Aluminum in Alzheimer's Disease and Other Neurological Disorders

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Aluminum: The "New" Mineral

We live in what one leading researcher on the biochemistry of aluminum has called "the Aluminum Age" (44). Aluminum, the third most abundant element in the Earth's crust and the most abundant metal, is one of the most remarkable elements in the periodic table. Objects made with aluminum are strong, durable, light and corrosion resistant. Aluminum is also an excellent conductor of electricity. For these reasons, aluminum currently finds its way into virtually every aspect of our daily lives. Aluminum is used in cans and cookware, aluminum foil, housing materials, components of electrical devices, airplanes, boats, cars and numerous hardware items of all descriptions (27).

Until relatively recently, aluminum was not readily available for use by humans (47) because aluminum is typically bound up in other molecular complexes such as bauxite. Until the 19th century, animals and humans did not usually come into direct contact with elemental aluminum or aluminum bound up in bauxite (27). But, this has dramatically changed. Aluminum is now found in drinking water, is a common additive to various processed foods, is added to cosmetics of many types, and, increasingly, shows up pharmaceutical products. As a result, aluminum is increasingly found in our bodies (46, 69, 86, 146).[1]

And, because aluminum can cause strong reactions in living things, the widespread use of aluminum has far reaching health implications for humans and other animals. In fact, growing evidence shows that aluminum seems to be toxic to basically all animals including humans (44).

The likely toxicity of aluminum is not a new idea: Dr. William Gies who had accumulated data from seven years of experimental testing in humans and animals on the effects of oral consumption of aluminum salts used primarily in baking powders and food preservatives wrote in 1911:

"These studies have convinced me that the use in food of aluminum or any other aluminum compound is a dangerous practice. That the aluminum ion is very toxic is well known. That aluminized food yields soluble aluminum compounds to gastric juice (and stomach contents) has been demonstrated. That such soluble aluminum is in part absorbed and carried to all parts of the body by the blood can no longer be doubted. That the organism can 'tolerate' such treatment without suffering harmful consequences has not been shown. It is believed that the facts in this paper will give emphasis to my conviction that aluminum should be excluded from food." (66).

Now 100 years after Gies' prophetic comments, it may be long overdue for the scientific community to revisit the notion of aluminum toxicity, in particular in relation to a spectrum of neurological diseases such as Alzheimer's, Parkinson's, ALS and autism spectrum disorders (ASD).

Aluminum and its Interactions with Animals and Humans

As noted above, aluminum is the third most common element in the Earth's crust, but most of the aluminum has not come into contact with humans until the last 100 years (45). This situation changed dramatically during the last half of the 19th century when aluminum salts began to be used routinely in the dyeing of fabrics and in food preservation (10, 27,135, 150). We still process various vegetables with aluminum potassium sulfate and this ingredient can be seen on the label of pickles at the supermarket (27). Aluminum routinely shows up in infant formula, where it may represent a contaminant in the production process (25), in cheese, bakery products, ready-made cake mixes, soft-drinks etc., as well as in less processed products such as coffee and tea (112, 135). It may also enter the body through the use of aluminum cookware and packaging (10). Aluminum also shows up in various cosmetics, as an antiperspirant in many commercial deodorants, and in a variety of medicinal formulations (27, 43, 69, 135). Antacids also contain high levels of aluminum hydroxide (27, 105).

Most of the aluminum that enters the human body comes through the food we eat. A smaller amount enters through the skin, such as in antiperspirants. Both of these routes would put aluminum into the circulatory system relatively quickly and most of this aluminum would likely be rapidly removed by the kidneys (135). The exceptions to this would be: 1) those who lack adequate kidney function; 2) infants who are born with immature kidney function until age one (33,137); 3) the elderly who have decreasing kidney function as they age (137). It is these three groups that are most susceptible to aluminum accumulation in the body.

Vaccines and Aluminum

Aluminum is added to vaccines to help the vaccine work effectively (77) but unlike dietary aluminum which will usually clear rapidly from the body, when aluminum is used in vaccines and injected it is more likely to remain there.[2] The relatively long persistence of aluminum from vaccines in the body is one of the key reasons it is used: It not only directly stimulates the immune response, but it also does so over prolonged periods (136, 137). The problem with vaccine-derived aluminum is really two-fold: It drives the immune response even in the absence of a viral or bacterial threat[3] and it can make its way into the central nervous system.

In the early part of the 20th century vaccine researchers tried to add compounds in the hope of making vaccines more effective. In 1926, Glenney and colleagues first experimented using aluminum salts in vaccines and the aluminum worked so well at strengthening the vaccine it is still used today (68). Unfortunately, the aluminum salts don't appear to have ever been tested for safety then, or now.

Safety concerns for aluminum in vaccines are twofold: First, the very real toxicity of aluminum compounds. Second: is the more general issue of the type immune response elicited, in particular if the aluminum induces either allergic or abnormal autoimmune responses, which are now considered by some investigators to play a role in Guillan-Barre disease, multiple sclerosis, and Gulf War Syndrome (11).

The damage may arise because aluminum may not only be an immune system booster, but may also suppress the immune system and leave the body exposed to other infections.

Aluminum and Autism Spectrum Disorders (ASD)

"Autism spectrum disorders" or Autism describe brain disorders that arise in infants or young children. Autism is characterized by delays in speech development and social functioning [91]. By some estimates, in North America there has been a sharp increase in the prevalence of autism by as much as 2000% since the early 1990s [137]. A countervailing viewpoint is that autism has not changed in its yearly incidence over the last 20 years and that any apparent increases are due to (a) more doctors diagnosing the conditions [80] and/or (b) greater awareness by parents and pediatricians of autism, (c) an increase in the general population, and (d) a changing gene pool.[4]

The most conclusive data [92] clearly shows that autism prevalence has been increasing with time, as shown by higher prevalence among younger groups. If we accept that autism rates have indeed increased since 1992, it seems reasonable to believe that some environmental factor, or various genes, may be responsible. What that factor(s) is remains unknown, but the increase in various toxins in the human environment seems a likely starting point.

"The FDA sets an upper limit for aluminum in vaccines at no more than 850 µg (microgram)/dose, however this amount was selected from data showing that aluminum in such amounts only enhanced the immunizing power of the vaccine. The FDA has not done any testing on the toxicological and safety issues of adding aluminum to vaccines."

Clearly, there will be many such toxins to consider with a focus on those to which children might reasonably be exposed. Given the almost universal increase in the number of vaccines children routinely receive during their formative years [137, 138], and given the demonstrated toxicity of at least some vaccine ingredients, much speculation has focused on two key vaccine components: mercury in the form of the preservative ethyl mercury (trademarked as Thimerosal) and aluminum, the most common vaccine additive [32, 33, 34, 60, 74, 137, 138]. Mercury's potential role in ASD has been widely discussed in the literature [17, 63, 160].

As cited in Tomljenovic & Shaw [136, 137, 138], aluminum salts are commonly added to vaccines. According to the Food and Drug Administration (FDA), vaccines represent a special category of drugs as they are generally given to healthy individuals and "this places significant emphasis on their [vaccine] safety" (FDA, 2002). The FDA sets an upper limit for aluminum in vaccines at no more than 850 µg (microgram)/dose [15], however this amount was selected from data showing that aluminum in such amounts only enhanced the immunizing power of the vaccine. The FDA has not done any testing on the toxicological and safety issues of adding aluminum to vaccines [15].

"The data sets, graphed against each other, show a strong and statistically highly significant link between the number vaccines with aluminum and the changes in autism rates. Furthermore, these data showed a significant link exists between the amounts of aluminum given to preschool children and the current rates of autism in seven Western countries. Those countries with the highest level of aluminum-adjuvanted vaccines had the highest autism rates."

Recently Tomljenovic and Shaw [137] conducted a study to compare recommended vaccine schedules by the Centers for Disease Control and Prevention (CDC) for children's vaccines in the United States in the period from 1991 to 2008 to changes in autism rates during this same period (US Dept. of Education) (original references in 137).

The data sets, graphed against each other, show a strong and statistically highly significant link between the number vaccines with aluminum and the changes in autism rates. Furthermore, these data showed a significant link exists between the amounts of aluminum given to preschool children and the current rates of autism in seven Western countries. Those countries with the highest level of aluminum-adjuvanted vaccines had the highest autism rates. This link was the strongest at 3 to 4 months of age, a period when rapid growth of the child's central nervous system was impacted by autism. These include rapid growth of the synaptic connections between cells (synaptogenesis), maximal growth velocity of the region of the brain responsible for short term memory and the onset of growth of the amygdala, which is involved in social interactions [111]. In addition, the period between 2 and 4 months in children also sees the development of neural systems for sleep, temperature regulation, breathing and brain wave patterns [70]. Many of these brain functions are impaired in autism (i.e., sleeping and brain wave patterns [12, 107, 108]). The link between the administration of vaccines with aluminum and autism appears to be very strong. In fact, the link was further tested using Hill's criteria and it met eight of nine conditions which means that vaccines containing aluminum are highly likely to be at least partially causal for autism.[5]

While the FDA does recognize aluminum as a potential neurotoxin, this concern does not appear to be present in regard to children's vaccines. The reason for this is that vaccines (and vaccine ingredients) have not been historically viewed as toxic by the FDA [50]. Such lenient views with respect to vaccine safety are of significant concern for a variety of reasons:

- Aluminum is highly neurotoxic as demonstrated in various studies and can impair prenatal and postnatal brain development in humans and experimental animals [20, 151].

- A pilot study showed higher than normal aluminum levels in the hair, blood and/or urine of autistic children (86).
- Children are regularly exposed to much higher levels of aluminum in vaccines per body weight than are adults (136).
- Practically nothing is known about the pharmacokinetics and toxicodynamics of aluminum in vaccines in children (37).
- Aluminum in vaccines have been linked to serious neurological impairments, chronic fatigue and autoimmunity (2, 11,29, 49, 77, 123, 138, 161).
- Injection of vaccines with aluminum at levels comparable to those that are administered to humans have been shown to cause motor neuron death (cited below in the section on ALS and aluminum), impairments in motor function and losses in spatial memory capacity in young mice (104, 121).
- Finally, injections of aluminum vaccines in 4-week old mice was followed by a transient peak in brain aluminum levels on the second and third days after injection (110). For example, in experimental models, repeated injections of 1 mg/kg of aluminum nanoparticles to adult Sprague–Dawley rats is sufficient to produce significant inflammatory effects in the rat brain (85). It is worth noting that comparable amounts of aluminum are administered to 2, 6 and 15 month old infants according to the US vaccination schedule (137).

All of these data point to the overall plausibility of aluminum from vaccines playing at least a partial role in autism.

A common assertion made about aluminum in children's vaccines is that children obtain much more of this element from diet and hence that the small amount in most vaccines does not represent a significant risk factor (94). However, this notion contradicts basic toxicological principles because aluminum which is injected bypasses the kidneys and other filtering systems and thus will likely require a lower dose to produce a toxic outcome (136, 137). In the case of aluminum, only ~0.25% of dietary aluminum is absorbed (157), while aluminum hydroxide (the most common form of aluminum used in vaccines) when injected may be absorbed by the body at nearly 100% efficiency over time (158). In addition, although the half-life of aluminum consumed through the diet is short (approximately 24 hours), the same cannot be assumed for aluminum in vaccines because the molecular size of most aluminum in vaccines (24 to 83 kDa (137)) is higher than what the human kidney or other bodily filtering systems can process (~18 kDa (44)). In fact, the pharmaceutical industry, specifically designs aluminum molecules in vaccines to be larger so they can stay in the body for a long time and enhance the power of the vaccine (33, 136). Additionally, the tightness of bonding between the aluminum adjuvant and the antigen is considered a desired feature that can be used to predict the efficacy of vaccines (36).[6]

Only two subcutaneous injections of the adjuvant aluminum alone (relevant to adult human exposure) in young male mice, spaced two weeks apart, can cause dramatic activation of the brain's innate immune cells (microglia) and support cells (astrocytes) that lasts up to 6 months. These injections also cause motor neuron death, impairments in motor function and loss of spatial memory capacity (104, 121). What then might be the effects of repeated, closely spaced administration of vaccines with aluminum (i.e., every 2–4 months from birth up until 12 months of age) in human infants who are given vaccines with aluminum every 2–4 months up until one year old?[7]

Thus peripheral immune damage can directly stimulate dangerous inflammation within the brain (18), even in the absence of a direct central nervous system infection. Moreover, inflammation due to vaccines with aluminum has been shown to be elevated in the blood, cerebrospinal fluid (CSF) and brain tissues of autism patients. The inflammatory profile in autistic brains was found concurrently with widespread activation of various glial cells in the central nervous system, namely activated microglia and astrocytes.[8]

Experimental evidence clearly shows that two to three injections of vaccines with aluminum can overcome the genetic resistance to autoimmunity in animals (115). While currently there is no direct evidence that aluminum can induce autoimmunity in humans, it is important to recognize that it certainly has a biochemical potential to do so. Autoimmune disorders, particularly those affecting the central nervous system, are common in autistic individuals do not appear to be limited to only a few nervous system antigens. For example, Vojdani and colleagues (115) demonstrated elevated levels of immunoglobulins (Ig)G, IgM and IgA against nine different neuron-specific antigens in ASD children. Such widespread manifestation of autoimmunity may have arisen from an alteration in the blood brain barrier (BBB) which would then have enabled access of immune-competent cells to many different CNS antigens (115).

The BBB in the human body serves to separate the blood circulatory system and the central nervous system. Aluminum has been shown to disrupt this barrier.[9] From all of the above evidence, it seems clear that the link between aluminum in children's vaccines and autism deserves the immediate attention of the medical and scientific community.

While aluminum exposure in children related to vaccines is a growing concern, it is important to recognize that children are also highly exposed to dietary sources of aluminum whose impact on the developing nervous system may be severe. Infants are at particular risk, as are all those under 5 years of age, as young children's unique physiology makes them more vulnerable to toxic insults compared to the adult population (31, 138).

Aluminum and Lou Gehrig's Disease (ALS)

Amyotrophic lateral sclerosis (ALS), best known as Lou Gehrig's disease after the famous baseball player who died from it, is a disease of still unknown origin that targets the neurons controlling motor function. These motor neurons can be inside the brain or within the spinal cord. Typically, at end stage disease, both sets of motor neurons are destroyed and the victim is unable to use their arms or legs. The disease is progressive and results in greater loss of function over time. The typical age ALS starts is mid-50s to 70s and the survival time after diagnosis is from 3 to 5 years. Death is usually due to respiratory failure. Many ALS victims show a significant loss of brain function as well at the latter stages of the disease.

About 90% of all ALS cases arise from unknown factors while 10% are "familial," meaning they show a genetic linkage. In familial ALS, the best studied gene is one coding for the protein superoxide dismutase (SOD) and the numerous mutations that change the outcome to what is termed a "toxic gain of function" mutation. Of the 90% of sporadic cases, the current view is that some environmental toxins, alone or in synergy with still unknown "susceptibility" genes, are to blame. What these toxins might be is controversial [120].

Some of the strongest evidence for an environmental toxin causing ALS has come from studies of the two historic geographic clusters of ALS parkinsonism dementia complex (ALS-PDC) in Guam and the Western Pacific and the ALS associated with Gulf War Syndrome. Neurologists in Guam noted an extremely high incidence of what appeared to be almost classical ALS amongst the indigenous Chamorro population. A second disorder, PDC, described a form of parkinsonism with an associated dementia. Approximately 10% of all patients in Guam developed both the ALS and PDC disorders, usually with the ALS appearing first [82].

The cause of the disorder in Guam was narrowed down to two items: toxins the seed of the cycad palm which the Chamorro people once frequently ate, and abnormally high aluminum in the soil and water in southern Guam [62]. These data remain controversial but clearly point to a potential link between aluminum and ALS.

"Gulf War Syndrome," is a range of disorders among veterans of the Persian Gulf War (1990–1991) characterized by a group of symptoms such as fatigue, muscle and joint pains, emotional disorders, posttraumatic stress reactions, headaches, and memory loss [57, 72]. The key features associated with Gulf War Syndrome are: Syndrome One consisting of "Fatigue/Depression" (also termed "Impaired Cognition" by other researchers) and includes excess fatigue and concentration and memory problems, anxiety, depression, and sleep disorders. Syndrome Two is "Neurological", and includes blurred vision, concentration and memory problems, irregular heartbeat, loss of balance and dizziness, speech difficulties, sudden loss of strength, and tremors and shaking. Syndrome Three is classified as "Musculoskeletal/ Rheumatologic", which includes generalized muscle aches, joint aches, numbness in the hands and feet, and swelling in the joints and in the extremities. Syndrome Two was particularly of interest for the neurological disease community since four of seven symptoms are consistent with early phases of ALS (loss of balance and dizziness, slurred speech, sudden loss of strength and muscle weakness, especially of the arms and legs, and tremors and shaking).

The suggestion that ALS might be part of Gulf War Syndrome became clear in 2003. First, the numbers of ALS cases were three times higher with Gulf War Syndrome sufferers than in the general population. Secondly, Gulf War Syndrome/ALS victims were far younger than those with classical ALS: age 20s to 30s instead of the normal North American onset age of 50s to 70s. The age shift was consistent with a pattern familiar from the variety of forms of ALS-PDC of the Western Pacific: As incidence levels increased, age of onset tended to decrease.

Studies of Gulf War ALS and GWS in general have suggested several potential environmental factors such as exposure to depleted uranium [58, 122], nerve gas [79, 118], organophosphates [1, 83], vaccines [76], heavy metals [52], and bacterial infections [93, 131]. Some genetic susceptibility factors have also been considered and could work in concert with various toxins [120].

However in recent years, increased scrutiny has focused on vaccines, in particular the anthrax vaccine which contained aluminum [AVA; 90], because vaccinated US troops who never went to Iraq have developed Gulf War Syndrome symptoms identical to those who were deployed. Soldiers from the United Kingdom who also received the anthrax vaccine with aluminum showed increased psychological distress and chronic fatigue compared with those who didn't get the vaccine [139]. French soldiers participating in the war did not receive the anthrax vaccine but did show some GWS related disorders (respiratory, neuro-cognitive, psychological, and musculoskeletal), but no ALS symptoms were reported [117].

Besides containing aluminum, anthrax vaccine also contains the lipid polymer squalene (a precursor to cholesterol), in some lots of the vaccine [103]. However, manufacturers of the anthrax vaccine along with the US Department of Defense and other government agencies, deny that squalene was ever part of the formulation of the anthrax vaccine during the period in question.[10]

To explore this now unusual ALS epidemic among Gulf War Syndrome victims investigators injected aluminum hydroxide, squalene, or both, into young, male colony mice. The mice were tested with various brain and behavioral tests over 6 months [104, 121]. The mice injected with aluminum hydroxide showed a 50% decrease in muscular strength and endurance compared with normal mice. Aluminum-injected mice also showed a 138% increase in anxiety levels and mice injected with aluminum and squalene had significant late stage long-term memory loss. A second study confirmed a clear loss of spatial memory capabilities in aluminum-injected mice [121].

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Mice injected with aluminum hydroxide showed a significant increase in cell death in the spinal cord and motor cortex, primarily affecting the motor neurons as well as inflammation in the spinal cord and motor cortex.

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The studies demonstrated that severe behavioral motor deficits and the loss of motor neurons throughout the nervous system resulted when aluminum was injected into mice. The effects closely resembled the damage seen in the motor areas mice used to model ALS-PDC of Guam and, in addition, looked a lot like the pathological outcomes in human ALS (120).

The available data on Gulf War Syndrome seem to point at the anthrax vaccine and its aluminum content of the anthrax vaccine as one of the strongest links to ALS. The neurological signs and symptoms, especially those for the ALS subgroup, are a good match to signs and symptoms of aluminum neurotoxicity. For example, dialysis solutions containing aluminum had been linked to an Alzheimer's–like disorder termed "dialysis-associated encephalopathy/ dementia" (DAE) (cited below in the section on Alzheimer's disease and aluminum). In animals, aluminum neurotoxicity has been well established, and appears to be particularly harmful to neurons that make the neurotransmitter acetylcholine, for example, motor neurons in the brain and spinal cord.

Additional evidence exists for aluminum's role in various central nervous system disorders, including multiple sclerosis associated with aluminum hydroxide injections that produce a persistent muscle inflammatory response termed macrophagic myofasciitis (11, 65).

Other studies using even smaller amounts of aluminum hydroxide describe the pathway of aluminum from the muscle into the brain. In brief, these studies show aluminum hydroxide is carried from the site of injection in the muscle to the draining lymphatic system. Once there, the aluminum is carried into the central nervous system (64).

Aluminum and Parkinson's Disease

There are only two geographic clusters of parkinsonism: 1) on Guam with the form called parkinsonism dementia complex, or PDC. 2) on the Caribbean island of Guadeloupe and is associated with the consumption of a local fruit called the soursop. Although there is currently little data on the potential impact of aluminum and Parkinson's disease, aluminum in cell cultures have been shown to lead to some of the same mis-folded protein accumulations as seen in the human Parkinson's (140). Exploring the potential role of aluminum in Parkinson's is likely to be a fruitful area for future research.

Aluminum and Alzheimer's Disease

The potential link between aluminum, in various forms, and Alzheimer's disease has been the subject of speculation for decades. The first case of Alzheimer's was reported in Frankfurt, Germany about 20 years following the widespread use of aluminum products. The discoverer for whom the disease is named, Alois Alzheimer, wrote that,

> "The case presented even in the clinic such a different picture, that it could not be categorized under known disease headings, and also anatomically it provided a result which departed from all previously known disease pathology" (5).

In other words, it clearly was a new and emergent disease. A rare disease as late as the 1920s, Alzheimer's is now one of the most prominent neurodegenerative disorders and a leading cause of dementia, impacting some 24.3 million people worldwide (see 135), more and more people are being diagnosed with Alzheimer's and the increase is not solely attributable to an aging population. Alzheimer's disease is characterized by a general loss of cognitive function, including memory. The brains of Alzheimer's victims contain amyloid "plaques" and neurofibrillary tau protein "tangles and in various parts of the brain there is significant neuronal loss. Various studies have shown the presence of aluminum associated with neurofibrillary tangles of neurotoxic tau protein (98, 146). Although such association could be coincident, the link certainly suggests a primary role in the Alzheimer's process. Although discounted in recent years, the notion that aluminum could be a contributing factor in Alzheimer's disease has begun to gain momentum. An extensive review published in 2011 (135) documents, that aluminum is toxic to plants, animals and humans.[11] Before the 1880s when aluminum began to be widely used various industrial and other commercial applications (106) aluminum could not easily impact humans because it could not be easily absorbed by human tissue (10, 27). An exception to this would be that aluminum changes from solid to liquid phase at low pH values. Such might occur due to acidic conditions in soil or water (10, 14, 27, 153) the latter (as cited above) a potential etiological factor in the Guamanian disease spectrum, ALS-PDC.

A particularly compelling neurological syndrome highlighting the potential role of aluminum in Alzheimer's disease arose with descriptions of "dialysis associated encephalolopathy" (DAE). In this disorder, patients with insufficient kidney function had sometimes inadvertently received dialysis fluids containing high levels of aluminum (4). DAE showed many of the characteristics of Alzheimer's disease, both behaviorally and pathologically (135). The overall list of behavioral outcomes included speech abnormalities, tremors, impaired psychomotor control, memory loss, impaired concentration, behavioral changes, epileptic seizures, and coma and even death. The latter severe outcomes occurred from three to seven months following the onset of the overt manifestations of the disorder (3, 4, 55, 153). The behavioral abnormalities were worse either during or immediately after a dialysis sessions (4, 55) and, conversely, those affected showed rapid improvement when aluminum was removed from the dialysis fluid. It is highly significant that DAE as a clinical syndrome vanished once aluminum was removed from dialysis solutions (4, 55). In cases that went to autopsy, high levels of aluminum in the brain were demonstrated, as well

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as amyloid β accumulations, the latter a typical hallmark of Alzheimer's disease [35, 73]. Admittedly, DAE was an extreme example of the potential negative impact of aluminum entering the circulatory system and then the central nervous system, but it clearly established the neurotoxic potential of aluminum. In particular, the relevance to chronic neurological disease lay in the ability of aluminum to induce behavioral and pathological features typically associated with Alzheimer's.

Epidemiological studies examining ground water and Alzheimer's incidence levels found a link between dietary consumption of aluminum and the disease [54, 88, 113]. While these studies were not later supported by further work, the notion of such a potential linkage raised concerns especially about aluminum in water sources, primarily aluminum sulfate, which is used to reduce organic matter in water [27]. Even more concerning, aluminum sulfate can increase the levels of the more toxic soluble forms of aluminum in the treated water as well [27, 124, 162]. In fact, a survey of 186 randomly selected community water supplies in the USA, by Miller et al. [89] revealed that there was a 40 to 50% chance that the total aluminum content in the treated water would be above the original content of un-treated water.

Aluminum sulfate when combined with fluoride, which is a common additive to municipal water supplies, can be especially dangerous to humans because this chemical combination can be easily transported across the Blood Brain Barrier. In rats, dietary exposure to aluminum and fluoride complexes causes severe damage to cerebrovascular endothelia and neurons, in a region-specific manner reminiscent of Alzheimer's disease [144].

A number of studies have linked elevated aluminum levels to an increased risk of cognitive impairment and Alzheimer-type dementia [54, 87, 113, 114], especially in conditions of low silica content [78, 114]. Experimentally, Campbell et al. [26] showed that exposure to even low levels of aluminum (0.01, 0.1, and 1 milimolar) in drinking water for 10 weeks increased inflammatory processes selectively in mouse central nervous system, and increased Alzheimer's cases in regions where the concentrations of the element are elevated in water supplies [54]. Similar studies by Walton in aged rats showed significant cognitive impacts and pathological features following prolonged exposure to aluminum chloride in water [150]. Treated animals showed significantly impaired performance in learning and memory tasks. Other behavioral changes in rats exposed to aluminum at human dietary levels included confusion and repetitive behaviors [149, 150].[12, 13]

In regard to oral/dietary exposure, a number of experimental studies have demonstrated that aluminum at levels "typically" consumed in an average "Western diet" over an extended period of time, produces strikingly similar outcomes (less seizures and mortality) to those induced by intracerebral injections of aluminum salts in rodents to [147, 149]. As Tomljenovic notes, the most recent and elaborate toxicological report for aluminum prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) reports that, "There is a rather extensive database on the oral toxicity of aluminum in animals. These studies clearly identify the nervous system as the most sensitive target of aluminum toxicity" [135].

Other sources of aluminum include those from various over the counter and prescription medicines, including the antacids [27, 105], from cosmetics and from antiperspirants [27, 41, 69] as well as vaccines [136, 137]. Any or all of these can contribute to the overall body burden of aluminum in humans and can be significant contributing factors to Alzheimer's disease.

Removal of Aluminum from the Human Body

If indeed aluminum plays a role in various neurological disorders across the lifespan, then there are two obvious solutions, albeit of differing levels of complexity. The first minimize exposure to all forms of bioavailable aluminum. This can be done by avoiding food and water with high aluminum content and limiting the use of aluminum-adjuvanted vaccines. While such procedures may prevent future disease, they cannot address those for whom aluminum is already present in their bodies. This latter issue is one that can only be resolved by the removal of aluminum by some form of chelating agent.

"Of particular interest may be silicate compounds such as those found in some varieties of mineral water. A 2005 study by Gillette-Guyonnet and colleagues found better mental performance in women who drank mineral water high in silica and a reduced rate of Alzheimer's disease. Silica is known to complex with aluminum and aid in its removal."

A number of aluminum chelators have been described in the literature over the last few decades. Of these, perhaps desferrioxamine (DFO) is best known [154, 156], although issues of safety and efficacy have been raised. A number of other candidate chelators have also been described [154], 3-hydroxypyridin-4-ones being considered to be preferable to DFO in both regards. Others include ascorbate and Ferralex-G [81]. Of particular interest may be silicate compounds such as those found in some varieties of mineral water [45]. A 2005 study by Gillette-Guyonnet and colleagues [67] found better mental performance in women who drank mineral water high in silica and a reduced rate of Alzheimer's disease. Silica is known to complex with aluminum and aid in its removal.

Overall, given the aluminum "body burden" most of us likely claim from years of aluminum exposure, it may well be important to reduce this burden in the body before it can cause the various neurological and other disorders typically associated with aging.

Emerging Issues and Summary

The current review has demonstrated a range of neurological disorders that might arise due to exposure to aluminum. Two broad categories have emerged from this analysis: neuro-developmental and age-related neurodegenerative. These outcomes are temporally separated. There are clear caveats to

both category and time of occurrence. For example, although ASD is clearly a neuro-developmental disorder, neuronal damage may also occur. Further, we do not yet know if such damage to cells in various parts of the CNS will play out as a precursor to ALS, Parkinson's, or Alzheimer's diseases during aging. Indeed, it might be wise to expect that such sequelae might well occur.

One aspect that separates the two ends of the aluminum-induced neurological disorder spectrum is the route of administration, that is, injection vs. oral. The first can be expected to have relatively rapid effects that, depending on age, can range from days to years. The latter may take years to reach a critical body burden or to trigger the end state outcomes, the latter likely the result of a cascade of pathological events. But, as above, these may not be hard and fast rules. For example, injected aluminum adjuvants in adults can trigger forms of cognitive impairment (96).

All of the various sources of aluminum in the human environment should, cumulatively, increase our concern for the potential long term impacts of aluminum in human health, most particularly as it may impact the types and incidences of various neurological disorders. As the above material has demonstrated, aluminum has the potential to impact the CNS at various phases of life: In infancy and early childhood, aluminum from various sources, including vaccine adjuvants, may play a decisive role in the dramatic increase in ASD. At older ages, aluminum may contribute to various neurodegenerative disorders including ALS, Parkinson's and Alzheimer's disease. Aluminum is also likely to play a role in various autoimmune disorders and in a series of vaccine adverse reactions (123, 138). In regard to the latter, it may be notable that aluminum adjuvants have recently been found to complex with viral DNA in human papilloma vaccines (S.H. Lee, personal communication) and could possibly be associated with the abnormally high percentage of adverse events with these vaccines.

There is still much we don't know about the impact of aluminum in neurological disease and hence much research remains to be done. However, a critical scrutiny of the available evidence suggests that we need to pay a great deal more attention to the possibility that aluminum may be involved in such disorders if we hope to prevent them in the future and to provide relief from those currently afflicted.

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End Notes

1. None of this would necessarily be a problem if aluminum were actually inert in biological systems. However, in spite of a widely held belief that this is true, it is demonstrably not the case. Aluminum is highly reactive with oxygen and carbon, two of the most abundant organic elements, yet appears to have no intrinsic or beneficial role in organic chemistry of *any* biota on the planet (44, 46). This may seem surprising, but Exley has strongly argued that aluminum has simply been selected out of biological evolution on Earth and thus has no known role in essential biochemical reactions (45).

2. Vaccines that use live viruses do not require aluminum, but many other vaccines do, especially those based on killed or weakened (attenuated) viruses or bacteria that are incapable of replication and hence unable to induce the disease they are designed to prevent. Examples of the types of vaccines which contain aluminum are hepatitis A and B (HA, HB), diphtheria/tetanus/pertussus (DTP), meningitis C, and Haemophilus influenza (HIB), amongst various others.

3. The theory in immunology and the application in vaccine research and development is that the antigen will retain the ability to induce a full and lasting immune response (15). The problem is that vaccine antigens don't fully do so, a fact that has been well known for almost 90 years. This problem leads directly to the need for one, or more, adjuvants (15,77). Adjuvants work by providing a link between the innate and adaptive immune systems (24, 77, 137). An adjuvant has typically also been thought to allow better presentation of the antigen to the immune cells of the body, by the "depot effect" which provides a slow release of the antigen over time. Current research however suggests that the mechanisms of adjuvant action are far more complex than initially thought (38). In particular, the immuno-stimulatory properties of aluminum adjuvants are numerous and affect both innate and adaptive immune responses (38, 48, 77, 97). Although all of these mechanisms of action seem likely to account for the immuno-stimulatory properties of adjuvants, their overall role in the immune system response remains surprisingly unclear (24, 37, 48).

4. Such changes would not account for yearly changes of approximately 20% in the intervening years. The notion of greater awareness is likely at least partially correct, but its impact on disease incidence cannot currently be determined. As for the general population argument, the population of the US has indeed increased in the last 20 years, but by less than 20% (US Census Bureau). However none of the reasons cited above explain the dramatic increase in autism.

5. We note that a more definitive study would be a "case control study," considered the gold standard in the field. However, given

the resources available to us at the time, the study discussed above still serves as a hypothesis generating study and thus has value in its own right.
The level of correlation we observed, however strong, does not necessarily mean causality. Indeed, many highly significant but spurious, correlations in the general medical literature have been demonstrated over the years. For example, during the same period, a number of factors impacting children could also have been changing that really have nothing to do with ASD rates. Any of these could, in principle, have been responsible for the changing incidence of the disorder. To address this concern, we applied Hill's criteria (75) to our analysis. Hill's criteria were designed to try to establish if in the relationship between two variables, one could be shown to be causal to the other. Applying the Hill criteria we found a highly statistically significant correlation between the CDC vaccine schedules of aluminum-adjuvanted vaccines and ASD rates (satisfying Criterion 1), the data were consistent (Criterion 2), and in addition demonstrated a biologically plausible mechanism by which the impact could be achieved (Criterion 6). Additionally, there was an appropriate temporal relationship between the proposed cause and the outcome (Criterion 4). Overall, these four criteria are considered sufficient in neuropsychiatry (141) to support the notion that the two events may indeed be causally related. Our results satisfy not only all four of these criteria, but also four others. These additional criteria are: biological gradient (5), coherence with the current knowledge (7), experimental or semi experimental evidence (8), and the analogy with similar evidence (9). The only criterion that our current study fails to satisfy is the "specificity" criterion which is actually not applicable to ASD given that the latter is recognized as a multifactorial disease (95,109, 132, 133). Overall, an analysis of our results indicates that the adjuvant effect of aluminum in vaccines may be a significant etiological factor in the increasing prevalence of ASD in some Western countries, including the US.

6. Experiments in adult rabbits demonstrate that even in an antigen-free form, aluminum hydroxide is poorly excreted. Finally, it is important to recognize that neonates have anatomical and functional organ (e.g., an immature renal system and blood brain barrier (10, 33), which would further compromise their ability to eliminate aluminum adjuvants. Additionally, the autoimmune conditions (many of which are typical of the "autoimmune syndrome induced by adjuvants" (ASIA)) are thought to be driven by a hyper-active/unrestrained immune response (40,152) and may be related to aluminum adjuvants in vaccines. This area of autoimmune disease research is rapidly expanding due to the pioneering work of Shoenfeld and colleagues and promises new insights into direct and indirect aluminum adjuvant impacts on the CNS (2, 123).

7. Neuroinflammatory mechanisms appear to play an important role in the pathophysiology of autism (95, 142).

8. In particular, microgliosis in autism coincided with increased immunoreactivity to MHC class II markers (142). Microglia, astrocytes, as well as members of the MHC and the complement cascade are crucial regulators of synaptic connectivity, function and plasticity and play key roles in establishing and modulating neuronal circuitry in the developing CNS (22, 23, 39, 56, 61) and abnormal brain connectivity is well recognized as one of the hallmarks of autism (16, 163). Cerebellar Purkinje cells, which are significantly reduced in autism, are a site of prominent MHC class I expression. One hypothesis is that specifically timed changes in neuronal MHC class I expression could contribute to autism (16). Given that aluminum adjuvants activate both MHC class I and II components of the complement cascade, increase pro-inflammatory cytokines as well as activate microglia and astrocytes in the brain, it is possible, indeed likely, that these may also interfere with synaptic pruning and developmental activity-dependent synaptic remodeling/plasticity.

9. Aluminum can increase BBB permeability by increasing the rate of trans-membrane diffusion and by selectively altering saturable transport systems (13, 155). Thus, contained in a vaccine, aluminum can enter the brain (Redhead et al., 1992). Finally, aluminum's ability to up-regulate chemo-attractants such as monocyte chemoattractant protein (MCP)-1, monocyte inflammatory protein (MIP)-1α and MIP-1β (119), could potentially promote the active recruitment of immunocompetent cells into the brain, leading to inflammation and/or autoimmunity. In fact, autopsy analysis of six children aged 4 to 17 months that died within 48 hours of exposure to vaccines with aluminum showed abnormal pathologic findings in the nervous system, including a defective Blood Brain Barrier and infiltration of aluminum into the brain, infiltration by macrophages and lymphocytes, perivascular lymphocytic infiltration, diffuse infiltration of these cell types into other regions including the mesencephalon and cortex by T-lymphocytes, and the presence of activated microglia in the hippocampus and pons (164). The neuropathological observations made by Zinka and colleagues (164) are thus consistent with the well-established immunostimulatory and neurotoxicological properties of vaccines with aluminum.

10. Antibodies to squalene have been demonstrated in many soldiers with Gulf War Syndrome (8). The origin of the reported squalene that might act to trigger antibody formation remains uncertain.

11. The types of exposures cited above are in keeping with the increased bioavailability of aluminum in the human environment. Exley and colleagues (47) note that, "In the absence of recent human interference in the biogeochemical cycle of aluminium the reaction of silicic acid with aluminium has acted as a geochemical control of the biological availability of aluminium." As discussed in the body of the article, all of this changed dramatically in the late 1800s.

12. Water borne exposure is not, of course, the only potential dietary source of aluminum: food. According to one study, 95% of the daily oral intake is from food or cookware (157). Estimates of total daily intakes vary between 2 and 25 mg Al/day (14–175 mg/week), but individual intake in urban societies can easily exceed 100 mg/day (700 mg/week; due to a widespread increase in consumption of processed convenience foods which are typically high in aluminum-containing additives (135). As further cited by Tomljenovic, the Food and Agriculture (FAO) WHO Expert Committee amended their provisional tolerable weekly intake (PTWI) for Al from 7 mg/kg/bw (490 mg/week, for an average 70 kg human) to 1 mg/kg/bw (70 mg/week), noting that, "aluminum compounds have the potential to affect the

reproductive system and developing nervous system at doses lower than those used in establishing the previous PTWI (provisional tolerable weekly intake) and therefore revised the PTWI." In regard to oral/dietary exposure, a number of experimental studies have demonstrated that aluminum at levels "typically" consumed in an average "Western diet" over an extended period of time, produces strikingly similar outcomes (less seizures and mortality) to those induced by intracerebral injections of aluminum salts in rodents to [147, 149]. As Tomljenovic notes, the most recent and elaborate toxicological report for aluminum prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) reports that, "There is a rather extensive database on the oral toxicity of aluminum in animals. These studies clearly identify the nervous system as the most sensitive target of aluminum toxicity" [135].

13. In addition to the concerns about aluminum exposure in children related to vaccines, it should be noted that children are also highly exposed to dietary sources of aluminum whose impact on the developing nervous system may be severe. Infants are at particular risk, as are all those under 5 years of age, as young children's unique physiology makes them more vulnerable to toxic insults compared to the adult population [31, 138].