Toxicity of Inorganic Copper from Drinking Water in the Causation of Alzheimer’s Disease

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Conflict of Interest

Dr. Brewer is an employee of and owns stock in Adeona Pharmaceuticals. Adeona hopes to profit from helping fix the copper in drinking water problem, from selling a new zinc product, and from diagnostic testing related to copper abnormalities in AD.
Alzheimer’s Disease Risk Factors

- Age
- ApoE4 Genotype
- Certain “Iron Management Genes”
  - Certain Hemochromatosis Alleles
  - Certain Transferrin Alleles
- Elevated Homocystine Levels
- Certain ATP7b Genotypes
- Ingestion of Excess Inorganic Copper- Hypothesis
- Zinc Deficiency- Hypothesis
The Toxic Copper Hypothesis Story

- AD is an epidemic particularly in developed countries
- The AD epidemic represents a new disease phenomenon
- Something new in our developed environment is triggering the epidemic
- Hypothesis: The AD epidemic is in part due to ingestion of inorganic copper leached from copper plumbing
- Use of copper plumbing coincides with the AD epidemic
- Inorganic copper is handled differently in the body than organic (food) copper and some enters the blood free copper pool directly
- Animal AD model work implicate low levels of copper in drinking water to AD causation
- Over 30% of household drinking water in N. America has enough copper to cause AD in the animal model.
The Epidemic of Alzheimer’s Disease (AD)

1. 10% in 60s, 20% in 70s, and 30% in 80s, have AD.

2. About 6 million cases in the US currently.

3. About an equal number of MCI, 80% of whom develop AD at about 15% per year.
U.S. Prevalence of Alzheimer’s

- 6,000,000
- 4,500,000
- 3,000,000
- 1,500,000
- 0


5.8 Million
The Epidemiology of AD

1. There is an epidemic of AD, about 6 million cases in the U.S. and about an equal number of cases of mild cognitive impairment (MCI), which 80% of the time becomes AD.

2. The epidemic of AD is new, starting about 100 years ago, exploding in the last 60-70 years.

3. AD is a disease of development, the epidemic occurring only in developed countries, such as U.S., Canada, Europe, and not in India, Indonesia, Africa, etc.

This is shocking! Something in our developed environment is poisoning our minds as we age! We must find it and reduce the risk!
The Epidemic of AD is a \underline{New} Disease Problem
DYING FOR A HAMBURGER

Modern Meat Processing and the Epidemic of Alzheimer’s Disease

"DYING FOR A HAMBURGER SHOULD BE REQUIRED READING IF YOU ARE EATING MEAT."
— Howard E. Lyman LL.D., author of Mad Cowboy

MURRAY WALDMAN, M.D., & MARJORIE LAMB
Osler: The Principles and Practices of Medicine – 1892, 1907
7,000 pages in 7 volumes. The sum total of medical knowledge
Volume 7: 1,000 pages on Disorders of the Brain
No dementia other than from syphilis
Dementia from syphilis carefully described
Freud: 24 Volumes of Observations and Theories – 1895 to 1939

Only dementia described is associated with advanced paranoia

Nothing under memory loss or senile dementia
This was the “bible” of neurology for many years.
No mention of dementia or senile dementia
There is no reference to AD plaques or neurofibrillary tangles in the brain, hallmarks of AD brain pathology
Maybe It Is Not a New Disease

Perhaps the fact that our population is now growing older reveals a disease of aging. Perhaps there weren't many old people around before 1900 and for that reason we didn’t see the disease
1900 U.S. Census Figures

- There were 3,184,363 people over age 60
- Should have been 36,252 AD patients at today’s rate
Bottom Line: The proportion of People Over Age 60 has Been About the Same for 3 Centuries
Prevalence Rapidly Increasing in the Last 30 Years

1982 in U.S.: 650,000 AD cases
In 1982 there were 31.8 million people over age 65
At today’s rate – we would expect 5.2 million cases
AD Is a Disease of Development

U.S. Canada, Europe – all have the same high rate
India, Africa – all have a low rate
What Is It In Our Developed Environment That Has Poisoned Our Minds as We Age, That Has Increased Almost Exponentially in the Last 100 Years?

Waldman and Lamb say its beef eating, that AD is a prion disease. While beef eating by an affluent society fits the epidemiology of AD that is it is associated with the epidemic, there is no evidence that AD is a prion disease.
Our Hypothesis: AD is Due to Copper Toxicity

The epidemic is associated with and caused by the use of copper plumbing and copper in drinking water, and coincidentally taking of copper in vitamin/mineral supplements. Spread of copper plumbing in the developed world coincides nicely with the epidemic of AD. Copper plumbing not used in undeveloped countries.
Percent of Japanese Persons with Alzheimer's by Age and Place of Residence

- Japanese Living in Honolulu USA
- Japanese Living in Hiyama Japan

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-69</td>
<td>0.18%</td>
</tr>
<tr>
<td>70-74</td>
<td>0.80%</td>
</tr>
<tr>
<td>75-79</td>
<td>0.24%</td>
</tr>
<tr>
<td>80-84</td>
<td>3.80%</td>
</tr>
<tr>
<td>85-93</td>
<td>7.00%</td>
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</table>

Percent with Alzheimer's Disease

20.50%
History of Copper Plumbing in the U.S.

Began to be used in early 1900
Curtailed by WWI, then WWII
Really took off after 1950
Now 80-90% of U.S. homes use copper plumbing
Coincides precisely with our epidemic of AD.
Association does not prove causality
So, let me present a web of evidence that shows that copper is at fault.
The Sparks and Schreurs Study of a Rabbit Model of AD

- 0.12 ppm of copper added to drinking water
  - Greatly increased brain AD-type pathology
  - Greatly decreased cognition
  - The EPA allows 1.3 ppm, up to 10 times the amount toxic to rabbits in our drinking water
Copper Water vs. Distilled Water

Memory
100%
75%
50%
25%
0%

Week 1
3
5
7
Week 8

- 45%

Sparks DL, et. al., PNAS (2003)
### Copper Levels in North American Household Drinking Water

<table>
<thead>
<tr>
<th>Copper Level (ppm)</th>
<th>Number of Households</th>
<th>Considered Safe</th>
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<tbody>
<tr>
<td>Undetectable 0.01</td>
<td>80 (28%)</td>
<td>12</td>
</tr>
<tr>
<td>0.02</td>
<td>16</td>
<td>Safety Unknown</td>
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<tr>
<td>0.03</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>0.04</td>
<td>15</td>
<td></td>
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<tr>
<td>0.05</td>
<td>12</td>
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<tr>
<td>0.06</td>
<td>7</td>
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<td>0.07</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>0.08</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>0.09</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>34</td>
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<tr>
<td>0.2</td>
<td>14</td>
<td></td>
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<tr>
<td>0.3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>Cause Alzheimer’s Disease in Animal Models</td>
</tr>
<tr>
<td>0.6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>5 (1.8%)</td>
<td>Above EPA Limit</td>
</tr>
<tr>
<td>1.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1.9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3.4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Copper-Containing Multivitamins and Cognitive Decline in the CHAP Study (2006)

• Chicago Health and Aging Project (CHAP)
• 3718 Chicago Residents over Age 65
• Cognition Tested at 0, 3 and 6 Years
• Copper-Containing Multivitamin Consumption Noted and Compared
• Consumers of Copper-Containing Multivitamins (i.e. 2mg/day) with a High Fat Diet had 6.51 Times the Rate of Cognitive Decline than Persons not taking Copper-Containing Multivitamins
n = 604 high fat dieters over age 65 of 3,718 CHAP participants

Chicago Health and Aging Project (CHAP)
Elevated Blood Free Copper in AD Story

- What is blood free copper?
  - It is the copper in the blood not part of the Cp molecule
  - Cp accounts for 70% or so of blood copper
  - The rest is “free” copper
  - Free copper is not really free but is more loosely bound, more freely available, and potentially toxic if the pool is increased in size
- Squitti and group found the following in AD patients:
  - Free copper is significantly elevated
  - Free copper is negatively correlated with cognition
  - Free copper predicts cognition decline
MMSE in Normal Woman

$r = 0.41, p < 0.001$

Squitti et al. Clinical Neurophysiology, In press
Working Hypothesis:

- Inorganic copper ingestion from drinking water and supplement pills is toxic and a causative factor in AD
Why is Inorganic Copper in Drinking Water and Supplements So Much More Harmful than Copper in Food?

It bypasses the liver and contributes directly to the “free copper” pool, which can more easily penetrate the blood/brain barrier.
Our $^{64}$Copper Data

9 patients Avg 6.04 2.74 (SD) at 1-2 hours (% of administered dose in blood)

How is Free Copper Toxic in the Brain?

All molecules involved in amyloid plaque and neurofibrillary tangles bind copper. Amyloid precursor protein binds copper, reduces it, and produces oxidative damage. βamyloid binds copper and cholesterol, oxidizing cholesterol to 7-OH cholesterol, toxic to neurons. Tau protein, which forms neurofibrillary tangles, binds copper. Amyloid plaque and neurofibrillary tangles are major sites of generation of reactive oxygen species, and this is copper (iron) dependent.
Low Density Lipoprotein Receptor-Related Protein (LRP), Copper and AD

Rochester group reproduced Sparks findings with 0.12 ppm copper in the drinking water of mice. They found 30% more amyloid plaques with copper supplementation. But they found that 30% of LRP receptors were damaged by copper supplementation. LRP receptors clear βamyloid from CSF into blood. Thus copper in the drinking water cripples this clearance mechanism.
A High Fat Diet also Probably Plays a Role

- Sparks and Schreurs, Morris - a background of high fat intake
- Grant: Finds a correlation of fat intake with AD around the world
- Hypothesis: Inorganic copper intake and a high fat diet set the stage for AD, with other genetic and environmental risk factors acting on that stage
Adjusted Hazard Ratio (HR) for Risk of Total Mortality for Women Aged 55-69


<table>
<thead>
<tr>
<th>Supplement Ingested</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamins</td>
<td>1.06 (1.02-1.09)</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>1.12 (0.98-1.29)</td>
</tr>
<tr>
<td>B Complex, Vitamins CDE</td>
<td>Neutral</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.92 (0.89-0.95)</td>
</tr>
<tr>
<td>Copper</td>
<td>1.42 (1.17-1.72)</td>
</tr>
<tr>
<td>Iron</td>
<td>1.09 (1.03-1.17)</td>
</tr>
</tbody>
</table>

What can the Individual Do to Minimize Copper Toxicity

• Throw Away Copper Supplements
• Test Your Drinking Water for Copper
  – Use Alternate drinking water if over 0.01ppm or use a copper removal system such as reverse osmosis
• Reduce your red and processed meat intake.
  – Copper is much more readily absorbed from meat than vegetable foods
• You can take zinc, but you should take it under a doctor’s supervision
SUMMARY

1. AD and MC1 are at epidemic proportions
2. They are a new disease, a disease of development, ie. something in the development environments is causal
3. Could be lots of things – beef eating, obesity, etc
4. Copper toxicity at first blush is like all the rest, ie. copper plumbing and copper supplements are associated with development and with AD
Summary (continued)

5. However, there is an excellent web of evidence supporting copper causality
   • Rabbits develop specific AD lesions at 0.12 ppm copper in water (EPA limit 1.3 ppm)
   • We found 31% of human drinking water exceeds 0.1 ppm
   • The Rochester group has identified a specific toxic effect in the brain at 0.12 ppm
   • Squitti et al, confirmed by us, finds elevated free copper in blood of AD patients
   • Morris et al find high rates of cognition loss with high copper intake
   • ApoE and homocysteine, risk factors for AD, both interact with copper.