Is the Aluminum Hypothesis Dead?

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The Aluminum Hypothesis, the idea that aluminum exposure is involved in the etiology of Alzheimer disease, dates back to a 1965 demonstration that aluminum causes neurofibrillary tangles in the brains of rabbits. Initially the focus of intensive research, the Aluminum Hypothesis has gradually been abandoned by most researchers. Yet, despite this current indifference, the Aluminum Hypothesis continues to attract the attention of a small group of scientists and aluminum continues to be viewed with concern by some of the public. This review article discusses reasons that mainstream science has largely abandoned the Aluminum Hypothesis and explores a possible reason for some in the general public continuing to view aluminum with mistrust.

Fifteen years ago, Munoz[1] stated: "Mainstream science has long ago left behind the Aluminum Hypothesis, which is generally considered to be a fringe theory. It is noteworthy that papers supporting the Aluminum Hypothesis are conspicuously absent at meetings of the Society for Neuroscience or American Association of Neuropathologists, and likewise constitute a marginal fraction of peer-reviewed publications." Although Munoz's language can be considered to be hyperbolic, the points that he makes are accurate; the Aluminum Hypothesis has diminishingly few adherents and is certainly not in the mainstream of Alzheimer disease (AD) research. In comparison to the number of research laboratories dealing with other theories of the etiology of AD, there are very few scientists investigating the Aluminum Hypothesis and there are few peer-reviewed articles dealing with this topic.

Nevertheless, similar to Mark Twain's response to the false rumor of his death,* the demise of the Aluminum Hypothesis of AD is an exaggeration. Although there are few scientists working in this area, research does continue, and among some members of the public, there is at least a suspicion that aluminum is involved some way in AD. For example, although authoritative organizations such as the Alzheimer's Association have stated that the idea that using aluminum cookware can lead to AD is a "myth" and that "... studies have failed to confirm any role for aluminum in causing Alzheimer's. ... and few believe that everyday sources of aluminum pose any threat,"† there is a thriving business in selling aluminum-free cookware with the ostensible purpose of avoiding AD. The present review discusses the reasons for mainstream science's disinterest in the Aluminum Hypothesis and touches on possible reasons that the general public continues to view aluminum with mistrust.

The Aluminum Hypothesis was initially based on three findings. The hypothesis began in 1965 with the serendipitous demonstration by Wisniewski, Terry, and Klatzo that introduction of aluminum salts into the brains of rabbits induces cognitive deficits in association with the formation of neurofibrillary changes that, with conventional silver staining, seemed similar to the neurofibrillary tangles present in the brains of AD sufferers,[2–4] viz: "The origin of this study is rather accidental. In attempting to determine the localization of antibodies in the brain by an immunochemical procedure it was found ... that in rabbits the intracerebral injection of various antigens bound with Holt's adjuvant produced a severe convulsive state following a latent period accompanied by striking neuronal changes throughout the central nervous system (CNS). Further investigation revealed that alum phosphate, which constitutes the basic ingredient of the Holt's adjuvant, was responsible for this phenomenon and that the neuronal change consisted primarily in a neurofibrillary degeneration."[3, p187] Several years later, aluminum levels were reported to be elevated in the brains of patients with AD,[5] and dialysis encephalopathy, a rapidly lethal disorder characterized in part by profound dementia, was found to be caused by contamination of dialysates by aluminum.[6]

Ironically, as discussed hereafter, these three foundational articles subsequently have been shown to be of little or no relevance to the etiology of AD. First, contrary to initial indications, aluminum salts do not induce neurofibrillary changes that are similar to the neurofibrillary tangles of AD. Second, the hypothesized similarity between aluminum-induced dialysis encephalopathy and AD was shown to be incorrect: while dialysis encephalopathy is clearly caused by aluminum, neither the symptoms nor the underlying neuropathology bear any resemblance to that of AD. The third, showing an increase in aluminum in the brain with aging, has despite extensive investigation proven to be of unknown functional significance. Nevertheless, the Aluminum Hypothesis has survived.

As previously noted, the Aluminum Hypothesis began with Wisniewski, Terry, and Klatzo's demonstration of AD-like neurofibrillary pathology induced by injection of aluminum salts into the rabbit brain. Nevertheless, subsequent work, some by these same investigators, showed that the similarities between aluminum-induced tangles and those of AD were more apparent than real. As reviewed in Wisniewski and Wen,[7] under light microscopy with silver staining, aluminum-induced tangles and AD pathology seem similar. Nevertheless, only AD tangles show strong fluorescence when stained with thioflavin-S and bi-refringence associated with a β-pleated sheet after staining with Congo red. Aluminum-induced tangles differ from those of AD in their distribution on both gross and ultrastructural levels. Although both types of tangles are found in the cortex and hippocampus, only aluminum-induced pathology is also found in the spinal cord. Indeed, with aluminum-induced tangles, the spinal burden seems to exceed that of the brain itself. Within single neurons, aluminum-induced tangles are found in the perikaryon and the proximal parts of the dendrites and axon. In contrast, AD tangles are found throughout the neuron, including the entire length of the dendrites, and throughout the axons, including the terminals. Aluminum-induced tangles are made up of straight 10-nm diameter neurofilaments, while AD tangles are 20 to 24 nm paired helical filaments. The protofilament building blocks of aluminum-induced tangles also differ from those of AD with the diameter of the former approximately 20 Å and the latter approximately 32 Å. The peptide composition of aluminum-induced tangles is chiefly neurofilament protein, while AD paired helical filaments are composed primarily of hyperphosphorylated tau, a microtubule-associated protein, and ubiquitin. Although a few investigators have reported that tau is also found in the aluminum-induced tangles of rabbits,[8,9] it should be

*Upon learning of the rumors of his death, Mark Twain quipped: "The report of my death was an exaggeration." *NY Journal*, June 2, 1897.

†http://www.alz.org/alzheimers_disease_myths_about_alzheimers.asp.

TABLE 1. Disease Progression

Dialysis Encephalopathy Progression	Alzheimer Disease Progression
Intermittent speech difficulties	Impaired recent memory with lack of insight
EEG abnormalities	Impaired executive functioning
Memory loss, dyspraxia, myoclonus	Problems of visuospatial perception, praxis, and language (eg, word finding and comprehension), with irritability and apathy
Seizures, loss of motor coordination and speech	Dementia and motor signs (Bradykinesia, rigidity, and gradual progression to fetal posture)
Death 6 months after initial symptoms	Death 5 to 10 years after initial symptoms

EEG, electroencephalogram.

noted that most investigators fail to confirm the presence of tau[10–13] and that those who do find this protein report that it is primarily in unphosphorylated form.[9] Accordingly, aluminum-induced tangles fail to react with the 5 to 25 monoclonal antibody to AD tangles.[14]

Like the tangles caused by aluminum in rabbits and the tangles of AD, the similarity of the dementia of dialysis encephalopathy to that of AD is also only on a superficial level. The clinical picture of dialysis encephalopathy radically differs from that of AD in presentation, clinical progression, and time course (Table 1).[15,16] Moreover, seizures, a cardinal sign and the typical cause of death in patients with dialysis encephalopathy, are only rarely seen in AD patients. Finally, the neuropathology associated with brain overload of aluminum in cases or renal failure and dialysis encephalopathy does not resemble that of AD[17,18] (see later).*

Crapper et al[5] reported that aluminum concentrations in bulk brain were elevated in patients with AD; this 1973 study, as well as several replications in the intervening years,[19–23] does not address the issue of *when* the metal was deposited. Thus, it is unclear whether the entry of aluminum into the brain causes AD or whether changes caused by AD allow aluminum to enter. For example, it is known that the integrity of the blood–brain barrier is compromised in patients with AD, thereby allowing substances that are ordinarily not allowed access to the brain, to pass into the parenchyma.[24] Equally important, the fact that other laboratories failed to find increased aluminum in the brains of AD patients[25–29] calls into question the conclusion that there is *any* significant increase of aluminum concentration in bulk brain. Indeed, consideration of the serious methodological difficulties with those studies that did report increased aluminum concentrations, discussed at length in Bjertness et al[29] and Wisniewski and Lidsky,[30] strongly suggests that there seems to be no consistent increase in bulk aluminum in the brains of AD patients.

Regardless of the inauspicious fate of the seminal articles in this area, the Aluminum Hypothesis persists, buoyed by ostensibly suggestive findings from in vitro, in vivo, and epidemiological studies despite the fact that there are contradictory findings in each of these areas. Nevertheless, the credence afforded the Aluminum Hypothesis in the scientific community can be gauged by the response of neuroscientists who are involved in research on the etiology and treatment of AD—very few investigators are concerned with the role

*Dialysis encephalopathy is a neurodegenerative syndrome that, several decades ago, was determined to be caused by patients with dialysis consuming aluminum phosphate binders and also by the use of aluminum-containing dialysates. Currently, the use of aluminum-free dialysates and the avoidance of aluminum phosphate binders have markedly reduced the incidence of this disorder. Aluminum phosphate binders do not pose a risk to patients with normal renal function.

of aluminum in AD. Is this abandonment of the Aluminum Hypothesis premature? Following is an attempt to answer this question.

In 1965, Austin Bradford Hill[31] proposed nine criteria for determining whether there was persuasive scientific evidence that influences from occupation and lifestyle have a causative role in various diseases. These criteria are summarized by van Reekum et al,[32] viz:

1. a strong association between the causative agent and the outcome
2. consistency of findings across research sites and methodologies
3. specificity of causative agent to outcome
4. appropriate temporal sequence of exposure to outcome
5. demonstration of a biological gradient
6. biological plausibility
7. coherence of findings—putative causation is in agreement with existing knowledge
8. experimental evidence—application of the causative agent causes the predicted outcome
9. evidence from analogous conditions

In discussing these criteria in the context of causation of neuropsychiatric diseases such as Alzheimer disease, van Reekum et al point out that " . . . some of Bradford Hill's criteria are more relevant, or more feasible, to use in neuropsychiatry than others. Demonstration of an association between the causative agent and the outcome, consistency of the findings, a biological rationale, and the appropriate temporal sequence are all necessary criteria that are feasible to achieve . . . The biological gradient, coherence, analogous evidence criteria are not necessarily appropriate for neuropsychiatry, but where demonstrable will add to the argument for causation." This review focuses on the subset that van Reekum et al argue are "necessary criteria"; each is discussed with respect to aluminum's putative causative role in AD. Of the remaining criteria, four (ie, specificity, a biological gradient, coherence, and analogous conditions) are dependent on one or more of the core necessary criteria. The remaining criterion, experimental evidence, is not feasible because of ethical considerations.

This review article is addressed to determining whether or not there is sufficient empirical evidence for the proposition that aluminum causes AD. To do so, the experimental literature has been reviewed in the context of the Bradford Hill criteria—generally accepted as the group of minimal conditions necessary to provide adequate evidence of a causal relationship between an environmental influence and a medical consequence. Although there have been several interesting hypotheses concerning a possible role of aluminum in AD, theoretical reviews have no place in a Bradford Hill determination of causation.

STRONG ASSOCIATION BETWEEN THE CAUSATIVE AGENT AND THE OUTCOME

Elevations of aluminum in the human brain result in neither the neuropathology nor the clinical symptoms of AD. Examination of the neuropathological and neuropsychological findings from patients with long-standing abnormal elevations of brain aluminum indicates that there is no strong association between aluminum exposure and Alzheimer disease risk. Because the primary route for eliminating ingested aluminum is through the kidneys, some patients with renal insufficiency who are exposed to high levels of dietary aluminum and aluminum-containing phosphate binders, accumulate this metal in their brains. Because the brain aluminum concentration of these patients is well above normal and remains elevated over a long time span (ie, years), consideration of the neuropathological sequelae and clinical sequelae in such patients is very relevant to the question of aluminum's involvement in AD.

The neuropathological hallmarks of AD are intraneuronal neurofibrillary tangles, extracellular β-amyloid plaques, amyloid angiopathy, and neuronal loss. Do patients with long-standing

renal insufficiency and increased aluminum intake show more AD pathology than age-matched controls? The brains of 50 such patients were evaluated[18]; the median duration of chronic renal failure was 9.8 years (range, 7 months to 30 years) and of treatment via hemodialysis was 3.2 years (range, 1 months to 14.9 years). Changes characteristic of aluminum exposure were "... lysosome-derived intracytoplasmic, aluminum-containing, pathognomonic, argyrophilic inclusions in choroid plexus, epithelia, cortical glia, and neurons." The degree of morphological change increased with increasing aluminum intake. In contrast, AD-like lesions were not associated with aluminum exposure. The authors concluded: "In our experience, aluminum does not cause an increase in AD morphology, at least not in terms of bioavailable aluminum in drugs or as a result of long-term..." hemodialysis.

Bolla and her colleagues[33] have shown that increased aluminum in the brains of humans also does not lead to cognitive changes similar to that of AD. These investigators evaluated the neurocognitive functioning of patients undergoing dialysis with increased body burden of aluminum but without symptoms of dialysis encephalopathy.[33] Increasing aluminum levels were associated with increasing impairment of visual memory. In addition, in those patients with lower premorbid levels of intellectual functioning, attention/concentration functioning also declined with increasing aluminum levels, while these cognitive functions were unaffected in patients with higher premorbid levels of intellectual functioning. A clinical picture similar to that of AD was not observed.

CONSISTENCY OF FINDINGS

A hallmark of the epidemiological literature concerning aluminum exposure and risk of Alzheimer disease is inconsistency. There have been numerous studies of workers who are occupationally exposed to aluminum in foundries and smelting plants and through welding[34–50] Many of these studies, focusing on various indices of cognitive functioning, reported adverse effects of aluminum exposure.[34–42] Nevertheless, a substantial number of studies, also focusing on various indices of cognitive functioning, reported no adverse effect of aluminum exposure.[43–49]

Not only is there lack of agreement between studies conducted by different investigators, there is also lack of consistency between findings reported by the same investigators. For example, the first study by Martyn et al[50] in 1989 concerned the risk of AD as a function of aluminum concentrations in drinking water. A case–control study was conducted in eight regions of England and Wales as a follow-up of an earlier investigation in which these same authors found that risk varied among populations according to the aluminum concentration in their water supplies. A subsequent confirmatory study was deemed necessary because of weaknesses in the initial investigation, including inadequate estimation of aluminum exposure. This second study, improved through the incorporation of important methodological changes, contradicted the earlier report and found no evidence of increased risk of AD according to aluminum concentration in the water supply.[51] Another important series of epidemiological articles shows similar inconsistency. Rifat et al[52] studied miners from northern Ontario who were exposed to aluminum, as part of a prophylactic program against silicotic lung disease. These individuals inhaled air containing a dust (McIntyre powder) said to be composed of 15% elemental aluminum and 85% aluminum oxide (20,000 to 34,000 parts per million) for 10 minutes preceding each work shift. This program began in 1944 and was ended in 1979 on the basis of the conclusion of a medical panel that the conditions in mines had changed such that silicosis risk had declined to the extent that prophylaxis was no longer necessary. In 1987, the Ontario Ministry of Labor commissioned studies of miners who had been exposed to McIntyre powder to determine whether there was any long-term negative impact on health. In their initial study, Rifat et al[52] reported that, although there was no increased

incidence of neurological disorders in exposed miners, a higher proportion showed cognitive impairment than did the control group of unexposed miners. Nevertheless, there were significant methodological concerns that were prompted by the cross-sectional design of the study, sampling procedures, and statistical analysis. Consequently, the investigators designed a more comprehensive assessment incorporating methodological changes that corrected the weaknesses of the initial study. In contrast to their earlier findings, this follow-up investigation revealed no statistically significant differences between exposed and nonexposed miners with respect to neurological disease or cognitive impairment (S. L. Rifat, P. N. Corey, M. R. Eastwood, D. R. C. McLachlan. Unpublished report to the Ontario Ministry of Labor; 1997). It is noteworthy that the original study was published in the Lancet, was widely publicized, and raised public concerns. The more reassuring findings of the follow-up, although based on more methodologically sound research, were never published in a peer-reviewed journal. Indeed, even a simple letter to the Lancet from the authors to allay the concerns raised by their original article never was published.

APPROPRIATE TEMPORAL SEQUENCE OF EXPOSURE TO AGENT AND OUTCOME

It is critical that an epidemiological study intended to evaluate the role of an environmentally available agent such as aluminum in the development of AD focus on the exposure of the study group during a period of time appropriate to the established natural history of the disease. If a putative role in etiology is at issue, it is critical to have accurate exposure data for the period preceding the onset of the disease; effects of exposure after disease onset may be relevant to questions of disease progression but are immaterial to conclusions about causality.

The cognitive symptoms that result in a diagnosis of AD occur long after the beginning of the disease process. The most authoritative work has been done by Braak and Braak,[53] who concluded that "... decades elapse between the beginning of histologically verifiable lesions and phases of the disorder in which the damage is extensive enough for clinical symptoms to become apparent...." Accordingly, the period of exposure studied in most epidemiological studies of drinking water, 10 years or less preceding diagnosis, corresponds to a point in time well after the onset of the disease. Although the water chemistry at the time of the study is used as a proxy for water chemistry years before, such an approach is not valid. Because of the changes in aluminum concentration resulting from acid rain,[54] simple extrapolation from current chemistry to estimate water aluminum concentrations in the past decades is speculative. Thus, the results of these studies are irrelevant to any questions concerning aluminum's putative role in the initiation of AD. In contrast, findings from the extant epidemiological literature may be relevant to aluminum's possible influence on disease progression rather than etiology. Nevertheless, as previously discussed, the findings from epidemiology, inconsistent and contradictory, do not provide unequivocal support for an effect of aluminum on disease progression.

BIOLOGICAL PLAUSIBILITY

As already discussed, elevated brain aluminum levels in humans produces neither the neuropathology nor the clinical symptoms of AD. In addition, to date, there has been no demonstration that aluminum in in vitro or in vivo models can cause AD-like neurofibrillary tangles or amyloid plaques of the type seen in AD.

In Vitro

In attempting to clarify the mechanisms of AD pathogenesis and aluminum's role therein, Kawahara and Kato-Negishi[55] reviewed the in vitro literature and note that "aluminum is reported to influence more than 200 biologically important reactions and cause

various adverse effects on the mammalian central nervous system . . . ." The authors summarize studies showing these adverse effects, citing well more than 100 articles. Aluminum-induced effects are documented, including disruption of gene expression, cellular functions, phosphorylation and dephosphorylation, protein accumulation, neurotransmitter release, cellular membranes, and membrane channels. Nevertheless, there are two important caveats concerning the relevance of these findings to the Aluminum Hypothesis. First, all of the effects are reported at aluminum concentrations that far exceed those seen in normal individuals or even those persons with disturbed renal function. Second, not a single one of the studies cited indicates that in vitro aluminum can induce pathological changes in animal models that are qualitatively similar to those of AD.

In Vivo

In evaluating the significance of the animal studies of aluminum, there is an important caveat. The toxicokinetics of aluminum in rats, and perhaps other animals used in in vivo research, differ from that of humans. Renal excretion is the primary route of elimination of aluminum, and it is well known that renal insufficiency in humans can result in very high levels of aluminum in the blood. Although kidney function in humans is not overly vulnerable to aluminum, the kidneys of rodents, the animal of choice for most studies, are exquisitely sensitive to the toxic effects of aluminum[56–58] Because urinary excretion is the primary mode of aluminum elimination, kidney dysfunction can result in highly elevated aluminum levels in the blood, producing, in effect, an animal model of dialysis encephalopathy. It is therefore critically important that the effects of aluminum on not only the brain but also the kidneys and other organ systems be carefully scrutinized. In addition, blood aluminum levels must also be measured. The problem posed by lack of information concerning blood or plasma aluminum levels affects both those studies that report adverse effects of aluminum and also those that report no effect.

Most in vivo rat studies assiduously document how much aluminum was administered via diet, inhalation, dermal application, or gavage. Unfortunately, one cannot use this information to determine how much of that aluminum actually reached the systemic circulation. In addition, assessment of kidneys and other organs is rarely attempted. Two notable exceptions are a series of studies conducted by Walton[59–61] and Poirier et al[62]; blood aluminum levels were measured, and effects on kidneys as well as other organs was assessed. In Walton's studies, rats were chronically exposed to dietary levels of aluminum beginning at 12 months of age. About one third of the rats in old age (24 months or older) showed impaired learning, and impaired attention, and all showed aluminum deposition in entorhinal cortex. Neuropathology was also identified in the hippocampus, as well as upregulation of amyloid precursor protein. Poirier at al conducted a " . . . double-blind, vehicle-controlled randomized design by exposing offspring to aluminum citrate in-utero, through lactation, and then in drinking water post-weaning." High doses of aluminum were used, and the following were assessed: motor activity, T-maze, auditory startle, autonomic function, activity, neuromuscular function, sensorimotor function, learning clinical chemistry, hematology, tissue/blood levels of aluminum, and neuropathology. "The most notable treatment-related effect observed in the offspring was renal pathology . . . ." There were no neuropathological changes or cognitive impairments that could be related to aluminum exposure, viz: "None of the lesions seen on histopathological examination of brain tissues of the day 364 group was reported as treatment-related and, as these were also seen in the control group, were likely due to aging." The authors concluded that " . . . these results indicate that concentrations of aluminum in the drinking water that are required to produce minimally detectable neurobiological effects in the rat are about 10,000 times higher than what is typically found in potable drinking water."

The differences between outcomes in the Walton and Poirier studies are typical of the aluminum literature. Clearly, there are methodological differences between the different investigations that could certainly have contributed to the different results. Nevertheless, it is difficult to understand why only one third of the rats in Walton's studies exhibited learning difficulties despite the fact that the same aluminum exposure took place in a genetically homogeneous group of animals. Furthermore, despite using a level of exposure that was significantly higher than that used by Walton, Poirier et al saw no effect other than impaired renal function and age-related changes.

A second problem in the use of animal models is that mice, rats, and rabbits do not develop the types of pathology that are characteristic of AD (neurofibrillated tangles, fibrillated plaques, and amyloid angiopathy). For example, in a series of in vivo studies, Sparks et al[63–65] reported that cholesterol-fed Watanabe and New Zealand rabbits develop amyloid beta protein accumulation in the hippocampus and cortex albeit in the form of diffuse plaques rather than the fibrillated plaques characteristic of AD. The critical factor that triggered these abnormal deposits was the addition of very low concentrations of copper to the animals' drinking water. Neither zinc nor aluminum led to the development of these diffuse plaques. These rabbits also develop neuroinflammatory changes with microglial activation. This reaction is triggered by copper and zinc but not by aluminum. Nevertheless, the level of aluminum exposure was low, only one dose level was used, and the rationale for choosing that particular dose was not provided. More important, it is unclear whether the mechanisms underlying diffuse plaque formation in rabbits bears any relationship to the processes that lead to the formation of fibrillated plaques in people with AD.

An alternative approach has been to use transgenic mouse models with genetic mutations that produce one or more of the pathological lesions characteristic of AD. Nevertheless, the relevance of research that uses transgenics is problematic. It is not known whether the mechanisms underlying the production of AD lesions due to genetic mutations is similar to that of sporadic AD nor if the genetically triggered pathological cascades respond to aluminum in the same way and with the same sensitivity as the neuropathological mechanisms of sporadic AD.

Ribes et al[66] used Tg2576 mice, an animal model of AD in which ß-amyloid plaques start to be deposited at 9 months of age. Animals were administered aluminum lactate via diet from 6 to 9 months of age. Assessment was made of memory and plaque load. The authors concluded that aluminum " . . . did not alter the recognition memory and ß-amyloid plaque loads of Tg2576 mice." Nevertheless, in addition to the aforementioned uncertainty concerning the relevance of this work to sporadic AD, there are additional concerns. There was no measure of blood aluminum levels nor assessment of effects on kidneys. Only one dose level was used, and no rationale was offered for the choice of that particular dose. Still, the aluminum dose was relatively high, and the absence of any effect on deposition of plaques cannot be dismissed.

Akiyama et al[67] studied the effects of long-term oral intake of aluminum or zinc on AD pathology in AßPP and AßPP/tau transgenic mice. The authors reported: "After administration for 4-10 months of approximately 100 mg/kg body weight Al or Zn per day, we were not able to find by quantitative immunohistochemical analyses differences in the deposition of Ab and tau between the treated and untreated groups. Nor did the Al or Zn treatment affect the amount of soluble Ab and Ab*56, an Ab oligomer, measured by ELISA* or immunoblot. The oral intake of excess Al or Zn does not accelerate AD pathology in the transgenic mouse models for Aβ and tau accumulation. Such results do not seem to support the notion that excessive oral intake of Al or Zn is a risk factor for AD." This study suffers from the same uncertainties as the Ribes et al study, albeit to

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*Enzyme-linked immunosorbent assay.

a lesser extent. Like Ribes, there was no direct measure of aluminum absorption. Nevertheless, the authors recognized this limitation and, citing Gómez et al,[68] noted: "A recent study reported increased Al levels in the brain of Tg2576 mice following 6 months oral intake of 1365 mg/day per mouse, a similar condition to that employed in the present study."

A determination of biological plausibility of the Aluminum Hypothesis does not solely rely on work using in vitro and in vivo animal studies. As mentioned previously, patients suffering from renal insufficiency have increased elevations of aluminum in the brain; assessment of clinical symptoms and postmortem studies of neuropathology in such patients does not provide biological plausibility to the idea that aluminum can produce AD.

DISCUSSION

In summary, consideration of the published research concerning aluminum's role in AD indicates that not one of the four Bradford Hill criteria deemed necessary to establish causation with respect to neurocognitive disorders such as AD[32] has been satisfied. Furthermore, the four remaining criteria, dependent on satisfaction of the four necessary criteria, are also not met.

In view of the problematic status of the Aluminum Hypothesis, it is not surprising that most scientists investigating the etiology are focusing on alternative theories. It is therefore reasonable to ask why this theory continues to hold sway with much of the general public and with some public health administrators. History provides some relevant information, but ultimately the answer may lie more in the realm of psychology than in either neuroscience or neurology.

Decades before there were any journal articles suggesting a possible link between aluminum and AD, the idea that aluminum was dangerous was already firmly implanted in the minds of many. What amounts to a crusade against aluminum was initiated by a dentist from Ohio, Charles Truax Betts. Suffering from severe gastritis, Dr Betts reported: "In 1913, I was forced to abandon practice and was informed that I might possibly continue to live three months." On the basis of his belief that he had been poisoned by aluminum, he " . . . discarded all our aluminum (which included everything in the utensil line) and within eight weeks was able to resume practice and have enjoyed good health ever since . . . ."[69] Shortly thereafter he began, what was initially a one-man campaign, to alert the public to what he perceived were the dangers of aluminum. Dr Betts was a tireless campaigner giving numerous public discourses and a prolific writer producing many articles and pamphlets conveying his viewpoint. Although attention was largely focused on aluminum cooking utensils (eg, Betts[70]), he also warned about aluminum in baking powder, water, and other possible sources. In addition to attributing digestive problems to aluminum exposure, Dr Betts also indicated that this metal causes various illnesses, including infertility, heart disease, cancer, blindness, insanity, and assorted neurological disorders. His cause was soon taken up by the Seventh Day Adventists who, through their publication (the Golden Age), gave Dr Betts's ideas wide distribution. These magazines were actively sold door to door; the production figure for 1934 was 2,406,400 and for 1935 was 3,451,300.[71] More than 130 articles about aluminum were published in the Golden Age between 1925 and 1969.[72] In addition to raising public concerns, the campaign against aluminum spawned a profitable new business opportunity—aluminum-free cookware and aluminum-free food stuffs. Typical of those who took advantage of this new source of income was Adolphus Hohensee (active from the 1940s to the 1960s). "Aluminum was the particular bugaboo, a scare doctrine at least half a century old. Hohensee had propagated this theory right from the start. He also denounced the hazards of peeling vegetables with metal knives. Like other fringe operators, he had his own 'safe' tenderizer and Lucite knives to sell."[73]

Thus, the idea that aluminum was dangerous to health had taken root in the public consciousness more than a half century before the 1965 demonstration of AD-like neurofibrillary pathology induced by injection of aluminum salts into the rabbit brain. Although later reinterpreted, the findings of Wisniewski et al[3] seemed at the time to confirm suspicions of chronic toxicity and the uproar over this reinforced previously held beliefs that aluminum was highly toxic. Furthermore, the thriving business in aluminum-free products, which fed off public concerns, continues to this day; its advertising continues to perpetuate the myths from the past.

Nevertheless, it is most likely that the most important factor in maintaining the Aluminum Hypothesis is that the average life span is longer. Because longevity has increased and the incidence of AD increases dramatically with age, the frightening specter of the inexorably deteriorating AD patient (and the emotional and financial costs associated with their care), once fairly uncommon, is now all too familiar to much of the normal population. Although tremendous advances have been made in understanding the pathological mechanisms of this disorder, the etiology is still unclear and the available treatments, although somewhat palliative, are not impressively efficacious. As a result, fear of developing AD is widespread.

Because science cannot explain how AD develops and, more important, offers no effective treatment, the Aluminum Hypothesis, because it would afford a strategy for avoiding AD, remains attractive. That most scientists give little or no credence to this theory is not persuasive, because the dubious reputation of the Aluminum Hypothesis is not well known outside scientific circles. It is likely that the Aluminum Hypothesis will continue until the causes of AD are better understood and effective treatments become available.

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