

# A review: Aluminum as a causative co-factor for the “dementia” of Alzheimer’s disease.

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## **Abstract**

This review explores an expert proposal made over a decade ago that aluminum is a “necessary but not sufficient” risk factor for the dementia of Alzheimer’s Disease (AD). More than twenty epidemiology studies report a statistical relationship between exposure of the aging population to aluminum in food and drinking water and increased risk of elderly cognitive impairment and risk of dementia. An autopsy microscopic visualization of aluminum in brain cells of AD patients using the Walton stain reveals two basic types of pyramidal neuron death produced by accumulated brain aluminum. These are first a cell death visually resembling necrosis and secondly brain cell death by mechanical enucleation from a persistent accumulation of cellular neurofibrillary tangles (NFTs). The metal was found to be associated with the formation of all NFTs, producing the characteristic protein folding. This autopsy finding supports a causative role of the metal in human AD dementia. Over a lifetime, aluminum bio-accumulates to relatively high concentrations in all human elderly brains. It is a reactive metal that readily complexes with basic brain biology and affects genes regulation. Abundant laboratory animal studies document mechanisms by which aluminum produces brain cell death and the erosion of white matter to reduce the connectivity of the brain. It is concluded from extensive literature that aluminum is a causative co-factor for the dementia of AD, which is a medical condition based on brain atrophy. Epidemiology studies identify an excellent public health opportunity for large scale prevention of the dementia of AD through the reduction of dietary and drinking water aluminum contamination and the wider use of nutritional factors that chelate the metal.

*Keywords:* Aluminum, Alzheimers, dementia, cognitive impairment

## **1. Introduction**

Chronic diseases of the aging process including Alzheimer’s Disease (AD) are generated by multiple causative factors. An abundance of epidemiology studies have identified over twenty different approaches to effectively reduce AD risk by 50 percent or more, after control of other factors [1]. These strategies include aluminum avoidance in the diet and water, and nutritional and lifestyle changes. Epidemiology also identify dietary and water exposure to aluminum as one of the largest and easily corrected risk factors [2]. AD is likely preventable in the 50 to 80 percent range which is a goal that can be achieved for the most part without drugs. In contrast, therapy for AD will always remain difficult due to severe brain atrophy in AD patients. Halting disease progression is the

best hope. Therapy with aluminum chelation has shown promise in a human clinical trial.

Country comparisons indicate a large capacity for AD prevention. Age-adjusted AD rates in northern India are 73 percent less than those of Pennsylvania [3]. Explanations include reduced dietary aluminum exposure and dietary factors that reduce absorption [1]. Many individuals are resistant to AD by virtue of genetics, lifestyle, environment and diet. Khachaturian et al mathematically projected from the Cache County Study that if all Americans lived to 100 years, about 28 percent of the population would avoid the disease [4].

## **1. Alzheimer's and AD with "dementia" are different medical conditions.**

The dementia of AD is characterized by gross brain atrophy marked by uncontrolled and extensive brain cell death and a reduction of brain connectivity. Dementia is what sends people to the nursing home and not brain deposits. Human autopsy studies and more recently brain imaging studies in live patients have found only weak statistical correlation between senile plaque and neurofibrillary tangle (NFTs) deposits and elderly cognitive impairment or dementia. It is common for persons of normal cognition for their age to die with significant densities of senile plaque and NFTs deposits [5].

### *1.1. Traditional brain deposits sequester aluminum to protect the brain from oxidation.*

Growing evidence indicates that the brain deposits characteristic of AD are initially protective of the brain in sequestering proteins and metals that cause oxidation and inflammation. This conflicts with the viewpoints of the past. For the past twenty years, the primary focus of researchers studying AD has centered on beta-amyloid ( $A\beta$ ), the presence of which is presently a mandatory definition of the disease. Yet a series of autopsy studies find little statistical correlation between the brain deposits defining AD and cognitive impairment of the patients while they lived.

Case Western Reserve University researchers and others have begun to assert an alternative viewpoint that  $A\beta$  may not be an initiating factor, but rather "secondary to other pathologic events". They propose that  $A\beta$  may be a "protective response to neuronal insult" [6]. The scientists question the validity of the oligomeric amyloid cascade hypothesis. Their new approach is beginning to gain traction because it fits the facts more adequately.

Studies of the biological interaction of aluminum and  $A\beta$  also suggest that the brain deposits that have defined AD over many years also protect the brain from oxidation generated by aluminum through sequestration of both aluminum and  $A\beta$ . Van Rensburg et al reported from an in vitro study that amyloid protein fragments bond with aluminum to quench the oxidative toxicity of both toxins [7].  $A\beta$  are sticky proteins. The authors proposed that they and aluminum were "meant to bond" which is not a stretch of imagination since amyloid precursor protein (APP) is a metal shuttle especially for

copper. Senile plaques perform a similar sequestration function for a range of oxidating metals and A $\beta$ .

Likewise, the NFTs protect the brain through aluminum sequestration. Walton's recent human autopsy study of AD patients using the Walton stain to visually locate aluminum within the cell discovered that human pyramidal brain cells could survive high densities of NFTs even to the point of death of the cell by mechanical enucleation [8]. The NFTs continuously chelated aluminum from the cytoplasm and incorporated the metal into the NFTs folded structure. This sequestration of aluminum reduced its toxicity to the neuron, allowing a cell to survive longer.

### *1.2. Aluminum induced brain cell death and connectivity loss involves direct biological action.*

Figure 1 summarizes the multiple ways that aluminum has been demonstrated to produce brain atrophy and loss of connectivity in laboratory animals and humans. A supporting bibliography of over seventy published studies of brain atrophy produced by aluminum exposure and a description of a range of biological mechanisms involved is available [9]. Aluminum is a substantial participant but is not the sole actor in producing severe brain atrophy and loss of brain connectivity in AD patients.

The metal generates both oxidation or reactive oxygen species (ROS) and brain inflammation in laboratory animal studies [10]. Lukiw et al finds that the ROS produced by aluminum, and aluminum combined with iron turned on and off a series of genes that are similarly affected in AD. A mixture of aluminum and iron has a synergistic adverse effect on brain cells. Continuous ROS exposure also induces inflammation and apoptosis genes, leading eventually to brain cell death [11]. Lue et al, found that brain inflammation distinguished between normal non-demented persons with heavy brain deposits of plaques and tangles and those with AD in an autopsy study [12].

### *1.3. Aluminum also participates in generation of traditional AD brain deposits and markers.*

Aluminum not only generates brain atrophy in a direct fashion, but also participates in generation of the traditional AD brain markers upon which the present rating systems of disease diagnosis are based.

- *NFTs:* Aluminum exposure is essential to the production of all NFTs by producing characteristic protein folding. Excessive generation of NFTs leads to brain cell death in humans by mechanical enucleation [8,13].
- *Soluble A $\beta$ :* Pratico et al discovered that the metal generates soluble A $\beta$  and senile plaques in the brain of transgenic Tg2576 mice design to express human APP. Increased oxidation was seen as the trigger for this effect measured by brain isoprostane levels[14]. Lukiw reports that toxins such as aluminum and iron that generate ROS in the brain will turn on genes that encode for generation of

A $\beta$  [15]. Soluble A $\beta$  has direct oxidative toxic properties which can be significantly quenched by sequestration in the senile plaques or by bonding with metals including aluminum [7]. In bonding with metals, A $\beta$  and its parent compound APP perform as antioxidants.

- *Platelets, A $\beta$  and Aluminum in Early Onset AD:* Platelets produce A $\beta$  and have been used as a model for AD. It has been proposed that aluminum augments levels of A $\beta$  in the human brain based on its generation of increased membrane fluidity of blood platelets [16], a condition which is specifically correlated with early onset AD [17]. A human clinical trial using modest zinc supplementation (twice the RDA) slowed AD disease progression by 7-9 months, but at the same time reversed the fluidity of the blood platelet membranes in persons with AD [18]. Zinc and aluminum are competitors in biology and likely dislodge each other from biological sites. A plausible mechanism is that membrane thinning will interfere with the proper functioning of  $\alpha$ -secretase, which cuts the amyloid precursor protein APP only at the surface of the membrane.

Van Rensburg notes that the fluidity of cell membranes of platelets generally decrease with age, especially in the endoplasmic reticulum (ER). Unexpectedly a number of laboratories have found that aluminum exposure increases the fluidity of platelet membranes, especially in the ER [19]. The ER is involved in brain cell death associated with either aluminum or A $\beta$  exposures [20].

- *Senile Plaques – How Much Aluminum Is Involved?* Unlike NFTs which are clearly contaminated with and folded by aluminum, controversy continues about the role of aluminum in formation of senile plaques because detection of aluminum in the plaques has proven difficult. Exley demonstrates that aluminum and iron added to A $\beta$  in solution not only precipitates it, but at the same time specifically produces the characteristic beta structures of senile plaques [21]. Copper and zinc do not produce these beta structures.

AI Bush et al in 1994 reported that zinc added to a glass container containing a solution of synthetic A $\beta$  residues 1-40 precipitated the A $\beta$  [22]. It was also reported that this effect “was attributed to precipitation onto the column glass, which contains aluminosilicate”. The principal role of aluminum was confirmed by adding kaolin to the solution, a hydrated aluminum silicate suspension, which also accelerated the precipitation of A $\beta$  in the presence of zinc.

The experimental result suggests that it does not take very much aluminum to affect the solubility of A $\beta$  in the presence of other metals: i.e. just the amount contained on the surface of glass or almost a catalytic effect which may be a reason that the measurement of aluminum in senile plaques has proven difficult. Another reason may be the obscuring of aluminum by the beta folding in the plaques, as was the case with measurement of aluminum in NFTs [13]. Use of the

autoclave by Murayama to unwind the NFTs allowed the discovery of aluminum that had been hidden from measuring equipment.

Many years of autopsy studies of AD patients have found very little correlation between senile plaque densities and the measured cognition of the patients while they lived. We will return to this issue. The senile plaque defines AD, but not its dementia which is not mediated by the senile plaque. Aluminum does not exert toxic effect on the brain through the senile plaques. In sum, AD and AD with dementia are two different medical conditions.

## **2. Aluminum is seen as a necessary but not sufficient risk factor for AD.**

The Canadian pioneer DRC McLachlan and colleagues in 1991 proposed a limit on aluminum exposure: i.e. “The evidence warrants a serious consideration of reducing human exposure to aluminum. We hypothesize that a public health effort to restrict human ingestion of aluminum would reduce the incidence of this chronic illness in the elderly [23]”. McLachlan ventured additionally in 1993 to conclude that aluminum was a “necessary but not sufficient” risk factor for the development of AD based on the extensive scientific literature of the time [24]. A human clinical trial at the University of Toronto to chelate aluminum from the brain of AD patients slowed disease progression as measured by life skills by 50 percent over two years by removing one third of brain aluminum [25].

The conclusion that aluminum is a necessary but not sufficient risk factor for AD is consistent with the genetic findings of WJ Lukiw et al [11]. The team exposed untransformed human neural cells to 100 nano-molar aluminum sulfate using high density DNA microarrays that interrogate the expression of every human gene. Aluminum down-regulates some genes and up-regulates others, which can then be compared to gene expression in the brain tissue of AD patients.

Of the most altered gene expression levels, 71 percent of aluminum-affected genes and 88 percent of aluminum induced genes exhibit expression patterns similar to those observed in AD. That leaves 13 to 28 percent of genes to be affected by other environmental, nutritional or other factors including age itself before AD manifests itself.

Alexandrov et al found aluminum and iron to be highly synergistic in up- or down-regulation of genes in a pattern similar to that of AD [26]. A further study by Lukiw and Pogue investigated the induction by aluminum and iron, both ROS producers, of specific micro RNA (miRNA) species in primary human brain cell cultures with similar biological outcomes [15]. The two metals have synergistic effects in up-regulation of specific regulatory elements and pathologic genes that promote cell dysfunction and apoptotic cell death. Both aluminum and iron are present at elevated levels in the aging brain and both metals bioaccumulate during the aging process.

McLachlan et al proposed that the goal for daily adult intake of aluminum from all sources should be 3 mg or less, and that municipal drinking water concentrations should be

maintained at less than 50 ug/liter based upon findings of epidemiology [23]. Both programs remain practical, though regulatory action has stalled. The US Environmental Protection Agency has neither acted to reduce aluminum levels in drinking water nor prohibited the use of aluminum coagulants for water treatment. Aluminum food additives are still recognized by the US Food and Drug Administration as “generally recognized as safe” (GRAS). FDA was petitioned in 2005 to rescind this position [27].

Not all researchers venture as far as the Canadians. V.W. Gupta et al summarized a middle road: “Finally, it is concluded based on extensive literature that the neurotoxic effects of aluminum are beyond any doubt, and aluminum as a factor in AD cannot be discarded. However, whether aluminum is a sole factor in AD and whether it is a factor in all AD cases still needs to be understood” [28]. It is a more cautious approach. We should not forget that the Canadians over ten years ago had a large group of studies upon which to base their public health recommendations. Evidence is vastly better today.

### **3. Epidemiology links aluminum exposure to prevention of AD and elderly cognitive impairment.**

Twenty two drinking water epidemiology studies link aluminum to either higher risk of AD with dementia or to elderly cognitive impairment [2,29]. The later condition often converts to AD. In the United States where epidemiology forms the basis and backbone for governmental regulation of toxins, this number of studies historically represents a sufficiently large body of evidence for a governmental regulatory action. In different political times, public health regulation of the metal would be in progress.

*Aluminum Absorbed from Drinking Water:* The absorption of aluminum from drinking water is related to the other constituents of the water. Canadian studies find that maintenance of a drinking water pH in the vicinity of 7.9 reduces the risk of both AD and elderly cognitive impairment by 50 percent [30-31]. The finding indicates that skin, lung, nose, and perhaps mouth absorption (more alkaline surfaces than the stomach) may be important than stomach or gut absorption. A shower or bath in aluminum contaminated drinking water may pose a greater risk for AD than oral consumption of the water. An additional 30 percent risk reduction was achieved in the Ontario studies by the presence of about 1 mg/liter of fluoride in the water. Fluoride is an aluminum chelator [32] but is not recommended for prevention since it has other adverse health effects [33].

Soluble silicon or silicic acid in the drinking water is associated with a large reduction in AD and elderly cognitive impairment risk. Silicic acid reduces absorption and increases excretion of aluminum. The relationship of aluminum and silicon may involve threshold chemistry. French women who drank sufficient bottled mineral water rich in soluble silicon to achieve a silicon intake greater than 12 mg/day experienced a 50 percent reduction in their risk of AD, but saw little benefit at lower dosages [34]. Exley proposes mineral water to provide chelation therapy for AD [35]. It is also a capable preventative agent.

*Aluminum Absorbed From Food Additives:* A study of dietary aluminum consumption from solid food over the previous five year period by newly admitted residents to a geriatric center in Syracuse, New York linked aluminum statistically to AD [36]. While a small sample size limited significance for some categories of food, an enriched dietary aluminum consumption from food items constituted with aluminum based baking powder including pancakes, waffles, biscuits, muffins, cornbread and corn tortillas over the previous five years was associated with 100 percent risk for AD. None of the controls got the disease. Baking powder is inexpensively manufactured with calcium, a formulation without AD risk and already available on supermarket shelves for purchase.

*Other Non-Occupational Exposures:* A 1990 retrospective case-control study of antacids and deodorants by Graves et al has often been cited by industry representatives as an argument that aluminum has no effect on AD disease [37]. It is a conflicted study:

- The use of aluminum based deodorants increased the risk for developing AD by 60 percent.
- The use of “any” antacid, which might indicate stomach damage and enhanced metal absorption, was associated with a steep and statistically significant dose-related AD risk, with an overall OR of 11.7 comparing the highest third antacid use with the lowest third exposure level.
- The use of specifically aluminum containing antacids reduced AD risk by 30 percent, which is consistent with other “retrospective” studies.

The findings are consistent with the concept explored statistically in William Forbes’ longitudinal study of men from age 45 to 75 that excessive aluminum exposure can shorten the lifespan of elderly persons. In a small sample, Forbes found evidence for a 41 percent increased risk of being deceased at age 73 for persons living in a water district where water aluminum exceeded 85 ug/liter [31]. Selective death of elderly persons such as from pneumonia, from the much higher dosage of antacids would bias the sampling pool of a “retrospective” epidemiology study.

Roberts compares the intestinal dosage of aluminum from antacids to be equivalent to the increased aluminum absorption in AD patients [38]. It is a high dose, particularly for those who are good absorbers of the metal as older people and AD patients tend to be. Persons who would have developed AD due to their aluminum exposure may already be dead when the study commences and the participants selected. Longitudinal studies which monitor the mortality rates of the participants would be obligatory to ascertain the effect of aluminum based antacids on AD risk.

#### **4. Aluminum interacts with other risk factors including dietary factors.**

The interaction of aluminum with many other risk factors of AD [1] adds plausibility to McLachlan’s proposal that the metal is a necessary but not sufficient risk factor for AD.

Many nutritional factors shown by epidemiology to be preventative of AD such as polyphenols from wine, flavonoids and polyphenols from fruits and vegetable, and vitamins E and C are also aluminum chelators. A nutrient of special interest is folic acid

which is preventative of AD [39]. Snowden's matched control study from the Nun Study found that higher serum folic acid reduced the severity of atrophy of the brain's neocortex [40] and that low folate was the only nutritional variable of 18 in this longitudinal study to show significant correlation with brain atrophy. Bayder et al report that folic acid supplementation sharply reduced the level of aluminum in rat brain: i.e. it is a chelator [41].

Consumption of fish and the docosahexaenoic acid (DHA) from fish oil supplements or alternative sources interacts with aluminum through countervailing gene expression and through the maintenance of membrane integrity. Lukiw and Bazan characterized DHA as promoting "survival signaling"[42]. A study from the Framingham Heart study concluded that the consumption of one daily fish oil pill would be sufficient to reduce the risk of developing AD by almost 50 percent [43]. Lukiw et al demonstrate that DHA and one metabolite neuroprotectin D1 induces anti-apoptotic and neuroprotective gene expression [44]. Some of these same genes are downregulated by aluminum and A $\beta$ . So the fish oil or DHA in the diet though likely not directly chelating aluminum tends to neutralize the adverse effects of aluminum generated oxidation on gene expression and membrane integrity.

Likewise, cognitive and physical activity leads to brain secretion of chemicals that interact with aluminum. Yang finds that glial cell line-derived neurotrophic factor (GDNF) suppresses aluminum induced apoptosis of pyramidal neurons in rat brains but brain derived neurotrophic factor (BDNF) may promote the apoptotic effect of aluminum [45]. Another researcher found BDNF to be protective in cell culture exposed to aluminum, and the neurotrophin generally protects against hippocampal atrophy in unexposed animals. Severe head trauma can be risk factor for AD, and has been shown to generate A $\beta$ . Yet, aluminum is found approximately doubled in the brain of boxers suffering from Dementia Pugilistica [46]. The mechanism of aluminum bioaccumulation in trauma is not known. In sum, many interactions and countervailing influences of the diet and environment on aluminum's effect on the brain.

## **5. The brain substantially regulates aluminum.**

The brain does not recognize aluminum as safe, and possesses significant chelation capacity to exclude and expel it. Natural brain defense mechanisms are insufficient to prevent a gradual bioaccumulation of the metal in the human brain over a lifetime.

Gaoloyan et al described the effect of hypothalamic secreted proline-rich polypeptide (PRP-1) in providing powerful control of brain aluminum [47]. Berg et al reported on dramatic reduction of brain aluminum in both Ts65Dn Down Syndrome and control mice provided by the appetite satiating hormone Peptide YY [48]. This finding may provide a link between obesity and aluminum, since both are risk factors for AD. Spray in the nose or oral versions of PYY soon to be commercialized for appetite control should offer inexpensive therapeutic options for AD.

Brain cell mitochondria also secrete aluminum chelation chemicals such as glutathione [49]. Another secreted anti-oxidant is alpha lipoic acid (ALA), which is likely an aluminum chelator in that it restores glutathione levels in the mitochondria in brain cells [50] and moves vitamin C, another chelator, into cells. ALA is a competent brain iron chelator [50] and iron chelators are generally capable of chelating aluminum. Both antioxidants are available at drugstores and vitamin stores for purchase as dietary supplements and could provide inexpensive prevention and therapy programs. A small German human clinical trial found that ALA completely halted the progression of AD over an eleven month period [51].

## **6. Aluminum is elevated in the blood of AD patients, and bio-accumulates in the brain in normal persons over a lifetime and at higher levels in AD patients.**

Average blood serum aluminum levels are higher in AD patients than in controls, though with considerable individual variation. Smorgon et al reported from a sample of Italians that high serum aluminum was a defining characteristic of persons with AD: i.e. a mean blood serum level of 0.745 mg/ml. Lesser aluminum blood levels were found in persons with cognitive impairment without dementia or with vascular dementia. Normal controls averaged 0.215 mg/ml in blood serum [52].

Aluminum absorption may increase with age. Taylor found that absorption of aluminum from a citrate-containing drink (290 mg Al, 4.8 g citrate) in normal subjects increased exponentially with age after 65 [53], paralleling the exponential increase in AD incidence, i.e. doubling every five years. Aluminum absorption from the diet is increased in AD compared to younger persons, though again with considerable individual variation. Down's syndrome patients have been shown to be more efficient absorbers of aluminum than the general population [54], and most develop dementia by the age of fifty.

### *6.1. Aluminum bio-accumulates in the human brain- in normal aging and in AD.*

Shimizu et al compared brain aluminum in non-demented elderly persons (aged 75-101) with younger non-demented adults (aged 32 to 46) using fluorescent stain [55]. Hippocampus aluminum content averaged 28 times higher in the elderly and 19 times higher in the frontal lobe than in the younger normal persons. These higher aluminum levels roughly correlated with increased AD type of brain deposits. The study confirms a bioaccumulation of brain aluminum during the human aging process. While the brain has powerful chelation capacity, it is insufficient to prevent gradual aluminum brain bioaccumulation which Edwardson et al estimated at 6ug per year of life [56].

The initiation of AD may involve only another doubling of brain aluminum beyond that experienced during normal aging, suggesting the possibility of thresholds [2]. Some brain compartments are better accumulators of the metal, and are involved early in the disease process. Andrasi et al found an approximately doubling of brain aluminum in four brain regions, but a seven fold increase in the entorhinal cortex, which is linked by white fibers to the hippocampus and provides sensory information to the same [57]. Jagannatha compared the rate of change of brain aluminum against other metals including

copper, zinc and iron [58]. As a mole percent of total metals, aluminum was 1.6 percent in the hippocampus of normal brains, 8.1 percent in moderate AD, and 48.4 percent in severe AD.

Aluminum is present in all aging brains to participate in the biological changes of cognitive impairment and dementia. Bryant et al demonstrated that aluminum widely complexes with brain chemistry as the small size and the charge of aluminum allow it to enter a wide range of biology [59].

## **7. Brain atrophy and loss of connectivity are key issues in the dementia of AD.**

Autopsy studies have consistently failed to find significant statistical relationship between AD diagnosed during life by cognitive testing and the density of brain deposits of senile plaques and NFTs upon death and brain autopsy. These brain deposits not the principal causes of the dementia of AD. Instead, an abundant evidence indicate that brain atrophy especially the death of brain cells and loss of brain connectivity are the principal sources of AD “dementia”.

While aluminum exposure participates in the production of the traditional AD deposits, the key biological role of the metal consists of killing brain cells and reducing brain connectivity. Here we briefly summarize a rapidly growing scientific literature, ranging from autopsy studies to scans of the brains of living humans concerning the difference between AD and AD with dementia.

Davis et al (1999) summarized the result of their study of 59 elderly well educated subjects examined longitudinally for 8 years until death, when a brain autopsy was performed [60]. It was found that the brains of a large percentage of cognitively normal individuals contained numerous degenerative changes, many of which would classify the individuals as having AD under the Khachaturian, CERAD, and NIA-Reagan Institute guidelines. Only a small percentage of the normal group judged free of dementia during life was free of these brain changes: i.e. 17 percent. In short, the traditional brain deposits of AD had little statistical relationship to dementia.

Edison et al (2007) compared brain amyloid loading in “living” AD patients with cognition measured by glucose utilization, and found little correlation. The authors’ conclusions are devastating to traditional viewpoints of the past twenty years concerning causation of AD dementia:

“The high frontal amyloid load detected by [11C]PIP-PET in AD in the face of spared glucose metabolism is of interest and suggests that amyloid plaque formation may not be directly responsible for neuronal dysfunction in this disorder...

Though the correlation between impaired performance on recognition tests for words and faces and cortical [11C] PIP uptake suggests that amyloid load

contributes to cognitive impairment, the loss of this correlation on withdrawing the AD subjects with normal baseline [11C]PIB PET suggests that amyloid deposition alone is unlikely to explain memory difficulties...It is conceivable that amyloid deposition occurs alongside or before the intracellular processes that lead to cognitive difficulties. This viewpoint is reinforced by the stronger correlation of recognition with temporal cortical hypometabolism which survived removal of an AD case with normal FDG uptake..."[61]

Decline in brain glucose metabolism, as measured by Edison, is a distinguishing preclinical factor separating persons with AD from persons with normal aging. Jagust et al used PET scans to conclude that decreased temporal and parietal glucose metabolism predicts a decline in global cognitive function, while medial temporal brain volume predicts memory decline in normal older persons [62].

Aluminum exposure is a participant in brain glucose deprivation in laboratory animals. Lai and Blass (1984) found that aluminum impairs brain glycolysis by inhibition of hexokinase activity in the cytosolic and mitochondria of rat brain [63]. In sum, while amyloid loading has little measured effect on glucose metabolism in living humans, there is evidence from animal studies that aluminum adversely affects glucose metabolism.

Goche et al (2002) reported from an autopsy of participants in the Nun Study that there are two tracks to dementia: i.e Alzheimer's and vascular dementia. Religious sisters with high Braak stages (high density of traditional AD brain deposits) but with relatively intact hippocampal volume had MMSE scores very close to the normal range for their ages [64]. Brain volume determines who becomes demented rather than density of senile plaques and NFTs. Brain volume was also a key issue in vascular dementia.

#### *7.1. Brain atrophy in AD is confirmed with MRI and with in vivo imaging programs as the causation of loss of cognition by AD patients:*

Brain imaging studies in living people, such as the study by Edison described above, have confirmed that brain atrophy and loss of connectivity are the primary causation of the loss of cognition and memory in the elderly and in AD, rather than the traditional brain deposits of AD.

Van der Pol demonstrates that brain atrophy occurs even in cognitively normal elderly persons aged 51 to 85, though brain volumes of normal persons remain considerably greater than those with AD [65]. The atrophy and loss of connectivity of the AD brain is best seen in the perspective of the ebb and flow of the normal brain into old age. McAuliffe summarizes that between the teen years and early adulthood, brain gray matter shrinks and white matter or connectivity expands [66]. At age 60, white matter begins to decrease at an accelerated rate as myelin and the axons are eroded, while gray matter shrinkage continues. Persons with AD experience a greater level of atrophy of both gray and white matter than cognitively normal persons.

Some remedies can slow this process. Physical exercise can generate greater brain connectivity [66]. Peirera found that exercise can generate new neurons in the dentate gyrus in younger adults [67]. Exercise has minimal benefit once AD has become established, and initiatives to slow brain atrophy become difficult because the AD brain becomes increasingly poisonous. The aluminum brain loading is higher and accelerating [58]. Brain copper and zinc levels increase into moderate AD [58] which may partially reflect an increase in Cu/Zn SOD to respond to increased brain oxidation.

DeCarli et al found that atrophy of the medial temporal lobe that includes the hippocampus was a significant predictor of which individuals with mild cognitive impairment (MCI) would progress to dementia within 3 to 5 years [68]. 190 individuals with MCI were classified into five categories of brain atrophy with a score of 0 being normal and 4 being markedly atrophied. MCI patients are known to have a higher risk of progression to dementia. For individuals with a brain atrophy score of 1.0 or less, only 29.1 percent progressed to dementia within 3 years, compared to 75 percent for those with a rating greater than 2.0. Vitamin E and donepezil had no effect on progression.

Mungas et al surveyed the brains of 103 California residents with MRI scans. They had an average age at baseline of 74 years. It was found that hippocampal volume was the primary determination of memory decline, whereas decline in executive function was related to a mix of cerebral vascular disease and AD [69]. After control for these factors, white matter hyperintensity had little effect on cognitive impairment.

Zarow et al found in comparing AD with ischemic vascular dementia that: “Regardless of causative diagnosis, the number of CA1 neurons correlates with magnetic resonance imaging-derived hippocampal volume...and memory score...We conclude that although CA1 neuron loss is more consistently observed in AD than ischemic vascular dementia, severity of loss shows the expected correlation with structure and function across causative subtype. Reduction in magnetic resonance imaging-derived hippocampal volume reflect loss, rather than shrinkage of CA1 neurons. [70]”

The brain imaging studies consistently conclude that brain atrophy is the key event in loss of memory and mental capacity in AD as opposed to the brain deposits.

*7.2. Isolation of the hippocampus by atrophy of white matter connections from entorhinal cortex is additionally important in memory loss.*

Stoub et al reported that atrophy of hippocampus was a statistically significant predictor of declarative memory performance in comparing 40 individuals with amnesic mild cognitive impairment (MCI) against 50 healthy individuals. Both groups were approximately 78 years of age [71]. The entorhinal cortex also experienced statistically significant increase in atrophy. This part of the brain receives sensory information that is relayed to the hippocampus through white matter fibers. Loss of this connectivity through brain cell death in the entorhinal cortex or through loss of the white fibers would isolate the hippocampus and thus extinguish memory.

A significant decrease in white matter volume in the brains amnesic MCI persons was discovered, compared with age-matched controls in the region of the parahippocampal gyrus that includes the perforant path. Regression analysis found that both hippocampal volume and parahippocampal white matter were statistically significant predictors of memory performance. As the authors concluded:

“These results suggest that, in addition to hippocampal atrophy, disruption of the parahippocampal white matter fibers contributes to memory decline in elderly individuals with MCI by partially disconnecting the hippocampus from incoming sensory information” [71]

## **8. Aluminum kills human brain pyramidal neurons in two ways and adversely affects brain connectivity.**

A human autopsy study by Walton found that elevated cytoplasmic aluminum was associated with all NFTs tangles in the AD brain [8]. Aluminum was measured using the recently developed Walton stain that allows visualization within the cell of aluminum's relationship to brain cell biology. The association of aluminum with all NFTs confirms the findings of Murayama using a different technique [13].

Walton reported that all human corticolimbic sections had neurons that stained for aluminum. There were two consistent tracks to pyramidal neuropathological processes in the human AD brain hippocampus related to the aluminum. Both processes could culminate in pyramidal neuron death.

- *Necrosis type of cell death:* One track involved a progressive increase in nucleolus aluminum that was often associated with granulovacuolar degeneration with granules that stain for aluminum. The outcome visually resembles a necrosis type of cell death.
- *Enucleation type of cell death:* The second track involved the formation of NFTs in regions of aluminum enriched cell cytoplasm. A continuing buildup of NFTs ultimately came to kill the neurons by displacing the cell nucleus outside the cell wall by mechanical enucleation.

*Chelation of aluminum by NFTs:* The evidence indicated that the continuing absorption of aluminum by the NFTs represented a type of natural in situ chelation that protects the neuron from an earlier death by a necrosis type of process [8].

### *8.1. The basis for increased NFTs deposits due to aluminum exposure is explored in rats and species difference is noted with regard to senile plaques:*

Walton reports that aluminum inhibited PP2A activity in the rats, leading to hyperphosphorylated tau, which in humans will polymerizes to form NFTs. PP2A activity in the aluminum exposed rats was only 41 percent of the control rats [72]. Tau activity normally requires phosphate addition and then removal. The later function is performed by PP2AS. The resulting hyperphosphorylation of tau interferes with protein

function, and neurons respond by synthesizing more protein leading to an accumulation in the neurons. In humans, the hyperphosphorylated tau is folded in the presence of aluminum to produce the NFTs which accumulate in the neuron. At high enough density, brain cell death occurs via enucleation.

Senile plaques are species specific, and did not form in the genetically normal rats used in these experiments. Walton notes that the oxidation generated by an aluminum enriched diet in Tg2576 transgenic mice, engineered to contain a human gene to overexpress APP, will produce senile plaques more numerous and larger than in the mice fed the same diet without the aluminum supplementation [14].

### *8.2. NFTs obstruct flow in the axons, leading to loss of brain connectivity.*

NFTs have a capacity to clog the axons and inhibit the flow of tau, building material and signaling chemicals from glial cells along the axons which will eventually reduce brain connectivity. As Singer et al put the issue: “The data suggest that as the size of the Al-NFT in a cell increases there is less tau in the perikarya available to perform normal functions such as microtubule polymerization and stabilization [73].” The authors propose that the aluminum-induced neurofibrillary tangle pathology shown in laboratory rabbits may provide a model to study Alzheimer’s, diffuse Lewy body disease and Parkinson’s disease.

Slowing of axonal flow has been shown to occur early in the AD process [74]. Experiments by Shea et al in cell culture found that aluminum inhibited neurofilament (NF) assembly, produced an accumulation of phosphorylated NFs in the perikarya and inhibited transport of the newly assembled NFs into axonal neurites [75]. In a human autopsy study, Apostolova et al found that “subregional hippocampal atrophy spreads in a pattern that follows the known trajectory of neurofibrillary tangle dissemination [76]”. The resulting loss of connectivity may starve the hippocampus of sensory information and lead to atrophy.

High aluminum levels found in the entorhinal cortex in AD patients reported by Andrasi [57] is relevant. Loss of neurons in that brain sector due to aluminum exposure will reduce the number of axons connecting that part of the brain to the hippocampus. Additionally, the clogging of the white matter fibers linking the entorhinal cortex to the hippocampus with an overload of NFTs generated by aluminum will deprive the hippocampus to access to sensory information that is collected by the enthorhinal cortex. Once the hippocampus is isolated as Stoub and others have proposed [71], memory ceases.

## **9. Aluminum causes atrophy of laboratory animal brain and loss of connectivity in multiple ways**

At the Seventh Keele Meeting on Aluminum held in Uxmal, Mexico in February 2007, Walton presented a video of the performance of elderly Wistar laboratory rats in a simple T maze with chocolate bait. The video documents the published studies by Walton [77].

The rats were exposed to aluminum in food and water similar to US human exposures from diet and water. At age of 28 months, two of the aluminum exposed rats began to behave like AD patients: i.e. become disoriented, groom excessively, and lose concentration. Their success in locating the chocolate bait fell to 30 percent compared to 90 percent for the unaffected rats.

The distribution of aluminum in brain cells in laboratory rats differs from that the human. Walton proposed that this intracellular distribution is a possible explanation why rats do not develop NFTs. The aluminum produced sufficient brain dysfunction in some of the elderly rats to mimic behavior seen in AD patients.

### *9.1. Apoptosis and necrosis are two basic mechanism of brain cell death.*

Figure 1 lists multiple mechanisms by which aluminum exposure has been demonstrated to kill brain cells in vivo in laboratory animals or to reduce brain connectivity. Here we can only briefly describe some biological mechanisms from an abundant number of studies. A bibliography of seventy studies for figure 1 is available [9].

Apoptosis and necrosis are basic cell death mechanisms which are often specific to animal type. Laboratory rabbits tend towards an apoptosis mechanism in response to aluminum exposure [78], whereas rodents tend towards a necrosis form of death [79]. Walton found a necrosis appearing cell death in human brain pyramid cells that had accumulated aluminum in the nucleolus. Most likely both apoptosis and necrosis mechanisms may be involved in human brain cell death as illustrated by a study by Johnson et al [80].

### *9.2. Aluminum adversely affects glial cells which substantially affects neurons.*

Glial cells outnumber neurons by 9 to 1 in the brain and are essential for neuronal function and the functioning of the axons [81]. Kashon et al found that cortical astrogliosis measured in autopsy by levels glial fibrillary acidic protein (GFAP) had a correlation with the cognitive performance and dementia status of patients before death [82]. This was especially the case for GFAP measured in the temporal lobe and to a lesser extent the parietal lobes where AD brain injury is most prevalent.

Glial cells absorb aluminum more readily than neurons. Evidence indicates that the death of neurons may be mediated by the adverse effect of aluminum on the viability and functioning of glial cells [83-84].

### *9.3. Less explored mechanisms of brain cell death produced by aluminum.*

Less explored routes to brain cell death include the depletion of red blood cell and heme by aluminum's effect directly on the bone marrow [85]. Florence et al reported that exposure of Wistar rats to aluminum citrate led to brain cell death that resembled necrosis [86]. This effect was only seen after 3 months and the authors proposed that the delay may represent the replacement time of red blood cells which have a lifetime of about 120

days in the rat. Pandav et al finds that the depletion of heme in aging humans is a risk factor for AD [87].

The brain is the largest user of glucose of any organ, with AD is associated with markedly impaired central glucose metabolism which can severely impair the viability of brain cells. As previously noted, Lai and Blass find that aluminum inhibits both the cytosolic and mitochondrial hexokinase activities in rat brain [63]. The aluminum exposure in these rats was similar to brain aluminum levels in AD and dialysis patients.

Mallioux and Appana have recently explored the production of hypoxia and anaerobic metabolism in liver cells after the exposure to aluminum [88]. Whether this effect would affect brain cells directly or only indirectly through liver damage is not known. It could affect glucose metabolism indirectly. Hyperammonemia has been proposed as a mechanism by which aluminum kills brain cells by Deloncle et al [89] and by Berg et al [48]. Aluminum bonds to L-glutamate and inhibits metabolism of ammonia. Deloncle concluded that aluminum appears to produce accelerated aging.

Little is known about the effect of aluminum on blood flow and oxygen levels in the brain, though the metal causes hypertension [90] and has been associated with amyloid angiopathy of the cerebral microvessels [91]. Aluminum rigidifies the membranes of red blood cells [16] which might limit their ability to mechanically negotiate the small size of the microvessels. Mitochondrial and vascular lesions are seen in the brain blood vessels of AD patients, and aluminum is known to damage the viability of mitochondria [92]. Hypoxia which can be associated with blood vessel damage can up- and down- regulate genes in patterns that mimic AD [93].

#### *9.4. Aluminum adversely affects brain connectivity.*

Already discussed has been the mechanical killing of neuron pyramid cells by the buildup of aluminum associated NFTs to eventually enucleate the cell. The NFTs can also clog up the axons to reduce flow, chemical communication by the glial cells, and brain connectivity. Aluminum also specifically oxidizes myelin [94], which can reduce the efficiency of neurotransmission. It produces a retraction of the dendrites [95] and damages synapses [96].

## **10. Summary**

Aluminum adversely affects the brain of aging humans and laboratory animals with a wide range of alterations of basic biology that leads to cell death and loss of brain connectivity. Additional research is needed on the alternative routes by which aluminum generates brain cell death. Other deleterious aluminum based mechanisms will likely be discovered. One might speculate an effect of the metal on arrested re-entry of differentiated neurons into cell division that ultimately leads to neuron death in AD [97].

Abundant evidence and the presence of relatively high dosages of the metal in all aging brains support McLachlan's proposal that aluminum is a "necessary but not sufficient"

risk factor for AD for the most part. Whether this is the case in all individual circumstances needs further research. For example, Wilson et al found that loneliness was associated with a more than doubling of the risk of AD in late-life [98], but upon autopsy it was a dementia unrelated to measures of AD pathology or cerebral infarction. Stress is known to increase corticosterone in rats, which reduces BDNF, and leads to atrophy of the hippocampus if the exposure is persistent. The authors labeled this condition as AD, but is it really? McLachlan may be fully correct.

The evidence is clearly sufficient today to conclude that aluminum is a causative co-factor for the dementia of AD. Walton's autopsy study visually demonstrates that aluminum participates directly in human brain cell death. Lukiw finds that iron is synergistic with aluminum. Gupta's conclusion that the neurotoxicity of aluminum is beyond any doubt is fully supported by the evidence.

Regulatory action for toxic metals like aluminum is based on a different standard of proof, with a greater emphasis on epidemiology and protection of the public health rather than absolute scientific certainty about biological mechanisms. Under the circumstances, governmental regulatory actions and parallel business actions to restrict exposure of the population in food and drinking water seem long overdue. Such initiatives would produce substantial health and economic benefit to the population.

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Figure 1 (9)

**Some Mechanisms By Which Aluminum Exposure Kills Brain Cells In Vivo  
and Erode Brain White Matter and Connectivity**

Apoptosis

- Caspase induction, release of cytochrome c, and suppression of feedback mechanisms preventing programmed cell death such as Bcl-2.
- Induction and suppression of genes involved in AD.
- Adverse effect on function of mitochondria and endoplasmic reticulum.
- Decrease of glutathion regeneration in mitochondria.
- Peri-nuclear clustering of mitochondria.
- Impairment of the ion pumps.
- Calcium homeostasis disruption.
- Oxidation of membranes and generation of soluble A $\beta$ .

Necrosis.

- Inflammation and oxidation.
  - Induction of inflammatory genes.
  - Impairment of the ion pumps.
3. Combination of apoptosis and necrosis.
  4. Glial cell death or impairment leading indirectly to neuron death.
  5. Eucleation by mechanical action of excessive accumulation of NFTs.
  6. Less explored cell death mechanisms.
    - Nuclear translocation of HIF-1 alpha and promotion of anaerobiosis.
    - Heme and red blood cell depletion.
    - Interference with cerebral glucose metabolism.
    - Slowing of cerebral blood flow due to damage to cerebral microvessels via amyloid angiopathy, inflammation, adverse effect on blood vessel mitochondria and production of red blood cell membrane rigidity.
    - Hyperammonemia.
    - Induction and suppression of hypoxia genes involved in AD.
  6. Death by loss of connectivity and lack of stimulation.
    - Clogging of axons with neurofibrillary tangles.
    - Damage to synapses directly, via reduction of axonal flow, or suppression of genes involved in synapsin.
    - Dendritic pathology and reduction of dendritic connectivity.
    - Interference with neurotransmitters.
    - Oxidation of myelin and fatty acids.
    - Disruption of the perforant path.
    - Death of connective layers of brain.
    - Isolation of hippocampus from the remainder of the brain.

Source: Jansson ET, Presentation at the 7<sup>th</sup> Keele Meeting on Aluminum, Uxmal, Mexico, 2007 Feb 27. Seventy supporting footnotes at: [www.deptplanetearth.com](http://www.deptplanetearth.com)

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