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## Recent Medical Study Suggests Link Between Copper and Alzheimer's Disease

Trace Amounts of Copper in Drinking Water Shown to Increase Deadly Plaques in the Brain and Retard Memory and Learning Functions

Alzheimer's—just the mention of the disease can strike fear and anguish in the hearts and minds of most Americans. It is one of the most devastating diseases for both the patients and their families, because it robs its victims of their memories and, ultimately, their lives.

From a medical standpoint, Alzheimer's disease is one of several disorders that cause the gradual loss of brain cells. Such loss and nerve cell damage impairs memory, thinking and behavior and leads, ultimately, to death due to the lack of brain function itself. A person with Alzheimer's will live an average of eight years and as many as 20 years or more from the onset of initial symptoms.<sup>1</sup> From the time of diagnosis, people with Alzheimer's disease survive about half as long as those of similar age without dementia.<sup>2</sup>

The disease was first described in 1906 by German physician Dr. Alois Alzheimer. Although it was once considered rare, research now shows that Alzheimer's disease is the leading cause of dementia with the number of new cases escalating dramatically each year.

According to the Alzheimer's Association, an estimated 4.5 million Americans have Alzheimer's disease. The number of Americans with the disease has more than doubled since 1980. And that number is expected to grow—by 2050 the number of individuals with Alzheimer's is expected to range between 11.3 million and 16 million.<sup>3</sup>

### What Is Known About Alzheimer's Disease Today

The greatest known risk for developing Alzheimer's is increasing age. As many as 10 percent of all people 65 years of age and older have Alzheimer's. As many as 50 percent of all people 85 and older have the disease.<sup>4</sup> A family history of the disease is another known risk.

Beyond these known factors, research has confirmed that there are two abnormal structures in the brain associated with Alzheimer's disease. Amyloid plaques (pronounced AM I loyd) are clumps of protein fragments that accumulate outside of cells. Neurofibrillary tangles (pronounced NUR o FI bri lair ee) are clumps of altered proteins inside cells.<sup>5</sup>

Research of these structures has provided clues about why cells die, but scientists have continued to investigate their exact role in the disease process. From these investigations, a great deal of evidence has been collected to link high cholesterol and high blood pressure—factors that also cause strokes and heart disease—to an increased risk for developing Alzheimer's.<sup>6</sup>

Dr. Larry Sparks, an Arizona-based medical researcher, was one of several medical experts to study the relationship between high cholesterol and Alzheimer's within the past few years. What he found was that rabbits on high cholesterol diets lost mental functioning and, on autopsy, showed Alzheimer's-like changes in the brain.

## Discovering the Copper Link

Of even greater interest, however, was that when Dr. Bernard Schreurs (of the Blanchette Rockefeller Neurosciences Institute and Department of Physiology and Pharmacology at West Virginia University) attempted to replicate the research of Dr. Sparks, he discovered that his rabbits were learning just fine, despite the introduction of high cholesterol levels into their diets.

Initially confused by his contradictory findings, Dr. Schreurs met with Dr. Sparks to compare notes. What appeared to be the only difference between the two studies was the water being consumed by the rabbits. One of the biggest differences was copper.<sup>7</sup> There was virtually no copper in the Morgantown (West Virginia) tap water. It was extremely high in Arizona tap water.

Together, the two researchers regulated the copper in their animals' water at .12 parts per million (0.12 ppm)—about one-tenth the federal limit for copper in drinking water. The result? All of the copper-cholesterol rabbits had trouble learning and displayed the beta-amyloid brain deposits characteristic of Alzheimer's.<sup>8</sup>

The results of the co-authored study were so significant that they attracted wide attention and were published in late 2003 in the prestigious "Proceedings of the National Academy of Sciences".

"Copper is a player in Alzheimer's," concluded Dr. Sparks, whose earlier career included work with the medical examiner program in Kentucky.<sup>9</sup> During that time, he noticed that people who died of heart disease also had beta-amyloid plaques in their brains. The protein-based

plaque would activate immune cells that would then try unsuccessfully to remove it. Poisons that kill nerve cells were then released, leaving plaque-clogged tangles.<sup>10</sup>

In his animal studies, it was only after trace amounts of copper were added to the drinking water of the cholesterol-fed rabbits that the learning deficiency was identified. "We were getting full-blown plaque formation and 80 percent memory deficits," Dr. Sparks said.<sup>11</sup> This led to his conclusion that cholesterol with copper definitely induced the production of beta-amyloid.

Dr. Schreurs described his studies as having a Pavlovic approach. He first gave the rabbits a brief tone and a half-second later a puff of air to measure how quickly the rabbits blinked. "We found the animals on the cholesterol and distilled water (without copper) learned just fine," Dr. Schreurs said. "But those on a little copper didn't learn very much at all."<sup>12</sup>

## How the Research Was Conducted

Drs. Sparks and Schreurs could have chosen any number of animals for this experiment. Earlier studies made primary use of mouse models, but these failed to produce more than one or two signs of Alzheimer's pathology. In contrast, for this study it was determined that cholesterol-fed rabbits had at least 12 pathological markers seen in Alzheimer's disease (12 different features of the Alzheimer's brain), suggesting that the cholesterol-fed rabbit is good animal model for studying Alzheimer's.<sup>13</sup>

A total of 68 male New Zealand white rabbits between the ages of three and four months (weighing 2.2 kg) were housed individually with free access to Purina rabbit chow and water, maintained on a 12-hour light/12-hour dark cycle and treated following National Institutes of Health guidelines. Each of the rabbits received a combination of food and water comprising normal chow or normal chow plus 2 percent cholesterol and tap water, distilled water, or distilled water plus copper.



Nineteen (19) of the 68 rabbits were fed normal chow and 49 were fed the normal chow plus 2 percent cholesterol.

Of the 19 rabbits fed normal chow, 9 received tap water and 10 received distilled water. Of the 49 rabbits fed cholesterol, 16 received tap water, 21 received distilled water, and 12 received copper in their distilled water. Cholesterol-fed rabbits given copper received copper sulfate in their distilled drinking water with a final copper concentration of 0.12 ppm (0.12 mg/liter). All rabbits were maintained on their respective food and water regimes for a total of ten weeks before euthanasia and subsequent histological analysis.

During their time in the lab, the rabbits received one 60-trial session of air-puff testing to assess sensitivity to air puff; eight daily sessions of trace classical conditioning to assess their ability to learn a difficult conditioning task; a 60-trial session of puff testing to test for any changes in sensitivity to air puff; four daily sessions of delay classical conditioning to test for their ability to learn a simple conditioning task; and 2 days of tone intensity testing during trace conditioning to assess their hearing. Each air puff test trial involved the presentation of 1 of 15 possible combinations of stimulus intensity.

At the end of the trials, the rabbits' brains were extracted and postfixed for 14 days in 4 percent paraformaldehyde.

### **Ramifications for Humans**

The Environmental Protection Agency (EPA) maximum contaminant level goal (MCLG) for copper in drinking water is set at 1.30 ppm (1.3 mg/liter). This is based on the lowest observed adverse health effect level (LOAEL) of 5.3 mg/day, a level which may induce gastrointestinal distress. Cholesterol-fed rabbits in these experiments were allowed 0.12 ppm or 0.12 mg/liter, and given that rabbits drink approximately 300-600 mg of water per day, they consumed between 0.04 and 0.08 mg of copper per day. That means that the levels of copper in the cholesterol-

fed rabbit drinking water that induced the plaque-like structures and learning deficiency are well below those considered safe for humans.<sup>14</sup>

Although there is still speculation surrounding how the results from these tests with rabbits translate into the exact effects on humans, there has been enough concern raised to prompt The National Institutes of Health to consider pursuing a more detailed, follow-up study which will evaluate the effects of varied combinations of cholesterol and copper on learning and memory.<sup>15</sup>

### **Conclusions**

Although cholesterol is important for a number of body functions and neurotransmission, it has been identified as a major risk factor for both atherosclerosis and Alzheimer's Disease. Cholesterol entering the brain from the circulation of cholesterol-fed rabbits induces the neuronal accumulation of amyloid plaque. Similarly, copper can also be viewed as an essential nutrient in a controlled setting but has recently been implicated as an important factor leading to Alzheimer's. It is believed that copper influences the body's ability to clear the brain of accumulated amyloid plaques.

With these concerns raised, it is beneficial for individuals to find ways to limit both cholesterol and copper intake. Copper may be consumed from a number of sources, but one of the most prevalent is copper pipe corrosion. Homeowners with copper pipes should take into consideration the condition of their current pipes when determining their overall copper consumption and exposure.

For more information about the Sparks and Schreurs research, or to review the entire study, go to:

[www.pnas.org/cgi/content/full/100/19/11065](http://www.pnas.org/cgi/content/full/100/19/11065)

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