BioFactors

Review Article

# Copper excess, zinc deficiency, and cognition loss in Alzheimer's disease

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## Abstract.

In this special issue about biofactors causing cognitive impairment, we present evidence for and discuss two such biofactors. One is excess copper, causing neuronal toxicity. The other is zinc deficiency, causing neuronal damage. We present evidence that Alzheimer's disease (AD) has become an epidemic in developed, but not undeveloped, countries and that the epidemic is a new disease phenomenon, beginning in the early 1900s and exploding in the last 50 years. This leads to the conclusion that something in the developed environment is a major risk factor for AD. We hypothesize that the factor is inorganic copper, leached from the copper plumbing, the use of which coincides with the AD epidemic. We present a web of evidence supporting this hypothesis. Regarding zinc, we have shown that patients with AD are zinc deficient when compared with age-matched controls. Zinc has critical functions in the brain, and lack of zinc can cause neuronal death. A nonblinded study about 20 years ago showed considerable improvement in AD with zinc therapy, and a mouse AD model study also showed significant cognitive benefit from zinc supplementation. In a small blinded study we carried out, *post hoc* analysis revealed that 6 months of zinc therapy resulted in significant benefit relative to placebo controls in two cognitive measuring systems. These two factors may be linked in that zinc therapy significantly reduced free copper levels. Thus, zinc may act by lowering copper toxicity or by direct benefit on neuronal health, or both.


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## 1. Introduction

In this article, I will briefly describe the Alzheimer's disease (AD) and the epidemiology of AD. Then, I will present evidence for and discuss two biofactors that I believe are contributing to cognition loss in AD. These factors are excessive ingestion of inorganic copper from drinking water and zinc deficiency.

AD was first described in 1906 and first published in 1907 [1] by Dr. Alois Alzheimer and the disease has since borne his name. It occurs in elderly people and usually begins with memory loss, during which time it is often called mild cognitive impairment (MCI). At least 80% of patients with MCI develop full-blown AD, at the rate of about 15% per year. As the AD disease progresses over time, cognition decreases, and gradually the patient loses functional capabilities and usually becomes dependent on a caregiver.

Diagnosis can only be certain at autopsy, where the brain is found to have extracellular amyloid plaques, consisting primarily of polymers of β-amyloid, and intracellular neurofibrillary tangles, consisting primarily of tau protein, the two pathologic hallmarks of AD. However, clinicians specializing in AD have become increasingly good at making the diagnosis and are over 90% correct, while the patients are still living. A key factor is to exclude other causes of cognition loss, primarily vascular dementia, the other common cause of dementia. This is done by finding that the major risk factors for atherosclerotic vascular disease, such as hypercholesterolemia, hypertension, and diabetes, are missing or have been well controlled.

Developed countries are experiencing an epidemic of AD. In the United States, the prevalence of AD in people older than 60 years is 10%, in people older than 70 years is 20%, and in people older than 80 years is 30%. The current

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US case load of AD is 5.6 million people, with an equal number with MCI, which usually converts to AD [2]. The prevalence is increasing rapidly. For example, in 1982, there were 650,000 cases diagnosed with AD in the United States. With the population present then, at today's rate, there should have been 5.2 million cases. This increase is often attributed to a larger population of older people and to better diagnosis; however, I believe there is more to it than that, as I'll discuss.

The major hypothesis for the pathogenesis of AD might be called the "amyloid hypothesis" [3]. Because amyloid plaque formation is so intimately tied in with AD, it is thought that these plaques are somehow toxic to neurons. A key part of this hypothesis is that there is evidence that oxidant damage occurs in the brains of patients with AD, and amyloid plaques and neurofibrillary tangles generate toxic oxidant radicals, particularly in the presence of excess copper or iron [4].

There are several known risk factors for developing AD. The most dominant one is age, as can be seen by the increasing prevalence with increasing age, as previously discussed. A second risk factor is having the E4 allele of apolipoprotein E [5]. Having one E4 allele increases risk, and having two increases risk further. Elevated homocysteine level, a known risk factor for atherosclerosis, is also a risk factor for AD [6]. Moreover, having certain hemochromatosis alleles [7] and certain transferrin alleles [8] increases risk of AD. This latter may fit with the oxidant stress part of AD causation, as these are "iron management" alleles, and excess iron causes increased oxidant stress. Another risk factor appears to be fat in the diet. Grant [9] has shown that there is a correlation between fat in the diet and AD prevalence across a large number of countries.

## 2. A brief history of the epidemiology of AD

Alzheimer first published on AD in 1907 [1]. The evidence is clear that AD was very rare before that in the 1800s and after that through the early part of the 1900s. Good evidence of this is provided by various authors who wrote extensively on the relevant topics during this period. First, there is Osler, who along with colleagues, wrote seven volumes on all the human diseases known, including the seventh volume on diseases of the brain, published in 1892 and republished in 1907 [10]. There is no mention of an AD-like disease. Gowers, a neurologist, published extensively on brain diseases, publishing a textbook on this topic in 1888 [11], and did not describe an AD-like disease. Freud et al. wrote extensively from 1895 to 1939 on mental illnesses, his writings collected and published in 1966 [12], and no mention of an AD-like disease. Finally, there is Boyd, a pathologist, who wrote several editions of a textbook of pathology, the last published in 1938 [13], and he did not report seeing amyloid plaque structures and neurofibrillary tangles, hallmarks of AD brain pathology, in brains at autopsy.

Some have said that perhaps there were not enough old people back in the 1800s and early 1900s to allow AD to develop with any frequency. However, Waldman and Lamb [14] have shown that in France in 1911, half the population lived to age older than 60 years. I have reviewed the US census figures for 1900 and found that there were 3.2 million people older than 60 years, and at today's rate, there should have been 36.3 thousand AD cases in the United States, plenty of cases to have been present in clinics and at autopsy.

Another common opinion is that AD was considered part of normal aging, just a part of normal senile dementia, and that no one took special note. This view could conceivably explain the absence of AD in the writings of the clinicians (Osler, Gowers, and Freud); however, it does not explain the absence of observing AD-type pathology in brains at autopsy (Boyd).

It appears that the AD epidemic began to take off around 1950, after the end of World War II, and that the prevalence has been increasing ever since, but mostly in developed countries. Undeveloped countries, such as those in Africa, India, and South America, retain a low prevalence. Developed countries, such as the United States and those in Europe, are sharing in the epidemic. Japan, a developed country, is interesting as it retains a low prevalence [15]. However, when Japanese migrate to Hawaii, they develop the higher prevalence seen in developed countries [16].

The above description of AD epidemiology suggests that there is something new in the environment of developed countries, not shared by Japan, which is increasing the risk of AD. Of the various risk factors discussed earlier, only increasing fat in the diet in developed countries, because of increasing meat consumption, is a possible environmental explanation for the epidemic. In my opinion, a high-fat diet is one explanatory risk factor. However, I think it works in conjunction with a second risk factor, increasing ingestion of inorganic copper, to greatly enhance the prevalence of AD.

## 3. Copper toxicity and cognition loss in AD

First, it is interesting that all the molecules involved in amyloid plaque formation and neurofibrillary tangles bind copper. β-Amyloid, the critical part of amyloid plaques, binds copper [17,18], as does the amyloid precursor protein [19,20], from which β-amyloid is cleaved. β-Secretase, the enzyme that cleaves off the β-amyloid, binds copper [4], as does tau protein [21], the protein that is critical in the formation of neurofibrillary tangles, which along with amyloid plaques, is the other pathologic hallmark of the AD brain.

Second, the genetic and biochemical risk factors can all be tied in to a copper causation hypothesis. ApoE4 lacks copper binding because it lacks cysteine, whereas ApoE3 has one copper binding site and ApoE2 has two copper binding sites. Risk of AD is lowest with the more ApoE2 alleles, next lowest with the more ApoE3 alleles, and highest with the more ApoE4 alleles [5]. The ApoE proteins, if they bind copper, may help to remove copper from the brain. Next, homocysteine binds copper, and the complex can oxidize

cholesterol to molecules toxic to neurons [6,22]. Finally, if certain hemochromatosis and transferrin alleles [7,8] increase iron toxicity, iron is toxic because of generating oxidant radicals, which is the same mechanism as copper toxicity. Thus, increased iron would supplement increased copper, in terms of toxicity in the brain.

An epiphany about our thinking on copper causation of AD occurred in 2003 when Sparks and Schreurs [23] published their landmark article on copper added to the drinking water of an AD rabbit model. To cause the rabbits to develop AD-like disease, they are fed with a high cholesterol diet. It turned out that when distilled water rather than tap water was used, almost no disease occurred. Both AD-type brain pathology and cognition loss were minimal. Investigation established that it was trace amounts of copper in the tap water that made all the difference. When 0.12 ppm copper was added to the distilled water used for drinking water, AD-type brain pathology and cognition loss were severe. This work has been replicated in other AD animal models, including the mouse model, in which the diet is not enriched with cholesterol or fat [24]. It has also been replicated by another group [25]. For reference, the Environmental Protection Agency (EPA) allows up to 1.3 ppm copper in human drinking water in the United States, over 10 times the amount that causes AD disease in the animal models.

Dr. Rosanna Squitti et al. in Italy have provided key data that indicate copper toxicity is playing an important role in the pathogenesis of AD. They have studied blood "free copper" levels in AD and find it elevated when compared with age-matched controls [26]. About 60–65% of copper in the blood is safely covalently bound to ceruloplasmin, a copper-containing protein secreted by the liver. The other 35–40% of copper is loosely bound to albumin and various small molecules in the blood, and is called "free copper" because it is more freely available for cellular uses. It is also the potentially toxic copper of the blood, particularly if the free copper pool becomes expanded, as it does in the inherited disease of copper accumulation and copper toxicity, Wilson's disease [27]. To reduce the liver and brain injury that occurs in this disease, it is critically important to reduce the free copper pool.

Squitti et al. have not only found that this potentially toxic-free copper pool is increased in size in patients with AD [26] but also that higher the level of free copper, the lower is the cognition in patients with AD [28], and the higher the level of free copper, the greater is the loss of cognition over a given period of time [29]. Furthermore, they found that in a group of elderly women who did not have AD, the free copper pool was negatively correlated with cognition, just as in AD [30].

This last study by the Squitti group takes us into effects of copper in the normal, non-AD, population. Very interesting work in this population was done by Morris et al. in Chicago [31]. They did a large study of nutritional intake and observed the relationship of specific nutrients to cognition loss over several years. They found that those in the highest quintile of copper intake, if they also ate a high-fat diet, lost cognition at six times the rate of other groups. These people were in the highest quintile of copper intake by virtue of taking vitamin/mineral supplements, each pill of which contains 1–3 mg of copper.

The study of Morris et al. [31] should stir memories of the study by Sparks and Schreurs [23] in that both found copper plus a high-fat/-cholesterol diet affected cognition. In addition, these two studies have something else in common: both involve exposure to a kind of copper we call inorganic copper. Copper in food is bound to proteins, and we call it organic copper. The copper-binding protein is digested to polypeptides and amino acids, and the bound copper is taken up by a copper transporter called Ctrl [32] in intestinal cells. This copper ends up in the liver for processing, being safely routed into various copper handling pathways, including covalent incorporation into the ceruloplasmin molecule. In contrast, I believe at least part of ingested inorganic copper is handled differently, bypasses the liver, and directly enters the free copper pool in the blood, with potential toxicity to the brain.

Findings from studies we did in Wilson's disease support our claim that at least some ingested inorganic copper bypasses the liver and enters the blood directly. When we administer $^{64}$Cu orally as an inorganic salt as part of a $^{64}$Cu test we do in Wilson's disease, some of the labels are found in the blood as soon as 1 h, too soon to have been processed by the liver [33].

So, could the toxicity of inorganic copper explain the epidemic of AD in developed countries beginning about 1950 and exploding ever since? Yes, because the epidemic coincides very well with the use of copper plumbing tube in developed but not undeveloped countries. Copper plumbing was initiated in the early 1900s, but because of two world wars did not see great use until about 1950, at which time it saw explosive use, such that now, 90% or so of US homes uses copper plumbing. Remember earlier on, we talked about Japan being an exception to the epidemic of AD in the developed countries [15], but when Japanese moved to Hawaii, they developed the increased incidence of AD seen elsewhere in the developed world [16]? It turns out that Japan, alone among developed countries, shunned the use of copper plumbing, apparently because of fear of copper toxicity. On the other hand, copper plumbing is widely used in Hawaii. Therefore, the epidemiologic data fit the hypothesis of use of copper plumbing being associated with the AD epidemic quite well.

Of course, association does not prove causation. To move to causation, we have to connect the link of the study of Sparks and Schreurs [23] of trace amounts of copper (0.12 ppm) in drinking water causing AD in animal models to whether the use of copper plumbing results in enough copper in human drinking water to be potentially toxic. Is there any current data on copper levels in human drinking water in developed countries? Yes, through coincidence, I collected data on copper levels in drinking water from 280 North American households, as a part of an effort to avoid excessive ingestion of copper in my patients with Wilson's disease. These samples were collected in trace element free containers and shipped to our Ann Arbor Laboratory for

assay. The following summarizes the results: 1.8% of the samples contained more copper than the EPA limit of 1.2 ppm; 31% of the samples contained more copper than caused AD worsening in the animal models (0.12 ppm); 28% of the samples contained 0.01 ppm, or less (a level I regard as trivial enough to be safe); and 41% of the samples contained between 0.01 and 0.1 ppm copper, levels of unknown safety. Thus, a total of 72% of the samples contained unsafe levels of copper according to the animal models or were of unknown safety.

So, the hypothesis of ingestion of inorganic copper as at least partially causative of AD fits the data nicely. First, there is the explosive epidemic of AD and the explosive use of copper plumbing coinciding in developed countries in the latter part of the 20th century, except for Japan, who did not share in either. Then, there is the data that low levels of copper in drinking water worsen AD in animal models. Then, there is our data that levels of copper in the drinking water in North American households is well above safe limits, based on the animal models, in a large percentage of the samples. Then, there is our data that ingested inorganic copper is at least in part, allowed to enter the blood free copper pool directly. Finally, there is the Squitti data [26,28,29], identifying an elevation of blood free copper as intimately associated with cognition loss in AD. Beyond this, there is the Morris et al. [31] data, suggesting that ingestion of inorganic copper in the form of supplement pills may also be damaging cognition.

All in all, the hypothesis that inorganic copper ingestion is playing a causal role in AD is very well supported. To be clear, I do not believe that it is the whole story. Ingestion of a high-fat diet also appears to be causative [9], as does involvement of risk factors such as age, ApoE4 genotype [5], and homocysteine levels [6]. However, I believe that ingestion of inorganic copper coupled with a high-fat diet sets the stage on which the others risk factors act.

## 4. Zinc deficiency and cognition loss in AD

Based on serum zinc levels, patients with AD are clearly zinc deficient. This was first shown in a sample of patients with AD from Albany, in comparison to age-matched controls [34]. In such a study, it is important to wash out the effect of any vitamin/mineral supplements (which always contain zinc). The patients in the Albany study had supplements stopped 1 month prior to study. Zinc deficiency in AD has also been identified by another group [35]. Serum zinc levels decline with aging, but patients with AD, on average, decline more rapidly, thus making them zinc deficient when compared with age-matched controls [34].

These studies demonstrate that patients with AD are zinc deficient by serum zinc status; however, what about the brain, is it suffering from inadequacy of zinc, and if so, is that at least a partial explanation for cognition loss in AD? Very interesting data and insight on these questions are provided in a publication by Adlard et al. [36]. First, these authors studied zinc transporter-3 (ZnT3) knock out (KO) mice. ZnT3 is the zinc pump that loads synaptical vesicles with zinc. These vesicles are secreted into the synapse and the released zinc plays many important neuronal functions. The ZnT3 KO mice exhibit defects in learning and memory at 6 months of age, and the authors suggest that these synaptically zinc-deficient mice provide "a phenocopy for the synaptic and memory deficits of AD."

These authors [36] also found that ZnT3 level decreased with aging in brains of both mice and humans and decreased even further with aging in the brains of patients with AD, when compared with age-matched controls. They also point out that the extracellular amyloid plaques in AD brain are avid zinc binders, further depleting available zinc for neurons.

One of the important neuronal functions of zinc is to limit glutamate neuronal firing [37]. Glutamate excitotoxicity damages neurons and may be a problem in many neurodegenerative diseases. Zinc also plays a role in NMDA neurons where it binds to a NMDA receptor required for functioning. Another important mechanism may be zinc's capacity to inhibit calcineurin [38]. Increased neuronal calcineurin activity as a causative factor in AD is postulated, because it is increased in AD brain, it affects many downstream biochemical functions adversely. Calcineurin activity is increased by exposure to β-amyloid and inhibited by zinc.

From the above, it seems increasingly likely that neuronal zinc deficiency is playing an important, perhaps a key, role in decreasing neuronal function and increasing damage, leading to cognition loss in AD. It is possible to put the two parts of our hypothesis together as follows. Perhaps excess copper and copper toxicity lead to amyloid plaque development and the plagues trap increasing amounts of zinc. This zinc depletion effect, together with the zinc depletion of aging, exaggerated in AD, and the loss of ZnT3 function with aging, exaggerated in AD, leads to severe neuronal zinc deficiency and neuronal damage. The damage could come about through the mechanisms already discussed.

Based on the above, it is reasonable to hypothesize that zinc therapy might be helpful in AD. Interestingly, zinc was tried as a therapy, both orally and parenterally, in patients with AD in 1992 [39]. Substantial improvement in cognition was reported, but of course these were uncontrolled studies. More recently, a study of zinc therapy in a mouse model of AD also reported improved cognitive performance when compared with placebo controls [40].

Based on all this information, Adeona Pharmaceuticals Inc. sponsored a controlled study of zinc therapy in mild to moderate AD. We used a new zinc formulation that we had developed at Adeona. To give some background on zinc therapy, I had developed zinc acetate as a therapy for Wilson's disease, an inherited disease of copper accumulation and copper toxicity. Zinc acts by blocking intestinal copper absorption, perhaps by inducing intestinal metallothionein, which binds copper and takes the copper out into the stool as intestinal cells are shed. I found that I had to give the zinc away from food to be effective, because many substances in food bind zinc and prevent its absorption. I found that

**Table 1**
**reaZin AD trial efficacy results: Zn + Cu endpoints**

| | Baseline $n = 45$ | 6 months $n = 36$ | $P$ |
|---|---|---|---|
| Serum zinc, μg/dl | | | |
| Treatment | 76.4 | 151.8 | 0.002 |
| Placebo | 70.8 | 75.3 | 0.153 |
| Serum-free Cu, μg/dl | | | |
| Treatment | 37.0 | 30.8 | 0.0042 |
| Placebo | 34.8 | 34.9 | 0.486 |

I had to give about 50 mg of elemental zinc at least twice a day to effectively block copper absorption. I ended up recommending 50 mg three times a day, as a safety factor. I did numerous studies showing long-term control of copper levels and copper toxicity by zinc therapy; the data are presented in a series of 18 papers on zinc therapy of Wilson's disease. Paper XV of this series nicely summarizes much of the data and presents long-term follow-up information [27]. Zinc acetate therapy was approved for Wilson's disease by the Federal Drug Administration (FDA) in 1997 and is the treatment of choice for Wilson's disease.

Older therapies for Wilson's disease have many problems. Penicillamine has a long list of side effects [41] and makes up to half of neurologically presenting patients worse, many of whom do not recover [42]. Trientine shares some of the side effects of penicillamine, but with a lower frequency. However, it makes about 25% of neurologically presenting patients worse, and many do not recover [43]. As zinc is rather slow acting for initial treatment of neurologically presenting patients, we developed tetrathiomolybdate (TM) for treating these patients. TM is a novel anticopper agent that works by binding copper and protein in a tripartite complex. It is very effective for treating neurologically presenting Wilson's disease patients [43], but so far has not gained FDA approval. This leaves zinc therapy as the best choice for the neurologically presenting Wilson's disease patients.

Although zinc therapy was very effective and is the maintenance therapy of choice for Wilson's disease, it had two problems. One was that given on an empty stomach, as zinc must be to be effective, it was irritating to the stomach in many patients. The zinc acetate capsules, dissolving quickly, release a high concentration of salt in a small region of the stomach, which is irritating in upward of 50% of patients. The other problem is that the zinc dose must be given two to three times a day to maintain elevated blood zinc levels, enough of the time to block intestinal absorption of copper, the mechanism of zinc therapy in Wilson's disease. This multiple dosing, particularly when each capsule must be separated from food by 1 or 2 h, is a big nuisance for patients on long-term therapy.

The new Adeona zinc formulation, called reaZin, is gastroretentive and contains an agent that releases zinc slowly. Thus, gastric irritation is minimized, and the slow release results in many hours of plasma zinc elevation, thus allowing one a day dosing. The single daily zinc dose was 150 mg/day, separated from food, in the AD study.

The study was designed to recruit 60 patients, randomly assigned equally to zinc or matching placebo, and treated for 6 months. Patients were diagnosed by standard clinical, functional, and Alzheimer's Disease and Related Disorders Association criteria. AD was mild to moderate with a Clinical Dementia Rating (CDR) of 0.5–1.5. Patients were monitored to prevent clinical copper deficiency. Only one patient during the 6 months of therapy had to have zinc dose lowered because of a decreasing copper status. The endpoints were improvement in serum zinc, reduction in serum free copper, and benefit in cognition in zinc treated versus controls. Cognition was measured by the Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog), the Mini Mental State Examination (MMSE), and the Clinical Dementia Rating Scale, Sum of Boxes (CDR-SOB). Dr. Diana Pollack, of Ptak Alzheimer's Center, Morton Plan Neuroscience Institute, Morton Plant Hospital, Clearwater, FL, was the principal investigator.

As presented by poster at the 63rd Annual Meeting of the American Academy of Neurology in Hawaii on April 14, 2011, by Dr. Pollack, serum zinc was greatly improved by zinc therapy, and serum-free copper was significantly reduced (Table 1). All three of the cognition scoring tests showed better scores in the zinc-treated group than the placebo group; however, none were statistically significant, although CDR-SOB was close, at $P = 0.1$ (Table 2).

Later, *post hoc* analysis presented at the American College of Nutrition Meeting in Morristown, NJ, in November, 2011, by Dr. Pollack revealed very interesting facts. First, what zinc was doing was stabilizing cognition while placebo patients deteriorated. Second, the deterioration in the placebo patients was very age dependent, the older patients deteriorating much more rapidly. Seeing this, we reanalyzed

**Table 2**
**reaZin AD trial efficacy results: Cognitive score endpoints ($n = 42$)**

- All three cognitive scoring systems showed less deterioration in the reaZin versus the placebo group

| | ADAS-Cog | MMSE | CDR-SOB | Global (composite of all three) |
|---|---|---|---|---|
| $P$ values | 0.36 | 0.42 | 0.10 | 0.15 |

- Conclusion:
  a) The finding that all three cognitive scoring systems showed advantage in the treated group is encouraging.
  b) None showed statistical significance, although CDR-SOB is close.

**Table 3**
***Post hoc* subgroup analysis—patients aged 70 and older: Change in 6 months**

| | Treatment | Placebo | *P* value |
|---|---|---|---|
| ADS-Cog | −0.76 | 1.27 | 0.037 |
| MMSE | 0.58 | −1.00 | 0.067 |
| CDR-SOB | 0.25 | 0.87 | 0.032 |

the data, limiting it to those patients aged 70 years and older. This analysis included 14 zinc-treated patients versus 15 placebo patients and revealed statistically significant better cognition scores in the zinc-treated patients versus controls in ADAS-Cog ($P = 0.037$) and CDR-SOB ($P = 0.032$), with near significant results in MMSE ($P = 0.07$; Table 3).

As this analysis was *post hoc*, it cannot be used as a definitive proof that zinc therapy is effective in preserving cognition in AD. *Post hoc* analyses are weaker than *pre-hoc* hypothesis testing, because when the data are looked at in multiple ways, there is an increasing likelihood that statistical significance is due to chance. To a certain extent this depends on how many different *post hoc* analyses are done. In our case, it was two (evaluating the different sites separately, and this age analysis), and therefore, the statistics are not badly weakened. Thus, we consider these data of zinc therapy efficacy as strong evidence, and Adeona is planning to sponsor another study to provide definitive proof.

Assuming the repeat study confirms that zinc therapy preserves cognition in AD, it means that lack of zinc is a very significant factor in cognition loss in AD.

## 5. Summary

In this article, we have put forward the concepts that ingestion of inorganic copper in drinking water and zinc deficiency both contribute to cognition loss in AD. Assuming that both of these concepts are correct, it is possibly useful, in trying to understand AD pathogenesis, to try to put them together. We have already suggested one possible link that of excess extracellular free copper causing amyloid plaque formation, and the plaques binding zinc, worsening neuronal zinc deficiency. There may also be a connection between efficacy of zinc therapy and copper toxicity as follows.

There is evidence of increased oxidant damage in the AD brain. Copper is probably toxic through an oxidant damage mechanism. For example, copper binding to amyloid plaques causes increased generation of oxidant radicals. Increased zinc in the brain may allow zinc to displace copper from sites where copper is generating oxidant radicals, and thus reduce the damage from copper. We know that zinc therapy is significantly lowering blood free copper in patients with AD, and this may be occurring in the brain as well, thus limiting copper toxicity in this manner. Zinc could be doing these things, interacting with copper, while also independently stabilizing neuronal health.

Our data so far indicate that zinc therapy does not improve cognition, but rather stabilizes it and at least partially prevents the cognition loss occurring otherwise. We should know within 1–2 years, when our definitive study is completed, whether this is proven, which will decide whether all patients with AD should be on zinc therapy.

In the meantime, what should people do about copper. The evidence we have put together suggests that inorganic copper ingestion is partially causal of AD. Everyone has to decide for themselves whether this evidence is strong enough to warrant action. For those who wish to act, we recommend throwing away all vitamin/mineral supplement pills that contain copper. Drinking water can be tested, and if it contains more than 0.01 ppm copper, an alternate source to be used. A reverse osmosis device, or other device that removes copper, can be placed on the tap that supplies drinking water. Meat intake can be reduced, because copper in meat is much more bioavailable than copper in nonmeat foods. Finally, one can take zinc to reduce copper levels, but this should be done under a physician's supervision, because clinical copper deficiency can occur if copper is depleted too much.

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