Personalizing Copper-2 Ingestion and Copper Levels to Avoid Alzheimer's Disease (AD)

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The Speaker has no conflicts of interest to disclose

"You're getting too much dairy."

Introduction and Outline of Presentation

1. Defining and quantifying the "AD epidemic" in developed countries in the 20th century
2. The overwhelming evidence that copper-2 ingestion is a major cause of the "AD epidemic"
3. The overwhelming evidence that AD is, at least in part, a copper toxicity disease
4. The evidence that a mild increase in body copper load for a lifetime is a risk factor for AD.
5. Personalization to minimize AD risk:
    a. Eliminating most copper-2 ingestion
    b. Personalization of free copper levels
    c. Personalization of risk from genetic factors

Presentation Learning Objectives

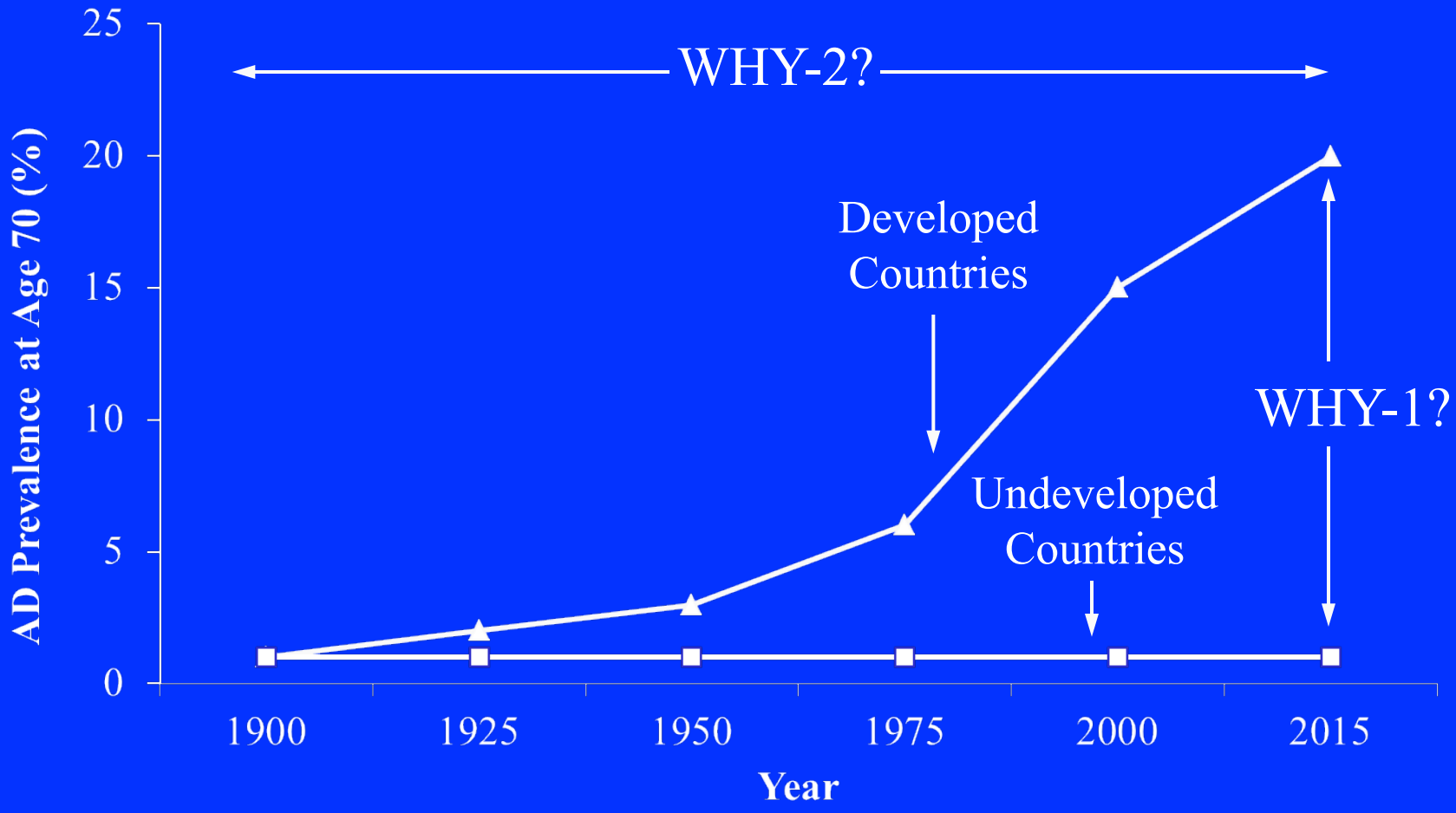
After participating in this presentation, learners should be better able to:

- Discuss the history and epidemiology of the current Alzheimer's epidemic.
- Discuss the rise of incidence that copper is the new environmental causative agent.
- Discuss copper-2 as especially hazardous.
- Evaluate a patients copper status and personally manage.

1. Defining and Quantifying the Current AD Prevalence

- Current AD prevalence in Developed Countries
  - Age 60 to 74: 15%
  - Age 75 to 84: 44%
- Current AD prevalence in Undeveloped Countries
  - India age 65 and over: 1.0%
  - Nigeria age 65-74: 0.52%
    age 75-84: 1.70%

AD History and Demographics 102



Basis for Claims of Low Prevalence in Late 1800s and early 1900s in Developed Countries

Dying for a Hamburger – 2004 book authored by Waldman and Lamb

They did an excellent demonstration of low prevalence during this period

- Osler, an internist, published all medical knowledge during this period – No AD-like disease
- Gowers, a neurologist, published a textbook of neurology during this period – No AD-like disease
- Freud, a psychiatrist, published widely on brain disorders during this period – No AD-like disease
- Boyd, a pathologist, published a series of editions of a textbook of pathology during this period – no amyloid plaques or neurofibrillary tangles

Possible Whys? For Change Over Time

1. Change in risk factors?
   a. Age of population? No
   b. Alleles of risk factors? No
2. Disease not noticed as different from aging? No
3. Change in environmental risk factors? Yes!

Conclusion: These data cry out, no "Scream out!", that environmental changes in developed countries in the 1900s is causing the "AD epidemic"

- This is a terrible disease
- It is robbing the "golden years" from a third of our elderly.
- It is a terrible burden on caregivers and family
- We must find the environmental factors causing all this misery and mitigate them!

Alzheimer's Disease: Facts and Impact

- Only cause of Death in Top 10 – That Can't be Prevented, Cured or Slowed
- 6th Leading Cause of Death
- 2015 Cost - $226 Billion in U.S.
- 1 of 3 Seniors – Dies With It
- 2/3 of Cases are Women

2. The Overwhelming Evidence that Copper-2 Ingestion is a Major Environmental Cause of the “Epidemic”

The "Brewer Hypothesis"

Ingestion of Inorganic Copper is a Major Triggering Agent in Alzheimer's Disease: Alzheimer's Disease is in Part a Copper-2 Toxicity Disease

Brewer, 2008. Curr Opin Clin Nutr Metab Care;11:727-732
Brewer, 2009. J Amer Coll Nutr;28:238-242
Brewer, 2011. Int J Alzheimer's Dis;2011:1-11
Brewer, 2012. Biofactors;38:107-113
Brewer, 2015. Nutrients;7:10053-10064
Brewer, 2015. J Alzheimer's Dis;46:593-604

Some Mechanistic Considerations:

Why is inorganic copper absorbed differently, with a portion ending up bypassing the liver and contributing immediately to the blood free copper pool?

- Inorganic copper is Cu2 (Cu^{++}) while organic (food) copper is Cu1 (Cu^{+})*
- Cu1 is absorbed in the intestine through Ctr1, and this route leads to the liver and safe channels
- Cu2 must be reduced to Cu1 before it can be transported by Ctr1
- Cu2 can be absorbed by a non-energy dependent carrier and by diffusion

  Perhaps when a large amount of Cu2 is ingested, before it can be reduced it as absorbed by this alternative route, and bypasses the liver.

  *Ceko, et al. Food Chemistry, 2014, 164:50-54

The "Web of Evidence": Support for "The Brewer Hypothesis"

1. Sparks et al showed that 0.12 ppm copper in drinking water of AD animal models greatly enhanced AD pathology

   (Level of copper allowed in human drinking water: 1.3 ppm)

   - This work has been confirmed in several animal models and in two different labs.
   - An animals food could be changed from 3 ppm to 6 ppm, a 25 fold greater change than 0.12 ppm, and it would cause no harm.
   - This shows that copper in drinking water is exquisitely more toxic than copper in food. Of course, it is copper-2 while copper in food is copper-1.

The Sparks et al Study is a "Randomly Controlled Trial" an "RCT" in Animals

- Treatment animals got copper in drinking water
- Placebo animals got distilled water to drink
- Other control animals got aluminum in drinking water and still other control animals got zinc in drinking water

Results: Only the copper animals had greatly enhanced AD

Conclusion: This is a RCT in animals

Further Support for "The Hypothesis"

2. Morris et al have measured nutritional intake and cognition over a period of years in a large Chicago population.
   - They found that in the quintile of highest intake of copper, who were in the highest quintile because of ingestion of copper supplements, if they also ate a high fat diet, lost cognition at 6 times the rate of other groups.
   - Copper in copper supplements is copper-2

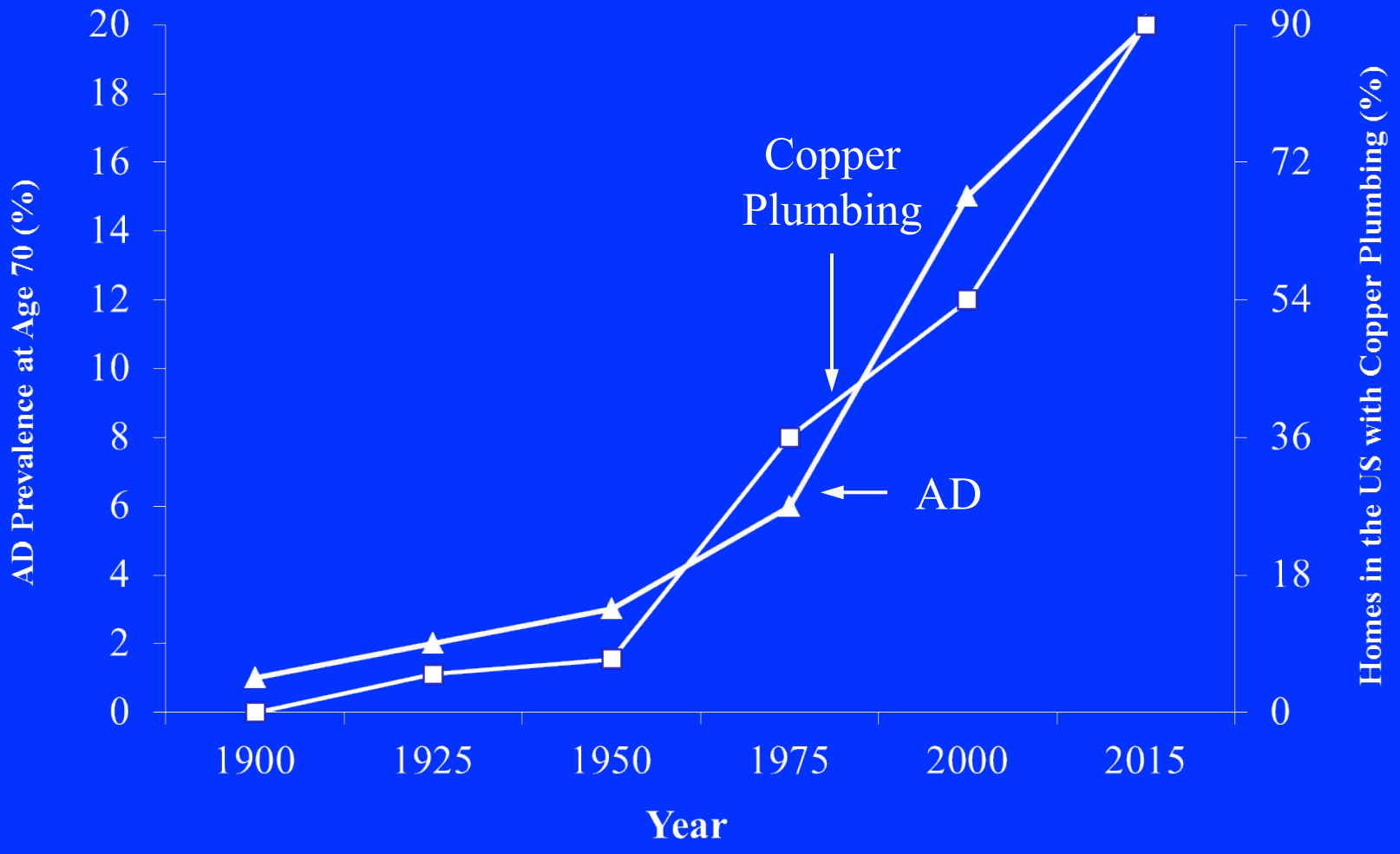
Morris, et al. 2006. Arch Neurol;63:1085-1088

Further Support for "The Hypothesis"

3. The epidemic is new and parallels the use of copper plumbing

- AD was rare, prior to 1900. probably at about 1% as seen in undeveloped countries
- Data for this include the writings of Osler, Gower, and Freud, all clinicians, during this period and no mention of an AD-like disease
- Plus the lack of amyloid plaques and neurofibrillary tangles, hallmarks of AD pathology, in Boyds' textbook of pathology, also written during this period.
- The epidemic parallels precisely the explosive use of copper plumbing in developed countries, except for Japan, that shunned copper plumbing, and have a low incidence of AD, but for Japanese in Hawaii, where copper plumbing is used, AD prevalence is similar to other developed countries.

Copper Plumbing vs AD Prevalence



Further Support for "The Hypothesis"

4. We have shown that copper concentration in drinking water of 1/3 of N. American households, exceeds 0.12 ppm and another 1/3 is above 0.01 ppm and of unknown safety, while only 1/3 is below 0.01 ppm and deemed safe.
   - Thus, 1/3 to 2/3 of drinking water has a copper-2 content either causing, or at risk of causing brain toxicity of the AD-type if the animal models are a good guide

Further Support for "The Hypothesis"

5. We have shown that a portion of ingested copper-2 contributes directly to the blood free copper pool.

   When copper-64 was given orally as an inorganic salt, 15-25% of the label appeared in the blood in 1-2 hours. This is much too soon for liver processing.

This is an Overwhelming Web of Evidence that Copper 2 Ingestion is a Major Cause of the AD Epidemic

- Drinking water copper-2 animal studies comprising an RCT
- Human studies of voluntary taking of copper-2
- Copper-2 vs copper-1 absorption mechanism differences

Can we do something about this?
Yes - personalized response later

3. The Over whelming Evidence that AD is at least in part, a Copper Toxicity Disease First, Clarification of the Blood Free Copper

The blood copper is in two pools, the majority covalently bound in Cp, and is safe, and a minority loosely bound to albumin and small molecules, called blood free copper. The free copper is available to cells, and becomes toxic if the pool is expanded, as it is in Wilson's disease, and Dr. Squitti has shown, in Alzheimer's disease (AD)

Alzheimer's Disease is in Large Part, a Copper Toxicity Disease: The "Squitti Hypothesis"

The elegant work of Dr. Squitti and her group has established this in the following published studies

1. Blood free copper is elevated in AD
2. Levels of blood free copper correlate with measures of cognition and
3. Predict rate of cognition loss over time and
4. Predict conversion of mild cognitive impairment (MCI) patients to full AD.

Thus, the intimate relationship of blood free copper levels to the pathogenesis of AD establishes AD as a copper toxicity disease, in large part.

Further Support for Copper Toxicity in AD

James et al from the Bush group have shown that elevated “labile copper” is associated with oxidative pathology in the brains of AD patients

4. The Evidence that a Mild Increase in Body Copper Load for a Lifetime is a Risk Factor for AD

Genetic Variants for ATP7B Are at Increased Prevalence in AD as Shown in Multiple Papers by Dr. Squitti's Group

- Heterozygotes for Wilson's disease causing mutations have a mild increased body copper load not requiring treatment.
- Although not Wilson's disease causing, I suspect Dr. Squitti's variants all affect body copper load.
- This suggests a mild increase in body copper load is a risk factor for AD.

Why Would Mild Body Copper Overload be a Risk Factor for AD, When Homozygosity for Wilson's Mutants Doesn't Affect Cognition?

- Homozygotes die or are treated young.
- Carriers of ATP7B mutations have a mild copper overload for a lifetime, allowing age, a critical risk factor, to be involved.

Have Humans in Developed Countries Had an Increase in Overall Copper Body Loading in the Last Century?

Answer: Yes, from increased meat eating.

Explanation: Copper is much better absorbed from meat than vegetable foods. So increased meat eating in developed countries has not only increased fat intake, another AD risk factor, but over all copper absorption as well.

Conclusions From All This:

There is increased risk for AD from:

- Copper-2 exposure
- A lifetime of general copper overload

5. Personalization to Minimize AD Risks

a. Personalizing (preventing!) Copper-2 ingestion to avoid AD

- Stop taking copper supplement pills
- Test the copper levels in your drinking water
  - If 0.01 ppm (10μg/L) or lower it is safe (about 1/3 of samples)
  - If higher than 0.01 ppm, put a reverse osmosis device on the tap (about 2/3 of samples)

5. Personalization to Minimize AD Risks

b. Personalizing blood free copper to avoid AD

- You can measure your blood free copper
  - Direct assay (only 2 labs offering this so far)
  - Usual method: Subtract ceruloplasmin copper from serum copper = free copper
  - (each mg/dl ceruloplasmin = 3 µg/dl copper)
- If on the high side, for example over 10 µg/dl, take steps to reduce free copper by reducing meat eating

Reduced Meat Eating Will:

- Decrease copper absorption
- Decrease fat intake
- Reduce overall mortality by 42% - Sinha et al

5. Personalization to Minimize AD Risks

c. Genetic risk factors:

- Mutation in Amyloid Precursor Protein (APP) – 1% of AD
- Apolipoprotein E-4 allele
  - 2% of population are E4/E4: 8-12 x increased risk of AD
  - 23% of population are E4: 3x increased risk of AD
- APT7B mutant allele
  - # in population unknown, increased risk unknown
- Many genetic areas, each with tiny effect, discovered on genome wide screening

Which genes to routinely screen?
Apolipoprotein and maybe ATP7B

What to Do if at Increased Genetic Risk

Evaluate copper status and if at risk

- Take copper precautions (no copper-2, measure free copper, reduce meat intake)
- Consider life style changes that have shown to decrease risk and/or mitigate severity
  - Increase physical and mental exercise
  - Increase certain nutrients

Nutrients That Decrease Risk of AD or Mitigate the Disease

Nutrient or Food	Intake Related to Risk of AD	Positive Animal Studies	Positive in Vitro Studies	Positive Clinical Trials	Positive Genetic Data
Vitamin D	X	X		X	X
Vitamin E	X	X			
Vitamin C	X				
B Vitamins (B6, B12, Folate)	X	X		X	
Omega Fatty Acids	X	X	X		
Epigallocatechin (ECCG)		X	X		
Curcumin		X	X	X	
Resveratrol		X	X		
Walnuts		X	X		
Coffee	X	X			

Presentation Clinical Actions

After participating in this presentation, clinicians should be better able to:

- Identify exposure to copper exposure, particularly copper 2, as a risk factor in the development of Alzheimer's.
- Evaluate a patients copper status and copper genotypes and manage accordingly.

Take Home Messages

- Copper-2 is toxic, as toxic as lead!
- Copper-2 is a major cause of the AD epidemic
- Do away with copper-2 ingestion
  - Throw away and don't buy multimineral supplement pills – they all contain copper-2
  - Test copper levels in your water, put a reverse osmosis device on your tap if necessary
- One fourth to one half of you are slated to get this terrible disease if you don't act preventively