ALUMINUM AS A CAUSE OF SENILE DEMENTIA

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■ Since aluminum is a reactive metal, it is surprising that after millions of years of evolution it has not found a useful function in any metabolic pathway. This avoidance of aluminum by the body's metabolism raises ominous questions. Aluminum constitutes 8.4% of the earth's crust, and almost every person will normally ingest 30 to 50 mg daily of this ubiquitous element.

NEUROPHYSIOLOGIC EVIDENCE IN ANIMAL EXPERIMENTATION

A replication of the entire sequence of symptoms of Alzheimer's disease was produced in cats, in a study by Crapper and associates.[1,2] A single injection of a microgram of aluminum chloride into the hippocampic ventricle of the brain typically caused death of the animal after about three months, with symptoms closely resembling those of Alzheimer's disease. The animals usually appeared normal for the first 8 to 14 days, although in sacrificed animals some aluminum could be detected in the chromatin of pyramidal neurons in 96 hours.

Pyramidal cells with extensive dendritic trees of cortical layers V and III were most frequently affected. The most common first sign in these cats was difficulty in maintaining balance after jumping. Eight to ten days after injection the cats began to lose short-range memory. For example, they were unable to recall under which cup their food had been placed. Progressive deterioration in movement followed, associated initially with disorder resembling a motor dyspraxia, then truncal ataxia, head tremor, difficulty in maintaining erect posture, tonic increase in extensor and flexor muscles, and myoclonic jerks followed by general motor seizures with status epilepticus. Death occurred in about three months. With intensive nursing some animals survived the acute encephalopathy. Following convalescence of two to four months they remained unimproved neurologically for up to three years of observation.

CLINICAL FINDINGS

The above findings were confirmed and broadened by observations on humans. LaPresle et al[3], and Galle and Duckett[4] showed the effect of aluminum on Parkinson's disease, while Crapper et al showed it in Down's syndrome. Perl and Brody[5] confirmed that aluminum has an effect on the nuclei of neurons in neurofibrillary degeneration in senile brains, similar to Alzheimer's dementia. Immunologic tests by Gambetta et al have demonstrated the

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chemical similarity between subnormal tubular intracellular growths in Alzheimer neurons and similar tubules induced in rats by administration of aluminum.[6]

An important corroboration was made by Alfrey and co-workers, who were the first to suspect the cause of the endemic encephalopathy that occurred in dialysis of uremics. A high percentage of those receiving two to three weekly dialyses on artificial kidneys developed Alzheimer-like symptoms, leading to death in three to six months.[7,8] After virus infection was ruled out, careful chemical analysis indicated presence of aluminum as a possible cause.

Not only had the patients taken aluminum hydroxide orally to control serum phosphorus, but also the dialysate used was prepared from tap water containing 120 to 240 μg aluminum/L water. Alfrey had discovered an involuntary, tragic clinical experiment, in which thousands of people were exposed to aluminum passing from dialysis water directly into the bloodstream, thus bypassing the body's two principal natural defenses: (1) low absorption of aluminum in the gastrointestinal system, and, (2) removal of aluminum through the kidneys. After Alfrey published his findings, reports of similar encephalopathies appeared that had been previously viewed as local infections. It became apparent that in most of these cases the water used for dialysis had contained over 80 μg aluminum/L. In 1977 the European Dialysis and Transplant Association, inquiring about the frequency of dialysis encephalopathy, received 153 reports from 17 countries.[9]

The experience of a well-managed clinic in a medium size Swedish town is typical.[10] In Växjö, Sweden, the aluminum content in incoming water and dialysis liquid from March to May 1978 was from 100 to 400 μg/L. From May 1977 to June 1978 nine patients with uremia were dialyzed in the clinic twice weekly for an average of 7.3 months. One of the patients died after one month from uremia. Four patients did not develop any clinical signs of dialysis encephalopathy. The remaining four developed neurologic symptoms 6½ to 11 months from time of admission and within 5½ to 10 months from the beginning of treatment. They died from three to six months later. Three of these fatalities were typical of dialysis encephalopathy. The fourth patient who had multiple symptoms (nephrosclerosis, coronary insufficiency, unilateral cyst) was considered atypical. However, two electroencephalograms over a one-month period showed a slow basal activity, frontal dominance, and numerous bilateral, rhythmic delta epidoses with high amplitude and occasional sharp waves.

The subsequent installment of apparatus for purification of dialysis water (reverse osmosis) has functioned satisfactorily for 15 months. The aluminum content has consistently remained below the detection limit of present analysis methods (<10 μg/L). Patients in home dialysis treatment also received reverse osmosis aggregates if aluminum was found in their water supplies or if the city water works used aluminum sulphate treatment. From June 1978 to September 1979, 11 patients were dialyzed in Växjö for 1 to 15 months (average 7.7). One died from hypertonicity after less than two months. No symptoms of dialysis encephalopathy have been observed in any of the patients in the clinic or in the patients dialyzed at home.

SOURCE OF ALUMINUM IN WATER SUPPLIES

The aluminum ion is a potent colloid-precipitating agent. With a certain precipitating power, for example, 3000 ppm sodium ion in an aqueous medium, this power can be doubled by adding only 200 ppm calcium or 5 ppm aluminum. These enormous changes in colloid stability can occur without noticeable change in specific conductance, a common parameter of water supplies.[11] For this reason, aluminum, until recently believed innocuous, is being widely used to precipitate colloid turbidity in water purification. Water is now purified for dialysis purposes by reverse osmosis devices or the equivalent, and outpatients on home dialysis are supplied with water purifiers when their home water is found to have aluminum in excess of 20 μg/L. More data are required to ascertain whether the onset and incidence of senile dementia would be postponed if control of aluminum was made mandatory in all water supplies.

Aluminum is present in almost all foods. A published list of the aluminum content of 283 foods also notes the content of many foods

prepared in aluminum cooking utensils versus those prepared in steel or enamel. The amount of aluminum in food cooked in aluminum pans is generally slightly higher, but is substantially elevated in acid dishes such as rhubarb or lemon.[12] While some restrictions were introduced in 1979 limiting permissible levels of volatile aluminum compounds in air, there are no restrictions for soluble aluminum compounds in foods or drugs.[13]

RELEVANT PROPERTIES OF ALUMINUM

Aluminum can strongly and uniquely affect the central nervous system and possibly also the sinoatrial node, the atrioventricular node, and Purkinje's fibers. Aluminum is a powerful flocculant, and, as such, causes shrinkage of colloids. The human brain contains large amounts of colloidal gels. Abnormal coagulation of these gels causes shrinkage, thereby severing interneuronal connections, a process similar to that occurring in aging. In addition, aluminum is a strong reactant, causing cross-linkage between large vital molecules.[1] In no other broad type of chemical reactions are there such great changes of biochemical behavior of molecules. The kind and positions of unwanted cross-linkages are specific in carcinogenesis, but in aging they are largely random and not specific. Deleterious effects of cross-linkage are: (1) formation of tangled molecular chains or nets which progressively impede intracellular transport; (2) loss of elasticity of all tissues, with increased susceptibility of rupture; (3) increased lipophilicity of proteins by causing preferential cross-linkage of hydrophilic areas; (4) conversion of essential molecules into inert aggregates; (5) inactivation of vital molecules by creating steric hindrances; and (6) secondary effects caused by any of the above on accuracy of mitotic processes, protein and other synthesis, or disturbance of any enzyme.

Aluminum is also an inhibitor of transaminations. The transaminases, largely pyridoxal-dependent, are widely distributed in the brain. Much work is needed to unravel the intricate patterns of brain function, but reactions involving transamination are amply indicated. These include the intermediate steps of oxidation, decomposition of Schiff bases involving pyridoxal and amino acids, or both. Such interaction is catalyzed in vitro by the metal ions Fe^{+++}, Co^{+++}, Ni^{+++}, Cu^{++}, Zn^{++}, and Al^{+++}. Of these, the first four are readily reducible to their lower valence stages, a good way to effect release from an intermediate compound. The significance of changes in oxidation stage in the brain has recently been stressed by Sylvia and co-workers.[14]

Of the metals which can catalyze pyridoxal-Schiff base reactions, only zinc and aluminum have a single oxidation stage. Zinc, however, is needed in normal metabolism, for example as a constituent of carboxyanhydrase, an essential blood enzyme, and also in uricase and renal phosphatase. It is also a frequent component of insulin. Organisms thus have been forced to develop systems for handling zinc, but zinc is neurologically toxic at relatively low concentrations.

Aluminum remains the maverick. It has no known metabolic function. It cannot be reduced, and it has valence 3, coordination number of 6. Thus, it can form extremely firm attachments that do not permit its removal by reduction of oxidation stage or by any other biological means. Perhaps this is why evolution has not assigned any metabolic function to aluminum, despite its ubiquitousness. Furthermore, the aluminum ion is one of the smallest ions known. Small dimensions and high charge combine to maximize the electric charges in the immediate proximity of the ion.[15]

DISCUSSION

The evidence reviewed shows that senile dementia may be similar in origin to Alzheimer's disease and to dialysis encephalopathy. There is general agreement that aluminum, once attached to the chromatin in a neuron, cannot be dislodged by any means available to the organism. Yet the presence of aluminum in serum shows that at least some trace will always be able to pass biologic barriers and ultimately reach critical neuronal chromatin. Alfrey shows that the aluminum content of heart and brain remains relatively low until the bone content nears a saturation point, after which aluminum deposition in heart and brain accelerates (Figure 1).[16] The data on aluminum content of the human aorta by Zinsser, Bjorksten, et al indicate that aluminum content

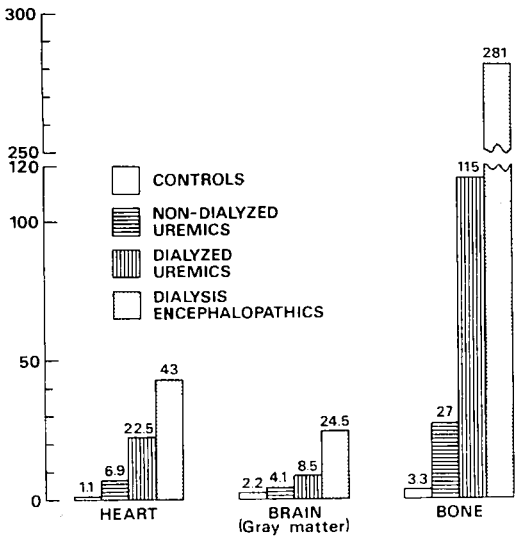

Figure 1. Tissue aluminum concentrations mg/kg dry weight. From Alfrey.[13]

peaks from age 40 to 50 years, and declines moderately thereafter.[17] Thus, it is possible that persons who have the highest body level of aluminum may not survive for five years, but more data are needed to prove this theory.

REFERENCES

1. Crapper DR: Functional consequences of neurofibrillary degeneration, in Terry RR, Gershon S (eds): *Neurobiology of Aging*. New York, Raven, 1976, pp 405-432.
2. Crapper DR, Karlik S, Deboni U: Aluminum and other metals in senile (Alzheimer) dementia, in Katzman R, Terry RD, and Bick KL (eds): *Alzheimer's Disease: Senile Dementia and Related Disorders*. New York, Raven, 1978.
3. LaPresle J, Duckett S, Galle P, Cartier L: Documents cliniques, anatomiques et biophysiques dans une encephalopathie avec presence de depots d'aluminum. *Biol* 1975; 169:282.
4. Galle P, Duckett S: X-ray microanalysis of pallidal arteries in Parkinson's disease. Sixth European Congress on Electron Microscopy, Jerusalem, 1976, pp 210-211.
5. Perl DP, Brody AR: X-ray spectrometric evidence of aluminum accumulation in neurofibrillar tangle bearing neurons. *Science* 1980; 208.
6. Gambetta P, Velasco ME, Dahl D, et al: Neurofibrillary tangles in Alzheimer's disease. An immunohistochemical study in lipid changes. *Aging* 1979.
7. Alfrey AC, LeGendre, Kaehny WD: The dialysis encephalopathy syndrome. Possible aluminum intoxication. *N Engl J Med* 1976; 294:184-188.
8. Alfrey AC: Cassette No. 4 from Conference of Academy of Medical Preventics. Denver, CO, Nov. 2-4, 1979.
9. European Dialysis and Transplant Association: Combined report on regular dialysis and transplantation in Europe. *Proceedings* 1978; 15:4-76.
10. Hagstam KE, Lindergard B, Lindholm T, Thysell H: Aluminum och encefalopati. *Läkartidningen* 1980; 77:2425-2427.
11. Riddick TM: *Control of Colloid Stability through Zeta Potential*. Wynnewood, PA, Livingston Publishing, 1968, pp 274-275.
12. Schlettwein-Gsell D, Mommsen-Straub S: Aluminum, in Ritzel GV: *Spurenelemente in Lebensmittel*. Berne, Verlag Hans Huber, 1973, pp 176-188.
13. American Conference of Governmental Industrial Hygienists: "TLVs" (Threshold limit values) for chemical substances in workroom air 1979; 9.
14. Sylvia AL, LaManna JC, Rosenthal M, Job sis FF: Metabolic studies of methamphetamine effects based upon mitochondrial respiratory state in rat brain. *J Pharmocol Exp Ther* 1977; 201:117-125.
15. Bjorksten J: Aluminum in degenerative disease. *Rejuvenation* 1981; 9:11-19.
16. Alfrey AC: Aluminum metabolism in uremia, in *Neurotoxicology*. In press.
17. Zinsser H, Bjorksten J, Bruck EM, et al: The freezing pool: A unified sequence of the aging process, in Blumenthal HT (ed): *Medical and Clinical Aspects of Aging*. Proceedings, Fifth Congress of the International Association of Gerontology. New York, Columbia University Press, 1962, pp 460-483.