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Trace Element Imbalances in Hair and Nails of Alzheimer's Disease Patients

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ABSTRACT: The concentrations of 17 elements in the hair and nails of 180 Alzheimer's disease (AD) and control subjects have been determined by instrumental neutron activation analysis (INAA). Comparisons of trace element levels of properly matched AD and control groups revealed significant imbalances in the concentrations of six elements (Br, Ca, Co, Hg, K, and Zn) between disease and control groups. It is noteworthy that each of these has previously been shown by our group, or others, to be altered in some AD brain region(s). Geometric means for each element in both hair and nails of AD and control subjects are presented, and significant differences noted. The significance of these alterations with regard to the possible role of trace elements in the etiology of AD is discussed.

Key Words: Trace Elements, Alzheimer's Disease, Hair, Nail, Radiochemical Analysis

INTRODUCTION

Despite intense research efforts, the cause of Alzheimer's disease (AD) remains unknown. One of the hypotheses regarding its etiology implicates trace elements. A recent publication (Ehmann *et al.*, 1986) summarized the elements that have been implicated in AD, with pro and con literature citations. This same study demonstrated imbalances in eight elements in AD brain compared to age-matched controls. In light of these findings, a follow-up study was initiated to determine whether or not the trace element imbalances observed in brain occurred in other tissues. Hair and nail results are reported here.

Many extensive reviews of the advantages, disadvantages, uses, and misuses of hair and nail analysis have appeared in the literature (Hopps, 1977; Valkovic, 1977; Laker, 1982; Taylor, 1986; Evans and Jervis, 1987). Hair and nail were chosen for this study because they have been shown to reflect environmental and dietary exposure to many of the elements we were interested in, such as Hg (Phelps *et al.*, 1980; Inasmasu *et al.*, 1986); As (Valentine *et al.*, 1979); Cd (Huel *et al.*, 1984); Pb (Creason *et al.*, 1975); Sb (Chattopadyhay and Jervis, 1974); and Cr (Rabinowitz *et al.*, 1983). There is also precedent for using hair to monitor trace element changes in disease states. Alterations have been seen in hair Ca levels of myocardial infarction patients (Bacso, 1984); in Cd, Pb, and Zn levels in hypertension (Medeiros and Pellum, 1984); in Ca, Cl, I, Na, Mn, Se, and Zn in cancer (Thimaya and Ganapathy, 1982; Moo and Pillay, 1983); in Al and Ca in chronic renal failure (Marumo *et al.*, 1984); and in Ca of Downs syndrome patients (Barlow *et al.*, 1981).

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Few comprehensive studies have been done on trace element levels in normal nail tissue (Kanabrocki *et al.*, 1979; Biswas *et al.*, 1984), or for alterations in disease states (Djaldetti *et al.*, 1987a, 1987b, Van Noord *et al.*, 1987). This work provides a considerable addition to existing nail trace element data.

The use of hair and nail as trace element indicators also has its pitfalls. Trace element analysis of a single hair or nail sample from one individual generally does not provide useful information. A more acceptable use of hair as a bio-indicator involves comparisons between well-matched groups of subjects (Evans and Jervis, 1987). When large numbers of samples are used, the effects of individual variations are minimized, and any differences that are observed between the matched groups can be more reasonably correlated with a single factor, such as disease state.

The analytical technique used for elemental determinations in this study was instrumental neutron activation analysis (INAA). This method, with its sensitive and selective detection of many elements in diverse matrices, is well suited for trace element determinations in biological tissue. Little sample pre-treatment is needed, so contamination is minimized. Additional discussion of the advantages and disadvantages of INAA for biological trace element work can be found elsewhere (Parr, 1980; Katz, 1985).

MATERIALS AND METHODS

The determination of hair and nail trace element levels and the subsequent interpretation of the data are not simple analytical problems. In this work, careful attention was given to minimizing sample contamination in all aspects of the analytical procedure. All implements which contacted the samples were pre-washed in an ultra-sonic cleaner using J. T. Baker *Instra-Analyzed* nitric acid, followed by rinsing with deionized distilled water and Distilled-in-Glass methanol. The polyethylene vials and bags used for sample storage and washing are very low in trace elements (Moody and Lindstrom, 1977). A laminar flow hood was used for sample packaging, and talc-free gloves were used for all sample handling.

Trace element levels in hair and nail are known to be subject to a number of external factors, such as age, sex, hair treatment, and geographic location. Information on all these factors, and on health status, diet, and medication, was obtained from each patient. A separate study examined the effects of age, sex, and treatment on trace element concentrations (Vance *et al.*, 1988), and only carefully matched disease-control groups were used for this study. Hair samples that had undergone any treatments (e.g., dyes, permanents, or rinses) or had been washed with Se- or Zn-containing shampoos were excluded from the study, as were samples from persons who noted any unusual exposure to trace elements in their work or home environments.

Hair and nail samples were obtained from AD and control subjects through the Sanders Brown Center on Aging at the University of Kentucky. The clinical diagnosis of AD was made according to criteria of the NINCDS/ADRDA work group (McKhann *et al.*, 1984). The population consisted of 117 control and 63 AD subjects. All AD subjects were over the age of 45; 38 were female and 25 were male. The average age of all the AD patients was 71 years. 73% of the control group was over the age of 45; of these, 55 were female and 30 were male. The average age of the over-45 control group was 68 years.

Hair was removed from the nape of the neck of the subject using stainless steel scissors and fingernails were removed using scissors or stainless steel fingernail clippers. Samples were placed into individual *Ziploc* bags for temporary storage. In preparation for analysis, the 5 cm of hair proximal to the scalp was cut into pieces of approximately 1 cm using stainless steel scissors, and placed in virgin polyethylene scintillation vials for washing.

Nail samples were individually scraped with a synthetic quartz knife, cut if needed, and also placed in scintillation vials. The samples were washed according to the International Atomic Energy Agency (IAEA) method (IAEA, 1978), which consists of successive acetone and water washes with mechanical shaking, and allowed to air dry in a dust-free hood. *Distilled-in-Glass* acetone (J.T. Baker) and deionized distilled water were used for this procedure. It is recognized that the IAEA wash procedure can alter the levels of the more labile elements, such as the alkali metal cations. Multivalent transition element cations are, however,

generally more tightly bound to proteins and are less likely to be altered by the IAEA wash procedure.

Samples and standards were packaged in pre-washed *Suprasil* quartz vials and subjected to a 40-hour irradiation at the Missouri Universities Research Reactor (MURR). All vials were counted immediately upon return from MURR for 20 min. to determine As, Au, Br, K, and Na. They were counted again approximately 10 days later for Ag, Ca, Co, Cr, Cs, Fe, Hg, Rb, Sb, Sc, Se, and Zn. Ortec HPGe and Ge (Li) detectors were used for counting. Gamma-ray spectra were acquired and analyzed using an ND680 multichannel analyzer system. Appropriate corrections were made for dead-time differences and spectral interferences.

Primary comparator standards used in this work were National Bureau of Standards Standard Reference Materials 1566 (Oyster Tissue), 1571 (Orchard Leaves), and 1577 (Bovine Liver). The secondary standard was Bowen's Kale. The results obtained for Bowen's Kale agree very well with accepted values (Vance, 1986). Samples of our Bowen's Kale had been analyzed previously in our laboratory using standard solutions prepared from high purity elements or stoichiometric compounds (Nadkarni and Ehmann, 1969).

RESULTS

The data were analyzed using the SAS Lifereg procedure (SAS Institute, 1985). This program was used because it provides a method by which detection limit values can be meaningfully incorporated into summary statistics. A more detailed description of the procedure has been provided elsewhere (Vance et al., 1988). Geometric means are reported (except for Zn), since most trace element concentrations in hair and nail are log-normally distributed.

The results of the hair and nail analyses are presented in Tables 1 and 2, respectively. Important external factors that affected the trace element concentrations in hair and nail (age, sex, treatments) had been identified previously (Vance *et al.*, 1988), and these factors were taken into account when comparing disease and control groups. For each element geometric means for properly matched AD and control groups are given, and significant differences ($p < 0.05$) between the groups noted. Table 3 presents an overview of the trace element imbalances observed by this laboratory in AD brain, hair, and nail.

There were no significant differences between AD and control groups for nine elements: Ag, As, Au, Cr, Fe, Na, Sb, Se, and Sc. The elements Cs and Rb were actually determined in less than 5% of the samples and these elements are not included in the statistical analysis. With regard to Na and K, we recognized the problems associated with measurement of these water-soluble cations. Our assumption was that the strictly controlled wash procedure should affect all samples in the same way, and that comparison studies should still be valid.

Hair

Four elements (Br, Ca, Co and Zn) were found to be imbalanced in the hair of AD subjects as compared to matched controls.

Bromine was higher ($p < 0.05$) in the hair of AD patients than in controls. Only hair that had not been treated with dyes, permanents, or rinses was used for this comparison. There were no age or sex effects for Br in hair.

Calcium was lower ($p < 0.05$) in the hair of AD subjects than in matched controls. Comparisons were again made only for non-treated hair, since treatments result in greatly increased Ca levels. Comparison groups were also matched by age (those over and under the age of 45) and sex, since these factors also affect hair Ca levels.

Cobalt was lower ($p < 0.01$) in AD subjects than in controls. Here too, only non-treated hair was included, and groups were sex-matched.

Zinc was higher ($p < 0.05$) in the hair of AD patients than in age-matched controls.

Nail

Four elements (Br, Hg, K, and Zn) were imbalanced in the nail of AD subjects. Two of these (Br and Zn) were also imbalanced in the same direction in AD hair. Potassium was rarely detected in the hair, so no nail/hair comparisons are possible. Mercury was not

TABLE 1. Disease/Control Comparisons in Hair.

Element, conc.	Groups[1]	AD Mean	Number of Samples[4]	Matched Control Mean	Number of Samples
Ag, ng/g	none	53.1 (1.23)	[32-12-0]	87.6 (1.15)	[72-17-1]
As, ng/g	none	26.0 (1.24)	[10-34-0]	10.3 (1.32)	[24-63-3]
Au, ng/g	M	15.3 (1.23)	[24-0-0]	13.2 (1.23)	[29-0-3]
	F	23.1 (1.27)	[19-0-1]	35.3 (1.23)	[54-0-4]
Br, µg/g[3]	N	3.59 (1.12)	[39-0-0]	2.55 (1.11)	[68-0-1]
Ca, µg/g[3]	M, > 45, N	83.5 (1.59)	[8-14-2]	208 (1.23)	[15-9-0]
	F, > 45, N	148 (1.58)	[7-5-3]	458 (1.34)	[13-9-0]
Co, ng/g[2]	M, N	9.37 (1.29)	[17-7-0]	19.2 (1.15)	[29-3-0]
	F, N	14.5 (1.35)	[12-3-0]	30.4 (1.25)	[35-2-0]
Cr, ng/g	none	195 (1.18)	[40-3-1]	212 (1.13)	[84-6-0]
Fe, µg/g	none	9.99 (1.15)	[31-13-0]	9.16 (1.10)	[77-12-1]
Hg, ng/g	M	355 (1.19)	[22-1-1]	439 (1.09)	[32-0-0]
	F	557 (1.25)	[20-0-0]	525 (1.11)	[58-0-0]
Na, µg/g	none	4.62 (1.16)	[42-2-0]	4.6 (1.10)	[87-1-2]
Sb, ng/g	N	25.7 (1.14)	[31-8-0]	30.0 (1.12)	[65-3-1]
Sc, ng/g	> 45	0.50 (1.16)	[26-18-0]	0.39 (1.20)	[29-34-1]
Se, µg/g	> 45, N	0.631 (1.04)	[35-0-4]	0.550 (1.04)	[44-0-3]
Zn, µg/g[3]	> 45	164 (5.7)	[41-0-3]	143 (6.3)	[61-0-3]

[1] These factors had been determined previously to have significant effects on the trace element concentrations.
N = only non-treated hair samples used for comparisons.
M = male, F = female.
> 45 = only subjects over age 45 used for comparisons.
[2] Significant difference between AD and control; $p < 0.01$
[3] Significant difference between AD and control; $p < 0.05$
[4] Number of actual-detection limit-missing values, respectively
Note: All means are geometric means (x/÷ SEM), except for Zn which is an arithmetic mean (± SEM).

imbalanced in AD hair.

Bromine is elevated ($p < 0.05$) in the nail of AD subjects as compared to age-matched controls. Potassium ($p < 0.01$), and zinc ($p < 0.05$) are both higher in AD subjects than in controls. No age or sex effects were observed for Hg in nail.

DISCUSSION

This study has demonstrated significant differences in trace element levels in hair and nail between AD and control groups, indicating that trace element imbalances in AD are not restricted to the brain. A major point of

interest is that all six of the elements exhibiting imbalances in hair and/or nail (Br, Ca, Co, Hg, K, Zn) have also been shown to be imbalanced in some AD brain regions, although the imbalances are not always in the same direction. The relationship of the peripheral trace element imbalances to those in the brain, and to the disease process itself, is not known. Some or all of the observed imbalances could reflect a generalized systemic alteration intrinsic to the disease. Or, they may be non-specific changes resulting from the terminal disease state with its attendant malnutrition, immobilization, dehydration, and

TABLE 2. Disease/Control Comparisons in Nail.

Element, conc.	Groups[1]	AD Mean	Number of Samples[4]	Matched Control Mean	Number of Samples
Ag, ng/g	M	21.9 (1.32)	[7-18-0]	23.5 (1.29)	[17-24-1]
	F	36.0 (1.32)	[18-19-1]	42.8 (1.26)	[36-39-0]
As, ng/g	> 45	33.8 (1.17)	[14-48-1]	28.6 (1.18)	[26-59-0]
Au, ng/g	M	11.5 (1.31)	[25-0-0]	12.9 (1.30)	[36-2-4]
	F	24.1 (1.12)	[34-2-2]	31.8 (1.15)	[70-1-4]
Br, µg/g[2]	> 45	2.48 (1.87)	[63-0-1]	1.94 (1.05)	[83-0-2]
Ca, µg/g	none	472 (1.08)	[35-16-12]	522 (1.06)	[70-32-15]
Co, ng/g	none	19.3 (1.15)	[51-11-1]	27.5 (1.10)	[96-20-1]
Cr, ng/g	none	1328 (1.13)	[62-0-1]	1760 (1.10)	[115-1-1]
Fe, µg/g	> 45	12.1 (1.11)	[46-15-2]	12.3 (1.10)	[66-18-1]
Hg, ng/g[3]	none	132 (1.14)	[62-1-0]	170 (1.07)	[112-5-0]
K, µg/g[2]	M, > 45	88.6 (1.27)	[14-9-2]	50.0 (1.24)	[16-9-5]
	F, > 45	75.4 (1.22)	[18-11-9]	25.9 (1.26)	[22-24-9]
Na, µg/g	M, > 45	204 (1.16)	[25-0-0]	134 (1.12)	[30-0-0]
	F, > 45	125 (1.13)	[38-0-0]	112 (1.08)	[55-0-0]
Sb, ng/g	> 45	19.5 (1.13)	[40-22-1]	21.3 (1.11)	[60-25-0]
Sc, ng/g	none	1.10 (1.17)	[40-23-0]	0.76 (1.15)	[72-45-0]
Se, µg/g	M	0.991 (1.07)	[25-0-0]	0.99 (1.05)	[41-0-1]
	F	1.081 (1.03)	[37-0-1]	1.10 (1.03)	[75-0-0]
Zn, µg/g[3]	M, > 45	158 (5.9)	[25-0-0]	145 (6.3)	[29-0-1]
	F, > 45	172 (5.3)	[38-0-0]	161 (4.4)	[54-0-1]

[1] These factors had been determined previously to have significant effects on the trace element concentrations.
N = only non-treated hair samples used for comparisons.
M = male. F = female.
> 45 = only subjects over age 45 used for comparisons.
[2] Significant difference between AD and control; $p < 0.01$
[3] Significant difference between AD and control; $p < 0.05$
[4] Number of actual-detection limit-missing values, respectively
Note: All means are geometric means (x/÷ SEM), except for Zn which is an arithmetic mean (± SEM).

TABLE 3. Summary of Elemental Imbalances in Brain, Hair, and Nail of AD Patients.

Element	Brain		Nail	Hair
	Cortex[1]	Special Regions[2,3]		
Br	elevated	----	elevated	elevated
Ca	n.d.	n.d.	—	lowered
Cl	—	n.d.	n.d.	n.d.
Co	—	elevated (nbM)	—	lowered
Cs	lowered	lowered (h)	n.d.	n.d.
Hg	elevated	elevated (nbM)	lowered	----
K	lowered (gray)	lowered (a,h)	elevated	n.d.
N	lowered	elevated (a, nbM)	n.d.	n.d.
Na	elevated	elevated (all 3)	—	----
P	elevated	lowered (a)	n.d.	n.d
Rb	lowered	lowered (a,h)	n.d.	n.d.
Se	—	elevated (nbM)	----	----
Zn	—	elevated (a)	elevated	elevated

[1]Ehmann *et al.*, 1986.
[2]Thompson *et al.*, 1988.
[3]nbM = nucleus basalis of Meynbert; h = hippocampus; a = amygdala.
elevated = AD subjects have higher levels than matched controls ($p < 0.05$).
lowered = AD subjects have lower levels than matched controls ($p < 0.05$).
— = no difference between AD and control subjects.
n. d. = element not determined.
Note: Only imbalances observed in our laboratory are included.

so on. We offer here some speculations about the ways in which trace substances might be involved in the clinical, biochemical, and pathological alterations observed in AD.

Bromine

The elevation of Br in hair, nails, and brain of AD subjects has been a consistent imbalance in our studies. Akanle *et al.* (1987) did not observe a Br imbalance in their study of 9 senile dementia subjects and 17 controls, but they do not specify whether or not treated hair samples were excluded from their study. Ward *et al.* (1987) found Br to be elevated in the hippocampus and cerebral cortex of AD subjects as compared to controls. Rindby *et al.* (1983) have reported an elevation of Br in the serum and CSF of four patients suffering from senile dementia.

Bromide has not been shown to have any essential physiological function, but it is known to be psychoactive, and was once used as a sedative and anticonvulsant. The amounts of Br to which humans are exposed has increased in this century due to increased use of

Br-containing fumigants and increased mining wastes (Rauws, 1983). Though there are reports of bromide intoxication resulting from excess intake of bromide-containing medications (Trump and Hochberg, 1976; Kunze, 1976), exposure to environmental Br, even at higher than normal levels, seems to produce only minor neurobehavioral alterations (Anger *et al.*, 1986).

Relatively little is known about the actual cellular mechanisms by which Br exerts its central nervous system effects. It can substitute for Cl or, to a lesser extent, for I, in cell processes. Sangster *et al.* (1983) have shown that interference of Br with, or substitution for, I can result in alterations in T_3 or T_4 levels. A link between thyroid disorders and AD has been reported (Heyman *et al.*, 1984), although a relationship between Br, thyroid disorders and AD seems unlikely. Interference with Cl seems a more likely problem.

The replacement of Cl by Br does seem to have an effect on neurotransmitter function. Roskoski (1974) showed that brominated components of the cholinergic system inhibit the action of CAT, an enzyme known to be affected in AD (Davies and Maloney, 1976). Goodwin *et al.* (1969) showed that the replacement of Cl by Br in the perfusing medium of slices of rat striatum diminished the release of noradrenaline and serotonin. Serotonin has been shown to be decreased in AD (Sparks *et al.*, 1986). Iodide did not produce this effect, suggesting that the inhibition was specific to Br. Because brain Cl levels are much higher than Br (Ehmann *et al.*, 1986), it is questionable as to how much interference the Br could actually produce in brain, unless the Br were selectively utilized in place of Cl. This phenomenon has been shown to occur in eosinophils. Weiss *et al.* (1986) showed that human eosinophils would preferentially oxidize Br to a halogenating intermediate in the presence of at least 1000-fold excess of Cl. HOBr is a powerful and toxic oxidant, reacting with a variety of biomolecules, and can act to halogenate proteins.

The Br elevation observed in hair and nail of AD subjects could also result from other causes. It has been shown that treatment with lithium carbonate results in elevated hair Br (Handorf *et al.*, 1985; Campbell *et al.*, 1986). Perhaps other medications commonly taken by AD patients have similar effects. It has also been shown that Cl depletion greatly lengthens the elimination half-life of Br (Rauws, 1983). If AD subjects were on salt-restricted diets, the longer residence time of Br in the body could lead to increased Br levels in hair and nail.

Calcium

Hair Ca is decreased in AD patients compared to age-, sex-, and treatment-matched controls. The same trend toward lowered Ca was observed in nails, but was not significant. These results disagree with those of Shore *et al.* (1984) and Akanle *et al.* (1987) who reported no difference in hair Ca between AD and control subjects. However, in neither of these studies is the problem of the effects of hair treatment on hair Ca levels addressed. In a study of Downs' syndrome (DS) patients Barlow *et al.* (1981) reported that both male and female DS patients exhibited lowered hair Ca values compared to matched controls. It is known that DS patients develop dementia and brain morphological and biochemical changes similar to AD if they live to middle age (Wisniewski *et al.*, 1985).

The lowering of hair Ca in AD subjects is opposite in direction to the elevation reported in AD brain (Hershey *et al.*, 1985; Ward *et al.*, 1987). This observation actually fits in with Gajdusek's proposal concerning the possible role of Ca in AD (Gajdusek, 1985). He proposed that a lowered amount of dietary and environmental Ca might result in malfunction of the parathyroid glands, with subsequent deposition of Ca in neurons. Gordus (1973) demonstrated that hair Ca levels reflect dietary intake. The lowered Ca intake could thus simultaneously result in lower hair Ca and elevated brain Ca.

Cobalt

This element is significantly decreased in the hair of AD subjects compared to controls. Nail Co levels are also lower in AD patients, but the difference is not significant.

There are few reports on Co levels in AD tissues. Cole and Prehal (1984) reported lowered serum Vitamin B_{12} in AD subjects as compared to controls. Ehmann *et al.* (1986)

found no alterations in Co for most brain regions, but we did report that Co levels were elevated in the nucleus basalis of Meynert in AD (Thompson *et al.*, 1988). Ward et al. (1987) reported no differences between AD and controls in Co levels in hippocampal and cerebral cortex samples.

Cobalt is not known to have neurotoxic effects. It does not seem plausible that Co has a direct role in AD.

Mercury

Mercury is decreased in the nail of AD subjects compared to controls. Though there are few studies in the literature on Hg in nail, many reports have indicated that hair is a good monitor for Hg exposure (Phelps *et al.*, 1980; Inasmasu *et al.*, 1986). Brain Hg levels have been reported to be elevated in AD by some workers (Ehmann *et al.*, 1986; Thompson *et al.*, 1988), but not by others (Ward *et al.*, 1988).

Perhaps one reason for the lowering of nail Hg in AD subjects could be the presumably lower exposure rate of the AD patients to environmental Hg. This would not explain the elevated brain Hg, however. An alternative approach would be to consider that the disease process somehow alters the distribution of Hg in the body. For example, several researchers have speculated that the blood-brain-barrier (BBB) is altered in AD (Wisniewski and Kollowski, 1982). It has been demonstrated that Hg ions will penetrate the BBB (Ware *et al.*, 1974) and impair its normal function. If this occurred, then it might be possible that Hg could preferentially accumulate in brain and be depleted in other tissues that reflect recent environmental exposure.

Of the several elements seen to be imbalanced in AD brain, hair, or nail, Hg seems to have the most severe and well-documented neurotoxic effects on systems that are known to be affected in AD. One example of this is the documented decrease in protein synthesis and reduction of RNA levels in AD brain (Mann *et al.*, 1982; Borthwick *et al.*, 1985). These changes can be effected by the presence of Hg. Kim (1980) demonstrated decreases in protein content and in DNA and RNA levels in rats fed mercury salts. Sajdel-Sulkowska and Marotta (1984) used a mercury compound to inactivate a protein that inhibits a cellular alkaline ribonuclease in brain. Decreased ribonuclease led to an increase in RNA degradation and a decrease in protein synthesis.

Mercury has also been demonstrated to have adverse effects on the function of Na^+-K^+-ATPase which in turn can lead to alterations in neurotransmitter uptake (Rajanna and Hobson, 1985). Hrdina *et al.* (1976) showed that exposure to methylmercury produced significant decreases in cortical ACh and brainstem 5-HT levels. Dwivedi *et al.* (1980) demonstrated a decrease in CAT activity in the brains of rats fed either methyl- or inorganic mercury.

Potassium

This alkali metal is elevated in the nails of AD patients as compared to their age- and sex-matched controls. Ehmann *et al.* (1986) reported a decrease in the separated gray/white matter of AD brain, and Ward *et al.* (1987) also noted a K decrease in AD hippocampus and cerebral cortex.

It is difficult to envision an alteration in K as a cause of AD. If anything, the change would be more likely to be a result of the disease process.

Zinc

This element is elevated in the hair and nail of AD subjects compared to controls. Ehmann et al. (1984) observed no Zn alterations in AD subjects in specimens derived principally from the cerebral cortex, but did find elevated Zn in the amygdala. Ward *et al.* (1987) reported decreased Zn levels in AD hippocampus and cerebral cortex.

Burnet (1981) suggested that the inability of neurons to incorporate Zn into DNA-handling enzymes could ultimately lead to dementia. This hypothesis does not necessarily imply that there is a Zn imbalance in bulk tissue, however.

It may well be that AD is not a simple disease that will eventually be traced to one cause, but rather is a complex disease with many interrelated causative factors. It is possible that an environmental factor such as a neurotoxic trace metal could serve as a trigger

in susceptible individuals and initiate a cascade of molecular changes resulting in the histopathological and biochemical alterations observed with AD.

In order to advance our understanding of the possible role of trace elements in AD, future studies will need to provide information on the localization of trace elements in the cell or pathological structure. An enhanced understanding of the biochemical interactions of non-essential elements like Br and Hg is also clearly needed.

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