Editorial: Aluminum – Alzheimer's Smoking Gun?

It is becoming apparent that with an aging population comes an increase in the incidence of mental impairment. In death certificates of people over 75 years of age, the number listed as having dementia has increased by a factor of 20 in the last 15 years (Forbes, Lessard, & Gentleman, 1995, appearing in the present issue). Most of this increase is probably the result of heightened diagnostic sensitivity to clinical dementia, although the demographic shift to an older population likely contributes as well. The importance of uncovering possible links between cognitive impairment and environmental exposure to putative toxins is of particular concern in older people, since normal protective mechanisms preventing toxicity may decline with age.

Into the field stride our epidemiological colleagues whose job it is to mine the data base for correlations. In a series of papers in this journal, Forbes et al. examine the relationship between mental function and certain geochemical aspects, notably aluminum, in drinking water. The principal hypothesis under investigation is that aluminum in drinking water is a causal factor for the onset of Alzheimer's disease (AD). The approach they have taken is to use data obtained from the Ontario Longitudinal Study of Aging (LSA), and correlate them with the levels of Al and other pertinent factors in the drinking water to which the individuals in the study were exposed. The first four papers do not assess AD directly in the subjects, but rather the presence or absence of normal cognitive function, based on questionnaires. This is reasonable, given that AD was under-recognized during most of the study, which commenced in 1959 with a cohort of 2000 45 year old men. In the fifth paper, the LSA data are compared with death certificates of individuals in which the underlying cause of death was either AD or presenile dementia. The water quality data were obtained from the Drinking Water Surveillance Program of the Ontario Ministry of the Environment, which started in 1986. Water quality variables examined included drinking water levels of Al, fluoride (F), silica, turbidity, dissolved organic content (DOC), and the pH.

Alzheimer's disease was first described in 1907 by the neurologist Alois Alzheimer. Public awareness of AD has increased enormously in the last few years, and it is now recognized as a major public health problem with devastating effects on afflicted individuals and their families. Historically, there are only three confirmed risk factors for AD (Berg, 1994): old age, familial history, and Down's syndrome (virtually all individuals with Down's syndrome develop AD by age 40) (Jorm, 1990). AD is defined as progressive clinical dementia with characteristic abnormalities in brain tissue. Dementia in AD begins subtly with gradual and increasing memory loss, typically

followed by impairment of specific motor skills, sometimes accompanied by behavioural and mood disorders. Tissue changes are manifested as the presence of senile plaques in the cerebral cortex of the brain and neurofibrillary tangles within affected neurons (Berg, 1994). Associated with senile plaques is beta-amyloid protein (AP), and there has been recent excitement over the identification of a gene associated with AP production (Sherrington et al., 1995; Levy-Lahad et al., 1995), confirming a long held suspicion of a genetic component to at least some cases of AD. Despite the now identified genetic basis for early-onset familial AD, this is likely to be only part of the story. What needs to be learned is the identity and function of the proteins that the relevant genes code for, what their role in the development of the disease is, and, in particular, what extrinsic factors are also involved.

Interest in the association of aluminum (Al) with AD stemmed from the observation that significant Al deposits (4–19%) occur in the core of senile plaques (Edwardson et al., 1986), and it accumulates as well in neurons displaying neurofibrillary tangles (Perl, 1983). The question is, does this implicate Al as a causal factor for AD, or is the Al an incidental consequence of AD progression? Aluminum is the most abundant metal on earth, comprising about 8 per cent of the crust, and there are numerous environmental sources of exposure to it. Some of these include food, drinking water, cookware, deodorants, and antacids. The Al toxicity theory of AD remains controversial, and there are a number of studies which fail to show an increase in AD in individuals exposed to a variety of sources of Al (Jorm, 1990; Halliwell & Gutteridge, 1989).

In the first paper (Forbes, Hayward, & Agwani, 1992), cognitive function was compared with levels of Al and F in both municipally treated and raw water to which individuals were exposed. Considered alone, high levels of Al in treated water had no statistically significant effect on the risk of cognitive impairment, although high levels of F reduced the risk. Treated water samples which had low F concentrations were associated with significant cognitive impairment if they contained high Al levels, however, and this enhanced risk of high Al levels was removed when high F levels were also present. These relative risks were absent when the water was raw rather than treated. In the second study (Forbes, McAiney, Hayward, & Agwani, 1994), the role of pH, along with Al and F levels in cognitive impairment was examined. While there was a trend towards reduced cognitive impairment risk by Al at neutral pH, the differences ascribed to pH were not statistically significant. In the third paper (Forbes & Agwani, 1994), new variables investigated were the degree of turbidity and the DOC of municipally treated water. These were of interest because they could represent alternate, nonsoluble forms of Al with different toxicity from soluble Al; elemental, colloidal Al might be found in turbid water, and water samples with high DOC could have a portion of their Al content bound to organic matter. Multivariate analysis showed that for cognitive impairment, the risk is somewhat higher with turbid samples, and lower with water with elevated DOC. These trends were modest, barely achieving statistical significance, and their im-

portance is diminished by the lack of information about what the organic and turbid components of the water samples actually contained. While the total Al in a given water sample might reside in an altered chemical form, contributing to turbidity or DOC, no quantitative data are offered to support this, and it would seem that similar arguments could be made for F or other ions.

Part IV of this series of studies (Forbes, Agwani, & Lachmaniuk, 1995) appearing in the present issue, examines the role of silica in the association of Al and cognitive impairment. Consistent with the other papers, it is noted that the data show that the risk of impairment significantly increases with Al levels in water, and decreases with higher F levels. Less clear, however, is how these risks are modified by dissolved silica content. Considered alone, "mild" levels of silica have an apparently protective effect, unlike low or high silica levels. An enhanced risk is reported when water samples with low Al content contain high as opposed to low silica levels . It is suggested that high silica content may protect against high Al levels, but this is not statistically supported. The authors offer possible physiological mechanisms for interactions between Al, F, silica and the "phosphate groups" of biological membranes, although these ruminations are highly speculative.

The fifth study compares death certificate data (1984–1991) in which AD or presenile dementia were listed as an underlying cause of death with the participants of the LSA, whose presence or absence of cognitive impairment was evaluated by questionnaire. This is a useful comparison; the death certificates provide a larger data set, death certificate identification of AD cases may be more accurate than questionnaire results with the LSA participants, and the LSA data may be skewed by respondents afflicted with AD or dementia declining to continue their participation in the study. By and large, there is agreement between death certificate data and the LSA responses, and this is noteworthy as it validates the use of a questionnaire for mental status in examining the associations of interest.

Overall, the data presented in this body of work show a statistically significant association between cognitive impairment and AD, with elevated levels of Al in drinking water. Interestingly, there also appears to be some protective effect afforded by high levels of F. A reservation that we have concerns the water quality data, because Al levels in the drinking water of LSA participants were unknown until the last few years. The water quality surveillance program began in 1986, with 35 sampling points, and now includes most municipal water sources in Ontario. The authors do not provide us with the degree of accuracy or the year-to-year variability of the measured variables over the interval during which they were sampled. Moreover, with how much confidence can these data be extrapolated back in time, given that the LSA started in 1959? These concerns would also seem to apply particularly to the estimates of pH, turbidity, and DOC. In Europe, for example, acid rain in recent years has led to an increase in aluminum in drinking water (Pearce, 1985), illustrating one way in which water quality parameters can change over time. Another important consideration Forbes et al.

could have elaborated on is what happens to Al following ingestion – would not the acidic environment of the stomach render moot drinking water characteristics such as pH, the chemical form of the Al, turbidity and DOC? How closely can it be demonstrated that individuals who drink water high in Al have increased blood levels of Al? Although we realize that the investigations, being epidemiological in nature, were not designed to directly address this question, these points do bear on the authors' comments about Al solubility and bioavailibility. As hinted at in the final paper, might Al exacerbate the plight of individuals afflicted with pre-existing AD rather than be a causal factor for the disease?

Although Forbes et al. have shown significant associations between Al and cognitive impairment, we feel that there are limitations in the data set as well as indications in other studies which fail to correlate Al and Alzheimer's Disease. These concerns leave us uncertain about the relationship between Al in the drinking water and Alzheimer's Disease. Thus, we can offer only lukewarm support for the water quality policy recommendation listed in the final paper.

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