Spitainy and his colleagues (64). The case involved a Vermont family whose home was supplied municipal water from a terminal main consisting of 1.5 inch type K copper pipe. The water was slightly acidic (pH = 5.8) and considered soft. This soft, acidic water in addition to their terminal position on the main caused the copper levels of the water to rise to 7.8 mg/liter (ppm), significantly higher than the U.S. Public Health allowable limit of 1.0 ppm. Members of the family exhibited symptoms of acute copper poisoning, gastrointestinal illness and emesis due to a consistently

high copper intake. A similar case of intoxication in a fourteen-month old child was diagnosed as Wilson's disease. However, postmortem studies suggested intoxication due to a contaminated water supply (6.75 ppm of copper) (65).

Dr. A.R. Sharrett (66) documented a positive correlation (0.85) between whole blood and drinking water copper concentrations in five U.S. towns conclusively identifying the main source of human intake. A subsequent study by Sharrett et al. (67) estimated the daily consumption of copper from drinking water in Seattle to be 2.2 mg, 0.2 mg greater than the U.S. RDA. The Food and Nutrition Board's standard of 2.0 mg/ day of dietary copper has even been questioned with independent studies estimating a daily requirement of 1.55 mg (68). Studies have also linked a reduced cardiovascular mortality to be associated with hard water due to the liming of pipes which trap the oxidative catalysts copper and manganese (69). Physicians should be conscious of copper poisoning if the water in their area is soft or acid (70).

Two other factors which substantially contribute to the daily intake of copper are multivitamin supplements and cigarette smoking. The following multivitamins contain at least 100% of the daily requirements of copper as reported by the *Physician's Desk Reference* (71) and thus are likely to lead to intoxication: Added Protection III (Professional Health, 2 mg), Berocca Plus (Roche, 3 mg), Chromagen OB (Savage, 2 mg), Total Formula (Vitaline, 2 mg), Mater-na 1.60 (Lederle, 2 mg), Medi-Tec (Robertson Kaylor, 2 mg), Mission Prenatal Rx (Mis sion, 2 mg), Myadec (Parke-Davis, 2 mg) Natalins Rx (Mead Johnson, 2 mg), Theragram M (Squibb, 2 mg), and Geriplex Fx (Park Davis, 4 mg).

Cigarette smoking only adds to copper and cadmium poisoning. Public Health Service (72) found a cigarette to contain 0.19 ug of copper. This accumulates in the body as smoke is inhaled as evidenced by Creason et al.'s (37) documentation of significantly higher levels of copper in smokers as compared to non-smokers. Yet another health hazard associated with smoking!

Therapy

Nutritional therapy for copper intoxication appears to be the treatment of choice, despite the claims of the pharmaceutical industry. Drug treatment consists of chelating agents, namely penicillamine, which binds copper ions causing their excretion. Chelating agents also have high affinities for other essential trace minerals leading to deficiencies of other Trace elements. The copper levels may be brought to the normal range, but zinc, molybdenum, manganese, and other cations may be depleted leading to numerous side effects such as prurititis, lupus, urticaria, thyroiditis, synovitis, anorexia, nausea, vomiting, epigastric pain, peptic ulcers, hepatic dysfunction, pancreatitis, loss of taste, hemolytic anemia, bone marrow depression, leukocytosis, proteinuria, hematuria, tinnitus, optic neuritis, myasthenia gravis, alopecia, epidermal necrolysis, bronchiolitis, pulmonary fibrosis, bronchial asthma, and excessive wrinkling of the skin. Penicillamine therapy, therefore, should be avoided except for severe cases of acute poisoning, rheumatoid arthritis, and some cases of Wilson's disease.

Nutritional therapy is more discriminating in its actions, thus avoiding adverse side effects. Zinc has been shown to protect against copper toxicosis by inhibiting intestinal absorption while promoting excretion in the bile. Bremner et al. (73) reported up to a 40% reduction in liver copper in zinc-supplemented sheep (420 mg/kg). Festa et al. (74) reported a similar relationship in man. Additional reports have documented copper deficiency anemia in humans suffering from zinc intoxication (75). Of course, in such cases patients were receiving up to ten times the recommended daily intake of zinc-deficient dwarfs of the Middle East (76) and zinc-deficient sickle cell anemia patients (77). Manganese is synergistic with zinc in copper elimination and therefore manganese should be combined with zinc therapy.

Studies of chickens (78), rabbits (79), guinea pigs (80), and monkeys (81) have documented a significant reduction of serum copper activity following ascorbic acid supplementation. This antagonistic relationship between copper and vitamin C was confirmed in man by Finley and Cerklewski's (82) illustrative study of young males.

In Wilson's disease and in copper intoxication of the Bedlington terrier, zinc and vitamin C represent the primary nontoxic

therapy. Schwenwink in 1963 first used zinc in the treatment of Wilson's disease. The successful use of zinc has continued in Holland for 20 years (Hoogenvaad, 1978).

Molybdenum is also antagonistic to copper in mammals, increasing urinary excretion but not influencing intestinal absorption. Initial studies of the molybdenum-copper interaction involved increased copper excretion in domesticated farm animals treated with molybdenum (84, 85, 86, 87). Copper has long been used as a growth stimulant in animals raised for slaughter. Doesthale and Gopalan (88) found significant increases in copper excretion in man with molybdenum intakes as low as 1.5 mg/day. In one of the more recent studies, the copper-molybdenum antagonism was observed to stoichiometrical-ly proceed with a 1.5:1, Cu:Mo ratio (89).

Dougherty and Hoekstra (90) have also demonstrated the protective actions of selenium and vitamin E against the toxic peroxidative activity of elevated copper.

Conclusions

Although copper is an essential trace mineral, a serious health threat is posed by the excess oral intake of copper in drinking water. Elevated copper levels produce a number of symptoms and the current environmental and social climate suggests that the incidence of copper precipitated disease will increase. Foods high in copper are nuts, liver, mushrooms, oysters, and wheat germ.

Copper ions are a general stimulant of nervous tissue, as well as of most tissues of the body, and its effects are identical to a similar dose of amphetamines. We first discovered copper as the cause of histapenia, a schizophrenia-like disorder characterized by high serum copper and low serum histamine levels. Although many patients were previously classified as suffering from unresponsive schizophrenia, our experience reveals they are simply copper poisoned. Ad-ditional nervous syndromes which have been documented in conjunction with high copper levels are stuttering, autism, childhood hyperactivity, tinnitus, hypertension, eclampsia, premenstrual tension, psychiatric depression, blepharospasm, psoriasis, arthritis, tardive dyskinesia, insomnia, senility, and functional hypoglycemia.

The most common manifestation of copper intoxication is hypertension, a common complaint in modern society. As early as 1974 the World Health Organization warned that high copper levels in the tissues are positively correlated with cardiovascular disease and hypertension. Copper has been shown to produce hypertension in laboratory animals and humans and its ability to be sequestered by melanin (skin pigment) may provide insight into the prevalence of high blood pressure in dark skinned populations. Copper also stimulates the heart itself and could predispose an individual to myocardial infarction, in addition to other cardiovascular diseases.

Therapy for copper intoxication involves the restriction of copper intake combined with copper antagonists which inhibit intestinal absorption of copper while promoting its excretion in the bile. Zinc, manganese and molybdenum along with vitamin C have been shown to decrease the body's copper burden.

Numerous studies have demonstrated an accumulation of copper as man ages. It is now speculated that this may play an integral role in the degenerative processes as we grow old. Massie and Aiello (1983) found that increased ingestion of copper in the form of gluconate reduced the survival time of male mice as much as 14.4%. Copper in its free, unbound form catalyses the production of various toxic free radicals. The body contains numerous enzymes to neutralize the deleterious free radicals; however, once these systems are saturated the compounds may wreak havoc upon target tissues. Elevated copper levels have the potential to produce a relatively continuous supply of free radicals. Thus, it appears that the oxidative properties of copper may actually promote aging while antagonists such as zinc, vitamin C, and molybdenum may prolong life. This increased knowledge of the trace elements introduces atomic biology which will help explain the many paradoxes of molecular biology.

With the persistent publicity concerning hypocupremia, it has become exceedingly clear that the attention of the clinical and research community is being polarized at the wrong end of the copper spectrum. Although one can hardly argue the definite effects of hypocupremia, these simply emphasize the ambivalent biochemical role of copper in the human body. It is the frequency of clinical

appearance which draws into question the importance of hypocupremia in the medical community. From the standpoint of treatment, physicians must be constantly aware of the possibility of copper intoxication *not deficiency.* In the current industrial and social environment where pollution continually poisons our water supplies and the health conscious consign their bodily care to a multivitamin containing 2 mg of copper, the incidence of copper poisoning has and will steadily increase.

CASE HISTORIES

Copper, Schizophrenia, and Birth Control (Oral Contraceptive Pill)

R.B. is a twenty-four year old, white female previously diagnosed as a chronic schizophrenic. Schizophrenic symptoms were being controlled with daily doses of Trilafon (8 mg AM and PM), lithium (3 tablets), and Deanol (4 drops of 20% in AM). Niacinamide, niacin, vitamin C, zinc, manganese, vitamin E, and thyroid were taken as daily nutritional supplements. With this program, blood copper levels stabilized at approximately 150 mcg%. Oral contraceptives (known to increase copper levels) were implemented on 3/7 at the request of the patient. Blood copper levels rose to 329 mcg% on 4/25. The patient complained of pain while climbing stairs and of tender breasts. Copper levels remained elevated at 284 mcg% on 6/6. Schizophrenic symptoms were exacerbated. Oral contraceptive use was stopped. By 9/26 copper levels had returned to the previously normal range, 156 mcg%. Schizophrenic symptoms abated.

Copper and Premenstrual Tension

T.L. is a twenty-three year old white female suffering from exercise-induced allergies (asthma) and premenstrual tension with accompanying migraine headaches. Blood copper was assayed on 8/19 and found to be 168 mcg%. She was placed on a rotation diet for multiple food allergies and nutritional supplements of methionine, calcium, vitamin C, zinc, and manganese. By 11/11 her copper levels had fallen to 143 mcg%, her premenstrual tension and headaches had been ameliorated, and she reported no asthma attacks despite her continued participation in an aerobics class.

Copper and Psychomotor Epilepsy

G.L. is a sixteen year-old white male with a history of psychomotor epilepsy. At presentation, seizures were not controlled (4-5 seizures/week) in spite of daily drug therapy (300 mg Dilantin, 1200 mg Tegretol). Blood copper levels were assayed on 6/6 and found to be high (156 mcg%). Diet was supplemented with vitamin C, manganese, zinc and molybdenum. Drug therapy was continued. On 8/23 the patient reported a total of two seizures since starting vitamin therapy 2 1/2 months earlier. Antiepileptic medication was reduced. Copper levels had declined to 144 mcg%. No further occurence of seizures has been reported.

Copper and Arthritis

P.V., a seventy-three year old white female, was suffering from arthritis and hypertension (blood pressure 150/100 mm Hg). She was taking 25 mg of hydrochlorothiazide a day for control of blood pressure. She complained of painful knees, wrists, and fingers. Chronic upper respiratory infections were also noted. Serum copper was assayed on 5/10 and measured 139 mcg%. Vitamin C, zinc, manganese, and molybdenum were used as supplements in her diet. By 11/7 copper levels had declined to 106 mcg%. Her joints were much less painful. With the exception of a sinus infection in mid-July, she reported no infections. Blood pressure was 130/75.

Copper and Hyperactivity (Hyperkinesis)

J.N. is a hyperactive eight year-old, white, male with tantrums and inability to concentrate (attention deficit). Constant tinnitus was reported at bedtime. Depression and paranoia were noted. On 1 /25 his serum copper was determined (144 mcg%). Vitamin C, zinc, manganese, and molybdenum were administered to reduce the copper intoxication. Ten drops of deanol per day was given to improve concentration. At a subsequent blood test on 4/19 the serum copper level had fallen to 132 mcg%. A slight improvement in hyperactivity was noted by the parents; however, they mentioned patient compliance was a problem. The following year the parents reported a significant decrease in the degree of hyperactivity. Tinnitus had ceased. Serum copper was found to be 124 mcg%.

Copper and Estrogens

L.B. is a nineteen year-old, white female who suffered an acute psychotic break on 3/1. The patient was hospitalized from 3/12 to 4/2, where a diagnosis of manic depression was made. Eskalith 450 (2 tab/day) and Haldol 0.5 mg (1 tab/day) were prescribed to control symptoms. The patient came to the Brain Bio Center on 5/7 where the interview revealed that oral contraception (Or-thonovum 28) was initiated approximately one week prior to the psychosis. Premenstrual tension was noted after implementation of oral contraception. The patient's blood type is A-l-. Experiential World Inventory revealed a grossly elevated score of 134 (normal 5-20). Copper levels were assayed and were 182 mcg%. The patient was placed on vitamin C, zinc and manganese supplements. A follow-up visit on 7/22 found the patient vastly improved. EWI scores dropped to 17. Copper levels had fallen to 152 mcg% Molybdenum was added to the nutritional therapy to further enhance detoxification. Haldol was discontinued.

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