The condition known as “senile dementia” has been recognized for hundreds of years. But in 1907 Alois Alzheimer reported on a patient who had the common symptoms of memory loss, confusion, and hallucinations yet was only 51 years old (4) – too young for this to be senile dementia, he thought. The patient died at age 55 and, curious, Dr. Alzheimer examined the brain microscopically. He found it loaded with tiny “neuritic plaques” and “neurofibrillary tangles.” The tangles appeared to have originally formed within nerve cells but remained even after the cells had degenerated. A few years later, however, others found the brains of many people who had died with classical senile dementia had these same markers. We now call this condition Alzheimer’s disease.

Later research has shown the plaques Dr. Alzheimer saw are made of a protein known as β-amyloid and the neurofibrillary tangles are formed from a protein known as tau. How this all comes about and results in nerve cell loss and the symptoms of dementia typical of Alzheimer’s disease remains unclear. The most popular theory (27) is, after processing, the amyloid precursor protein is normally supposed to fold on itself to form a soluble protein. Occasionally, however, the parts that are supposed to stick to each other will instead stick to corresponding parts on other β-amyloid molecules, and once started the process continues. Eventually this “raft” of β-amyloid molecules will get too big and form the insoluble plaques seen in the microscope. Then, in some way that is not understood at all, the plaques cause the excessive phosphorylation of the tau protein and the resulting neurofibrillary tangles. Evidence suggests that it is the neurofibrillary tangles that actually cause the symptoms of Alzheimer’s disease, since it is they rather than the plaques that correlate with the duration and severity of the disease (6,55). These tangles appear to produce the loss of nerve cells seen in Alzheimer’s (23). An additional point supporting a crucial role for neurofibrillary tangles is that a mutation in the tau protein leads to dementia and tangles very similar to those in Alzheimer’s, but without amyloid plaques (60).

Where Does Aluminum Fit into Alzheimer’s Disease?

Ever since the first reports of high levels of aluminum in brains of Alzheimer’s victims (15), the idea of a possible role for aluminum has been controversial. The fact that senile dementia was common for many years before aluminum came into common use and that old age is by far the greatest risk factor for dementia suggest aluminum is not the primary cause of most Alzheimer’s cases. It has been argued that aluminum is naturally present in surface waters and might gradually accumulate in the brain over the course of a lifetime (61). Nevertheless, even if aluminum is not the primary cause of Alzheimer’s disease it could still play a role. For example, it might speed progression of the disease, especially in its early stages before symptoms develop. This could result in people being diagnosed with Alzheimer’s disease who would otherwise have died before anyone noticed the symptoms. Such accelerated progression could account for a weak but difficult to ignore link between aluminum exposure and Alzheimer’s disease.

Aluminum Consumption and the Risk of Alzheimer’s Disease

The epidemiological evidence, both positive and negative, for a possible connection between aluminum and Alzheimer’s disease has been well reviewed by Frisardi and colleagues (21). One reason for the continuing controversy is that not all studies of the subject agree. A 2008 systematic review of studies that included aluminum exposure through drinking water, diet, and occupation found 23 studies demonstrated an increased risk for Alzheimer’s disease with elevated aluminum exposure, 3 found that there was no connection…"
“The good news is that the Alzheimer’s disease patients in this one study of deferroxamine had progress of their disease slowed to half that seen in control patients.”

of a relationship, but it is too weak to reach statistical significance and thus allow any confidence that the possible association is real (1, 10, 51). Notably, two studies found no connection at all between Alzheimer’s disease and heavy use of aluminum-containing antacids (10, 51). One might intuitively expect individuals who use antacids daily for extended periods to have much higher aluminum intakes than anyone else.

In summary, epidemiological studies appear to suggest that drinking-water aluminum levels higher than would be permitted in the US may increase the risk of an Alzheimer’s diagnosis. Studies on exposure from other sources, however, do not confirm this suggestion. On balance, the jury is still out.

Aluminum in the Brain

Another reason the relationship between aluminum and Alzheimer’s disease remains controversial is measurements of the amount in patients’ brains have led to inconsistent results. These studies have two distinct methods of measure. First method like Crapper’s initial study (15), measures the total amount in specific parts of the brain. Second method microscopically examines thin sections of brain tissue to locate aluminum in cells, neurofibrillary tangles, or β-amyloid plaques. In the first group, six studies in addition to Crapper’s have found aluminum levels in brains or brain regions of Alzheimer’s disease patients (5, 14, 16, 54, 62, 69). Interestingly in view of results from the second group of studies, one of this group reported that aluminum levels were elevated specifically in brain regions where neurofibrillary tangles were common independently of the number of β-amyloid plaques that might be present (16). However, these positive studies are contradicted by four studies that reported no difference in brain aluminum levels between individuals with Alzheimer’s disease and other people the same age (7, 12, 26, 40). It is difficult to say what these apparently conflicting results mean, since many different techniques were used and each method could lead to finding either higher or lower amounts of the metal than are actually present. However, one of the negative studies cited as a strength the fact that it had found similar results using two quite different techniques (26).

Several microscopic studies have explicitly reported finding aluminum in connection with neurofibrillary tangles (9, 45, 64). Notably, one of these studies found still higher levels of aluminum associated with neurofibrillary tangles in brains of patients with dementia pugilistica (“punch-drunk” boxers) (9), suggesting aluminum accumulation is specific for tangles rather than Alzheimer’s disease. There has also been a study reporting aluminum associated with the nuclei of nerve cells containing neurofibrillary tangles (46). This was true even in the brains of non-demented seniors, although such brains naturally had far fewer neurofibrillary tangles than did those of people who had died with Alzheimer’s disease. There has also been reports Alzheimer’s disease is associated with elevated amounts of aluminum bound to a specific nuclear protein (46) and a microscopic study that did not report the subcellular location of the additional aluminum (59). However, again, results have not been consistent. One study found no significant differences among nerve cells, with or without neurofibrillary tangles, from Alzheimer’s disease patients, nerve cells from control subjects, or non-neural supporting tissues from the two groups (37).

Another study similarly reports no differences in either nuclear or cytoplasmic aluminum content among nerve cells with or without tangles or from control subjects (35). Two other studies have looked specifically at β-amyloid plaques, with one stating that aluminum is associated with the amyloid fibers (70) while another reports that it is not (33). There was also a study that found “no peculiarities in the distributions of aluminum” in brain slices taken from patients who had died of Alzheimer’s disease (42).

Aluminum in Animal Models

Studies in animal models of Alzheimer’s disease must be evaluated with a degree of caution. These models typically involve mice that have been genetically altered to incorporate the human amyloid precursor protein carrying mutations known to cause familial Alzheimer’s disease, sometimes along with other mutated Alzheimer-associated proteins. None, however, have been shown to reproduce all major features of the human disease (50). The only ones in which the original reports documented the presence of neurofibrillary tangles were those in which the animals also carried a mutated form of the tau protein, while the only ones in which loss of nerve cells was documented were those that also carried a mutated form of presenilin-1, mutations in which also produce familial Alzheimer’s disease. Additionally, some studies looking at the effects of aluminum have injected the metal directly into the animals’ brains, which is clearly different from the human situation, while others have measured the effects solely by declines in performance on memory tests such as water mazes without looking at the changes in the brain that define Alzheimer’s disease. Although relevant to the general question of aluminum’s bad effects on the brain, it is unclear whether such performance-only studies tell us anything about the disease.

Since these genetically altered (“transgenic”) mice are a relatively recent development, many of the early studies used other animals. These models, however, do not reproduce the typical features of human Alzheimer’s disease very well. In the first such study to be reported, aluminum was injected into the brains of cats, with the amount ending up in specific brain regions being associated both with the number of neurofibrillary tangles in those regions and with poorer performance on an avoidance test (15). There was no mention of β-amyloid plaques, however. Another relatively early study injected aluminum into
rabbit brains, again finding many neurofibrillary tangles without mentioning plaques (31). Still another study gave rabbits repeated injections of aluminum (65). Neurofibrillary tangles appeared first in the spinal cord, then the brain stem, and finally the hippocampal region of the brain, with aluminum being found in the nuclei only of nerve cells containing tangles. However, the order in which these tangles appeared does not reflect the human disease, although this could be attributed to the way the aluminum was given. In a final set of recent non-mouse studies, rats were continuously given aluminum in their drinking water beginning at 12 or 16 months of age, middle-aged for a rat (65, 67). The amount of aluminum in the rats’ diet was said to be comparable to human dietary intake. In the most comprehensive study (66), different groups of rats received low, medium, or high doses. Most but not all of those in the high-dose aluminum group, a few of those in the medium-dose group, and none of those in the low-dose group showed poorer performance on a T-maze test in old age than they had in middle age, suggesting a loss of spatial memory. Notably, however, none of the rats showed neurofibrillary tangles or β-amyloid plaques, although other types of brain lesions were seen and a related study (68) found that production of amyloid precursor protein was increased specifically in rats whose performance declined with age. Although these cat, rabbit, and rat studies suggest aluminum isn’t good for you, it’s hard to know whether they tell us anything about human Alzheimer’s disease.

One intriguing study in transgenic mice found injecting aluminum into the brains of mice carrying mutated forms of both amyloid precursor protein and presenilin-1 resulted in greater loss of nerve cells and of ability to learn and remember a task than was seen in either transgenic animals not receiving aluminum or wild-type mice treated with aluminum (31). Despite the unnatural way the aluminum was given, this tends to suggest that aluminum can accelerate the progress of Alzheimer’s disease. However, another study employing a somewhat different transgenic mouse strain – this one containing mutated forms of amyloid precursor protein and tau proteins – found that high levels of aluminum in their drinking water did not increase the number of amyloid plaques or amount of over-phosphorylated tau in their brains (17). This study did not examine effects on learning or memory. Two other studies did examine memory and learning, however. Both, from the same research group, used a strain with only mutated amyloid precursor protein. One study found very high levels of aluminum in the food (more than 1% of the entire diet), decreased ability to learn and remember a water maze, although there was no detectable loss of nerve cells (49). The other fed aluminum at 1/10th the level employed in the previous study – still quite high by human standards – and found no effect on either plaque deposition or ability to recognize familiar objects (50). By contrast, another study is interesting because it supports the theory that aluminum exerts its effects by increasing oxidant levels in the brain. Mice with a mutant form of amyloid precursor protein were fed high levels of aluminum, which increased both plaque formation and levels of a compound associated with the presence of oxidants (48). Feeding the antioxidant vitamin E reversed these changes. Significantly, however, feeding aluminum had very little effect on oxidant levels in wild-type mice, again supporting an interaction of aluminum with Alzheimer’s disease rather than aluminum as the direct cause.

Removing Aluminum from the Body
If aluminum is bad for you, can you get rid of it? Will that help? The only way to get rid of aluminum is with chelators – compounds that chemically “grab” aluminum and make it soluble so the urinary system can flush it out of the body. The FDA has not approved any chelators specifically for removing aluminum. However, the aluminum ion is very similar in size and charge to the ferric ion (the more highly charged form of iron) and two chelators have been approved for treatment of iron overload from diseases such as thalassemia.

Deferoxamine, also known as desferrioxamine and sold under the trade name Desferal, has been used to treat iron overload since 1963 (28). In the 1980s a number of renal dialysis patients acquired excessive amounts of aluminum from their dialysis fluid, with symptoms that somewhat resembled those of Alzheimer’s disease but without the diagnostic tangles and plaques. Deferoxamine was successfully used to remove this aluminum overload, with marked improvement in the symptoms (2, 25). Deferoxamine use has been reported to cause a variety of side effects (18), with hearing loss and disturbances of vision being particularly common (11). Official prescribing information for deferoxamine indicates that side effects are typically seen only with high dosages or prolonged use, but this is in the context of the officially approved use for iron overload. Evidence suggests that patients who do not have excessive amounts of iron in their systems may be more vulnerable (47). Nevertheless, when patients with Alzheimer’s disease were given low doses of deferoxamine for 2 years, the only side effect noted was loss of appetite (17).

Other drawbacks to deferoxamine are high cost and the fact that it is given by injection. The good news is that the Alzheimer’s disease patients in this one study of deferoxamine had progress of their disease slowed to half that seen in control patients (17). Critics have suggested, however, that this slowing may have been a result of seeing the doctor more often and the resulting increase in human interaction, since control patients did not get injections.

Deferiprone, also known as L1 and sold under the trade name Ferriprox, has been under investigation for more than a decade but has only recently been approved for treatment of iron overload. A comparative study concluded that deferiprone and deferoxamine were more or less equally effective in removing either iron or aluminum and that, while they had different side effects, there was little to choose between them on this ground either (29). A review from the same author, however, indicated that deferiprone’s side effects were less significant (30). Furthermore,

“A compound known as Feralex-G has drawn attention because it has been reported to be more effective than deferoxamine for removing aluminum from brain slices obtained at autopsy from Alzheimer’s disease patients.”
deferiprone is much cheaper and is given by mouth, so it is likely to be preferred.

A number of other iron/aluminum chelators were studied in the 1990s but have since been abandoned for various reasons. A compound known as Feralex-G has drawn attention because it has been reported to be more effective than deferoxamine for removing aluminum from brain slices obtained at autopsy from Alzheimer’s disease patients (157). No studies in live animals or humans have been reported, however. Other novel chelators are also being investigated (240) but appear unlikely to be available for human use in the near future. An innovative approach that has recently been suggested is attaching chelators to nanoparticles that can move freely back and forth through the blood-brain barrier (34), but much work still needs to be done to bring this idea to fruition.

Using more than one chelator in combination also appears to be an attractive idea. In aluminum-injected rats, however, the combination of deferoxamine and deferiprone was no better than deferoxamine alone (48). There was similarly no advantage to combining deferiprone and the compound deferasirox (58). On the other hand, combined use of two quite different types of chelators, both still largely in the “blue sky” stage, did provide superior results (13). And in a highly artificial laboratory study, the combination of ascorbic acid (vitamin C) and Feralex-G was better than any of several other compounds or combinations for removing aluminum from nerve cell nuclei (12). The authors suggest that ascorbic acid may enter the nucleus readily and chelate the aluminum there, then transfer it to the Feralex-G for disposal. The antioxidant effects of ascorbic acid may also be relevant. The possibility that ascorbic acid might enhance the effectiveness of deferoxamine or deferiprone needs to be tested in a more realistic setting.

Conclusions

The Alzheimer’s Association says, “Since [the 1970s], studies have failed to confirm any role for aluminum in causing Alzheimer’s” (http://www.alz.org/alzheimers_disease_myths_about_alzheimer s.asp, accessed May 23, 2012). This seems somewhat overstated. Although the evidence is not entirely convincing, there is too much data supporting a role for aluminum in Alzheimer’s disease for it to be entirely ignored. However, the evidence best fits with that role being to speed progression of the disease rather than constituting a direct cause.

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