Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease?

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Although the cause of Alzheimer's disease (AD) remains unknown there is mounting evidence that implicates aluminum as a toxic environmental factor of considerable importance. Four independent lines of evidence — laboratory studies of the effects of intracerebral aluminum on the cognitive and memory performance of animals, biochemical studies, epidemiologic studies and the slowing of the progress of the disease with the use of an agent that removes aluminum from the body — now support the concept that aluminum is one of the pathogenic factors in AD. The evidence warrants 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 common chronic illness in the elderly.

Même si l'on ne connaît toujours pas la cause de la maladie d'Alzheimer (MA), de plus en plus d'indices semblent démontrer que l'aluminium est un facteur environnemental toxique très important. Quatre niveaux de preuve indépendants — études de laboratoire au sujet des effets de l'aluminium intracérébral sur la cognition et la mémoire chez les animaux, études biochimiques, études épidémiologiques et ralentissement du progrès de la maladie lorsqu'on utilise un agent qui élimine l'aluminium du corps — appuient maintenant le concept selon lequel l'aluminium est un des facteurs pathogènes de la MA. Ces preuves justifient d'envisager sérieusement de réduire l'exposition des êtres humains à l'aluminium. Nous posons l'hypothèse suivante : une campagne d'hygiène publique visant à limiter l'ingestion d'aluminium par les êtres humains réduirait l'incidence de cette maladie chronique répandue chez les personnes âgées.

The cause of Alzheimer's disease (AD) remains unknown, but both genetic and environmental factors appear to be important. Mutation on chromosome 21[1,2] may account for a small number of families with familial AD; recently, two families of patients with AD were found to have a point mutation in the amyloid precursor protein, a gene on chromosome 21.[3] This mutation causes an amino acid substitution of isoleucine for valine in the transmembrane domain of the β-amyloid precursor protein at a site just two amino acids from the β-amyloid peptide. It is still uncertain whether this point mutation "causes" AD or whether the mutation is closely linked to the yet-to-be-discovered gene responsible for AD on chromosome 21. For most families, however, linkage to chromosome 21 has not been established, and the genetic form of the disease appears to involve mutations on more than one chromosome.

The much more common, sporadic form of AD appears to be related to unidentified environmental factors. Even in genetically identical twins nongenet-

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ic factors appear to be important; in one study the disease developed in only 40% of twin pairs.[4] Although a virus or scrapie-like infectious agent has been proposed as a pathogen AD is not transmissible to other humans or laboratory animals, and neither viral DNA nor viral antigens have been reproducibly found in AD-affected tissues. Immunologic mechanisms have also been suggested as factors, but whether the observed changes are cause or effect is uncertain.[5]

Aluminum, a widely recognized neurotoxin, has been found in increased concentrations in all AD-affected tissues examined by means of methods sufficiently sensitive and appropriately applied.[6]

However satisfying the idea, we may not be justified in searching for a single cause. A direct experimental approach to measuring the importance of aluminum, or any other postulated etiologic or pathogenic factor, is not possible because AD is found only in humans and cannot be replicated exactly in laboratory preparations. Aluminum induces neither the paired helical filament configuration found in Alzheimer-type neurofibrillary tangles nor the formation of senile plaques with amyloid cores. Nevertheless, it has been found in at least four sites in AD-affected brains and induces at least three cellular derangements also found in AD. However, no single observation or experimental result is, in itself, conclusive.

Four independent lines of evidence implicate aluminum's role in AD: (a) toxicologic studies and laboratory observations of the learning and memory performance of animals, (b) a large number of documented biochemical changes at concentrations of aluminum similar to those found in various subcellular compartments in AD-affected human brains, (c) epidemiologic evidence of the increased incidence of AD in relation to exposure to aluminum in drinking water and (d) the slowing of the clinical progression of AD by a drug that selectively removes aluminum from the body.

Effect of aluminum on learning and memory performance of animals

The direct intracranial injection of small but lethal amounts of soluble aluminum salts produces delayed memory and learning impairment in sensitive species such as cats and rabbits.[7-9] A dose of intracranially injected aluminum sufficient to raise the content in grey matter about fourfold (from 1.5 μg/g dry weight to the 50% lethal concentration of about 5.5 μg/g) had no immediate effect on memory and motor tasks in trained cats; however, 7 to 10 days after injection the cats began to exhibit progressive impairment in precise motor control during jumping[10] and alterations in the performance of learning and memory tasks.[7] Initially the learning and memory deficits were selective: the performance of visual discrimination tasks was not affected and the speed of motor response not altered. The selective effect of aluminum on the learning and memory system is element specific, because nine other trivalent toxic metals (boron, chromium, gallium, indium, lanthanum, scandium, thallium, vanadium and yttrium) have been shown not to elicit the sequence of clinical signs that follow aluminum administration.[11]

Ten days after aluminum injection rabbits have exhibited deficits in learning (acquisition of an active avoidance task) and failed to retain the task when tested 3 days later.[12] Impaired learning in a water maze,[13] defective classic[14] and eye-blink conditioning[15,16] and impaired long-term potentiation in hippocampus slices[17] (considered to be an electrophysiologic model of a learning response) have also been reported in rabbits given aluminum.

Shortly after the memory defects appear, cats and rabbits exhibit progressive deterioration in motor control, with difficulty executing body righting, increased muscle tone, ataxia of gait, tremors, myoclonic jerks and seizures. If the seizures are not treated with anticonvulsant medications the animals may die in convulsions; treated animals may survive, but with persistent severe neurologic and behavioural defects.

The unique, progressive clinical course after a single intracerebral lethal threshold dose of aluminum in susceptible mammals is marked first by disturbance of learning and memory and then by altered motor control, increased muscle tone, myoclonic jerks and seizures. It resembles the clinical course of AD in humans, although much shorter in duration.

The intracerebral aluminum levels (5 to 6 μg/g dry weight[18]) that produce the toxic effects in animals are sometimes found in the brains of AD patients. Approximately 23% of randomly selected samples of neocortical grey matter from patients with AD have been found to contain aluminum in the amount of 5 μg/g dry weight or more.[19]

Aluminum-induced neurochemical changes in the brain

Aluminum affects many biochemical and neurochemical processes of the brain (Table 1).[12,17,20-105] Of particular importance is the observation that human neuroblastoma cells in culture treated with low doses of aluminum produce antigens that react with an antibody to an abnormally phosphorylated microtubule-associated protein known as Tau found in AD.[56] The antibody reacts specifically with AD neurofibrillary tangles. Considerable evidence now

Table 1: Actions of aluminum at the cellular level

Nuclear effects
- Binds to DNA phosphate and bases[20,21]
- Increases histone-DNA binding[22]
- Decreases RNA in neuroblastoma[23]
- Blocks initiation sites for RNA polymerase[24]
- Blocks RNA polymerase activity in vitro[25]
- Blocks ribosylation of adenosine diphosphate[26]
- Alters sister chromatid exchange[27]
- Alters steroid-induced chromosome puffing[28]
- Inhibits corticosterone binding to DNA[29]
- Alters poly(A) RNA content in the forebrain of rabbits[30]
- Reduces messenger RNA coding for neurofilaments in anterior horn cells of rabbits[31]
- Decreases cell division and alters DNA synthesis[32,33]
- Induces considerable changes in chromatin[34]
- Alters the development of rat offspring[35]

Cytoplasmic effects
- Induces conformational changes in calmodulin; blocks calmodulin-dependent calcium–magnesium adenosine triphosphatase (ATPase), which is important in extrusion of calcium ion from cells[36,37]
- Increases intracellular calcium content[17,38]
- Reduces sugar phosphorylation[39]
- Decreases respiration[40]
- Inhibits hexokinase activity[41–46]
- Stabilizes terminal phosphoryl group on ATP[41–46]
- Forms long-lived complex with ATP[41–46]
- Inhibits ATP[41–46]
- Inhibits brain glycolysis, depression of yeast and rat brain cytosolic and mitochondrial hexokinase activity[41–46]
- Stimulates brain pyruvate kinase[46]
- Enhances adenylate cyclase stimulation by fluoride but inhibits activation by serotonin and guanine nucleotides in *Fasciola hepatica,* a requirement for activation of the regulatory component of adenylate cyclase by fluoride[47,48]
- Increases the number of lysosomes; reduces thiamine pyrophosphatase and nucleotide diphosphatase in the Golgi apparatus[49]
- Inhibits the synthesis of tetrahydrobiopterin[50]
- Elevates cyclic AMP and GMP* levels[51]
- Increases ubiquitin response in neurites of cultured nervous tissue[52]
- Binds to ferritin and is partially sequestered by this mechanism; may alter iron storage[53]
- Proliferates peroxisomes (aluminum clofibrate)[54]
- Inactivates phosphofructokinase and inhibits hepatic glycolysis[55]
- Induces an alteration in Tau that is recognized by antibodies to Alz 50[56]
- Perturbs elongation factor Tu[57]
- Inhibits protein kinase-C activation[58]
- Inhibits proton translocating ATPases in *Streptococcus* and *Lactobacillus*[59]

Cytoskeletal effects
- Induces neurofibrillary degeneration composed of 10-nm fibres identical in chemical composition to normal neurofilaments[60–64]
- Alters slow axonal transport, although disputed; has no effect on anterograde transport[65–67]
- Alters phosphorylation of cytoskeletal proteins, microtubule-associated protein 2 and the 200KD component of neurofilaments[68]
- May have secondary effect on cyclic AMP-dependent protein kinase[68]
- Promotes assembly of microtubules, which are more slowly depolymerized than magnesium-assembled tubules[69,70]
- Induces chronic myelopathy in rabbits[71]
- Induces neuronal cytoskeletal lesions (through intravenous and intrathecal injections)[72]
- Alters neurofilament conformation in vitro[73]
- Inhibits calpain-mediated proteolysis; induces human neurofilament proteins to form high-molecular-weight complexes[74]

Effects on membranes and membrane-bound enzymes
- Alters physical properties of membrane lipids[75]
- Binds to positive-charged and negative-charged sites in membranes in vitro[76]
- Alters membrane structure[77,78]
- Alters adenylate cyclase activity required for activation of regulatory component of adenylate cyclase in vitro by fluoride[47,58]
- Inhibits sodium–potassium-activated ATP activity at relatively high concentrations[79]
- Enhances brain-specific lipid peroxidation[80,81]
- Accelerates peroxidation of membrane lipids stimulated by iron salts[80,81]
- Decreases activity of superoxide dismutase in rat brain[80,81]
- Alters blood–brain barrier[82–85]
- Inhibits saturatable transport system for *N*-tyrosinated peptides and encephalin from brain[82–85]
- Increases permeability of blood–brain barrier to neuropeptides[82–85]

Synaptic and neurotransmitter effects
- Alters dendritic shape and synaptic density in chronic preparations[12,86]
- Blocks high-affinity uptake of γ-aminobutyric acid (GABA) and glutamate from synaptosomes[87,88]
- Blocks synaptosome uptake of neurotransmitter amines choline, dopamine and noradrenaline[79,89]
- Inhibits acetylcholinesterase[23,90,91]
- Blocks uptake of calcium and binding of acetylcholine[92]
- Reduces glucose uptake by synaptosomes extracted from rat cortex[93]
- Depresses norepinephrine and dopamine levels in cortex and activity of enzymes dopamine-β-hydroxylase and phenylethanolamine-*N*-methyltransferase when fed to rats with diets deficient in copper, zinc and iron[94,95]
- Reduces choline acetyltransferase in hypoglossal nucleus and spinal cord grey matter in rabbits[96–98]
- Inhibits fast phase of voltage-dependent calcium influx into synaptosomes[99]
- Inhibits protein phosphatase (in synaptosomal cytosol fractions)[100]
- Is toxic to key synaptosomal enzymes (dependent on sodium–potassium, magnesium and calcium ions)[101]
- Stimulates sodium chloride-dependent release of taurine and GABA in rat cortical astrocytes[102]

Effects on blood
- Alters activity of cholinesterase[103,104]
- Interacts with transferrin[105]

*AMP = adenosine 3',5'-cyclic monophosphate, GMP = guanosine monophosphate.

indicates that these tangles are composed of a polymer of normal Tau that has undergone abnormal phosphorylation[106] and that aluminum in healthy neurons induces hyperphosphorylation of Tau.

The determination of which of the other toxic effects listed in Table 1 are important in the pathogenesis of AD will require a more advanced understanding of the cellular and molecular characteristics of AD and aluminum neurotoxic effects than now possible. The key biochemical events responsible for neuronal dysfunction and neuron death may involve energy metabolism, calcium homeostasis, membrane receptor and channel functions or gene expression. Aluminum, or any other postulated pathogenic factor, must be shown to induce changes in model systems similar to those observed in the human disease and must be found at the putative site within brain cells in sufficient concentrations to induce the changes observed in AD-affected tissues.[107]

Abnormal accumulation of aluminum has now been found in at least four sites in the AD-affected brain.

Neurofibrillary tangles

Different analytic methods capable of precise tissue localization[108-110] have shown remarkably high concentrations of aluminum (up to 300 μg/g dry weight) in the bundles of paired helical filaments that make up AD neurofibrillary tangles. The observation that aluminum induces abnormal phosphorylation of Tau,[56] the principal subunit of AD neurofibrillary tangles,[106] supports the idea that aluminum accumulation may occur early in the disease process and result in the formation of tangles, not late in the process in a terminally damaged neuron.

Amyloid cores of senile plaques

Focal deposits of aluminum and silicon, as aluminosilicates, are also a consistent and specific feature of the central core of senile plaques.[111,112] Aluminosilicates, in vitro, can seed the formation of polymeric fibrillary aggregates of model peptides, including the amyloid peptide, which resemble the amyloid core of senile plaques. The amyloid precursor protein is considered to be the major protein found in senile plaques. Increased amounts of the protein have been found in some patients with elevated brain aluminum concentrations due to chronic renal failure. In some cases of prolonged dialysis precocious development of immature senile plaques has been observed.[111,112] These observations, together with the finding that aluminosilicates seed the formation of fibrillary aggregates, support the possibility that elevated amounts of aluminum in serum and brain can induce some of the cellular responses contributing to amyloid deposition.

Ferritin

Ferritin is an ubiquitous intracellular iron storage protein capable of scavenging other metals, including zinc and beryllium. The amount of aluminum found in ferritin extracted from AD-affected brains was 5.6 times higher than in ferritin from matched control preparations.[113] The researchers considered that the increase may have been due to a general increase in the availability of aluminum to the brain of patients with AD and raised the possibility that aluminum may release iron as Fe^{+++}. This could facilitate the production of highly toxic free radicals that can denature proteins and destroy membranes, thereby contributing to neuron death in AD.

Chromatin fractions

AD is associated with a change in the structure of the DNA–protein complex that constitutes the physical matrix within which genes are expressed.[114] This change results in the reduced transcription of certain neuron-specific genes, including the low-molecular-weight messenger RNA for neurofilament protein.[115,116] Aluminum has been shown to accumulate on DNA-containing components of the cell nucleus in the cerebral cortex.[117] A ninefold increase in aluminum content is associated with the DNA–protein fraction containing repressed neuronal genes.[114] Although aluminum increases the affinity of binding of certain repressor proteins to DNA and contributes to the gene repression, some other event likely occurs first to allow the protein to dock at a particular DNA site.

We postulate that aluminum replaces magnesium at a key DNA–protein binding site. Because the aluminum atom has a small ionic radius and high charge it is nearly a million times slower than the magnesium atom in dissociating from the DNA–protein complex. By replacing magnesium, aluminum locks the repressor protein in place.

Environmental aluminum

Although aluminum is a common constituent of the environment it has no recognized biologic function. Aluminum is absorbed primarily through the gastrointestinal tract but probably also through the respiratory epithelium and skin. Preliminary data using accelerator mass spectrometry with aluminum-26 ligated to citrate indicate that as much as 1% of aluminum ingested orally is absorbed into the blood stream (James Barker and J. Philip Day,

Department of Chemistry, University of Manchester, Manchester: personal communication, 1991). Aluminum and fluoride, and probably silicon, are mutually antagonistic in competing for absorption in the gut; the more fluoride or silicon in the diet, the less aluminum absorbed.

In 1980 Shore and associates[118] did not show increased aluminum concentrations in AD patients. However, later studies[119-121] showed significantly elevated aluminum levels in the serum or whole blood of AD patients, as compared with the levels in carefully matched control patients. Aluminum appears to be transported in serum and carried into the brain by several proteins that may have different, genetically determined affinities for aluminum. One speculation is that individual variation in susceptibility to elevated aluminum concentrations may be related to the proteins responsible for transportation in serum. A portion of aluminum in serum is carried by high-molecular-weight proteins, including α_2-macroglobulin, immunoglobulin, hepatoglobin, transferrin and albumin. In addition, a low-molecular-weight protein (of about 18 kilodaltons) that transports aluminum has recently been discovered.[122]

In cerebrospinal fluid most of the aluminum is bound to these newly identified low-molecular-weight proteins. Aluminum uptake by the brain is currently attributed to transferrin, and the highest densities of transferrin receptors are in regions of the brain selectively vulnerable to AD.[123] Recent evidence has indicated that the binding of gallium, an analogue of aluminum, by transferrin is defective in AD.[124] Thus, a serum transport defect could contribute to the accumulation of aluminum in the AD-affected brain.

Although it has been recognized for several years that the markedly elevated serum aluminum levels (200 μg/L) that occur in kidney failure may result in dialysis dementia, much lower concentrations are now recognized to be associated with impaired cognitive function. The psychomotor performance of 27 patients receiving long-term hemodialysis who had only a mildly raised serum aluminum level (mean 59 [normally less than 10] μg/L) was impaired, as compared with the performance of matched control subjects.[125] In another study[126] signs of neurologic dysfunction and impaired memory occurred in dialysis patients who had labile aluminum released by desferrioxamine, an aluminum chelating agent, in challenge tests. These observations further indicate that even moderate elevations in the serum aluminum level pose a risk of cognitive impairment.

Sequestration of aluminum

Aluminum may be sequestered in the human body by several mechanisms. It is injected intramuscularly or subcutaneously into most of the world's population as an adjuvant in vaccines for diphtheria, pertussis, tetanus and hepatitis and in allergenic extracts. Alum-precipitated allergenic extracts contain up to 850 μg of aluminum per dose, and injections of ragweed pollen every 2 weeks for 2 years results in a calculated dose of 44 mg of aluminum. The injected aluminum may persist in the tissues for weeks or years as subcutaneous nodules.[127] The granulomas comprise aluminum-laden histiocytes and dense lymphocytic infiltrates with germinal centres.[127] The transportation and distribution of injected aluminum in the body are unknown, but tissue depots of aluminum are likely to release the metal for many years. Immunologic mechanisms may play a role in AD,[5] and histiocytes that penetrate brain tissue may serve as an additional transport system for aluminum, which bypasses the blood–brain barrier.

Considerable concern has been expressed about the aluminum content of infant formulas and parenteral nutrients. Bishop and collaborators[128] reported that a premature infant who had received an estimated total of 645 μg of aluminum through parenteral feeding had seizures and died. At autopsy the temporal grey matter contained an average of 40.1 μg/g wet weight of aluminum, as compared with a mean of 2.4 μg/g wet weight in 12 infants dying unexpectedly within the first year of life. This 17-fold increase closely approaches that mentioned in the first reported fatal case of encephalopathy associated with respirable aluminum.[129]

X-ray energy spectroscopy has detected aluminum in 9% of oral apical granulomas.[130] Possible sources of aluminum in the mouth include toothpaste, impression materials and amalgam.

Aluminum is also found in pigmented macrophages in Peyer's patches in all patients over 6 years of age[131] and is presumed to be of dietary origin. Whether aluminum is sequestered in these cells from potential neurotoxic actions is unknown. The recent development of accelerator mass spectroscopy for the long-life isotope ^{26}Al to be used in tracer studies will greatly help answer the many questions concerning aluminum metabolism.

Epidemiologic findings

Seven studies have related elevated aluminum concentrations in drinking water to an increased incidence of AD.[132-139]

In a recent study[137] 2792 randomly selected subjects aged 65 years or more were screened for AD by psychologists using dementia screening tests.[138] They were then examined by senior neurologists using criteria established by the National Institute of

Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[140] The aluminum level in drinking water varied from 10 to 160 μg/L for the sample. The relative risk for probable AD at 100 μg/L was 4.53 times greater than at 10 μg/L. Martyn and colleagues[136] reported similar results in an incidence study of presenile Alzheimer's disease (in people 65 years of age or less) in 88 counties in England. By examining the records of computerized tomography (CT) units that served the districts they identified patients with probable AD (445 people) or possible AD (221). The control group comprised 519 people with dementia and multiple minor strokes visible on the CT scans and 2920 with adult-onset epilepsy without clinical dementia; the incidence of each of these diseases in the catchment areas was correlated with the aluminum content in the drinking water. No statistically significant relative risk between aluminum in the drinking water and dementia caused by multiple strokes or adult-onset epilepsy was found. However, the prevalence of AD in areas with an aluminum level of 111 μg/L of drinking water was 1.7 times higher than in areas with a level of less than 10 μg/L (confidence limits [CLs] 1.1 and 2.7).

Two epidemiologic studies in Norway used an ecologic approach. Vogt[133] divided the population of Norway into five zones according to the aluminum concentration in the lakes, which corresponded well with the aluminum levels found in drinking water. The lowest concentration was 20 μg/L and the highest 200 μg/L. The risk of death from senile dementia in the zone with the highest concentration was 1.48 times higher than in the zone with the lowest. Correlations between the rates of death from AD and the aluminum concentrations were statistically significant; multiple-stroke dementia and the risk of death from paralysis agitans were not related to the aluminum levels. Flaten[134] found a highly significant correlation between aluminum in processed drinking water and AD.

Table 2 lists the studies in order of increasing diagnostic accuracy. The relative risk of AD in relation to aluminum content of drinking water appears to increase as the diagnostic accuracy increases in each of the studies.

In the United States Still and Kelly[132] examined first admissions to the state mental hospitals between 1971 and 1979 in three counties of South Carolina. Index cases were patients aged 55 years or more classified as having primary degenerative dementia (considered by the authors to be predominantly AD), vascular dementia, alcoholic dementia or other forms of dementia. Fluoride levels in water were measured instead of aluminum levels, because fluoride reduces aluminum uptake by the gut. In addition, the ingestion of aluminum compounds counteracts dental fluorosis and results in reduced fluoride stores in teeth and bones.[141] One county had 4.18 mg of fluoride per litre of drinking water; the levels in the other two counties were 0.49 and 0.61 mg/L. The incidence of primary degenerative dementia in the county with the highest fluoride level was about 20% of that in the other two; there were no significant differences between the counties in the number of first admissions because of the other types of dementia.

A study in Newfoundland revealed clusters of high rates of death from dementia, recorded on death certificates as an immediate, antecedent, underlying or contributing cause of death.[139] Index cases were grouped according to birth place. In 1985 and 1986 there was a significant excess of deaths in a small area of Bonavista Bay that could not be explained by differences in age, sex, ethnic origin, family origin or mobility patterns. The area was reported to have a high aluminum concentration in the drinking water (165 μg/L), the lowest pH (5.2) and the highest colour (turbidity) index in the region. The last two conditions would increase the probability of the formation of both polynuclear inorganic aluminum and organic aluminum ligands, which, as argued later, have greater aluminum neurotoxic effects than mononuclear aluminum.

A recent case-control epidemiologic survey of 130 matched pairs examined the association between AD and the lifetime exposure to aluminum in antiperspirants and antacids.[142] For aluminum-containing antiperspirants the overall adjusted odds

Table 2: Relative risk of Alzheimer's disease in relation to aluminum content of drinking water in three epidemiologic studies

Study	Diagnostic criteria	No. of subjects	Aluminum level, μg/L drinking water	Relative risk*
Vogt[133]	Death certificates	18 664	20–200	1.48
Martyn et al[136]	Computerized tomograms	307	0–> 110	1.7
Michel et al[137]	DSM-III[138] and NINCDS–ADRDA[140]	2 792	10–160	4.53

*The more rigorous the diagnostic accuracy of the study, the higher the relative risk for AD.

ratio for AD was 1.6 (CL 1.04 and 2.4), the risk increasing with increased frequency of use (p = 0.03), and the odds ratio for the 33% of those who used the highest amount was 3.2. For antacids the overall adjusted odds ratio, regardless of aluminum content, was 3.1, with a dose–response gradient (p = 0.009), and the odds ratio for the highest tertile was 11.7. When only aluminum-containing antacids were analysed no significant risk or dose–response trend emerged. However, in another study the brain aluminum concentration was higher after ingestion of antacids with a high level of aluminum. Dollinger and coworkers[143] examined brain tissue specimens from 20 subjects scheduled for brain surgery who were given antacids for 10 days for stress prophylaxis. Half of them received 70 mL of a high-aluminum-content antacid daily, the others an equal dose of a low-aluminum-content antacid. After the 10 days of antacid treatment the low-dose group had a mean aluminum concentration of 0.412 μg/g wet weight (an estimated 2.60 μg/g dry weight) and the high-dose group 1.05 μg/g wet weight (an estimated 5.25 μg/g dry weight). The mean aluminum level in brain tissue from 20 control subjects was 0.583 μg/g wet weight.

The new tracer techniques demonstrate that uptake of aluminum between the bowel and the blood and between the blood and the brain occurs at a considerably higher rate than previously suspected. Accelerator mass spectrometry with the use of ^{26}Al ligated to citrate in rats revealed that approximately 1/55 000 of a single intraperitoneal injection of ^{26}Al is incorporated into the cerebrum.[144]

Epidemiologic studies demonstrate association but do not establish cause and effect. Nevertheless, each study reviewed reached the same conclusion: aluminum in drinking water is associated with an increased risk of dementia of the Alzheimer type.

The most satisfactory studies would include autopsy findings confirming the diagnosis and ruling out clusters of familial AD as confounding variables. The aluminum ligands in food, water and all substances ingested or injected into people should be measured and correlated with the incidence of AD. Such studies will be extremely expensive to conduct and will require several years to execute.

Organic and inorganic forms of aluminum

Are all forms of aluminum equally toxic? It is well known that organic mercury, methyl mercury, is much more toxic than metallic mercury. The same is true for aluminum. Some forms of aluminum, like aluminum hydroxide, are poorly absorbed from the gastrointestinal tract, whereas certain organic ligands of aluminum, such as aluminum citrate, pass very rapidly from the food chain into the blood.

The forms of aluminum in drinking water are of considerable significance for epidemiologic studies. They are incompletely studied, and those that could be risk factors for AD have not been identified. Driscoll and Letterman[145] studied the chemistry and fate of aluminum in water pumped from Lake Ontario and treated with alum for drinking in Syracuse, NY. They found that 52% of the aluminum was in the form of monomeric alumino-hydroxide complexes, 29% was associated with organic matter, 19% was in a fluoride complex, and a small amount was particulate. The relative intestinal absorption by mammals of these organic and inorganic forms has not been studied.

Recently, aluminum-27 magnetic resonance spectra of soil samples demonstrated the presence of inorganic polynuclear aluminum forms, which may account for up to 30% of aluminum in water.[146] Since these inorganic polynuclear forms appear to be 10 times more toxic than mononuclear forms in certain aquatic plants and fish their toxic effects in mammals and humans need to be investigated. Considerable seasonal variation has been observed in the distribution of aluminum forms in drinking water. Therefore, it is very important that the various organic and inorganic types of aluminum be correlated with the incidence of AD in each of the epidemiologic studies reviewed in this article and be considered in future studies.

Respiratory aluminum

Rifat and associates[147] examined prolonged exposure to respirable aluminum to determine whether it was associated with serious cognitive deficit. Between 1944 and 1979 finely ground alumina (particle diameter less than 2 μm) was dispensed prophylactically for silicosis to groups of gold miners in northern Ontario. The alumina powder was dispersed in the miners' change rooms for 10 to 20 minutes at a concentration of 35 mg/m^3 before each underground shift. These miners had significantly poorer performance on cognitive tests than an age-matched group of miners who had not been exposed. The differences persisted after adjusting for potential confounding factors such as head injury, education and alcohol abuse. The relative risk of severe cognitive deficit was 4.5 times greater among miners with more than 20 years' exposure, 3.1 among those with 10 to 20 years' exposure and 2.4 among those with 1 to 10 years' exposure. Clinical and histopathologic examinations were not done, and thus no conclusion can be reached as to whether the cognitive deficit was more closely related to dialysis dementia or to AD. Although long-term follow-up examinations were not performed and brain tissue was not examined, the authors have concluded that prolonged

exposure to respirable aluminum is associated with serious cognitive deficit.

Clinical progression of AD after removal of brain aluminum

A fourth line of independent evidence has tested the hypothesis that if aluminum is an important pathogenic factor in AD, its removal by an ion-specific binding agent should slow the progress of the disease. A 2-year prospective, single-blind clinical trial was conducted to determine whether the sustained use of desferrioxamine, a trivalent metal ion binding agent, would slow the progression of the dementia.[148] A total of 48 people living at home with probable AD were randomly assigned to three treatment groups: desferrioxamine, lecithin (in oral homeopathic doses of 1 g/d) and no treatment. A structured performance test measuring daily living skills was videotaped in the home and was the outcome measure over the 2-year period. The tapes were analysed at random by trained behaviour raters blind to the purpose and protocol of the study. There was no statistical difference in the average rate of decline in performance between the lecithin group and the no-treatment group. However, when data from these two groups were combined the average 2-year decline in the desferrioxamine group was 25% of the maximum score, as compared with 57% in the no-treatment group.

A double-blind placebo-controlled multicentre trial must now be conducted to confirm these results. However, on the basis of current evidence desferrioxamine appears to slow the progression of AD. These results support the hypothesis that aluminum is a significant toxic environmental factor in the pathogenesis of the disease.

Conclusions

Four independent lines of evidence support the conclusion that aluminum is an important risk factor in AD: (a) prolonged exposure to trace amounts of aluminum induces cognitive deficits in experimental animals and humans, (b) aluminum accumulates in at least four sites in AD-affected brain tissue at concentrations known to affect several biochemical reactions, (c) seven epidemiologic studies have demonstrated an association between AD and aluminum exposure in drinking water and antiperspirants (high levels of aluminum in the air have been found to increase significantly the risk of cognitive defects, but an association between this type of aluminum exposure and AD has not been investigated) and (d) treatment with a trivalent metal ion binding agent slows, but does not arrest, the clinical progression of AD.

Recommendations

- Human exposure to aluminum should be limited. After considering the available evidence a prudent person may wish to limit daily exposure to aluminum. In addition to reducing head trauma, which is considered to be a risk factor for AD,[149] reduction in aluminum exposure may be the only change in lifestyle that offers hope of reducing the incidence of AD. Unfortunately, the sources of aluminum are largely unknown to the public. As well as occurring naturally in food and water, aluminum is added to drinking water, many processed foods, cosmetics, toothpaste, antiperspirants and adjuvants in various parenteral preparations and other pharmaceutical agents. Current evidence supports the hypothesis that a major reduction in the ingestion of aluminum would significantly reduce the incidence of AD.
- Public policy action is required. No risk factor other than aluminum that might be controlled by public action to reduce the incidence of AD has yet been identified. Sources of public health information have an obligation to inform the public about the current state of knowledge concerning the relation between aluminum and AD so that each individual may make an informed decision. Additional important pathogenic factors in AD will become recognized as knowledge grows about this disease.
- The aluminum content should be listed on the packages of all substances marketed for human contact and ingestion including processed foods, potable water, cosmetics, toothpaste and pharmaceutical products.
- Municipal processed water should be regulated so that the aluminum concentration is less than 50 μg/L; the long-term goal should be a concentration of less than 10 μg/L.
- A goal for the daily intake of aluminum from all sources by adults should be 3 mg or less.
- Further research should be conducted to understand fully the health risks of aluminum.

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[This issue's Encore selection (starting on page 823) features a 1936 case report on Alzheimer's disease. — Ed.]

Conferences

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Oct. 24-25, 1991: Gairdner Foundation Lectures
University of Toronto
Sally-Anne Hrica, Gairdner Foundation, 220-255 Yorkland Blvd., Willowdale, ON M2J 1S3; (416) 493-3101, fax (416) 493-8158

Les 24 et 25 oct. 1991 : 9e Assemblée scientifique annuelle du Collège des médecins de famille du Canada (section Québec) — Culture et santé : défis et perspectives
Montréal
Micheline Guilbault, secrétaire administrative, CP 146, Succ. Champlain, LaSalle, QC H8P 3J1; (514) 762-9889, fax (514) 762-9870

Oct. 24-27, 1991: Canadian Association of Gerontology 20th Annual Scientific and Educational Meeting
Regal Constellation Hotel, Toronto
Canadian Association of Gerontology, 110-1565 Carling Ave., Ottawa, ON K1Z 3R1; (613) 728-9347

Oct. 25, 1991: Research Day in Family Medicine
Radisson Hotel, London, Ont.
Margot Meijer, Thames Valley Family Practice Research Unit, 1489 Richmond St., London, ON N6G 2M1; (519) 439-0121, fax (519) 439-0124

Oct. 25-27, 1991: Canadian Medical Society on Alcohol and Other Drugs 3rd Annual Scientific Meeting
Clarke Institute of Psychiatry and the Addiction Research Foundation, Toronto
Canadian Medical Society on Alcohol and Other Drugs, 13-100 College St., Toronto, ON M5G 1L5; (416) 595-6000, ext. 7363, fax (416) 595-1214

Oct. 30-Nov. 1, 1991: Catholic Health Association of Canada Administrators' Seminar — Threats to the Mission of Catholic Health Care: a Strategic Response
Radisson Hotel, Ottawa
Freda Fraser, director of communications, Catholic Health Association of Canada, 1247 Kilborn Pl., Ottawa, ON K1H 6K9; (613) 731-7148

Nov. 1-2, 1991: Pediatric AIDS Conference (sponsored by the Sunny Hill Hospital for Children, Vancouver, and the Division of Continuing Education in the Health Sciences, University of British Columbia)
Coast Plaza Hotel at Stanley Park, Vancouver
Pediatric AIDS Conference, Continuing Education in the Health Sciences, 105-2194 Health Sciences Mall, Vancouver, BC V6T 1Z3; (604) 822-2626, fax (604) 822-4835

Nov. 1-2, 1991: Women, Food and Weight — New Perspectives
519 Church Street Community Centre, Toronto
National Eating Disorder Information Centre, 200 Elizabeth St., Ste. CW1-328, Toronto, ON M5G 2C4; (416) 340-4156

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For prescribing information see page 873 →