How Aluminum Causes Alzheimer's Disease: The Implications for Prevention and Treatment of Foster's Multiple Antagonist Hypothesis

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Introduction

Aluminum has been identified as a neurotoxin for over 100 years.[1] Its toxic impacts were demonstrated most dramatically when long-term hemodialysis patients (with chronic renal failure) were treated with aluminum-containing phosphate binders, and/or dialysate made using water with high dissolved aluminum levels.[2] Many of these kidney patients developed dialysis dementia and other complications including osteomalacia and osteoporosis.

There are similarities between the brains of Alzheimer's and dialysis dementia patients. Senile plaques have been observed in both, as have decreased levels of choline acetyltransferase activity and gamma-aminobutyric acid concentrations.[3-6] Such similarities have provided further support for the hypothesis that aluminum toxicity is the key to Alzheimer's disease, although many researchers reject this suggestion.[7] Opponents of this viewpoint argue that aluminum deposition in the brains of Alzheimer's patients only occurs late in the disorder, because the blood-brain barrier prevents aluminum entry until it is damaged by extensive nerve cell death or by other causes, such as amyloid deposition. Secondly, they claim that even when incorporated into the brain, aluminum is relatively benign. Thirdly, they point out that pathological changes caused experimentally in animals by aluminum are not identical to those seen in the brains of Alzheimer's disease patients.[9] This article provides evidence to refute such objections.

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Geographical and Epidemiological Evidence of Aluminum's Involvement in Alzheimer's Disease

Drinking water usually contains between 0.01 and 0.15 mg per litre of aluminum, but some potable water may have as much as 0.40 mg per litre or more.[9] While this represents only a small percentage of total dietary aluminum, it is possible that because of repetitious exposure and increased species solubility, aluminum from drinking water may provide a large component of the total aluminum absorbed. Priest[10] has shown that the fraction of dietary aluminum entering the tissues may vary from as much as 0.01 for aluminum citrate to 0.0001 for insoluble species, such as aluminum silicates and oxides. Most of this absorbed aluminum tends to be excreted if kidney action is normal, but about 5 per cent is deposited in the body, mainly in the skeleton.[11] It was established by Sohler and coworkers[12] as early as 1981, however, that in 400 psychiatric outpatients in New Jersey, memory loss increased as blood aluminum levels rose.

It has been shown that, in Norway,[13-14] England and Wales[15] and Canada,[16] the prevalence of Alzheimer's disease rises as dissolved aluminum in potable water supply increases. Conversely, there is some evidence that where drinking water contains the aluminum antagonist fluoride, Alzheimer's disease prevalence may be depressed.[17-18] This latter point is open to debate since the acidity of drinking water greatly affects the aluminum species formed when fluoride is present, some of which are easily absorbed and others not.[19]

Other sources of exposure to aluminum include tea, certain food additives (such as those often found in chocolate), aluminum

foil, cans and cookware, antacids, enteric-coated aspirin and some antiperspirants and deodorants.[20]

Aluminum also is always present in ambient air but numerous industrial workers inhale far more than the 4.4 microgram average daily intake from the air.[10] Inhaled aluminum appears to be neurotoxic under certain special conditions. To illustrate, silica has a well known ability to protect against aluminum and vice versa. For this reason, between 1944 and 1979, many miners were given aluminum powder as a prophylaxis against silicotic lung disease. An aluminum "bomb" was let off after each shift and the miners inhaled its dust in an effort to protect themselves against silica. During a study[21] conducted during 1988 and 1989, miners who had been exposed to aluminum dust in this way were found to show abnormal cognitive deficits, their neurological problems increasing with the duration of their exposure.

Probably the most significant evidence of the possible link between dementia and aluminum comes from an Ontario study involving 668 autopsy-verified Alzheimer's disease brains. These showed that the risk of developing Alzheimer's disease is about 2.5 times greater in individuals from communities drinking water containing more than 100 mcg per litre of aluminum, than it is in individuals from communities where the potable water contains less than this level of aluminum.[22]

It is not the author's objective here to present all the epidemiological and geographical evidence that is available to support a role for aluminum in Alzheimer's disease. Readers wanting a more comprehensive introduction to this literature are directed to Doll's[9] "Review: Alzheimer's disease and environmental aluminum" in *Age and Ageing* and to the double edition of *Environmental Geochemistry and Health* that was devoted largely to this topic.[23]

Foster's Multiple Antagonist Hypothesis

Numerous hypotheses have attempted to explain the neurodegenerative processes that ultimately culminate in Alzheimer's disease. These focus, for example, on calcium homeostasis,[24] beta-amyloid protein and the apolipoprotein- E4 allele.[25] None of these hypotheses, however, appear able to account for all the diverse geographical, sociological, pathological, biochemical and clinical aspects of the disease. For this reason, the author is presenting a new multiple antagonist hypothesis which appears capable of explaining more fully the etiology of Alzheimer's disease.

Antagonism among elements is widely established. To illustrate, many diseases in livestock occur because fodder, enriched in particular minerals, results in shortages of others. Cobalt deficiencies, which cause wasting in sheep and cattle, for example, can usually be linked to a high iron and manganese soil content.[26] Such relationships between minerals are commonplace and appear to occur because ions with similar valence of electronic shell structures, or similar electronic configurations,[27-30] are antagonistic towards each other. Aluminum shows this type of antagonism towards divalent metals including zinc, phosphorus, calcium and magnesium.[31-34] Aluminum's biological activity is influenced further by at least two other elements, silicon and fluorine, some compounds of which are able to chelate it while others promote its solubility. Dietary levels of minerals formed from these six elements greatly affect aluminum's absorption by the digestive tract and its ability to cross the blood-brain barrier. If it reaches the brain, aluminum's negative impact again is due largely to its antagonism with calcium, magnesium, phosphorus and zinc, since it has a strong tendency to replace them in important enzymes and proteins. The resulting novel compounds then create cascades of biochemical dysfunctions which eventually cause neuronal degeneration, ultimately culminating in Alzheimer's disease. Evidence to support this hypothesis is presented now,

together with a discussion of its implications for the prevention and treatment of this form of dementia.

Alzheimer's Disease: the Challenge

Alzheimer's disease affects at least 4 million people in the United States and probably over 11 million more world-wide, chiefly in the developed world.[25] It is most common in the elderly, but between 2 and 7 percent of cases are associated with inherited genetic mutations which can cause the disease in people as young as 30 years old. Three rare genes have been implicated in such early-onset Alzheimer's cases, but these stand apart from the major susceptibility genes linked to Alzheimer's in the elderly. Most Alzheimer's patients, however, develop the disease after age 65, without any previous family history of this disorder.[25] Apart from genetic susceptibility and aging, other identified risk factors for the disease are malnutrition, lack of education and head trauma.[25, 35-36]

Alzheimer's disease, a normally irreversible brain disorder, is characterized by insidious onset and progressive loss of intellectual capacity. This decline in the ability of the brain to function is linked to the formation of senile plaques, neurofibrillary tangles and to the granulovascular degeneration of neurons in the cerebral cortex.[37] Other nerve cell degeneration in the subcortical area of the brain also has been recorded.[38] Such brain abnormalities were documented first by the German physician Alois Alzheimer in 1907,[39] hence the name of the disease.

Biochemically, Alzheimer's disease is known to involve malfunctions in the cholinergic and catecholaminergic systems which are linked, for example, to deficiencies of the neurotransmitters acetylcholine and dopamine. Another hallmark of Alzheimer's disease is a decrease in brain glucose metabolism. Such changes in the brains of Alzheimer's patients are not typical of aging. Indeed, Byell and Coleman[40] suggest that while degenerative dendritic changes do occur in some cells as a usual consequence of aging, these seem associated with a simultaneous thickening of branches in other cortical neurons. This suggests that in normal aging there is an attempt to compensate for neural degeneration which does not occur in Alzheimer's brains.[41]

Typically, memory loss is the first obvious sign of the early stage of Alzheimer's disease. Then subtle personality shifts begin to appear, including signs of apathy and withdrawal. By the middle stage of the disease appearance and behaviour tend to deteriorate and wandering may become more apparent. Intellectual personality disturbances increase and depression or delusions may appear, followed by delirium. As progression occurs, the patient may become mute, incontinent and incapable of self-care. Death ultimately follows. From onset to mortality, the average course of Alzheimer's disease is usually between 5 to 8 years.

Any hypothesis attempting to explain the etiology of Alzheimer's disease must, therefore, be able to account for the disorder's known risk factors (such as its increasing frequency with age), its links to genetic aberrations, its associated neurological and biochemical abnormalities and its clinical symptoms.[25] The rest of this article is an attempt to meet this challenge.

Aluminum's Absorption by the Intestinal Tract

While exposure to aluminum is ubiquitous, how much of it is absorbed by the intestinal tract and how easily this is excreted depends upon a variety of complex interrelationships. To illustrate, there is considerable evidence to show that when dietary calcium intake is low, or when aluminum intake is very high, the latter may substitute for the former, or may use some of the same transport mechanisms to gain access to the brain.[42] This is most likely to occur in individuals drinking acidic water, which may explain why the

prevalence of Alzheimer's disease increases in areas that experience acid rain.[43] Relationships between aluminum and calcium are complex, as illustrated by the impact of aluminum-containing antacids on the absorption of calcium and other minerals.[44] Even small doses of such antacids significantly increase fecal fluoride, indicating a decline in its intestinal absorption. Antacids that contain aluminum also impact on phosphorus and calcium metabolism, and their primary effect is the complexation of intestinal phosphorus, which results in its depletion. This change in phosphorus metabolism results in a rise in urinary and fecal calcium excretion, which often is sufficient to produce a negative calcium balance. Animal experiments suggest that aluminum absorption also is greatly affected by parathyroid hormone and active vitamin D levels, both of which are involved in calcium homeostasis. Rats[45] fed on a diet containing elevated aluminum, for example, produced high levels of parathyroid hormone, which in turn increased gastrointestinal aluminum absorption. This element was subsequently deposited in the brain. Chickens given supplements of active vitamin D also developed increased aluminum brain content.[46] In contrast, dogs with low levels of vitamin D suffered significantly more aluminum accumulation in their bones, independently of parathyroid hormone status.[47]

Such animal studies also demonstrate that diets deficient in calcium alone, or low in calcium and magnesium (with or without added aluminum) can reduce absorption of magnesium and increase that of aluminum.[48] Low calcium and high aluminum diets in rats, for example, diminish magnesium in the bone and in the central nervous system, and induce loss of calcification in the former and tissue degeneration in the latter.[49] Furthermore, aluminum has been shown to decrease the zinc concentration of the bones and soft tissues of rats fed a low calcium-magnesium diet.[50] Beyond this, it has been established that in rats fed magnesium-deficient diets there is diminished kidney function,[51] which seems likely to provide greater access of aluminum to soft tissues. This decline in kidney function is associated with calcium deposition in tubules. The antagonism between magnesium and aluminum, therefore, is clearly established[52] but it would appear that magnesium intake also influences the bioavailability of both calcium and zinc.

Aluminum also has a high affinity for silicon which influences its absorption by the intestinal tract. This was demonstrated by a British clinical trial, conducted by Edwardson and coworkers,[53] in which volunteers were given an aluminum tracer (^{26}Al) dissolved in orange juice. Elevated levels of this element were later detected in their blood. Six weeks later the same volunteers drank orange juice, again containing aluminum but to which sodium silicate also had been added. After this second challenge, blood aluminum level rose to only 15 percent of that previously reached in the absence of silica. Edwardson and colleagues argued that the geographical association between Alzheimer's disease and levels of aluminum in water supplies reflects this inverse relationship between aluminum and silicates. It is believed silica promotes the formation of aluminosilicate species, limiting the gastrointestinal absorption of aluminum.

Fluorine also has an affinity for aluminum and influences its absorption. Fucheng and coworkers,[54] for example, have described high incidences of osteoporosis, osteomalacia, spontaneous bone fractures and dementia in certain villages in Guizhou Province, China. These diseases are very similar to those occurring in European dialysis patients, treated with water and gels containing aluminum.[55] Fucheng and colleagues discovered that such Chinese health problems stemmed from eating maize which had been baked in fires of coal

mixed with kaoline. The latter contained 19.3 percent aluminum and 7000 ppm fluorides. In this area, fluoride levels in drinking water also were elevated. Bone aluminum and fluoride levels were found to be 25 times higher in maize-eating villagers than they were in controls. Tests with rats confirmed that in the presence of elevated fluorides, the toxic dose of aluminum in food may be reduced to 100 ppm or less. The implications of this fluoride-aluminum relationship to Alzheimer's disease are unclear, but demonstrate that aluminum can be neurotoxic in individuals who do not suffer from kidney malfunction.

The solubility of aluminum and probably the ease with which it is absorbed varies markedly with pH, being lowest at about pH 6.5.[56] Aluminum's solubility, therefore, is greatest in highly acid or highly alkaline waters. However, since the latter usually contain elevated calcium and/or magnesium it tends to be the greatest health threat when dissolved in acidic water. It is also believed that fluorine complexes aluminum at acidic pH values, forming species such as solvated AlF^{2+} and AlF_2.[57] At a higher pH, the predominant form of aluminum is $Al(OH_4)^-$. These relationships have been discussed at length by Forbes and coworkers.[19] In general, therefore, aluminum is most soluble in acidic water, especially if it contains fluorides. Tennakone and Wickramanayake[58] for example, have shown that the presence of only 1 ppm of fluoride in water adjusted with sodium bicarbonate or citric acid to pH3, and boiled in an aluminum vessel, releases nearly 200 ppm aluminum in 10 minutes. Prolonged water boiling can elevate dissolved aluminum to 600 ppm. In contrast, if such water contains no fluoride, only 0.2 ppm aluminum levels are reached. In addition, in 10 minutes, 50 grams of acidic crushed tomatoes cooked in 200 ml of water containing 1 ppm fluoride produced a paste containing 150 ppm aluminum. In summary, acidic food or water, especially if fluoride is present, can leach excessive

aluminum from cooking vessels. Furthermore, tea brewed in soft (acidic) water or flavoured with lemon juice contains significantly higher levels of bioavailable alum-inum[59-60] than normal. These links between fluorine and aluminum may be of great significance in Alzheimer's disease since, in a recent study, Varner and co-workers[61] have demonstrated that the chronic administration of the fluoraluminum complex (AlF_3) to rats, in drinking water, resulted in elevated aluminum levels in brains and kidneys. These high levels of aluminum were associated with damage to rat neuronal integrity, not seen in controls drinking double distilled deionized water.

Beyond such antagonistic and synergistic relationships with specific bulk and trace elements, it is clear that certain aluminum compounds inherently are more easily absorbed than others. McLachlan and Kruck,[62] for example, have fed a wide variety of aluminum compounds to rabbits to establish variations in absorption rates. They discovered that aluminum citrate, formed when aluminum reacts with the citric acid in oranges or tomatoes, caused the absorption of aluminum to increase by a factor of 2.5. This is of particular interest because oranges and tomatoes also are known to increase calcium absorption, which needs acid for assimilation.[63] McLachlan and Kruck's rabbit experiments further established that aluminum maltolate, produced when this metal reacts with maltol (an additive that usually is found in hot chocolate, beer and some commercially baked goods), raised aluminum uptake some ninetyfold. Aluminum citrate and aluminum maltolate, therefore, seem particularly capable of entering the body.

Aluminum and the Blood-Brain Barrier

Investigators who oppose the pathogenicity of aluminum in Alzheimer's disease have claimed that the blood-brain barrier will prevent this neurotoxic metal from impacting on the brain until after se-

rious damage already has occurred from other causes.[64-65] This argument is incorrect. Yumoto and coworkers[66] injected the radioisotope [26]Al into healthy rats and showed that a considerable amount of this aluminum isotope was incorporated into the cerebrum within five days after one injection and continued to show a gradual increase in the brain for a further 70 days. This accumulation of aluminum was accompanied by a decline in dendrites in cortical nerve cells and in attached spines. These changes implied a decrease in the amount of information that could be received. Many similar changes have been reported from Alzheimer's brains.

Aluminum's ability to cross the blood-brain barrier is influenced by the form in which it is absorbed and the levels of other compounds in the blood. To illustrate, it has been discussed previously that aluminum maltolate is absorbed easily by the intestinal tract. It appears also to be capable of quickly crossing the blood-brain barrier.[67] Furthermore, as it does, it increases the permeability of this barrier, a process with subsequent serious toxicity implication. That is, aluminum maltolate may affect the blood-brain barrier adversely, making it permeable to other damaging toxins. This may account for the variety of symptoms seen in subtypes of Alzheimer's disease and even in some other forms of dementia. Interestingly, Rao and colleagues[68] have suggested that maltolate-treated, elderly rabbits can be used as a good animal model of Alzheimer's disease because of their neurofibrillary pathology.

Aluminum maltolate is not the only substance that can enhance aluminum's ability to cross the blood-brain barrier. To illustrate, Deloncle and coworkers[69] have shown that when there is an increase in sodium L-glutamate in whole blood, plasma aluminum penetrates red blood cells. This suggests that aluminum crosses the erythrocyte membrane as a glutamate complex. Experiments with rats have dem-

onstrated that similarly, aluminum can pass the blood-brain barrier as a glutamate complex and then be deposited in the cortex. This aluminum-L-glutamate complex is neurotoxic in vivo.[70] Nevertheless, aluminum enters neurons and alone induces possible conformational changes in tau which are detected by the Alz-50 antibody. Aluminum combined with glutamate or glutamate by themselves do not.[71]

Aluminum and the Brain

On reaching the brain, aluminum begins to antagonistically replace calcium, magnesium, zinc and phosphorus in various enzymes and proteins. As a consequence, it sets in motion a series of biochemical cascades involving abnormal processes, which together eventually culminate in the pathologic and clinical symptoms known as Alzheimer's disease. Several examples will now be provided, but no claim is made here that all such antagonistic relationships have been identified, or that they are necessarily limited to calcium, magnesium, zinc and phosphorus.

(i) Aluminum and glucose metabolism

Decreased glucose metabolism is a hallmark of Alzheimer's disease.[72] It appears to occur because of aluminum's binding with the phosphate enzyme, glucose-6-phosphate dehydrogenase and its interference with hexokinase.[73] To illustrate, Cho and Toshi[74] purified two isozymes from pig and human brains and established that they contained an enzyme-aluminum complex. They were then able to demonstrate that glucose-6-phosphate could be completely inactivated by aluminum, but that this enzyme's potency could be restored by the three aluminum chelators: citrate, sodium fluoride and apotransferrin. Aluminum's negative impact on glucose metabolism, however, is not limited to inhibiting the glucose-6-phosphate enzyme. Lai and Blass[75] have shown that this metal also inhibits hexokinase activity in the rat

brain, but that high levels of magnesium can reverse this process. Aluminum also appears to inactivate hepatic phosphofructokinase, an important control site in the glycolytic pathway.[76]

(ii)Aluminum and the cholinergic system

Cholinergic neurotransmitter deficits are characteristic of Alzheimer's disease.[25] Indeed, a deficiency of acetylcholine is the basis for a recognized diagnostic test for this disorder.[77] Such malfunctioning of the cholinergic system appears to be caused by aluminum's ability to inhibit the activities of the enzyme choline acetyltransferase,[78-80] a deficiency of which has been confirmed in Alzheimer's disease by several researchers including Perry,[81] Gottfries[80] and Quirion and coworkers.[82] In addition, some neuritic plaques have been shown to contain acetylcholinesterase-beta amyloid protein complexes, further compromising the functioning of the cholinergic system.[83] As is described in the following discussion, the development of such plaques is also the result of aluminum's disruptive influence.

Interestingly, Gottfries and colleagues[84] have established that in the early stages of Alzheimer's disease, elevated serum homocysteine appears to be a sensitive marker for cognitive impairment.[85] Choline deficiency raises homocysteine levels by altering the metabolism of methionine[86] and would, therefore, account for both homocysteine's presence at high levels in the serum and associated cognitive impairment. Certainly, there is an extensive literature [87-91] that indicates that the malfunctions that occur in the cholinergic system in Alzheimer's disease are accompanied by selective degeneration of cholinergic neurons in the cortex, hippocampus and base of the forebrain. This is highly significant because such acetylcholine-containing neurons play a key role in memory and affect the highest levels of cognitive functioning.

(iii) Aluminum and the catecholaminergic system

Altman and coworkers[92] have shown that, in patients on hemodialysis, levels of the enzyme dihydropteridine reductase are inversely related to serum aluminum concentrations. When such patients were given the aluminum-chelating agent desferrioxamine, their dihydropteridine reductase activity doubled. This depression of dihydropteridine reductase by aluminum is extremely significant since this enzyme is essential for the maintenance of normal brain concentrations of tetrahydrobiopterin, which is itself required for the synthesis of the neurotransmitters, dopamine, norepinephrine and serotonin.

As might be expected, if Alzheimer's is caused by aluminum neurotoxicity, levels of tetrahydrobiopterin are depressed significantly in the cerebrospinal fluid of patients suffering from this disease.[93] As a consequence, the brains of Alzheimer's patients contain more neopterin[94] and less dopamine, norepinephrine and serotonin than those of controls.[95-96]

Several studies have demonstrated that the subnormal production of these neurotransmitters appears to be linked to the death of dopamine receptors and noradrenergic and serotonergic neurons in the cortex and elsewhere in the Alzheimer's brain. Joyce and coworkers,[97] for example, argued that the loss of the D2 receptor-enriched modules in the brains of Alzheimer's patients contributed to disturbances in information processing that may be responsible for cognitive and non-cognitive impairments. Similarly, Palmer[98] has suggested that the absence of noradrenergic and serotonergic neurons probably contributes to the non-cognitive impairments in behaviour seen in Alzheimer's patients.

It is possible that aluminum impacts more directly on the catecholaminergic system. Marinho and Manso,[99] for example, have studied the effects of different concentrations of aluminum sulphate on the nonenzymatic oxidation of dopamine, con-

ducting these experiments to evaluate the action of aluminum on neuromelanin synthesis. Their results indicate that aluminum partially inhibits dopamine self-oxidation, decreasing the formation of such intermediate compounds as dopaminequinone and dopaminochrome. This suggests that if, as believed, neuromelanins have a cytoprotective function in the central nervous system, where they are thought to act as free scavengers of redox metal ions and free radicals, then their reduction by aluminum could accelerate the damage of neuronal tissues by oxidative stress.

Furthermore, Singh and colleagues[100] have described the high toxicity of aluminum phosphide which is used widely as a fumigant in India. Accidental poisoning with this aluminum compound is relatively common and its dominant clinical feature is severe hypotension related to dopamine. This appears to further confirm that aluminum has a direct impact on the catecholamine system.

Wenk and Stemmer[101] have shown that, in rats, the neurotoxic effects of ingested aluminum are dependent on the dietary intake of copper, zinc, iron and magnesium. To illustrate, norepinephrine levels in the cortex and cerebellum are depressed in rats receiving a high aluminum, low copper diet. Similarly, suboptimal iron levels reduce norepinephrine in the cerebellum. Furthermore, diets containing aluminum but little copper or zinc decreased cortex dopamine levels. These data suggest that aluminum's impact on the catecholaminergic system is complex and depends very much on the presence, or absence, of adequate levels of various bulk and trace elements in diet.

(iv) Aluminum and parathyroid hormone

Adenylate cyclase is a catecholamine sensitive enzyme[102] that plays a significant role in parathyroid hormone secretion. Calcium inhibits adenylate cyclase activity but magnesium promotes it, so stimulating the production of parathyroid hormone.[103] Indeed, Zimmerman and colleagues[104] have suggested that the adenylyl cyclase catalytic mechanism involves two magnesium ions. Animal studies have established that aluminum can cause an irreversible activation of adenylate cyclase that Ebstein and coworkers have suggested may be one reason for this metal's neurotoxicity.[105] Indeed, although while adenylate cyclase activity declines in the non-demented elderly, no such reduction is seen in Alzheimer's patients, who typically show abnormally high brain adenylate cyclase activity.[106]

(v) Aluminum and the glutamatergic system

There is a profound reduction in glutamatergic neurotransmission in Alzheimer's disease that results from the loss of pyramidal neurons and cholinergic innervation.[107] This deficit is associated with significantly depressed plasma glutamate levels and abnormally low glutamine cerebrospinal fluid/plasma ratios.[108] Furthermore, there appears to be a strong correlation between behaviour and coping ability in Alzheimer's patients and cerebrospinal fluid glutamate levels, which provides clear evidence of a role for the disruption of amino acid metabolism in the disease.

Rabbit studies with intracisternally administered aluminum-powder have shown that this element causes significant decreases in glutamate decarboxylase activity in the cerebellum.[109] In addition, aluminum impairs the glutamate-nitric oxide-cyclic GMP pathway in neurons[110] and appears to inhibit glutamate release from the rat hippocampus.[111] Aluminum chloride also has been shown to slow the rate of accumulation of L-glutamate in rat forebrain nerve-ending particles, in a dose-dependent fashion, so influencing neurotransmitter substance transport.[112] As has been discussed previously when reviewing aluminum's ability to cross the blood-brain barrier, aluminum can react with glutamate to form an aluminum L-glutamate complex

that is neurotoxic in vivo.[69,70] This may be because aluminum, as has been shown, potentiates both glutamate-induced calcium accumulation and iron-induced oxygen free radical formation in primary neuronal cultures,[113] suggesting that the aluminum-glutamate association may increase neuronal oxidative stress.

(vi) Aluminum and neuritic plaques

The brains of Alzheimer's patients are characterized by neuritic plaques, which are composed of abnormal proteins. The cores of such plaques consist of beta-amyloid, a sticky snippet of a larger protein, amyloid precursor protein. It has been established that beta-amyloid involved in such plaques is created when the brain is deficient in acetylcholine, a shortage that causes amyloid precursor protein to break down.[78,114] As has been discussed previously, acetylcholine deficiency is a hallmark of Alzheimer's disease because of aluminum's ability to inhibit the activities of the enzyme choline acetyltransferase,[78] so interfering with the normal operation of the cholinergic system.[83] In addition, as pointed out already, some neuritic plaques contain acetylcholinesterase-beta amyloid protein complexes, which further disrupt the cholinergic system.[83]

Perry[115] has demonstrated that in post-mortem Alzheimer's brain tissue, there is an inverse relationship among the activities of choline acetyltransferase and acetylcholinesterase and senile plaque numbers. Furthermore, plaques that contain acetylcholinesterase have a higher resistance to low pH and to anti-cholinesterase inhibitors and are more cytotoxic than normal plaques.[116]

(vii) Aluminum and neurofibrillary tangles

Neurofibrillary tangles also are a characteristic of Alzheimer's brains. Such tangles consist mainly of an abnormal form of the protein tau which is highly and unusually phosphorylated.[117] Calcium/calmodulin kinase II acts as a catylist in the phosphorylation of tau,[118] a process that is stimulated by two phospholipids,[119] phosphatidylserine and phosphatidyl-ethanolamine. However, aluminum interacts with calmodulin by displacing the Ca-ion to form a stable Al-calmodulin complex.[117-120] Under these circumstances, calmodulin becomes less flexible, is prevented from reacting with several other proteins and is inhibited in its regulatory functions. In addition, aluminum creates fatty acid abnormalities in the phospholipids, which normally stimulate the phosphorylation of tau.[117,121]

Beyond this Yamamoto and colleagues[122] have shown that aluminum appears to inhibit the dephosphorylation of tau in the rat brain. It seems likely, therefore, that in the presence of elevated aluminum both phosphorylation and dephosphorylation of tau are disrupted, largely by the replacement of calcium by aluminum in calmodulin.

Furthermore, hemodialysis patients exposed to elevated aluminum develop depressed serum alkaline phosphatase levels.[123] Abnormally low phosphatase concentrations also have been reported from Alzheimer's patients' brains.[124] Aluminum-induced abnormalities in levels of phosphatases, enzymes required to remove phosphate groups from protein, also appear to be involved in the formation of neurofibrillary tangles. It would appear that such aluminum-induced lack of phosphatase,[125] in the brains of Alzheimer' patients, occurs because of an excess of phosphates in tau that prevent this protein from performing its normal role of securing vital parts of the neuronal cytoskeleton. The cell, therefore, is harmed and hyperphosphorylated tau is precipitated to form tangles. According to Roushi[126] animal studies suggest that such extra phosphates may cause neural damage even before tangles form, by interfering with one of tau's normal functions, assembling and stabilizing the microtubules that carry cell organelles, glycoproteins and

other vital substances through neurons.

It has been demonstrated that the more phosphate groups that are attached to synthetic neurofilament fragments, the easier it is for aluminum ions to bind and cross-link neurofilaments.[125] The presence of aluminum, therefore, appears to change the paired helical filaments that make up neurofibrillary tangles so that they accumulate and are not removed, in the normal way, by protein-digesting enzymes.

Interestingly, a laser microprobe study of the elemental content of neurofibrillary tangles in Alzheimer's disease, conducted by Good and coworkers,[127] established that the only metallic elements found to be consistently present were aluminum and iron.

(viii) Aluminum and brain cell membranes

In Alzheimer's patients, cellular brain membranes display abnormal viscosity which appears to disrupt the activities of various enzymes, receptors and membrane carriers and may be linked to dendritic spine loss.[128] These abnormalities seem associated with irregularities in the biochemistry of the phospholipids that concentrate in such brain cell membranes. Corrigan and coworkers,[130] for example, have shown that in Alzheimer's disease phospholipids from the parahippocampal cortex, including phosphatidylcholine, phosphatidylserine and phosphatidylinositol, contain below normal levels of alpha-linolenic acid. In addition to this depression of the level of n-3 polyunsaturated fatty acid, abnormalities also occur in levels of n-6 essential fatty acids. It has further been demonstrated further that, not only are the biochemical compositions of phospholipids from Alzheimer's patients abnormal, but that total concentrations of such membrane phospholipids are low[130] and that their regional distribution in the brain is irregular.[131]

It has been suggested that the biochemical abnormalities seen in phospholipids in Alzheimer's disease result from elevated oxidative stress.[121] However,

aluminum also appears more directly involved. To illustrate, aluminum chloride has been shown to inhibit the incorporation of inositol into phospholipids.[132] Deleers and coworkers[133] also have demonstrated aluminum-induced lipid phase separation and fusion of phospholipid membranes. However, it seems more likely that disruption of phospholipase A2 by aluminum [134] is probably the main cause of the biochemical abnormalities seen in phospholipids in Alzheimer's disease, and the chief cause of associated brain membrane dysfunctions. Certainly, phospholipase A2 plays a key role in the metabolism of membrane phospholipids,[135] is decreased in Alzheimer's disease[136] and is inhibited by aluminum chloride.[134]

In addition, aluminum has a direct effect on cell membranes. Dill and coworkers, [137] for example, have proved that the addition of micromolar quantities of aluminum chloride to phospholipid membranes containing VDAC channels greatly inhibits the voltage dependence of the channels' permeability, encouraging them to remain open. It would appear, therefore, that both through its antagonism with phosphorus and by its own direct impact, aluminum adversely affects the functioning of cellular brain membranes in Alzheimer's disease.

(ix) Aluminum and oxidative stress

There is overwhelming evidence that Alzheimer's disease brain cells are subjected to elevated oxidative stress and that amyloid plaques are a focus of cellular and molecular oxidation. Much of the destruction of neurons which characterizes Alzheimer's disease has been linked to the lipid peroxidation of cell membranes caused by free radicals. This process seems to occur because of disturbed defense mechanisms in Alzheimer's disease which are associated with a self-propagating cascade of neurodegeneration.[138-139] It has been established, for example, that Alzheimer's patients display depressed plasma antioxi-

dant status associated with significantly low vitamin E levels.[140]

There is considerable evidence that aluminum itself reduces the body's defense against free radical damage. In dialysis patients, for example, serum glutathione-peroxidase levels are significantly depressed.[141] Similarly, animal studies have demonstrated that the oral administration of aluminum sulphate, especially in the presence of citric acid, inhibits brain superoxide dismutase and catalase activities.[142] Interestingly, vitamin E, which is depressed in Alzheimer's patients, can protect rats against associated aluminum-induced free radical damage.[143] Other evidence of the significance of oxidative stress includes a significant increase in erythrocyte Cu/Zn superoxide dismutase and catalase activity in the blood of Alzheimer's patients[144] and a pronounced increase in superoxide dismutase immunoreactivity in olfactory epithelium.[145]

Exactly how aluminum is involved in the catastrophic loss of neurons from free radical damage is being established by van Rensburg and coworkers[139,146] and Fu and colleagues.[147] The former have shown, for example, that both beta-amyloid and aluminum dose-dependently increase lipid peroxidation in platelet membranes. Their research has established that beta-amyloid is toxic to biological membranes and that aluminum is even more so.[146] Beyond this, van Rensburg and colleagues have demonstrated that iron encourages lipid peroxidation both by aluminum and by beta-amyloid protein. This is of considerable interest since the only metallic elements found in the neurofibrillary tangles of Alzheimer's disease are aluminum and iron.[127] Van Rensberg and coworkers' in vitro model also showed that melatonin prevented lipid peroxidation by aluminum and beta-amyloid protein in the absence of hydrogen peroxide. If the latter were present, melatonin could only slow the process.[146]

Fu and coworkers[147] have begun to explain how beta-amyloid specifically damages neurons. Their cell culture research has shown that beta-amyloid interferes with calcium homeostasis and induces apoptosis in neurons by oxidative stress. This latter process involves the catecholamines (nonepinephrine, epine-phrine and dopamine) which increase beta-amyloid's toxicity to cultured hippocampal neurons. These findings are very consistent with the much earlier research of Hoffer, Osmond and Smythies[148-149] who argued that the oxidation of adrenalin to adrenochrome was responsible for the hallucinogenic symptoms seen in schizophrenia. More recently, Hoffer[150] has suggested that the oxidation of dopamine to dopachrome lies behind the psychotic symptoms seen in Parkinsonism, in many long-term levodopa users. Fu and coworkers[147] also have been able to show that the antioxidants vitamin E, glutathione and propyl gallate can protect neurons against damage caused by amyloid beta-peptide and the catecho-lamines.

Aluminum also may increase free radical damage in Alzheimer's disease by inhibiting the protective copper/zinc metalloenzyme, superoxide dismutase. Normally, this is one of the major enzymes that provides protection against free radicals. However, Shainkin-Kesterbaum and coworkers[151] showed that in vitro, at the levels of the enzyme found in dialysis patients, aluminum severely inhibited its protective effects. This inhibition of superoxide dismutase's antioxidant activity was directly proportional to the level of aluminum. Silicon was found also to have a similar inhibitory effect on the enzyme. The disruptive influence of aluminum on superoxide dismutase may account for the fact that, while zinc supplementation generally improves mental alertness in the elderly, in Alzheimer's patients it accelerates deterioration of cognition, encouraging amyloid plaque formation.[152] This may be because in the latter stages of Alzheimer's disease it cannot be

used in disrupted superoxide dismutase production and so merely stimulates free radical formation.

Aluminum and Established Risk Factors in Alzheimer's Disease

Any hypothesis seeking to explain Alzheimer's disease must be able to account for established risk factors, namely: malnutrition, susceptibility genes, head trauma, aging and lack of education.[25] An attempt will be made now to do this for Foster's multiple antagonist hypothesis.

(i) Malnutrition

Throughout this article, evidence has been presented to show that diet influences aluminum's absorption, ability to cross the blood-brain barrier and likelihood of causing brain damage. Furthermore, Grant[153] has shown that epidemiological evidence is consistent with the view that low fat, low calorie diets may lessen the risk of Alzheimer's disease. Interestingly, Mazur and coworkers[154] have established that, in the rat, low selenium diets increase plasma apolipoprotein E levels. Similarly, Durlach and colleagues[155] have suggested that, in humans, vitamin E, selenium, magnesium and other antioxidants can protect against the deleterious metabolic consequences of apolipoprotein E4-4.

(ii) Genetic susceptibility to Alzheimer's disease

Recent studies have shown that elderly Japanese and African-Americans living in the United States have a much greater prevalence of Alzheimer's disease than those still residing in their ethnic homelands. Environmental not genetic factors must, therefore, be the major agents responsible for Alzheimer's disease.[156-157] Nevertheless, the likelihood of any first-degree relative of a late-onset Alzheimer's patient also developing the disease is some four times greater than in the population at large.[158] There must be, therefore, at least one genetic component to Alzheimer's disease. In fact, there appear to be several such links. To date four genes have been identified as playing a role in either early or late-onset Alzheimer's: beta-amyloid precursor protein, presenilin-1, presenilin-2 and apolipoprotein E genes.[159] Workers have linked most of these variants to familial early-onset Alzheimer's but the apolipoprotein E-4 allele is a relatively common definite risk factor for developing late-onset Alzheimer's disease.[25]

Considerable progress has been made in interpreting the significance of such genetic variants. To illustrate, mutations in the presenilin-1 gene seem associated with increased superoxide production and greater vulnerability to amyloid beta peptide toxicity.[160] Interestingly, mutations in the presenilin genes, which are linked to more than 40 per cent of all familial Alzheimer's disease cases, cause enhanced production of an abnormal form of beta-amyloid precursor protein.[161] This protein is longer than normal, aggregates more rapidly, kills neurons in culture more effectively and precipitates preferentially to form amyloid plaques. The same elongated protein is also produced as a result of mutations in the gene encoding beta-amyloid precursor protein.

As has previously been described, aluminum interacts with L-glutamate to form a complex that can cross the blood-brain barrier.[69] This reaction appears to lead to depressed plasma and cerebrospinal fluid levels of glutamate and glutamine.[162] The largest familial Alzheimer's disease kindred discovered to date occurs in Antioquia, Columbia.[159] These individuals appear to develop Alzheimer's disease because of a genetic mutation that results in a glutamic acid-to-alanine substitution in presenilin-1. That is, members of the Antioquia disease kindred are short of glutamic acid. A similar deficiency might be expected to be associated with aluminum-induced depression of glutamate and glutamine.

An apolipoprotein E variant predisposes a significant section of the population to late-onset Alzheimer's disease.[25] This may occur in several ways. Pratico and coworkers[163] have shown that in apolipoprotein E deficient mice, oxidative stress in increased, encouraging arteriosclerosis. Interestingly, the oral supplementation of vitamin E suppresses this degenerative process. Naiki and colleagues[164] also have demonstrated that normal apolipoprotein E inhibits beta-amyloid fibril formation in vitro. Indeed, it would seem that in normal brains apolipoprotein E efficiently binds and sequesters beta-amyloid peptide, preventing it from forming senile plaques.[165] In Alzheimer's disease, associated with this genetic variant there is impaired apolipoprotein-beta-amyloid peptide binding, resulting in an accumulation of beta-amyloid peptide which facilitates senile plaque formation.

The literature suggests, therefore, that the gene variants that predispose to both early and late-onset Alzheimer's disease do so because they either increase susceptibility to, or mimic, the aluminum-related degenerative processes previously described. That is, the genetic mutations involved in promoting the development of Alzheimer's disease duplicate some of aluminum's deleterious impacts on the brain and in so doing, encourage at least one of the following: the growth of neuritic plaques or neurofibrillary tangles, excessive free radical formation and higher neural oxidative stress. As a consequence, unfortunate individuals carrying any one of the genetic variants are much more likely to develop Alzheimer's disease, whether or not they are exposed to the aluminum excess or vitamin and mineral deficiencies, that are normally associated with its etiology.

(iii) Head Trauma

Controversy continues over whether or not traumatic brain injury increases the probability of developing Alzheimer's disease.[166] Launer and coworkers[167] sought to answer this question by performing a pooled analysis of four European population-based prospective studies of individuals aged 65 years and older. These data included 528 incident dementia patients and 28,768 person-years of follow-up. Their analysis established that a history of head trauma with unconsciousness did not increase significantly the risk of subsequent Alzheimer's disease. Similarly, Nemetz and colleagues[168] followed up the medical histories of 1,283 traumatic brain injury cases, that had occurred in Olmsted County, Minnesota, from 1935 to 1984. Thirty-one of these trauma patients subsequently had developed Alzheimer's disease, a number similar to that normally expected in individuals without head injuries. However, the data clearly shows that such head trauma had reduced the time-of-onset of Alzheimer's disease by about 8 years, amongst persons at risk for developing it. That is, head trauma does not appear to increase the probability of developing Alzheimer's disease in the general population, however, those prone to it tend to suffer from it earlier than normally expected.

Why this happens is a question which appears to have been answered by Nicoll and coworkers.[169] These researchers have shown that the deposition of beta-amyloid in the brain had been promoted by head trauma, in approximately one third of individuals dying shortly afterwards from severe injury. The probability of deposition of such beta-amyloid, following trauma, is greater than would be anticipated statistically in individuals with the apolipoprotein E-epsilon 4 allele, that is the allele that has been linked to late-onset Alzheimer's disease. In short, in individuals with this genotype, severe head trauma often appears to initiate beta-amyloid deposition. Not surprisingly, if they survive the trauma, such deposition reduces the time-of-onset of sporadic Alzheimer's disease in those genetically prone to it since, of course, beta-

amyloid is the major constituent of neuritic plaques.

(iv) Aging and increased prevalence

In the United States, the prevalence of severe dementia, much of it Alzheimer's disease, found amongst those aged 65 to 74, is roughly 1 percent, compared to 25 percent for those over 84.[170] There is a disputed suggestion that the risk of developing dementia may decline after age 84 is reached,[171] but this hypothesis appears to be in conflict with results of detailed surveys.[172] Evans and coworkers,[173] for example, found that in East Boston, Massachusetts, an urban working class community of some 32,000 inhabitants, an estimated 10.3 percent of the population aged over 65 had probable Alzheimer's disease. The prevalence of this disorder increased steadily with aging, from 3.0 percent at age 65 to 74 years to 18.7 percent for those aged 75 to 84. This trend continued so that 47.2 percent of those 85 years or older were diagnosed as suffering from probable Alzheimer's disease. This age-related increase in dementia was identified again in San Marino.[174] At age 67 only 1.8 percent of the population suffered from it, a figure that rose to 25.0 percent in those 87 years of age. The general situation was summarised by Jorm, Korten and Henderson[175] who, after a survey of the international literature, concluded that dementia prevalence rates reflected the age of the sample population, doubling every 5.1 years.

If the multiple antagonist hypothesis presented here is correct, this increase in risk of developing Alzheimer's disease with aging is inevitable. As the individual ages, intestinal absorptive capacity is reduced, and in consequence calcium absorption drops. In addition, kidney function declines and with it there is a corresponding reduction in the production of active vitamin D, further decreasing calcium absorption in the intestines.[36] These changes typically lead to a loss of bone calcium and, as has been discussed previously, make aluminum absorption far more likely to occur.

Not only is the brain's aluminum burden likely to increase with aging in this way but its ability to protect itself also characteristically declines. Hypovitaminosis, for example, is common in the elderly,[176] who are all too frequently deficient in antioxidants and, therefore, more prone to oxidative stress. Beyond this, two hormones that decline with age, melatonin and estrogen, play roles in protecting the brain from aluminum. As their levels fall, damage from this element inevitably increases. The aluminum relationship to estrogen probably explains why, as Cohen[177] pointed out, Alzheimer's disease is more common in women then in men, a gender bias that cannot be explained entirely by the greater longevity of females.

Sleep disruption, nightly restlessness and other circadian disturbances are common in Alzheimer's disease patients. This behaviour often appears to be associated with abnormally low cerebrospinal melatonin[178] Interestingly, the level of melatonin in such patients have been found to be linked to genotype. Melatonin levels in Alzheimer's disease patients expressing apoliprotein E-epsilon 3/4, for example, were found to be more than double those of patients expressing apolipoprotein E-epsilon 4/4. It has been shown also that the normal daily variations in melatonin disappears in both older subjects and Alzheimer's patients.[179]

This decline of melatonin production in the elderly[180] has many significant implications for Alzheimer's risk. Melatonin, for example, has been shown to alter the metabolism of beta-amyloid precursor protein,[181] prevent beta-amyloid-induced lipid peroxidation and associated toxicity to biological membranes, protect against glutamate excitotoxicity and reduce neural damage due to gamma-aminolevulinic acid.[182] In addition, Pappolla and colleagues[183] have demonstrated that melatonin is remarkably

effective in preventing death of cultured neuroblastoma cells and mitigating oxidative damage and intracellular Ca2+ increases induced by cytotoxic fragments of beta-amyloid protein. That is, melatonin is likely to prevent neural damage caused by glutamate and by beta-amyloid protein, both of which are implicated in the neuronal destruction characteristic of Alzheimer's disease.

The decline of estrogen production in postmenopausal women also increases their risk of developing Alzheimer's disease. Confirmation of this has come from the Italian Longitudinal Study on Aging which provided convincing evidence that estrogen-replacement therapy reduces the prevalence of Alzheimer's disease.[184] It has been shown also that female Alzheimer's patients receiving this hormone have improved cognitive skills.[185] Why estrogen acts in this way is still the subject of extensive research. It has been proved, however, that, in rats, estrogen acts as a growth factor for cholinergic neurons.[186] Gibbs and Aggarwal[187] have hypothesized that there are similar effect in humans and that, as a result, in postmenopausal women receiving estrogen replacement therapy, this hormone delays the decline in basal forebrain cholinergic function, typical of Alzheimer's disease.

(v) Lack of an education

Beyond the possibility that less educated individuals may be more likely to eat inappropriate diets, there appear to be three hypotheses that may explain why the lack of an education might increase the risk of developing Alzheimer's disease. Firstly, it is possible that the apolipoprotein E variant that predisposes a significant section of the population to late-onset Alzheimer's disease might, in some way, also adversely effect an individual's ability to cope with the demands of an education. There seems, however, to be no available evidence to support this hypothesis.

Secondly, education might stimulate

the brain's development, so increasing its ability to withstand more degenerative damage before Alzheimer's symptoms become apparent. There is certainly growing evidence that stimulation affects brain development. To illustrate, Rosenzweig[188] showed that the number of neurons in rats' brains were influenced by the stimuli in the environment. Rats that grew up in an "enriched" milieu were found to have more neurons in the cerebral cortex than those that did not. In addition a rat from an "enriched" environment had a heavier cortex with thicker cortical coverings. Brain enzymes were also elevated. Globus[189] further discovered that such "enriched" environments increased the number of dendritic spines in the rat brain. Perhaps as Restak[190] muses, learning, memory and other brain functions in humans may depend to a large degree on the quality of environmental stimulation.

A third hypothesis that may account for the apparent link between a lack of education and the risk of developing Alzheimer's disease would focus on exposure to toxic metals and inadequate dietary mineral intake. If a child were exposed to elevated aluminum while its calcium, magnesium, zinc and phosphorous intakes were depressed, it might be unable to handle the rigours of higher education. Ultimately, these imbalances might also result in the development of Alzheimer's disease. There is clearly this type of negative relationship between lead exposure and depressed childhood intelligence.[191] Furthermore Varner and coworkers[61] have shown recently that the chronic administration of drinking water containing aluminum-fluoride or sodium-fluoride to rats causes significant deficits in neuronal integrity that show regional brain differences. It has been established also that elevated hair aluminum levels seems to be associated with classroom withdrawal by young children.[192] Much of this aluminum may come from cans but it should be noted that

aluminum concentrations in most cow's milk-derived formulas are 10 to 20-fold greater than in human breast milk. They are also 100-fold greater in soy-based formulas.[193] Deficiencies in trace and bulk elements also appear to adversely influence school performance. To illustrate, Marlowe and Palmer[194] compared 26 hair trace elements in two sets of young Appalachian children: an economically disadvantaged group of 106 drawn from Head Start programs and 56 control group children from more prosperous backgrounds. Developmental disabilities, including communication and behavioural disorders were recorded in 13 members of the Head Start Group, but were absent from the control group. Hair analysis also established that the mean levels of calcium, magnesium and zinc were significantly depressed in children from the economically disadvantaged group. Conversely, Benton[195] reviewed five studies that suggested that vitamin/mineral supplements improved many children's performances during intelligence tests. In summary, the evidence suggests that many children are exposed to excess aluminum, while being simultaneously mineral deficient. Such individuals appear to experience schooling difficulties early in life and may possibly develop Alzheimer's disease when older. This may be particularly true if they eat a high fat diet.[153]

The Prevention of Alzheimer's Disease

The number of elderly is undergoing an unprecedented increase, with the proportion of the very old doubling within one generation. In 1950, globally there were 214 million people 60 or older; by 2025 there will probably be one billion.[196] Not only are more people surviving into old age and, therefore, increasing their chances of developing Alzheimer's disease but those who do so are living longer after its onset. Gruenberg[197] termed this paradox the "failure of success", a tragedy caused largely by progress in medical care. As he and his colleagues[198] point out "the old man's friend, pneumonia, is dead–a victim of medical progress." In consequence, the old man is still with us, but all too often he is demented.

As Khachaturian[25] states the costs of this paradox will be enormous, "... if current demographic trends continue, the number of people with Alzheimer's disease will double every twenty years. The US already spends $100 billion a year on care for Alzheimer's patients: with the rising cost of health care, society will have a monster on its hands". The USA will not be alone. StatsCan predicts that by the year 2031, close to 800,000 Canadians will be demented, two-thirds of them suffering from Alzheimer's disease.[199] This trend is typical of the Developed world.[200]

The author believes that the preceding review has demonstrated that aluminum neurotoxicity is the cause of Alzheimer's disease.[201] At the political level, a series of highly unpalatable steps, therefore, must be taken if the "monster" is not to have its way. These include setting much lower limits for aluminum in drinking water,[202] prohibiting the use of aluminum salts as coagulants in water treatment,[203] reversing the drive for water fluoridation and banning the use of both aluminum cans[204] and the food additive aluminum maltolate.[62] It is obvious also that the recommended daily allowances of many minerals and vitamins, especially antioxidants, are too low and that this inadequacy is reflected in the contents of the average multivitamin pill.[205]

The chances that such changes will be made in the near future are poor. Fortunately, there are many steps that the individual can take to reduce his or her own probability of developing Alzheimer's disease. These include drinking low aluminum potable water, avoiding hot chocolate and acidic drinks in aluminum cans and not using aluminum-containing antacids or deodorants. Cooking utensils should be

stainless steel or glass and foods should not be cooked or stored in aluminum foil. Mineral supplements should include calcium, magnesium and zinc. Probably the best evidence that vitamin supplements also can reduce the risk of developing Alzheimer's disease comes from a prospective study of 633 people aged 65 or older, whose vitamin intake was carefully established.[205] After a 4.3 year follow-up period, 91 of the participants met criteria for the clinical diagnosis of Alzheimer's disease. None of the 27 vitamin E supplement users suffered from it, however, nor did any of the 23 elderly individuals taking vitamin C. Nevertheless, there was no relationship between the incidence of Alzheimer's disease and the use of multivitamins. These data suggest that high dose vitamin E and C supplements lower the risk of Alzheimer's disease; but that multivitamin antioxidant levels are too low to do so.

The Treatment of Alzheimer's Disease

Very few people ever come back from the abyss, but it has been done. The author is aware of only two well documented cases of the "spontaneous regression" of Alzheimer's disease. Fortunately both of these individuals have written books about their experiences.[206-207] In the belief that Siegel[208] is correct that "We should be paying more attention to the exceptional patients, those who get well unexpectedly, instead of staring bleakly at all who die in the usual pattern", their cases will now be reviewed.

Louis Blank[207] was confirmed to have Alzheimer's disease after detailed hospital testing. As his disorder progressed, he lost the ability to recognize his own family or to speak, and to dress, wash or eat without assistance. For six months, at the peak of his illness in 1993, he sat virtually motionless. His recovery appeared to begin after his family replaced all its aluminum cooking utensils and started to avoid aluminum cans. In addition, he was fed a high magnesium diet, designed to chelate aluminum.

By May, 1994 Louis Blank was again able to carry on conversations and venture outside. By January 1996, he had written and published his book *Alzheimer's Challenged and Conquered?*[209] despite the fact that one of his specialists continued to argue that since there is no cure for Alzheimer's disease, he must still have it. An interesting aspect of Blank's description of his experiences is that while most of his long-term memory remains he still has no recollections of his worst six months. This confirms that, as Alzheimer's disease progresses, the patient loses the ability to form short-term memories. Older-term memories appear to remain intact for much longer.

In his book *Beating Alzheimer's: A Step Towards Unlocking the Mysteries of Brain Diseases,* Tom Warren[206] also describes his experiences with dementia. In June 1983, a computer assisted tomography scan confirmed that Warren had Alzheimer's disease. His physicians gave him a maximum of seven years to live. Yet nearly four years later, a new scan indicated that the disease process had reversed. Warren's self-treatment had included rectifying low hydrochloric stomach acid, the removal of all his teeth and mercury amalgam fragments from his gums, ethylene diamine tetracetic acid (EDTA) chelation therapy and high doses of vitamins and minerals. The latter included zinc, calcium, magnesium, and vitamins B_3, B_6, B_{12} and folic acid.

In summary, both Blank and Warren attempted to reduce their exposure to metals, especially aluminum and/or mercury, underwent chelation therapy and added minerals to their diet, especially in Blank's case, magnesium. These protocols seem consistent with the hypothesis presented here, that Alzheimer's disease is caused by aluminium and reflects its antagonistic relationships with zinc, calcium, phosphorus and magnesium. It would seem essential that the Alzheimer's patient, in addition to avoiding contact with aluminum and other toxic metals, undergoes treatment to lower

the body's existing burden of these elements. To illustrate, clinical trials have shown that the chelating agent desferrioxamine can slow the progression of the disorder.[210] This may be because, as Savory and coworkers[211] have shown in rabbits, aluminum-induced neurofibrillary degeneration can be effectively reduced in as little as two days by intramuscular injections of desferrioxamine. An excellent oral chelation therapy designed to remove metals from the body has been described recently by Pouls.[212]

Campell[213] has suggested that a daily supplement of 500 mg of calcium and a similar amount of magnesium can lower elevated hair aluminum back to normal in a year, while Bland[214] recommended the daily use of 600 mg of calcium and 300 mg of magnesium to reduce body aluminum burden. Durach[215-6] has argued that there are two types of magnesium deficit: magnesium deficiency and magnesium depletion. Magnesium deficiency, in his view, is due to insufficient magnesium intake and responds to simple supplementation. Magnesium depletion, in contrast, is the result of a dysregulation in the mechanisms responsible for magnesium metabolism. This second form of magnesium deficit can only be addressed by the correction of the responsible pathogenic dysregulation. However, since in Alzheimer's the dysregulation is apparently due to excess exposure to aluminium which itself can be corrected by elevating magnesium intake, magnesium supplementation alone also may correct such dysregulation and with it the deficit. This appears to be what happened in the case of the "spontaneous regression" of Louis Blank's Alzheimer's disease when he both avoided aluminum and ate a high magnesium diet.[209]

Once exposure to aluminum and the existing body burden of this element have been reduced, the final stage of Alzheimer's disease treatment appears likely to involve attempts to buttress the patient's cholinergic, catecholaminergic and glutamatergic systems and associated oxidative stress defense mechanisms (Table 1, p. 39). Scinto and coworkers,[77] for example, have used acetylcholine deficiency as the basis for the early detection of Alzheimer's disease, demonstrating that the pupils of patients with Alzheimer's disease dilate markedly in response to a dilute solution of the acetylcholine-blocking drug, tropicamide, while normal subjects are virtually unaffected by it. As a consequence, several attempts have been made to treat Alzheimer's disease by trying to increase brain acetylcholine levels. To illustrate, various clinical trials have been conducted to determine whether phospha-tidylcholine or lecithin (which contains it) improve brain function in Alzheimer's patients.[217-8] Taken as a whole, these trials seem to suggest that phosphatidylcholine may slow the rate of progression of Alzheimer's disease. Again, in an attempt to elevate brain acetylcholine, clinical trials also have been conducted using acetyl-L-carnitine in the treatment of Alzheimer's patients.[219-21] Results have been promising, with statistically significant improvements being recorded in behaviour, attention and memory. It is not surprising that acetyl-L-carnitine may be valuable in the treatment of Alzheimer's disease because patients' brains are deficient in carnitine acetyl-transferase, which is necessary to catalyse interchange between L-carnitine and acetyl-L-carnitine.[222] Acetyl-L-carnitine may be of benefit in Alzheimer's disease for two reasons. It is a precursor of acetylcholine,[223] increasing the brain availability of this neurotransmitter. In addition, it also seems to evoke dopamine release from the vesicular pools of nigrostriatal dopaminergic neurons.[224] Acetyl-L-carnitine, therefore, may be capable of helping to correct deficits in both the cholinergic and catecholaminergic systems, commonly found in Alzheimer's disease.

It is unfortunate that clinical trials to date have used acetyl-L-carnitine in isolation. The production of acetylcholine from

Table 1. Alzheimer's Disease and Aluminum. An Overview.

aluminum impaired enzyme	consequence	potential treatment
Glucose-6-phosphate	Glucose metabolism impaired	Calcium, magnesium
Hexokinase	Glucose metabolism impaired	Calcium, magnesium
Phosphofructokinase	Glucose metabolism impaired	Calcium, magnesium
Choline acetyltransferase	Acetylcholine deficiency Malfunction of cholinergic neurons Formation of senile plaques	Vitamin B12,[zinc],estrogen, folic acid, calcium, magnesium phosphatidylcholine, lecithin, acetyl-L-carnitine
Adenylate cyclase	Elevated parathyroid activity	Magnesium
Dihydropteridine reductase	Depressed dopamine, norepinephrine and serotonin	Desferrioxamine, magnesium, copper, zinc, iron, calcium, magnesium
Glutamate decarboxylase	Reduction in glutamatergic neurotransmission	Calcium, magnesium
Calcium/Calmodulin Kinase II	Loss of calmodulin flexibility, formation of neurofibrillary tangles	Desferrioxamine, calcium, magnesium
Alkaline phosphatase	Neurofibrillary tangles	Calcium, magnesium
Phospholipid A2	Abnormal brain cell membranes	n-3 and n-6 essential fatty acids, calcium, magnesium, phosphatidylserine, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidylinositol
Glutathione-peroxidase	Increased lipid peroxidation	Vitamin E, vitamin C, selenium, melatonin
Superoxide dismutase	Greater free radical damage	[Zinc], copper, ginkgo biloba

Zinc can accelerate amyloid plaque formation in later stages of Alzheimer's disease.[152]

choline involves other nutrients, including vitamin B_{12} and folic acid. These substances should not be assumed to be readily available in Alzheimer's patients. Indeed, a B_{12} deficiency seems characteristic of the disease,[225-6] as are high levels of its metabolites.[227] McCaddon and Kelly[228] have suggested that when B_{12} levels are depressed, a well-known biochemical process, the "methyl-folate trap" occurs. This trap diverts folic acid from the brain, preventing the manufacture of acetylcholine, even in the presence of abundant choline.

Nevertheless, there is increasing evidence for a role for acetylcholine in the treatment of Alzheimer's. Recently, done-

pezil HCI, a piperidine-based reversible acetylcholinesterase inhibitor[229] has been used to produce an increase in central nervous system acetylcholine in mild to moderate Alzheimer's patients, which seemed associated with improvements in cognition. Similarly, vitamin B$_{12}$ injections, which may increase brain acetylcholine levels, have been reported linked to significant improvement in various neuropsychiatric disorders, even when anaemia is absent.[230] Since the production of acetylcholine from choline involves folic acid, it is not surprising that Snowdon's study of postmortem brains from the School Sister's of Notre Dame, Mankato, Minnesota has identified that a deficiency of this vitamin also appears to occur in Alzheimer's disease.[231]

Three potential treatments for Alzheimer's disease also rest on reducing the availability of acetylcholinesterase for incorporation into plaque complexes with beta-amyloid. Tetrahydroaminoacridine (Tacrine), for example, is a potent inhibitor of acetylcholinesterase which reportedly improves memory deficits in Alzheimer's disease.[232] Similarly, in a dementia mimetic mouse model, created with aluminum chloride solution, the Chinese herbal medicine of tonifying kidney depressed acetylcholinesterase levels in the cerebral cortex, leading to an improvement in memory.[233] Bonnefont and coworkers[234] also have shown that estrogen protects neuronal cells from the cytotoxicity induced by acetylcholinesterase-amyloid complexes.

Ginkgo biloba is a herb that has been used traditionally to treat both memory loss and diabetes mellitus.[235] Its active components are ginkgolides which have antioxidant, neuroprotective and cholinergic properties. The value of ginkgo biloba extracts in the treatment of Alzheimer's have been demonstrated in placebo-controlled clinical trials and seems to be similar to those of donepezil or tacrine, but without any undesirable side effects. One of the major benefits of ginkgo appears to be its ability to increase blood flow, not only to healthy parts of the brain but also to disease-damaged areas.[235] Beta-amyloid, in its interaction with superoxide radicals constricts and damages the lining of the small blood vessels supplying the brain. It is likely that ginkgo, acting as a circulation enhancer, helps to overcome this problem.[236-7] This, of course, may be why the blood thinner aspirin[238-9] may also be beneficial in the treatment of Alzheimer's disease. However, there seems to be more to ginkgo biloba extract than its antioxidant and circulation enhancing properties since clinical trials also have established that it improves memory and cognitive performance in healthy young females.[240] In addition, in both young and old rats it increases neurotransmitter receptor binding.[241]

There appear to have been few attempts to correct deficits in the catecholaminergic system in Alzheimer's disease. One exception to this generalization has been the recent testing of lisuride, a dopamine receptor antagonist, more often used in the treatment of Parkinson's disease. Initial results suggest that this drug may reduce the rate of decline of verbal memory in Alzheimer's but results were not statistically significant.[242]

In contrast, several attempts have been made to assess the possibility of correcting the abnormal viscosity of cellular brain membranes in Alzheimer's disease. Trials have been conducted, for example, to test the value of phosphatidylserine in this role.[243-4] In Italy, for example, Cenacchi,[245] conducted a clinical trial involving 425 people aged 66-93 years, in 23 institutions. All participants had experienced moderate to severe cognitive decline. Phosphatidylserine dosage was 300 mg per day and patients were assessed when the study began and three to six months later. Significant improvement in memory and learning scores were reported. Interestingly, phospholipids such as phosphatidylserine, phosphatidylcholine, phosphatidyl-eth-

anolamine and phosphatidylinositol are available in healthfood stores and are widely used as memory aids by the general public.

The potential value of antioxidants such as melatonin, estrogen and vitamins C and E in the treatment of Alzheimer's disease have been discussed earlier. However, there may be more to estrogen than its ability to protect against free radical damage. In addition to promoting the growth of cholinergic neurons and decreasing neuronal damage by acting as an antioxidant,[246] this hormone also has been shown to have powerful protective neuronal cell effects against the cytotoxicity of the acetylcholinesterase-amyloid beta-peptide complex found in the senile plaques that are characteristic of Alzheimer's disease.[116] It would appear that estrogen protects neurons against damage from both senile plaques and from amyloid beta-peptide fibrils. This helps to explain why Alzheimer's disease is considerably less common in women receiving estrogen replacement therapy.[184]

Little is known of the clinical impact of melatonin on Alzheimer's disease. However, Jean-Louis and coworkers[247] describe its effects on two cases. In one patient, melatonin enhanced and stabilized the circadian rest-activity rhythm, along with a reduction of daytime sleepiness and mood improvement. In the other patient, no significant changes were observed. Interestingly, Pierpaoli and Regelson[180] describe treating a patient who suffered from Parkinsonism with melatonin and claim that, on a dose of 5mg daily, her uncontrolled hand shaking disappeared and ten years later she was still completely disease free.

It is well established also that melatonin plays a significant role in normalizing blood zinc levels in the elderly because it aids this mineral's absorption[180] Zinc deficiency may cause depressed glutamate dehydrogenase, resulting in an excitotoxic rise in glutamate.[248] Furthermore, zinc enzymes also are involved in the metabolism of neurotransmitters, including acetylcholine. A shortage of zinc, therefore, may partially account for the depression of this neurotransmitter in Alzheimer's disease. Supplementation with zinc aspartate appears beneficial in preliminary trials with Alzheimer's patients.[248] However, great care must be taken in the use of this mineral since, although it seems beneficial in improving mental alertness in the elderly, in a clinical trial in Australia it caused a serious deterioration of cognition in Alzheimer's patients within two days.[152]

In contrast, the available evidence suggest that the antioxidant selenium may be very beneficial in dementia, including Alzheimer's disease. In 1987, Tolonen and colleagues[249] described a double-blind clinical trial in which the demented elderly were given high doses of sodium selenate, organic selenium and vitamin E. These supplements resulted in statistically significant improvements in depression, self care, anxiety, mental alertness, fatigue and interest in the environment. While the roles of selenium and vitamin E in producing these improvements cannot be identified separately, this study suggests that high doses of both of these antioxidants may be of significant benefit to Alzheimer's patients.

Conclusions

In his book *Disaster Planning: The Preservation of Life and Property,* published in 1980, this author[250] wrote "Communities, like individuals, may often work towards their own destruction through neglect, ignorance, or a deliberate emphasis on fulfilling superficially advantageous short-term goals. Incrementally, in doing so, they magnify risk and eventually suffer the disasters they deserve." It has been known for over a century that aluminum is a neurotoxin.[1] The unfortunate truth that its widespread use is the major cause of Alzheimer's disease is now unavoidable.

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