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# The History and Demographics of Alzheimer's Disease Fits with the Copper Toxicity and Copper-2 Hypothesis

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## ABSTRACT

In this review we document that the prevalence of Alzheimer's disease is high in developed countries but low in undeveloped countries. The history of the disease indicates that it was at a low prevalence in developed countries a century ago, so that the current epidemic has happened in that time period. We show that age of the population and known risk factors are not explanations for the current demographics and history. Clearly, something or some things have changed in the environment to cause the current epidemic. We show that Alzheimer's disease is, at least in large part, a copper toxicity disease. Then it is asserted here that copper-2 (divalent copper) ingestion, from drinking water and copper supplement pills is a major new environmental agent triggering the disease. It is also asserted that increased meat eating, which increases copper absorption as well as increasing fat intake, is a second major causative environmental agent.

**Keywords:** Copper; Copper-2; Alzheimer's disease; Increased meat eating

# INTRODUCTION

It is clear we have an epidemic of Alzheimers Disease **(AD)** in developed countries. In the US, for example, 10% of those aged 60, 20% of those aged 70, and 30% of those aged 80 are afflicted with AD. Interestingly, undeveloped countries are not sharing in the AD epidemic. For example, in rural India, the prevalence is only 1% in those age 65 and over [1] and in Nigeria, Africa, the prevalence is 0.52% in age 65-74, and 1.69% in those aged 75-84 [2]. Strikingly, in the Nigeria study, African-Americans in Indianapolis, USA, had a prevalence of 8.02%. This great increase in prevalence in people of the same ethnic background shows the effect of "Westernization" on the prevalence of the disease. This picture of the current demographics of AD raises very important questions about the causes of the great increase in prevalence resulting from living in the developed world. It appears likely that this great increase in prevalence is resulting from something we are doing to ourselves.

Just as the current demographics of AD raise important questions about the cause of the high prevalence in developed countries, so does the history of AD in developed countries. There is clear evidence that the disease was quite rare in the 1800s and early 1900s. This fascinating history was nicely worked out in their book, dying for a Hamburger, written by Waldman and Lamb [3]. AD was discovered in 1906 by Alois Alzheimer [3]. A few cases were seen early in the century, and it was a little more common by 1950. And then it really took off, increasing to the figures cited earlier, and creating a major epidemic. The assertion that the disease was relatively rare at the turn of the century is somewhat controversial, but is well supported by Waldman and Lamb [3]. They found that Osler, an internist who edited a whole series of volumes on medical knowledge, including a volume on diseases of the brain [4], Gowers, a neurologist who wrote a textbook of neurology [5], and Freud, a psychiatrist who published widely [6], all three publishing during the period in question, and none mentioned an AD-like disease. In addition to these clinicians, Boyd [7], wrote a textbook of pathology in the late 1800s and revised up until 1938, and didn't describe amyloid plaques and neurofibrillary tangles, invariate pathological hallmarks in the brains of AD patients.

Many AD scientists have apparently assumed that the current epidemic of AD is due to the increasing age of people in developed countries. But, in 1911, half the population lived to age 60 [3]. The US census shows that in 1900 3.6 million people were 60 and older, producing 360,000 AD patients at today's rate, more than enough to be common in the clinics of the clinicians, and to show up frequently at the autopsy table. Others have argued that the disease was attributed to normal aging, and not taken notice of as a special disease. While this could possibly explain the clinicians not noticing the disease, although it seems unlikely, given their thoroughness and comprehensiveness, it wouldn't explain the lack of plaques and tangles in the autopsy material.

Figure 1 portrays pictorially the above discussions of current demographics and the history of the AD epidemic in developed countries. Figure 1 shows two big "WHYs". WHY-1, refers to

why the huge difference currently in prevalence between developed and undeveloped countries, and WHY-2, why the astounding increase in AD prevalence in developed countries over the last century? So far, little or no attention has been paid by the scientific community to these amazing facts. It would appear that something, or some things, has changed dramatically in the last century in developed countries to cause this picture. It would also appear that it is critically important to identify these changes, to see if the changes can be reversed, to mitigate this huge epidemic. Here, new changes which appear very likely to be causative of the epidemic will be laid out. But before that, known AD-risk factors, and the possibility that changes in one or more of them could be responsible, will first be discussed and ruled out in the next section.

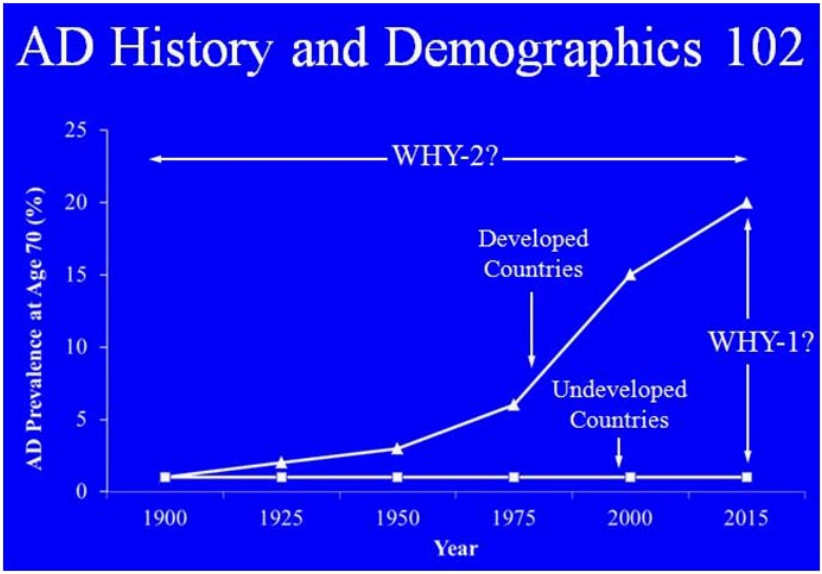


**Figure 1:** This figure portrays first the current demographics of Alzheimer's disease, contrasting the current high prevalence in developed countries versus the low prevalence in undeveloped countries, and second, the history of the disease in developed countries, showing the dramatic increase over the last century.

## KNOWN ALZHEIMER'S DISEASE RISK FACTORS AND THE EPIDEMIC

Age is the strongest known factor, and certainly, the increased age of the population in developed countries contributes directly to the total patient load. But it isn't a factor in the great increase in prevalence in today's aged versus the aged of a century ago, or in today's aged in developed countries versus today's aged in undeveloped countries, the two big points in Figure 1. So age is not the explanation for the epidemic, only for a larger case load.

The alleles of certain genes, such as apolipoprotein E4 [8], hemochromatosis [9], transferrin [10], and ATP7B [11-14], are increased in frequency in AD patients, and therefore are probable

risk factors for AD. But allele frequencies generally change slowly, so there is no possibility that changes in frequency of these alleles are causative of the epidemic.

Blood levels of homocystine are a risk factor for AD [15], as they are for atherosclerosis. While levels could change a little as a result of dietary changes, they would not be expected to change very much.

If known risk factors can't account for the epidemic that leaves new changes in the environment as the likely explanation. To set the stage for discussing the environmental factors causative of the AD epidemic proposed here, the evidence showing that AD is, at least in part, a disease of copper toxicity, will first be discussed.

## ALZHEIMER'S DISEASE IS, AT LEAST IN PART, A COPPER TOXICITY DISEASE

Dr Rosanna Squitti's group in Italy has done an elegant and comprehensive job showing that copper toxicity plays a major role in AD. They have shown this by four major papers involving the free copper pool in AD. By way of explanation, the copper in the blood is divided into two pools. The first pool comprises 80-90% of blood copper and this copper is covalently, and therefore safely, bound to the protein, Ceruloplasmin **(Cp)**. The smaller 10-20% pool is copper loosely bound to albumin and small molecules, and is freely available to provide copper to the organs of the body, and is therefore called "free copper". It is not really free, but just more loosely bound. If this pool increases in size, the copper becomes toxic. The prime example of this is Wilson's disease, an inherited disease of copper accumulation and copper toxicity, where the free copper pool is greatly expanded [16]. Successful treatment lowers the free copper pool and stops copper toxicity accordingly.

The four papers the Squitti groups have published showing copper toxicity in AD are, first, that the free copper pool is significantly increased in AD [17]. Second they have shown that the size of the free copper pool correlates negatively with measures of cognition, that is, the higher the free copper, the poorer is cognition [18]. Third, they have shown that the free copper pool correlates positively with the loss of cognition over time, that is, the higher the free copper, the faster the loss of cognition [19]. Fourth, they showed that the free copper predicts the conversion of Mild Cognitively Impaired **(MCI)** patients, the precursor to AD, to full AD, that is, the higher the free copper, the higher the risk of conversion [20].

These data show clearly that the level of free copper in AD is intimately related to the key pathogenic element in AD, that is, loss of cognition, thus showing that AD is, at least in part, a copper toxicity disease. In addition, it has been shown that "labile" fee copper is associated with oxidative pathology in the AD brain [21]. (Labile copper is another name for free copper).

Next, it is important to note that the Squitti groups has contributed another series of investigations to help show that copper toxicity is central to AD pathogenesis. The Squitti group

has found an increased frequency of ATP7B mutants in AD patients [11-14]. ATP7B is the Wilson's disease gene, and homozygotes for ATP7B crippling mutations have Wilson's disease, with great copper accumulation and copper toxicity [16]. Heterozygotes for a Wilson's disease causing mutation have an increased accumulation and body load of copper not requiring treatment. While not necessarily Wilson's disease causing, it is probable that the ATP7B mutants found by the Squitti group to be at increased frequency in AD have some effect on increasing body copper load, because the ATP7B protein is a critical factor in regulating the blood free copper levels. That these ATP7B mutants are at increased incidence in AD, indicates that they increase the risk of AD, which further indicates that a lifetime of increased body copper level increases the risk of AD. The evidence that copper toxicity is a major component of AD pathogenesis is very relevant to the environmental causation agents put forth in a later section.

An important aspect relevant to this area is why the two diseases of copper toxicity, AD and Wilson's disease, have such different effects on brain pathology and cause such different neurologic symptoms. Wilson's disease causes damage to those parts of the brain coordinating movement, producing a movement disorder, and has no effect on cognition loss of the AD type. Those who think it causes cognition loss are confusing cognition loss with the psychiatric symptoms, which are quite common and cause loss of focus and sometimes bizarre behavior. But with treatment, the psychiatric symptoms disappear and cognition returns to the patient's normal level. In contrast to Wilson's disease, AD produces amyloid plaques and neurofibrillary tangles, neuronal death, brain shrinkage and cognition loss, but no movement disorder.

The likely explanation for the differences in the diseases are that homozygotes for Wilson's die young or are treated young and free copper levels normalize, and the major risk factor for AD, aging, is not involved and so cognition loss does not occur, while parts of the brain controlling movement are vulnerable to the very high copper levels. In AD, elevated copper levels never reach to the levels of movement disorder vulnerability, but with the concordance of aging, mild to moderately elevated copper levels increase the risk of AD.

## PROPOSED NEW ENVIRONMENTAL RISK FACTORS FOR ALZHEIMER 'S DISEASE.

### Copper-2

It is asserted here that exposure to inorganic copper, which is copper-2, or divalent copper, is a major new risk factor for AD. Actually, Brewer has been asserting that for some time [22-26] Following is the series of studies supporting that assertion.

In 2003, Sparks and Schreurs [27] showed that adding tiny amounts of copper-2 to the drinking water (0.12 ppm final concentration) of rabbits in an animal model of AD greatly increased the AD type pathology in the brains of the rabbits, and strongly further impaired the animals' memory. Sparks et al [28] later confirmed this effect of copper-2 on AD-type disease in several other animal models, including the mouse model. This effect of 0.12 ppm in the drinking water on the mouse

model of AD was later confirmed in another laboratory [29]. For reference, the US Environmental Protection Agency allows 1.3 ppm copper in the drinking water of humans, 10 times the amount found toxic in the AD animal models. Another point to be made about this work is that it shows the exquisite toxicity of inorganic copper versus the relative lack of toxicity of organic copper in food (which is copper-1, see reference [30]).One could increase the copper in animal chow from 3 ppm to 6 ppm, a 25 fold greater increase than the 0.12 ppm of copper-2 in the drinking water, and it would cause no toxicity.

These AD animal model studies are important. They mean that if there is copper at these levels in human drinking water, it could be AD causative. Below, it will be shown that there are indeed potentially toxic levels of copper-2 in human drinking water, leached from copper plumbing.

The toxicity of copper in drinking water in AD causation in AD animal models raises the question of potential copper toxicity in human drinking water. First, it is interesting how closely the growth in the use of copper plumbing in developed countries parallels the growth in AD prevalence in developed countries during the same time period. Copper plumbing started to be used in the early 1900s, was curtailed by two world wars, and then took off after 1950, so that now, about 90% of homes in the US, as an example, have copper plumbing [31]. AD prevalence is quite similar during this period; rare in the early 1900s, slowly increasing, and then taking off after 1950, to today's epidemic figures.

The next question is, does copper leach from copper plumbing in toxic amounts? This has been studied. In a study of 280 N American household drinking water copper, it was found about one third had levels over 0.1 ppm, the level found toxic in animal models, about one third was 0.01 ppm or lower, a level deemed safe, and about one third was between these levels, and of unknown safety [25]. Thus, one third to two thirds of N American drinking water has copper levels of known toxicity or possible toxicity, if the animal models are any guide.

The case for inorganic copper leaching into drinking water as causal of AD is made stronger by observations in Japan. Japan is a developed country that has a low prevalence of AD [32], and interestingly, they have shunned copper plumbing. But when Japanese migrate to Hawaii where copper plumbing is used, this prevalence of AD increases to that of other developed countries [33].

A second important study, the first being the AD animal model studies, was that of Morris et al [34]. A large Chicago population was studied for nutrient intake and cognition loss over time. They found that in the highest quintile of copper intake, who were there because they ingested a copper supplement pill (which is copper-2), if they also ate a high fat diet, lost cognition at six times the rate of other groups. This is another important study because probably a third to a half of the population take a multimineral supplement pill, and these all contain copper. Further, a large part of the population eats a high fat diet. This means that a significant part of the population is suffering serious cognition loss due to the simple act of taking a copper supplement pill.

The question comes up, why is copper-2 ingestion, as exemplified by the drinking water copper in the AD animal model studies, and the Morris et al supplement copper-2 study, more toxic than food copper? Clues to the answer come from copper-64 studies in Wilson's disease. Copper-64, administered orally as a copper-2 salt, appears in the blood in significant amounts in 1-2 hours [35]. If food copper were radio-labeled no radioactive copper would appear in the blood for about two days, because this copper ends up in the liver, where it is put into safe channels. In contrast, as shown by the copper-64 studies, a portion of copper-2 appears in blood immediately, too soon to have been processed by the liver, and is absorbed immediately into the fee copper pool of the blood, where it is toxic to cognition.

The situation with respect to the differences in absorption of copper-2 versus food organic copper has been clarified by a recent study by Ceko et al [30]. They carried out speciation studies of copper in foods and drinking water. As expected, drinking water was copper-2. But unexpectedly, most food copper was copper-1. This was somewhat unexpected, because in living tissue, copper-1 and copper-2 form a redox doublet, important for life. Apparently at death or harvest, in the absence of oxygen transport, copper-2 becomes reduced to copper-1. Thus, during evolution, our ancestors ingested primarily copper-1, and thus evolved safe systems for handling copper-1, not copper-2. This explains the presence of the Ctr 1 receptor in the intestine [36], which will absorb copper-1, sending that copper to the liver, where it is metabolized and put into safe channels. Ctr 1 can't transport copper-2 unless it is reduced to copper-1. Copper-2 can be absorbed by other routes, including diffusion, and some of the absorbed copper-2 is absorbed directly into the blood bypassing the liver, and added directly to the blood free copper pool, where it is toxic to cognition.

A third study was carried out by Shen et al [37] in China. They studied the soil concentration of copper in all of the provinces of China and related it to the AD prevalence in these provinces. They found a significant positive correlation. For example, if the soil copper concentration was 40-60 ppm, the prevalence of AD was 2.6 times as high as when the soil concentration of copper was 20-40 ppm. It is likely that the copper concentration in the drinking water over these provinces is highly correlated with the soil concentration of copper.

## Overall Increase in Copper Absorption Due to Increased Meat Intake

The studies described in the previous section indicate that an increased level of copper in the body for a lifetime increases the risk of AD. So it becomes relevant to determine whether copper intake or copper absorption are different between developed and undeveloped countries, and whether there have been changes concerning copper intake an/or absorption in the last century in developed countries. A clear answer to both questions is yes, and it is due to increased meat eating in developed countries. To clarify why meat eating is important, it has been shown that copper is much better absorbed from meat than from vegetable foods [38]. This is not a small difference, it is a large one. A vegetarian diet contains an equal amount of copper to a diet with average amounts of meat, but an estimated 40% less copper is absorbed from the vegetarian diet. This

means that as the diet has changed in developed countries, to include much more meat eating due to economic factors and the increased availability of meat from the increase in domestic animals raised strictly for meat production, copper absorption has increased by an estimated 40%. This increase in copper absorption may well increase the risk of AD.

## Increase in Fat Intake from Increased Meat Eating

Grant (39) has shown that there is a positive correlation between AD prevalence and fat ingestion over many countries of the world. This suggests that increased fat intake is a risk factor for AD, and fat intake increases in relation to meat intake. So as discussed in the previous section, meat eating is much greater in developed than in undeveloped countries, and has increased steadily in developed countries over time, and that means fat intake has increased right along with increased meat eating. There are multiple reasons to believe that increased fat eating would be a risk factor for AD. First, copper and fat are synergistic in developing oxidant molecules that are damaging to neurons. Second, this fits with the animal model Sparks and Schreurs [27] first used to show the copper-2 AD-inducing toxicity of copper-2 added to drinking water. This model was a cholesterol-fed rabbit model, the copper-2 and cholesterol acting together to greatly enhance the AD-like disease. Third, in the Morris et al (34) studies in which it was shown that copper-2 supplement pill ingestion was associated with greatly accelerated cognition loss, the people showing the cognition loss also ate a high fat diet. Thus, in summary, it seems likely that ingesting a high fat diet is a risk factor for AD, and since increased fat intake, due to increased meat intake, has increased greatly during the last century in developed countries, and is much higher in developed than undeveloped countries, it could also be a factor in causing the current AD epidemic in developed countries, i.e., it is proposed here as a new environmental risk factor for AD.

Bringing all this together, the list of proposed new environmental risk factors for AD is as follows:

1. Copper-2 ingestion.

2. Increase in body copper load over a lifetime due to meat eating.

3. Increase in fat intake from increased meat eating.

In the interest of mitigating the AD epidemic, it is appropriate to ask, which of these proposed new risk factors for causing the epidemic are most important, and also, which are most easily eliminated?

Basically this is #1 versus #2 and #3, both of the latter due to increased meat eating. Of this comparison, #1 seems most important, based on the Japanese data when migrating to Hawaii [32-33]. Here, the copper plumbing changes (#1), but it seems unlikely meat eating (#2 and #3) change very much, but the AD prevalence changes dramatically. Changing copper-2 ingestion is also relatively easy to accomplish, as discussed below.

# MITIGATING THE ALZHEIMER'S DISEASE EPIDEMIC

## Reducing Copper-2 Ingestion

This would appear to be the most important new environmental causative agent, and it is also relatively easy to greatly reduce, almost eliminate, ingestion of copper-2. There are two steps to take related to the source of ingestion.

The easiest of the two is simply not to take copper supplement pills. There are a few relatively rare patient groups that need copper supplementation, but these patients are generally well identified. They include those with extensive surgery of the gastro-intestinal tract, including gastric bypass surgery. They also include those with malabsorption syndromes, and people taking large zinc supplements (more than 50 mg daily). But the general population is not copper deficient, and doesn't require copper supplementation. So copper containing supplement pills should not be taken.

The second step is to test drinking water copper levels. There are various companies that offer this service. If the copper levels are 0.01 ppm or below, they are safe. If they are above this level, copper plumbing need not be thrown out. A device, such as a reverse osmosis device, can be placed on the tap used for drinking water, and it will remove copper to safe levels. Even if copper plumbing is not used in the home, it is a good idea to test copper levels, because sometimes source water contains high levels of copper.

## Reducing Meat Intake to Accomplish Both Reduction in Copper Absorption and Fat Ingestion

Reducing meat eating is harder to accomplish because it is a lifestyle change and lifestyle is usually difficult to change. It is also not easy to specify how much meat it is allowable to eat in order to reduce overall copper absorption. Some guidance might be taken from the study of Sinha et al [40]. This study looked at meat eating in relation to overall mortality and mortality due to cancer, cardiovascular disease and a few other causes, so it didn't look at copper absorption. They found a substantially higher all cause mortality in those in the highest quintile of red meat and processed meat intake compared to the lowest quintiles. The highest quintile was taking in about 140 grams of red meat and 40 grams of processed meat daily compared to 20 grams of red meat and 10 grams of processed meat for the lowest quintile. Perhaps aiming for intakes closer to the lowest quintile would reduce copper absorption significantly as well as reduce all-cause mortality. In this study, it appeared white meat was somewhat protective against mortality, but of course, copper is quite well absorbed from white meat.

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