Risks of Copper and Iron Toxicity during Aging in Humans

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Received September 17, 2009

Copper and iron are essential but also toxic metals. Their essentiality is known, but their toxicity, except for the genetic overload diseases, Wilson's disease and hemochromatosis, is not so well known. Yet, their toxicities are so general in the population that they are a looming public health problem in diseases of aging and in the aging process itself. Both metals are transition elements, and their resulting redox properties have been used during evolution in the development of oxidative energy generation. But both contribute to the production of excess damaging oxidant radicals. Evolution has kept stores of copper and iron in excess during the reproductive years because they are so vital to life. But the oxidant damage from these excess stores of metals builds up as we age, and natural selection ceases to act after about age 50 since diseases after that do not contribute to reproductive fitness. Diseases of aging such as Alzheimer's disease, other neurodegenerative diseases, arteriosclerosis, diabetes mellitus, and others may all be contributed to by excess copper and iron. A very disturbing study has found that in the general population those in the highest fifth of copper intake, if they are also eating a relatively high fat diet, lose cognition at over three times the normal rate. Inorganic copper in drinking water and in supplements is handled differently than food copper and is therefore more toxic. Trace amounts of copper in drinking water, less than one-tenth of that allowed in human drinking water by the Environmental Protection Agency, greatly enhanced an Alzheimer's-like disease in an animal model. In the last part of this review, I will provide advice on how to lower risks from copper and iron toxicity.

Contents

1. Introduction

I was very pleased to be invited to contribute a paper to this issue of Chemical Research in Toxicology, on metal toxicity, because I think there is an important story to tell about copper and iron toxicity. This story, which I think is reaching the level of public health significance, is virtually unknown to the general medical community, to say nothing of the complete unawareness of the public. I have written on this topic before (*1–3*), but this review gives me the chance to put all the pieces together. In addition, I am coauthoring a book on this topic, which has been recently published (*4*).

When we think of metal toxicity, most of us think of the villains, such as lead and cadmium. Not so much do we think of the good guys, the essential metals, such as copper and iron, that make essential contributions to our lives. Of course, physicians are aware of copper and iron toxicities in Wilson's disease and hemochromatosis, respectively, where the body is grossly overloaded with these metals. But in this review, I want to tell the story of the more subtle toxicity of copper and iron that does not just affect a limited number of us, as with Wilson's disease and hemochromatosis, but may affect almost all of us as we age.

I will tell the story in four parts. In the first part, I will review oxidant damage, and the mechanism of copper and iron toxicity, which involves oxidant damage. In the second part, I will review the contribution of copper and iron toxicity to specific diseases of aging, such as Alzheimer's disease (AD) and atherosclerosis. In the third part, I will review oxidant damage as a likely component of aging in general, and the likely contribution of copper and iron toxicity to aging. In the fourth part, I will discuss what can be done to minimize copper and iron toxicity, including some of our own research.

1.1. Oxidant Damage and the Role of Copper and Iron. Higher organisms, such as ourselves, live in the fast lane in that we use oxygen to fuel a very high level of energy generation. Much of this oxidative metabolism occurs in the mitochondria of cells where high energy phosphate bonds are created in the form of adenosine triphosphate (ATP). Nutrients and oxygen are utilized in this process. Toxic byproducts of this metabolism are generated, called reactive oxygen species

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10.1021/tx900338d
Published on Web 12/07/2009

(ROS). These include the superoxide anion, singlet oxygen, hydrogen peroxide, and the hydroxyl radical. ROS can cause damage to most biological molecules, including DNA, protein, and lipids, resulting in damage to membranes and various cellular organelles. The reviews by Poon et al. (*5*) and Butterfield and Kanski (*6*) are quite instructive as to the mechanisms of oxidant damage.

Cells have defenses against ROS, enzymes that scavenge and destroy these molecules. These include the enzymes catalase, superoxide dismutase, glutathione peroxidase, glutathione transferase, and others. However, these defenses are not perfect, and some ROS escape and cause continual damage.

Copper and iron are essential elements, necessary for life. Good reviews of the importance of copper and iron for life are given in refs *7* and *8*, respectively. They are important components of many proteins and many enzymes, including many that participate in the generation of high energy metabolites. In other words, copper and iron are integral components of what allows us to live in the fast lane. This is the good guys side of these metals.

But both copper and iron have their dark side, their toxic side. They are both transition elements. A characteristic of transition metals is that they exhibit two or more oxidation states. The oxidized states are Cu^{2+} and Fe^{+++}, and the reduced states are Cu^{+} and Fe^{2+}. This redox capability is what makes them useful in various steps of energy generation. But it is also what allows them to catalyze the generation of damaging ROS.

Copper and iron are particularly damaging when they exist in what we will loosely call their free state. Explaining this further, starting with copper, 85−95% of the copper in human blood is safely covalently bound to a molecule called ceruloplasmin (Cp). The other 5−15% is loosely bound to albumin and small molecules in the blood. This 5−15% pool is what we call free copper, although it is actually loosely bound. The free copper is available to meet cellular needs, for example, for incorporation into enzymes. This free copper is also available to cause toxicity such as the generation of ROS. The evidence indicates that the larger this pool of free copper, the greater the damage that is produced. For example, in Wilson's disease, this free copper pool in the blood is greatly expanded (*9*). Whereas normal people have 5−15 μg/dL of free copper, untreated Wilson's disease patients may have 50 μg/dL or higher and as a consequence suffer severe damage to their liver and/or their brain. I will present evidence that those normals living on the high side of the 5−15 μg/dL normal range may also be suffering from more subtle copper toxicity.

Another important piece of information about copper is that organic copper, that is, food copper where the copper is bound to proteins, is handled differently by the body than inorganic copper consumed in drinking water or mineral supplements (*2*). Food copper is processed by the liver, which does not allow excess release into the free copper pool in the blood. Inorganic copper in large part bypasses the liver and contributes immediately to the free copper pool in the blood. For example, when we give an oral dose of radioactive ^{64}Cu as an inorganic salt, a substantial part of the ^{64}Cu appears in the blood almost immediately, having bypassed liver metabolism (*10*). This inorganic copper contributes immediately to the free copper pool. This becomes important when we discuss later the negative effects of copper in drinking water and the copper in vitamin/mineral supplements on cognition and on Alzheimer's disease.

Turning to iron, it is primarily carried by molecules in the blood called transferrin and ferritin. Transferrin is a molecule that delivers iron to meet cellular needs. The percent transferrin saturation is one measure of iron adequacy, and the normal range is 15−45% in both men and women. Ferritin is a storage molecule for iron. Its normal value is different between men and women because during menstruation, women lose considerable iron, and their storage iron is reduced. Menopausal women begin to catch up with men. The normal serum ferritin range for men is 15−320 mg/mL and for women is 6−155. The actual observed mean values on a large sample of people, as reported by Zacharzski et al. (*11*) from National Health and Nutrition Examination Survey (NHANES) III data, are about 150 for men, about 30 for menstruating women, and about 60 for menopausal women. I will present evidence that the higher the available iron, in other words the free iron, the greater the risks of developing important diseases of aging.

In considering the roles of copper and iron toxicity in humans, it is important to simultaneously consider the role of evolution (*1, 4*). Evolution promotes fitness, which is measured by success in reproduction. Adequate copper and iron are important for successful reproduction because they are so important to life. If an individual has extra stores of copper and iron, they are partially protected against negative events such as lack of food and trauma leading to blood loss, and increased need of nutrients for wound repair. Thus, evolution has favorably selected individuals with extra stores of these metals because they are more likely to successfully reproduce, i.e., they are more fit. If these extra stores of copper and iron cause some toxicity during the reproductive years, it does not affect fitness as long as it does not produce a disease during the reproductive years. The reproductive years in humans are perhaps up to age 50, when one considers that good health in the parents during early care giving years to the children is also important in reproductive success.

But after about age 50, natural selection ceases to act against diseases in humans because they no longer affect successful reproduction. Thus, there is no natural selection against diseases of aging. In addition, there is no natural selection against having too high and toxic levels of free copper and iron, as long as those levels were acceptably safe during the reproductive years. Thus, it is my view that the levels of copper and iron we consider normal for humans are acceptable during the reproductive years but are, on average, too high after age 50 and contribute to diseases of aging.

2. Contribution of Copper and Iron Toxicity to Specific Diseases of Aging

2.1. Copper and Alzheimer's Disease. When Sparks and colleagues moved their research activities from one laboratory to another, they were frustrated when they could not reproduce their results in the second location (*12*). They were studying a rabbit model of Alzheimer's disease (AD) in which rabbits fed a high cholesterol diet developed Alzheimer's-like amyloid plaques in the brain and lost cognition, that is, they had a fall off in performance of certain tasks. In the new location, the whole disease process was much more mild. They finally realized that the rabbits in the new location were given distilled water to drink, while in the old laboratory, they were given tap water. They carefully evaluated what it was in tap water that made the difference and determined that it was trace amounts of copper. They then did studies where they showed that 0.12 ppm (parts per million) of copper in distilled water used for drinking had a dramatic effect in increasing amyloid plaques and decreasing cognitive performance in the AD rabbit model (*12*). The Environmental Protection Agency (EPA) allows over 10 times (1.3 ppm) that much copper in human drinking water

(*13*). These rabbit model results should give us strong warnings that we may be worsening AD in human patients by having too much copper in our drinking water. The reader should recall our earlier discussion that inorganic copper, like the copper in drinking water, partially bypasses the liver and contributes directly to the free copper pool in the blood.

A group at the University of Rochester has done a study which provides a mechanism whereby low levels of free copper in the brain could be toxic in AD (*14*). They find that 0.12 ppm copper damages low density lipoprotein receptor-related protein, a molecule responsible for efflux of β-amyloid from the brain. β-Amyloid is the protein that forms amyloid plaques, one of the hallmarks of the AD brain.

It is of interest and of possible importance that all of the molecules known to be involved with pathology in the AD brain are binders of copper. This is true of the amyloid precursor protein (APP), which has a copper binding domain that reduces Cu^{++} to Cu^{+} and then produces oxidative damage (*15, 16*). This is also true of the β-secretase enzyme that cleaves β-amyloid from APP (*17*) and the β-amyloid itself, which binds copper and cholesterol, facilitating copper oxidation of cholesterol to 7-OH cholesterol, extremely toxic to neurones (*18, 19*). It is also true of the τ-protein that forms the neuro-fibrillary tangles, another hallmark of the pathology in the AD brain (*20*). Amyloid plaques and neuro-fibrillary tangles are major sites of catalytic redox activity (*21*). This redox activity is abolished by desferrioxamine, an iron chelator, or by EDTA, a general metal chelator, and is restored with copper or iron replenishment. The copper binding by all these proteins does not prove that copper is causative or even a risk factor for AD, but it helps increase suspicion that copper dyshomeostasis could be playing a role.

Rosanna Squitti and her colleagues (*22*) in Italy have found, importantly, that free copper levels are elevated in the blood of AD patients compared to age-matched controls. They have also found that a measure of cognition in AD, the mini-mental state examination (MMSE), correlates negatively with free copper levels in AD (*23*). In other words, the higher the free copper, the lower the cognitive ability. Furthermore, they later showed that free copper levels were a predictor of annual decline in mini mental state examination (MMSE) values in AD patients (*24*).

Certain risk factors for AD are connected with copper. The ApoE protein has three alleles, ApoE2, ApoE3, and ApoE4. ApoE4 is a risk factor for AD, while ApoE2 is protective (*25*). ApoE2 has two copper binding cysteines at a copper binding location, while ApoE3 has one and ApoE4 none. Thus, the increased risk of AD for ApoE4 genotypes may relate to the inability of ApoE4 to bind copper and remove it from the brain.

Another molecule that is a risk factor for AD and also interacts with copper is homocysteine. Elevated homocysteine-levels are a risk factor for the development of AD (*26*). Homocysteine interacts with copper to produce increased oxidant stress and oxidizes low density lipoprotein (LDL) that contributes to the development of AD (*27*).

Not all authors agree that excess copper is involved in the pathogenesis of AD. Here, I cite authors with a contrary opinion (*28–30*).

2.2. Copper and Other Diseases of Neurodegeneration. Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), and prion diseases such as Jacob-Crutczfeld disease, are all diseases of neurodegeneration. All have misfolded proteins that form inclusion bodies. The formation of these inclusion bodies is copper dependent (*31*). Additionally, we have found an elevated blood free copper level in Parkinson's disease patients (*32*). There are tantalizing bits of evidence in various diseases suggesting free copper involvement (*33–37*).

2.3. Copper and Cognition in the General Population. Dr. Martha Morris and co-workers in Chicago have done a very important study in the general population (*38*). They looked at the intake of various foods and micronutrients such as copper in a large sample of people and looked at decline in cognition over a six year period. They found that those people in the highest quintile of copper intake, if they also consumed a high fat diet, lost cognition at a rate of 19 years in a six year period. In other words, they lost cognition at over three times the rate expected!

These people were in the highest quintile of copper intake primarily because they took copper in their vitamin/mineral supplement pill. These data are frightening! Almost all vitamin/mineral supplements contain copper. Copper deficiency is extremely rare; therefore, almost no one needs copper supplements, yet tens of millions of people are taking copper supplements and in my view are running the risk of poisoning themselves with copper.

2.4. Copper and Atherosclerosis. I have previously summarized the evidence that copper is involved in atherosclerosis (*1*). The best evidence is probably the interaction of copper and homocysteine to generate oxidant stress and oxidize LDL, which is a component of the atherosclerotic plaque (*27, 39–42*). Elevated homocysteine levels are a known risk factor for atherosclerosis (as well as AD), and it may be this toxic interaction with copper that makes it a risk factor.

There is also epidemiologic evidence supportive of an association of elevated copper and/or ceruloplasmin (Cp) levels with atherosclerotic disease (data reviewed in ref *1*). One of the coppers of Cp can interact with LDL and oxidize it, thus generating oxidized LDL, which, as we have said, is a component of the atherosclerotic plaque (*43–45*). A rabbit model study of atherosclerosis found that at high (as well as low) levels of copper supplementation, atherosclerosis was enhanced (*46*).

The evidence that iron promotes atherosclerosis, which we will discuss shortly, is very good. Since both iron and copper promote oxidant stress, a positive role for iron supports the concept of a positive role for copper.

2.5. Copper and Diabetes. Cooper and colleagues (*47*) have shown abnormal copper metabolism in a rat model of diabetes, and diabetic rats with heart failure were greatly improved by treatment with the anticopper drug, trientine. They followed these animal studies up with clinical studies in which left ventricular hypertrophy in diabetic patients was reduced by trientine therapy (*47*). Eaton and Qian (*48*) have found in an animal model that copper interacts with glycated proteins and produces neuropathy, one of the complications of diabetes in humans.

2.6. Copper and Other Diseases. Copper has been suggested as a factor in several other diseases (*4*). Free copper is elevated in Parkinson's disease (*49*). Free copper may be elevated in autism and Tourette's syndrome. Drusen in age related macular degeneration requires copper for formation (*4, 50*).

So far, not much has been published about copper and cancer risk, but since it promotes oxidative stress and inflammation, it is likely that it could play a role, such as in prostate cancer for which inflammation is important. Thus, we suspect the study reported by Zhang et al. (*51*), in which they reported zinc use for 10 years or more, either in a multivitamin preparation or as a supplement, increased the risk of prostate cancer, is in error. Zinc is an anti-inflammatory, antioxidant agent (*52*) and would

be expected to be protective as reported by Hu and Song (*53*), and by Gonzalez et al. (*54*). The latter study evaluated 35,242 men and found that supplemental zinc of 15 mg or more significantly protected against advanced prostate cancer. Thus, it may well be that the other components, such as copper, in the multivitamin preparation taken in the Zhang et al. (*51*) study are the real culprits.

2.7. Iron and Atherosclerosis. Sullivan was the first to propose (*55*) and has continued to reiterate (*56, 57*) that iron levels play a major role in producing atherosclerosis. His major basis for this proposal was that menstruating women, who have a reduced iron load as a result of blood loss, have strong protection against atherosclerosis, compared to men in the same age group. Post-menopausal women lose this protective effect. It has been clearly shown that the protective effect of menstruation is not due to hormonal effects (*58–61*).

There is some positive epidemiological data correlating some measure of atherosclerosis with some measure of iron stores, such as serum ferritin or transferrin saturation (reviewed in ref *62*). There are also positive studies of blood donors having less atherosclerotic disease (reviewed in ref *62*). Other types of evidence are discussed in my previous review (*1*).

One problem with the iron hypothesis of Sullivan has been that homozygous hemochromatosis, in which iron loading is severe, has not been associated with a greater amount of atherosclerosis. Recently, Sullivan (*63*) has explained this. There is a very low level of hepcidin in homozygous hemochromatosis. Hepcidin promotes iron accumulation in macrophages. Iron laden macrophages are a key factor in the development of atherosclerotic plaques and in the instability of the plaques, promoting their rupture. These events lead to clot formation and vascular occlusion. In the absence of hepcidin, there are no iron laden macrophages to promote the development of atherosclerotic lesions. This explanation offered by Sullivan (*63*) seems to nicely explain the lack of excess atherosclerosis in hemochromatosis in spite of the iron loading in this disease.

2.8. Iron and Alzheimer's Disease. This area has been reviewed by Ong and Halliwell (*64*), who suggest that an important mechanism is the interaction of iron and cholesterol in promoting oxidative damage, causative of both atherosclerosis and neurodegeneration. Another important type of evidence is that mutations in genes involved in controlling iron predispose to AD (*65*). Thus, mutations in the hemochromatosis gene, HFE, increase the risk of AD (*66*), and patients with the transferrin subtype C2 also have an increased risk (*67–69*). The presence of both of these increases the risk of AD 5-fold (*70*). A clinical trial of the iron chelator, desferrioxamine, given for two years to AD patients, clearly slowed the clinical progression of dementia (*71*).

3. Oxidant Damage Theory of Aging and the Role of Copper and Iron

Harman has been an early proponent of the oxidant damage theory of aging (*72, 73*). The concept proposes that the constant production of toxic free radicals, particularly reactive oxygen species, slowly produces mitochondrial damage. The slow loss of mitochondria and their energy production is associated with aging and may be a major cause of aging. Free iron and free copper, the greater their levels, accelerates the production of toxic radicals. Several reviews on this topic, particularly regarding iron, have been published (*5, 6, 8, 65, 74–77*). Lowering total iron has increased the life span of fruit flies (*78*) and houseflies (*79*).

Transferrin saturation has been linked to overall mortality in the NHANES I study. People with a transferrin saturation over 55% (1−2% of the population) had increased mortality (*80*). Also, those with elevated transferrin saturation had increased mortality if they had high iron or red meat intake (*81*). Thus, it is possible, perhaps even likely, that the toxicity of free copper and free iron extends to the very basic process of aging itself.

4. What Can Be Done to Minimize Copper and Iron Toxicity?

4.1. Avoid. The first recommendation under Avoid is very simple. Simply avoid taking in supplements containing copper and iron. Most multivitamin/multimineral pills have copper, and this copper is potentially dangerous, as we have described. Scan the label on your supplement bottle, and stop taking it if it contains copper. Copper deficiency is extremely rare, and almost no one needs copper. Keep in mind that those in the highest quintile of copper intake, in the Morris et al. study (*38*), those that were losing cognition at over 3 times the normal rate, got there for the most part by taking copper supplements.

Men rarely need iron supplements unless they have chronic blood loss. But some menstruating girls and women, particularly if menstrual flow is heavy, may become iron deficient. However, the patient should consult with her doctor to see if iron supplementation is necessary.

The second recommendation under Avoid is harder and requires a lifestyle change, and that is to lower the consumption of meat. Both copper and iron are much more bioavailable from meat than from vegetable foods (*82, 83*). That means that these metals are much more easily absorbed from meat sources. Liver and shellfish are particularly high in copper content. Red meat is particularly high in bioavailable iron. But copper and iron are readily bioavailable from all meat foods.

There are no good data on how much one needs to reduce meat intake to have a desirable effect on copper and iron levels. There is evidence on mortality. According to the NIH-AARP (American Association of Retired Persons) study (*84, 85*), those who averaged 2/3 of an ounce of red meat/day had 30% less mortality than those who averaged 5 ounces of red meat/day. Processed meats also increased mortality. Mortality was 20% higher in those who averaged 2 ounces of processed meat per day (an average of one hot dog/day), compared to those who ate almost 15% that much. It is possible that the reduction in mortality seen in the study is at least partially due to the reduction of copper and iron intake.

So far, one can follow my recommendations without measuring anything, but to follow our third recommendation under Avoid, which is avoid drinking water with elevated copper content, one has to measure the copper in their drinking water. Eighty percent of homes in the U.S. have copper water pipes. Whether toxic amounts of copper leaches from the copper pipes depends mostly on the acidity of the water. The more acidic the water, the more copper leaches from the pipes. Also, if the plumbing system is used as the electrical ground for the house (which is legal in many places, but should not be), more copper can leach from the pipes.

There are various laboratories where copper in the water can be measured. It is best to measure both the first draw water in the morning and water after allowing the tap to run for five minutes. Because stagnant water may contain more copper, it is good to know if this is the case so that it can be avoided if necessary. Since 0.12 ppm (parts per million) caused worsening in Alzheimer's-like disease in the rabbit model (*12*), we recommend the drinking water contain no more than about 0.01

ppm. (The EPA allows 1.3 ppm!) If the drinking water contains too much copper, a reverse osmosis device can be installed on the tap used for drinking and cooking water. Alternatively, distilled water, which contains no copper, can be purchased for drinking and cooking. Bottled waters, which many people now drink, are an unknown for copper content, and at this point cannot be used to avoid copper in drinking water.

If one wishes to go further in limiting risks from free copper and iron, one will have to follow steps in the section entitled Intervene. In order to do this, certain measurements of copper and iron status have to be made. These will require the participation of one's doctor to draw blood and order tests.

4.2. Measure. Free copper levels in the blood can be determined by measuring serum copper and serum ceruloplasmin (Cp) on the same sample. It is best to measure Cp by the oxidase method, although most clinical laboratories measure it by an immunologic method, which will have to do if the other method is not available. The copper in the Cp molecule is subtracted from the serum copper to determine the free copper. Each mg of Cp contains 3 μg of copper. An example calculation is as follows. A typical Cp value might be 25 μg/dL of serum. Multiplied by 3, this equals 75 μg/dL of copper in Cp. A typical value for serum copper is 90 μg/dL. Subtracting 75 from 90 equals 15 μg/dL of free copper. The normal range is 5−15 μg/dL. Because of built in bias in Cp values determined immunologically, occasional values of free copper will be very low or even below zero. This is acceptable; it simply means that the free copper value is low.

The iron variables to be measured are serum iron, percent transferrin saturation, and ferritin. These are standard tests which can be simply ordered.

4.3. Intervene. The intervention steps reviewed here are a more aggressive approach to copper and iron control. Whether one wishes to be more aggressive is an individual choice, partly based upon how one views the risks I have described and after discussion with a doctor. I believe these risks should be taken seriously. I view the situation as being similar to cigarette smoking. Those who stopped when risks were emerging but before definitive proof was developed accomplished much in risk avoidance.

Regarding copper, those in the upper half of the free copper distribution, after stopping supplements, lowering meat intake as much as is acceptable, and avoiding elevated levels of copper in drinking water, may wish to take the next step. The intervention step required to further lower free copper is to take oral zinc supplements. As we have shown when we developed zinc as an FDA-approved therapy for Wilson's disease, a disease of copper accumulation and copper toxicity, zinc therapy will lower free copper levels (*86*). It does so by inducing intestinal cell metallothionein, which acts to strongly limit copper absorption. The minimal dose of zinc to do this is about 40 mg twice a day. Two daily doses are required to keep metallothionein induced. The zinc dose must be separated from food and beverages other than water by at least 1 h before and 2 h after.

The starting dose might be 50 mg twice per day, to lower free copper to less than 7 or 8 μg/dL. Free copper should be measured at baseline and after 3 months and then monthly while on this dose. As soon as the free copper gets down to target range, the dose should be reduced to say 25 mg twice per day or, if necessary, 25 mg in the morning and 50 mg in the evening. The dose should be adjusted to lower free copper as necessary. The Cp value is a safety factor. If it starts to go down, say to 20% less than baseline, one is overshooting and should reduce the dose of zinc. If the Cp goes down substantially, one is running the risk of copper deficiency, which if it becomes severe, can be serious. Zinc can be purchased over the counter in pharmacies and health food stores. The best salts are zinc acetate and zinc gluconate. It is safest to take zinc with the supervision of one's doctor.

Another type of data to keep in mind when deciding to lower free copper is that we have shown in multiple animal model studies that lowering free copper levels is beneficial in fibrotic, inflammatory, and autoimmune disease processes (*87*). This was done primarily with a more potent anticopper drug, tetrathiomolybdate, but zinc therapy was also effective (*88*). Again, zinc is best taken with the supervision of one's doctor.

Regarding iron, one might use the percent transferin saturation in the same way that the free copper levels are used. The normal range is 15−45% in both men and women. Those higher than about 25% might choose to intervene. Serum ferritin can also be used. The normal range for men is 18−320 ng/mL and for women is 6−155 ng/mL. The average values for men is about 150 and is about 30 for menstruating women, and about 60 for menopausal women.

The intervention for lowering free iron is blood donation or removal of a significant amount of blood on a regular basis. It is probably not necessary for menstruating women to intervene in this manner because of their monthly blood loss. But men and menopausal women could donate 500 mL of blood every 2 months (or have that much removed if they are not suitable blood donors), until their percent transferrin saturation is in the 15−25 range. They could also attempt to lower serum ferritin to 50 or below. It would probably take a year or two of regular (at least every 2 months) blood donations, particularly for men, to reach this goal.

4.4. Monitor. I have already covered this to a certain extent in the previous section, but I will expand on it a little here. If one is going to intervene by taking zinc to lower free copper and or donate blood to lower free iron, it is important to monitor free copper and/or free iron levels.

In the case of copper, because zinc acts slowly, it is not necessary to check free copper (and Cp) levels until three months. After that, it should be checked monthly until a stable maintenance dose is reached. After that, monitoring can occur every three months and later every six months to make sure that things are staying on track.

In the case of iron, blood donation (or blood letting) will have a slow effect. Iron variables can be measured everly six months for monitoring purposes.

In summary, it appears very likely that copper and iron toxicity are occurring, but in somewhat subtle ways, in a large proportion of our population. Both copper and iron toxicity are likely contributing to Alzheimer's disease (AD). There is a major epidemic of AD in the industrialized world. Careful research by Waldman and Lamb (*89*) has shown that this disease did not exist until 100 years ago. It still is rare in India and Africa. There is something about industrialization that has brought this disease on in the developed world in epidemic proportions. Waldman and Lamb (*89*) think it is due to the consumption of beef because they think it is a prion disease. I think it may be due, in part, to increased meat ingestion because of the increased bioavailability of copper and iron from meat, but may also be due in part to the increased use of copper pipes for plumbing in developed countries and the increased ingestion of copper supplements.

Another major disease is atherosclerosis, likely contributed to by both copper and iron toxicity. Atherosclerosis causes heart disease and stroke, the leading causes of death. Diabetes mellitus

is also epidemic, mostly due to the epidemic of obesity, but the disease and its complications are likely contributed to by copper toxicity.

Parkinson's disease, another disease which appears to be related to development, also is characterized by a high free copper level. Perhaps it owes its increasing frequency to increased free copper exposure. Many other diseases we have discussed here (and some we have not, such as autism), may be contributed to and owe their increased frequency to increased free copper and/or iron exposure.

The process of loss of cognition during aging may be greatly speeded up by increased free copper exposure, as suggested by the work of Morris, et al. (*38*), and the very process of aging itself, if due to a lifetime of oxidant stress (*72, 73*), is likely increased by higher levels of free copper and free iron since the toxicities of these two metals is through the production of oxidant stress.

I have provided some relatively simple ways of lowering the risks of free copper and iron, by throwing away supplements containing these metals, by lowering meat intake, and by avoiding drinking water with elevated levels of copper. I have also reviewed more rigorous methods of lowering free copper and free iron exposure, by taking zinc to lower copper and using blood donation to lower iron. These latter steps are not medical advice (for which one should see one's doctor) but are simply information to use or not use as one sees fit.

It seems clear that large segments of the population are at risk for toxicities from free copper and free iron, and to me, it seems clear that preventative steps should begin now.

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