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Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water

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ABSTRACT: Aluminium (Al) is clearly a powerful neurotoxicant. Considerable evidence exists that Al may play a role in the aetiology or pathogenesis of Alzheimer's disease (AD), but whether the link is causal is still open to debate. This paper reviews the epidemiological evidence linking Al and AD. Nine out of 13 published epidemiological studies of Al in drinking water and AD have shown statistically significant positive relations. Given the difficulty in producing high-quality data for the occurrence of AD and also for Al exposure, with the resulting unavoidable misclassification errors biasing any true association towards the null value, these studies are remarkably consistent. A major problem in their interpretation is that drinking water, even at high Al concentrations, only contributes a fraction of the total dietary intake of Al. In particular, regular consumers of antacids ingest gram amounts of Al daily, thousands of times the amounts taken in through drinking water, and epidemiological studies of antacid exposure and AD have been largely negative. However, Al is very poorly absorbed in the gastrointestinal tract, and the possibility that some Al fractions present in drinking water may be particularly bioavailable cannot be dismissed at present. The combined evidence linking Al and AD warrants substantial research efforts. Such efforts should focus on clarification of the cellular and molecular mechanisms in Al toxicity and of the basic metabolism and kinetics of Al in the human body, and on further epidemiological studies including diverse routes of Al exposure and also variables that are known or suspected to influence the individuals' susceptibility to AD, such as apolipoprotein E allele status and family history of AD. © 2001 Elsevier Science Inc.

KEY WORDS: Epidemiology, Antacids, Bioavailability, Silicon, Fluoride.

INTRODUCTION

There is no question that aluminium (Al) is a potent neurotoxicant, both in experimental animals and in humans [25,101]. The first studies demonstrating Al neurotoxicity in experimental animals were conducted by Siem and Döllken more than 100 years ago [2]. In 1965 [53,94], it was reported that intracerebral inoculation of Al phosphate in rabbits resulted in neurofibrillary degeneration of "striking resemblance" [94] to the neurofibrillary tangles of Alzheimer's disease (AD), thereby initiating the contentious debate of the role of Al in AD that has been going on since. In 1973, the first report of increased concentrations of Al in the brains of patients with AD was published [15]. At the same time, shortly after the introduction of routine dialysis therapy in patients with chronic renal failure, Alfrey and coworkers first described dialysis enceph-

alopathy [3,4], the first human condition generally accepted to be causally related to Al exposure, and perhaps the first iatrogenic disease recognised in the dialysis patient population [2]. In 1980, a pilot epidemiological study in the United States reported lower incidence of primary degenerative dementia (largely AD) in a county with a high concentration of fluoride in drinking water relative to two counties with less fluoride in the drinking water [91]. The authors' interpretation was that because fluoride may decrease the bioavailability of Al, the study indicated a relationship between Al uptake and AD. In 1986, the first attempts to relate the actual levels of Al in drinking water to AD was reported in two parallel studies in Norway, where it was found that the mortality of dementia was higher in areas with high concentrations of Al in drinking water [22,96]. Later, epidemiological studies confirming this association have been published in Great Britain [62] and in several other countries [16,64,74].

It is generally accepted that Al is a causal agent in dialysis encephalopathy, a fatal brain disorder occurring in some patients with chronic renal failure [2]. In these patients, tissue accumulation of Al to levels high enough to cause toxicity is mainly due to a combination of (1) high exposure, partly directly into the bloodstream (thus by-passing absorption in the gastrointestinal tract, which is generally below 1%), and (2) these patients' lack of kidney function, which is the main excretion route for Al [20,38]. Thus, the exposure situation is very different from that in the general population, where any disorder related to Al exposure is likely to be due to a slow accumulation over a long period of time. Although a few reports exist of AD-like neuropathology in dialysis patients [9,11,44,85], such pathology does not seem to be a common feature in dialysis encephalopathy. Indeed, the general scarcity of such pathology in dialysis patients has often been used as an argument against Al playing a causal role in AD [99]. In any case, it seems clear that massive Al exposure or high brain Al concentrations alone are not sufficient to cause full-blown AD neuropathology. However, there is considerable evidence that more clearly implicate a role for Al in AD. The relevant literature is voluminous, and a full review of the biochemical and other evidence is beyond the scope of this paper. Several reviews and books have been published fairly recently [12,16,64,73,74,83,101,102]. The emphasis in the present paper is on epidemiological studies, a number of which have been published after these reviews.

EVIDENCE LINKING ALUMINIUM AND ALZHEIMER'S DISEASE

The different lines of evidence implicating a role for Al in AD can be categorised as follows:

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TABLE 1

EPIDEMIOLOGICAL STUDIES OF ALUMINIUM IN DRINKING WATER AND ALZHEIMER'S DISEASE, DEMENTIA, OR COGNITIVE IMPAIRMENT

Study No.*	Country of Origin	Reference No.	Result†
1	Norway	[22,23,96]	+
2	United Kingdom	[100]	−
3	United Kingdom	[62]	+
4	Canada, Ontario	[72]	+
5	Canada, Newfoundland	[37]	+
6	Switzerland	[98]	−
7	Canada, Ontario	[28–34]	+
8	France	[48,49,67,79]	+
9	United Kingdom	[36,93]	−
10	Canada, Ontario	[30,33,35]	+
11	Canada, Ontario	[65]	+
12	United Kingdom	[61]	−
13	Canada, Québec	[39]	+

*See text.

† +, Significant positive association; −, No significant positive association. This is a crude classification, see text for further discussion of the results.

1. Elevations in Al concentrations, both in bulk brain samples and in neurofibrillary tangles and senile plaques, the hallmark neuropathological lesions of AD, have been reported from more than 11 laboratories in six countries employing 6 analytical techniques [64,83]. Some studies, however, have failed to reproduce these findings, and although credible attempts have been made to argue that this failure could be due to analytical problems [54,64,103], the issue remains controversial [58,83]. Also, any real accumulation of Al in Alzheimer plaques or tangles could be a secondary effect occurring as a result of the disease, rather than Al playing an active role in the aetiology or pathogenesis of the disease.
2. In susceptible experimental animals, many pathological and clinical aspects similar to those of AD can be produced, depending on factors such as Al dose, route of exposure, and type of Al compound [47,64,83,84].
3. More than 100 different toxic actions of Al have been identified at the molecular and cellular level, many of which occur at Al concentrations which are plausible for human brain [64].
4. One clinical study indicates that treatment with desferrioxamine, a trivalent metal chelator clinically used to treat iron and Al overload, may slow the clinical progression of AD [66].
5. Several epidemiological studies have indicated a relationship between drinking water Al and AD. These will be reviewed in the next section.

EXPOSURE TO ALUMINIUM IN DRINKING WATER

At an average concentration of about 8%, Al is the third most abundant element in the earth's crust, and is present in all foodstuffs, drinking water and other beverages, and as dust in the air [38,101]. Partly due to the resulting uniform exposure of humans to Al, epidemiological studies of the relationship between Al and AD are difficult to conduct.

So far, most epidemiological studies of Al and AD have focused on exposure through drinking water. These studies have been reviewed earlier [16,60,64,74,88,101], but several epidemiological studies have been published after these reviews were written.

There are two main sources of Al in drinking water:

1. Dissolved Al is present naturally as a result of leaching from minerals in the soil and bedrock in the catchment of the water source. At approximately neutral water pH values, the resulting concentrations of dissolved Al are usually much less than 0.1 mg/l. However, this leaching can be greatly enhanced as a result of acid precipitation, as is the situation in large parts of Norway [24] and in many other areas of the world.
2. Al is widely used in water treatment as a coagulant, to reduce the number of small particles and to improve the colour of the water. The main mechanism is that Al ions, having a high positive electrical charge, bind to the negatively charged particles and coloured humic compounds and form connective "bridges" between them. Thus, particles are formed that are large enough to be filtered from the water, and most of the added Al is removed by filtration and sedimentation together with the particles and humic compounds. This often results in increased water concentrations of Al, but if the treatment process is functioning optimally, the addition of Al may actually result in lower Al values in the treated water than in the raw water [55,68].

The epidemiological studies relevant to the issue of Al in drinking water and AD are very different in design, so a quantitative meta-analysis is not possible [74]. The studies are listed in Table 1, in approximate chronological order and according to country. The studies are briefly discussed below, in the order they are listed in Table 1, column 1.

Study 1. The studies in Norway by Vogt [96] and Flaten [22,23] used largely the same sources of data both for exposure and outcome, and essentially gave the same results. The studies are ecological; the municipalities were grouped according to Al in drinking water, and the outcome measure was mortality with dementia as coded from death certificates either as the underlying or as a contributory cause of death. Age-adjusted mortality rates grouped by Al in drinking water [<0.05 (control), 0.05–0.20, and >0.20 mg/l] showed relative risks for dementia of 1.00, 1.15, and 1.32 in men, and 1.00, 1.19, and 1.42 in women [23]. Thus, the results indicated a dose-response relationship.

Study 2. Wood et al. [100] studied mental test scores recorded on admission to hospital in 386 patients with hip fracture between 1982 and 1985. The fraction of patients with reduced mental test scores was almost identical between one health district with high drinking water Al (0.18–0.25 mg/l) and two districts with drinking water Al <0.05 mg/l. However, the water supply in the high-Al

district had only "been treated with Al since 1982" (the Al treatment being the reason for the elevated Al concentrations), that is, for only 0–3 years before the mental tests were given, so this study does not provide much evidence against the Al–AD hypothesis.

Study 3. Martyn et al. [62] estimated incidence rates of AD in 88 county districts in England and Wales from the records of the seven computerised tomography scanning units serving these districts. The relative risk of AD was 1.5 times higher in districts with mean Al concentrations >0.11 mg/l relative to districts where concentrations were <0.01 mg/l. There was no obvious dose-response gradient, but a tendency for this was observed when the analysis was restricted to subjects under 65 years of age.

Study 4. In Ontario, Neri and Hewitt [72] compared 2232 patients who had been discharged from hospital with a diagnosis of AD or presenile dementia, with an equal number of patients matched for age and sex and discharged with a non-psychiatric diagnosis, using a case-control design. The resulting relative risks with increasing Al concentrations in drinking water were 1.00 (<0.01 mg/l, control), 1.13 (0.01–0.10 mg/l), 1.26 (0.10–0.20 mg/l), and 1.46 (>0.20 mg/l), thus showing a dose-response relationship. The results have, however, only been published in abstract form.

Study 5. Frecker [37] examined the birthplaces of the 40 individuals having died with a diagnosis of dementia recorded on their death certificates, in seven communities around Bonavista bay in Newfoundland. The relative risks for dementia in these seven communities tended to increase with increasing concentrations of Al in drinking water (see Table III in Doll [16]). The small number of patients together with the ecological design limits the conclusions that can be drawn from this study.

Study 6. In Switzerland, Wettstein et al. [98] compared the mnestic and naming skills (measures of cognitive impairment) in two groups of 80–85-year-old long-term (>15 years) residents in Zürich, one group living in an area with a mean Al concentration in drinking water of approximately 0.10 mg/l, the other group in an area with <0.01 mg/l. There were no differences in cognitive impairment between the two groups. It should be noted that a concentration of 0.10 mg Al/l is not very high. Also, in contrast to most other epidemiological studies, the study relied on only two sources of drinking water, and because the bioavailability of Al is likely to vary between different drinking water qualities due to differences in the speciation of Al ([45], see below), it is possible that the only high-Al source in this study contained a low fraction of bioavailable Al.

Study 7. In a series of papers based on the Ontario Longitudinal Study of Aging, where about 2000 men have been followed for about 30 years, Forbes et al. studied the relationship between cognitive function and Al, fluoride and other constituents in drinking water [28–34]. In the initial report of the study [32], the OR for impaired mental functioning was 1.14 (not significant) for median drinking water Al >0.085 mg/l relative to lower Al concentrations. In later analyses, adjusting for other water constituents, significantly elevated odds ratios (OR =1.97, 95% confidence interval [CI] 1.21–3.22, and OR = 2.27, 95% CI 1.27–4.02 using 2 different logistic regression models) were found for Al [28]. Also, comparing individuals with simultaneously high Al (>0.085 mg/l) and low fluoride (<0.88 mg/l) concentrations with those having low Al and high fluoride, the OR was as high as 2.72 ($p < 0.01$) [32].

Study 8. A series of papers have been published from the Paquid cohort of 3777 elderly men and women in the parishes of Gironde and Dordogne in southwestern France. The first three papers used mental impairment as the outcome variable [48,49,67], the last one used AD [79]. The preliminary report [67] indicated a greatly elevated relative risk of 4.5 (95% CI 3.4–6.1) for a calculated increase of 0.1 mg/l of Al in drinking water. However, it was realised that the Al measurements (archival data from the individual waterworks) on which the study was based were erroneously high. When all of the water sources were resampled and analysed in the same laboratory with up-to-date methods and thorough quality control, the resulting analytical values for Al were generally many times lower than the old ones [48,49]. It is very puzzling that this preliminary analysis, using exposure data of such dubious quality, should produce such a strong and highly significant association. The epidemiological results using the new drinking water data were ambiguous: For drinking water pH less than 7.3, there was a weak positive relationship between Al and cognitive impairment; for pH above 7.3, the relationship was *negative* [48]. In the most recent analysis of the Paquid cohort [79], the outcome variable was not cognitive impairment, but AD, diagnosed using the The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [63]. With this improvement in the outcome variable, the relative risk of AD adjusted for age, sex, education, place of residence, and wine consumption was 2.14 (95% CI 1.21–3.80) for individuals exposed to drinking water Al > 0.10 mg/l, while that of dementia was 1.99 (95% CI 1.20–3.28). Furthermore, in a subsample for which information about bottled mineral water consumption was available, the relative risk for dementia adjusted for age, sex, education, place of residence, wine consumption, drinking water silica, and mineral water consumption increased to 3.36 (95% CI 1.74–6.49) [79].

Study 9. In a case-control study of 109 cases of clinically diagnosed presenile (<65 years of age) AD patients in northern England, Forster et al. reported no significant relationships with Al in drinking water [36,93]. Relative risks for different Al concentrations varied from 0.8 to 1.3. However, it should be noted that the Al concentrations in this study were relatively low, the highest concentration being 0.125 mg/l, with few concentrations >0.050 mg/l. Furthermore, it is possible that gastrointestinal absorption of Al increases with age [92]. Therefore, the effect of Al on AD may be smaller in presenile (this study) than in senile AD cases.

Study 10. Employing death certificates from Ontario on which AD was listed as the underlying cause of death, Forbes et al. [33] reported a rate ratio of 2.42 (95% CI 1.42–4.11) for drinking water Al > 0.336 mg/l relative to Al < 0.067 mg/l. Restricting the analysis to individuals over 75 years of age increased the rate ratio to 3.15 (95% CI 1.85–5.36). Furthermore, repeating the analysis with only individuals >85 years gave a rate ratio of 4.76, and after adjustment for drinking water source (ground vs. surface water) and the water contents of silicon, iron, pH, fluoride, and turbidity, a rate ratio as high as 9.95 was obtained [35]. While the effect size in this study was higher than in other published studies, it should be noted that also the Al concentrations were higher.

Study 11. McLachlan et al. [65] conducted a case-control study on autopsy-verified material from a brain bank in Ontario, with AD patients (385 individuals, 296 with pure AD and 89 with other coexisting pathology) and controls (125 individuals with no brain histopathology and 170 with neurodegenerative diseases for which Al has never been implicated) defined on the basis of strict neuropathologic criteria. Comparing all AD cases with all non-AD controls, and using the Al concentration in drinking water at last residence before death as the measure of exposure, the OR associated with Al > 0.10 mg/l was 1.7 (95% CI 1.2–2.5). Attempts to improve the data for Al exposure using 10-year weighted residential histories resulted in increased estimates of ORs of 2.5 or greater. Furthermore, ORs increased gradually when calculated using increasing Al cutoff points: At 0.125 mg/l, the OR was 3.6 (95% CI 1.4–9.9), at 0.150 mg/l it was 4.4 (95% CI 0.98–20), and

at 0.175 mg/l it was 7.6 (95% CI 0.98–61). One of the strengths of this study is the diagnostic quality of the data. A possible weakness is the potential for bias using material from a brain bank. The individuals whose brains end up in a brain bank are probably not representative of the general population, but it does not seem very likely that this could have distorted the results substantially.

Study 12. In a case-control study of 106 cases of clinically diagnosed male AD patients below 75 years of age in eight regions of England and Wales, Martyn et al. found no evidence of an association between AD and higher Al concentrations in drinking water, also when the analyses were restricted to water supplies with low concentrations of silicon [61]. There were three comparison groups (other dementia, brain cancer, and other diagnoses), and the analyses were done employing three different methods for computing exposure data (Al concentrations averaged from age 25 years to diagnosis, from age 25 years to 10 years before diagnosis, and over 10 years before diagnosis). Most of the 54 ORs for increased Al concentrations were below unity, 8 significantly so. Of the studies published so far, this is the one providing the strongest evidence against the Al–AD hypothesis.

Study 13. Gauthier et al. [39] conducted a case-control study (68 cases) in Québec, as part of a large, multidisciplinary study of AD. AD was diagnosed using the NINCDS-ADRDA criteria [63]. Exposure was calculated from water chemistry data for samples collected at four different seasons, combined with the individual subjects' residential history from 1945 to onset of AD. The ORs were adjusted for educational level, family history of AD, and presence of at least one apolipoprotein E ϵ4 allele. In contrast to earlier studies, this study carried out speciation of Al, the exposure data consisting of total Al, total dissolved Al, monomeric organic Al, monomeric inorganic Al, polymeric Al, Al^{3+}, and complexes of Al with hydroxide, fluoride, silicon, and sulphate. The ORs for total Al > 0.077 mg/l were elevated (2.10 for onset exposure and 1.52 for long-term exposure), but not significantly so. The only Al fraction that was significantly associated with AD, was monomeric organic Al measured at disease onset (OR = 2.67, 95% CI 1.04–6.90). The threshold concentration used was 0.012 mg/l (measured as elemental Al). This study has several strengths: high-quality disease data, the most detailed and specific water chemistry data of the studies published to date, and adjustment for known risk factors. Sadly, however, the low power (only 68 cases) of the study seriously restricts the conclusions that can be drawn.

INTERACTIONS WITH OTHER CONSTITUENTS OF DRINKING WATER

Interactions between Al and other chemical constituents in drinking water, in the different parts of the gastrointestinal tract, in the blood, and in extra- and intracellular fluids, have the potential to crucially modify the biological effects of Al. In drinking water, the constituents that have been most frequently discussed are fluoride and silicon. Also, the fact that drinking water only provides a small fraction of the total intake of Al (see below) suggests that the epidemiological relationship between drinking water Al and AD may be indirect. That is, high Al values could be a marker of the active agent, and because water that contains high amounts of Al tend to have low concentrations of silicon and vice versa, the Al–AD link found in epidemiological studies has been suggested to actually be caused by silicon [7].

Silicon

Birchall [7] has proposed that silicon reduces the gastrointestinal absorption and increases the renal excretion of Al, and has also proposed, on theoretical grounds, an approximate threshold concentration of 0.1 mmol/l (equal to 2.8 mg/l of elementary silicon or 6.0 mg/l of silica, SiO_2) for silicon in drinking water for these effects to be effective. Indeed, 0.1 mmol/l of soluble silicon added to orange juice containing the ^{26}Al tracer isotope was found to reduce by severalfold the absorption of Al in human volunteers [18]. Silicon has been studied in six of the epidemiological studies listed in Table 1, and the results are briefly discussed below using the same numbering as in Table 1.

Forbes et al. [29] reported a protective effect of silicon in drinking water on cognitive functioning at silicon concentrations between 0.007 and 0.013 mmol/l, but not at higher silicon concentrations. However, the highest concentration group used in this study was >0.031 mmol/l, which is much below the threshold of 0.1 mmol/l proposed by Birchall [7], so this study does not provide much information relevant to the silicon hypothesis. However, the study gave some indications that at relatively high Al levels, high silicon concentrations lowered the OR [29] (Table 1, study 7).

In the Paquid prospective study in France, Rondeau et al. [79] reported slightly decreased relative risks [RR = 0.69, 0.74, 0.73, and 0.77 (borderline significance) using four different Cox proportional hazard models] for AD in individuals with silicon concentrations >0.19 mmol/l relative to individuals with lower silicon concentrations in drinking water. It should be noted that all except one of the water samples used in this study had silicon concentrations above Birchall's proposed threshold of 0.1 mmol/l [49] (Table 1, study 8).

In their case-control study of 105 presenile AD patients, Taylor et al. [93] reported an OR of 0.8 (95% CI 0.34–1.83) for the threshold value of 0.1 mmol/l of silicon. The relatively low number of individuals with drinking water silicon above this threshold limits the statistical strength of this study (Table 1, study 9).

In their study using death certificates mentioning AD or presenile dementia in Ontario, Forbes et al. [33] reported a rate ratio of 0.63 (95% CI 0.33–1.22) for drinking water silicon >0.1 mmol/l relative to silicon <0.025 mmol/l. The relatively wide confidence interval was due to the low number of individuals (n = 9) for whom drinking water silicon was above 0.1 mmol/l (Table 1, study 10).

In their case-control study of 106 AD patients, Martyn et al. [61] found no evidence of a protective effect of silicon in drinking water, even though the study had satisfactory power to detect such an effect, in that approximately equal numbers of both cases and controls were exposed to drinking water silicon above and below 0.1 mmol/l, respectively (Table 1, study 12).

In their case-control study of 68 AD patients, Gauthier et al. [39] reported ORs of 1.88 (95% CI 0.79–4.49) for onset exposure and 1.37 (95% CI 0.55–3.43) for long-term exposure to drinking water silicon >0.142 mmol/l. In addition, they calculated the concentrations of Al-silicon complexes employing the analytical data for Al, silicon and other drinking water constituents in a computer speciation model. The OR for this species was slightly, but non-significantly decreased (OR = 0.68, 95% CI 0.28–1.70) (Table 1, study 13).

In conclusion, although some of the studies indicate slightly reduced (mostly non-significant) risks of AD or cognitive impairment at higher drinking water silicon concentrations, the combined evidence suggests that the effect is not very strong. However, silicon does seem to reduce the gastrointestinal absorption of Al in man [18,51], and further studies are needed to settle this matter.

Fluoride

It has long been known that ingestion of Al hydroxide decreases the gastrointestinal absorption of fluoride [89]. Assuming that the converse also might be true, i.e., the more fluoride in the diet, the less Al is absorbed, Still and Kelley [91] conducted a pilot

epidemiological study in South Carolina. They reported a lower incidence of "primary degenerative dementia" in a county with a very high concentration of fluoride (4.2 mg/l) in the drinking water relative to two counties with lower fluoride concentrations in their water (0.49 and 0.61 mg/l, respectively). The study, however, was retrospective and based on hospital admitted cases only, and the numbers of cases were small (five cases of primary degenerative dementia in the high-fluoride county). Furthermore, the assumption that fluoride decreases the absorption of Al may not be true; it may well be that fluoride complexes of Al, particularly the electrically neutral AlF_3^0 complex [59], are more readily absorbed from the gastrointestinal tract than uncomplexed Al [22]. Indeed, fluoride has been reported to enhance the absorption of Al in rats and mice [5], and to increase accumulation of Al in the bones of rabbits [1]. Nevertheless, Forbes et al. reported a protective function of drinking water fluoride on cognitive function ([32], Table 1, study 7), and on dementia as reported on death certificates ([33], Table 1, study 10), consistent with the results of Still and Kelley [91]. Indications of a protective effect of drinking water fluoride on cognitive function were also found in a recent epidemiological study in China, but this effect was not significant after adjustment for other elements in the drinking water, and the authors concluded that fluoride was not significantly related to cognitive function in that study [19]. Also, no protective effect of drinking water fluoride was found in epidemiological studies in France [48] and in Québec [39]. In conclusion, the evidence that fluoride in drinking water may provide significant protection against AD through reduction of gastrointestinal absorption of Al is not strong.

Other Drinking Water Constituents

In some of the epidemiological studies of Al in drinking water and AD, other drinking water constituents than silicon and fluoride have also been considered, either in univariate analyses or in multivariate analyses together with Al. Because pH has a very strong influence on both the solubility and the speciation of Al in water, it is interesting to note that both Jacqmin et al. [48,49] and Forbes et al. [30,33,34] reported interactions between Al and pH on the relationship with the outcome variable. However, from what is known about the aquatic chemistry of Al, it is difficult to offer a meaningful interpretation of the results. Other constituents that have been studied are calcium [48,49], iron [30], dissolved organic carbon [28,33] and turbidity [29,34], but no clear picture has emerged from these studies.

EXPOSURE TO ALUMINIUM FROM OTHER SOURCES

Even at high Al concentrations (0.1–0.4 mg/l), drinking water only contributes a fraction of the total Al intake, which is typically in the order of a few milligrams per day in most countries where this has been studied [43,69]. The average intake of dietary Al seems to be somewhat higher in the United States, mostly due to a more widespread use of Al-containing food additives [43]. There is a clear need for epidemiological studies relating total dietary intake of Al to AD. In addition, special groups with heavy exposure to Al should be (and have been) studied. Two such groups stand out; workers occupationally exposed to Al, and regular consumers of antacids. A typical daily dose of antacids is 1 g of Al or more, and other medications like buffered aspirins also contain high levels of Al [57]. Epidemiological studies of dietary intake, occupational exposure, and antacid consumption are reviewed below.

Dietary Aluminium

Up to present, I am aware of only one study devoted to investigating the relationship between Al in food and AD [78]. This was a pilot study of only 23 case-control pairs from a geriatric centre in the United States. The study focused on foodstuffs that are high in Al due to Al-containing food additives, which are rather common in the United States [43]. The crude OR for daily intake of any such high-Al foodstuffs was 2.0. The OR adjusted for kilocalories, body mass index, education, and intake of vitamins A, C, and E was 8.6 ($p = 0.19$). Several subcategories of foodstuffs containing Al additives were also studied, but the small sample size resulted in very unstable ORs. Curiously, all ORs were greatly increased after adjustment for the covariates listed above. For example, for the category "chocolate pudding, chocolate milkshake and hot chocolate" the crude OR was 1.0, while the adjusted ratio was 77.7! Although suggestive, the results of this study clearly need to be reproduced in larger studies before too much confidence can be placed in them.

Tea infusions contain rather large amounts of Al, typically 2–6 mg/l [27]. Tea consumption has been investigated in at least four case-control studies, three of which showed slightly, but non-significantly elevated ORs. In the study by Forster et al. [36] described above (Table 1, study 9), the OR for consuming >4 cups of tea per day was 1.4 (95% CI 0.8–2.6). In a population-based case-control study in Canada [10], the OR was 1.40 (95% CI 0.86–2.28, amount of tea consumed not specified). In a case-control study in Australia [8], the OR was 1.42 (95% CI 0.93–2.17). Finally, in the pilot case-control study of dietary Al described above, Rogers and Simon [78] reported an adjusted OR for tea consumption of 0.7 ($p = 0.69$).

Antacids

Regular users of Al-containing antacids typically consume in the order of 1 g Al per day [57], more than 100 times the typical intake of Al from the diet [43,69]. The majority of brands of antacids on the market are Al-based [57]. Antacid intake has been investigated in a sizeable number of epidemiological studies of AD, but has rarely been the main focus of investigation in these studies. Many of the studies have been of the case-control type, and the amount and regularity of antacid intake is of course difficult to assess in AD patients. Due to the lack of memory in AD patients, questions have to be asked to proxy respondents (both for cases and controls), usually close relatives, whose recall of the patients' habits many years into the past may be more or less imperfect.

The epidemiological studies relevant to the issue of antacid use and AD are listed in Table 2, in approximate chronological order. The studies are briefly discussed below, in the order they are listed in Table 2, column 1. Three of the studies have used an indirect approach, by studying groups of patients with peptic ulcer [26,80] or regular users of the H_2 blocker cimetidine [13]. The majority of such patients have been heavy and regular consumers of antacids, especially before the introduction of H_2 blockers in the late 1970s. Since the early 1960s, Al-based antacids have generally been recommended for ulcer patients as they have a longer duration of action than other antacid types. Thus, most (but not all) peptic ulcer patients have consumed very large amounts of Al.

The small case-control study (40 AD cases and 80 controls) of Heyman et al. [46] from 1984 appears to be the first epidemiological study investigating the role of antacids in AD. Five cases and 15 controls reported regular use of Al-containing antacids for at least 3 months, yielding an OR of 0.59 (not significant) (Table 2, study 1).

Amaducci et al. [6] employed a matched-pair analysis in their

TABLE 2

EPIDEMIOLOGICAL STUDIES OF ANTACID USE AND ALZHEIMER'S DISEASE (AD) OR DEMENTIA

Study No.*	Study Design	Reference No.	Main Result†	Statistical Significance or 95% Confidence Interval
1	Case-control (AD)	[46]	OR = 0.59	n.s.
2	Case-control (AD)	[6]	OR = 0.5 and 0.0	n.s.
3	Death certificates mentioning AD in a cohort of cimetidine users	[13]	"closely matching national rates"	Not stated
4	Case-control (AD)	[42]	OR = 0.7	0.3–2.0
5	Case-control (AD)	[8]	OR = 0.96	0.56–1.65
6	Death certificates mentioning dementia in a cohort of ulcer patients	[26]	SMR = 1.10	0.85–1.40
7	Case-control (AD)	[50]	OR = 0.56	0.20–1.60
8	Case-control (AD)	[56]	OR = 0.82	0.28–2.43
9	Case-control (AD)	[10]	OR = 0.75	0.45–1.23
10	Hospital records, dementia in ulcer patients	[80]	RR = 0.86 (men), 0.72 (women)	0.48–1.42 (men), 0.38–1.22 (women)
11	Case-control (AD)	[36]	OR = 1.6	0.8–3.5
12	Twin study (AD)	[81]	RR = 1.20	0.31–4.97
13	Case-control (AD)	[78]	OR (adjusted) = 8.3	n.s. ($p = 0.22$)

* See text.

† OR, odds ratio; SMR, standardised mortality ratio; RR, relative risk. For some of the studies, the paper contains more results relevant to the Al–AD hypothesis; see text for further discussion of the results.

case-control study of AD, and reported use of antacid drugs in only three discordant case-control pairs using hospital controls (OR = 0.5) and in two pairs using population controls (OR = 0.0, meaning that in both these pairs, the control had used antacids while the AD patient had not). Furthermore, the validity of the surrogate control histories was tested by taking histories directly from the controls as well, and antacid drug use showed the poorest validity of all the variables investigated in this study (Table 2, study 2).

Colin-Jones et al. [13] analysed death certificates in a cohort of 9928 patients who had taken cimetidine (an H_2 blocker), nearly three-quarters of whom had proven or suspected peptic ulcers, and would generally have been heavy antacid users (see above). After 9 years of follow-up more than 2000 patients had died, but only 4 patients had mention of AD on their death certificates, and 4 had mention of presenile dementia. Only one patient had AD listed as the underlying cause of death, which "closely matched the number expected from national rates" (Table 2, study 3).

In their case-control study of 130 matched pairs, Graves et al. [42] reported an overall matched OR for AD of 3.1 (95% CI 1.2–7.9) for use of any antacid, Al-containing or not, daily or almost daily for at least 1 year prior to the reference year. A steep dose-response gradient was found (p for trend = 0.009), with an adjusted OR for the highest tertile of 11.7. However, when only Al-containing antacids were analysed, the overall adjusted OR was only 0.7 (95% CI 0.3–2.0) and there was no significant dose-response trend (Table 2, study 4).

In their case-control study in Australia of 170 matched pairs, Broe et al. [8] reported an OR for AD of 0.96 (95% CI 0.56–1.65) for daily antacid use for at least 6 months. This result was based on 53 matched case-control pairs, and it was not specified whether the antacids were Al-based or not (Table 2, study 5).

Flaten et al. [26] analysed death certificates in a cohort of 4179 patients who had been operated on for gastroduodenal ulcer in the period 1911–1978, who were still alive in 1970, and who were followed to the end of 1987. It was assumed that the majority of these patients would have been heavy consumers of (mostly Al-based) antacids. In 64 of the 1953 patients who had died, dementia

was coded from death certificates either as the underlying or a contributory cause of death. Comparing with the national rates, the standardised mortality ratio for dementia was 1.10 (95% CI 0.85–1.40) for all patients, while for patients operated on in the period 1967–1978 it was 1.25 (95% CI 0.66–2.13) (Table 2, study 6).

In a small case-control study (43 AD cases) in Columbia, Joya-Pardo et al. [50] reported an OR of 0.56 (95% CI 0.20–1.60) for use of Al-containing antacids. The length and timing of the use of antacids was not specified, but it was stated that questions were asked about "chronic ingestion of Al-containing antacids". This study has not been published in a peer-reviewed journal (Table 2, study 7).

In a case-control study of 70 AD patients in China, Li et al. [56] reported an OR of 0.82 (95% CI 0.28–2.43) for use of antacids (type unspecified) for more than 2 years (Table 2, study 8).

In a large (258 AD cases) population-based case-control study conducted within The Canadian Study of Health and Aging [10], the OR for use of Al-containing antacids (length and timing of the use of antacids not specified) was 0.75 (95% CI 0.45–1.23). Also, the frequency of peptic ulcer disease, indicating high antacid consumption, was not significantly elevated among the AD cases (OR = 1.19, 95% CI 0.72–1.96) (Table 2, study 9).

Ryan [80] studied relative risks of acquiring a hospital diagnosis of dementia in 101,104 patients randomly selected from total admissions to Scottish hospitals between 1968 and 1977. The patients were allocated to putative at-risk groups according to main diagnosis at first time of hospital admission. Relative to a mixed reference group of patients with 20 different diagnoses not a priori considered to constitute increased risk for AD or dementia, the relative risks for the peptic ulcer group were 0.86 (95% CI 0.48–1.42) for men and 0.72 (95% CI 0.38–1.22) for women (Table 2, study 10).

In the case-control study of 109 AD patients by Forster et al. [36] described above (Table 1, study 9), "prolonged antacid use" (type of antacid not specified) was associated with an OR of 1.6 (95% CI 0.8–3.5) (Table 2, study 11).

In a study in Finland of 74 twin pairs discordant for AD, Räihä

et al. [81] reported a relative risk of 1.20 (95% CI 0.31–4.97) for any antacid use. The study's low power to detect an effect was due to the low number of twin pairs (6 and 5, respectively) discordant for antacid use (Table 2, study 12).

In the pilot case-control study (23 AD cases) of dietary Al described above, Rogers and Simon [78] reported a crude OR for Al-containing drug use (any vs. never) of 1.0, and an adjusted (see above) OR of 8.3 ($p = 0.22$) (Table 2, study 13).

Although many of these individual studies have had little power, the results are fairly consistent, and taken together they strongly suggest that a high intake of Al through antacids is not a strong risk factor for AD. Heavy antacid users have a very large intake of Al: A typical daily dose is 1 g of Al or more [57]. An intake of 1 g of Al from drinking water necessitates an intake of several thousand litres of water, even at very high Al concentrations in water. Because a considerable fraction of the Al ingested through antacids would be solubilised in the stomach, and some of it would probably be absorbable, partly through complexation with organic ligands in the stomach, the combined evidence from these studies of antacids admittedly provides considerable, although not conclusive (see below) evidence against the Al-AD hypothesis.

Occupational Exposure

Neurotoxic effects from occupational exposure to Al have been reported in a considerable number of studies of different groups of workers [64,87]. Such workers have often been very heavily exposed to Al by the inhalatory route. So far, only two epidemiological studies have attempted to specifically investigate the relationship between occupational exposure to Al and AD [41,82].

1. In Salib and Hillier's study [82], 22 of 198 AD cases (NINCDS-ADRDA diagnostic criteria [63]) and 39 of 340 controls reported having had an Al-related occupation at some stage in their working life, giving an OR of 0.98 (95% CI 0.53–1.75).
2. Graves et al. [41] conducted a rather small (89 cases) case-control study, with only 17 cases and 12 controls ever having been occupationally exposed to Al, of any exposure intensity. A non-significant positive association between Al and AD was found (OR = 1.46, 95% CI 0.62–3.42).

Taken together, these two studies seem to suggest that lifetime occupational exposure to Al is not likely to be an important risk factor for AD, as concluded by Graves et al. [41]. However, a weakness of these case-control studies is that it is not known which types of occupations the workers actually had, and how well the questions asked actually measure the exposure [82]. Clearly, the "exposed" workers could have held a variety of different occupations, and the exposure is very difficult to characterise. Before a clear conclusion can be made about the relation between occupational exposure to Al and AD, there is a need for follow-up studies of cohorts of workers heavily exposed to Al. The follow-up period of such studies would have to be long, to ensure that the subjects reach an age high enough to develop AD. One might argue intuitively that if occupational Al exposure were an important risk factor for AD, one would expect that the resulting increased frequency of AD among such workers would have been noticed, given the high number of heavily exposed workers. However, in the absence of solid epidemiological evidence, such a conclusion cannot be made.

FINAL COMMENTS AND CONCLUSIONS

Epidemiological studies of different designs are more or less prone to bias and confounding. Although the majority of the epidemiological studies of drinking water Al and AD have shown a positive relation (Table 1), the relative risks were generally not high, so there is a possibility that the results could have been due to confounding factors. However, because the number of positive studies is as high as nine, and these studies were conducted in different geographical areas using very different designs, it seems highly unlikely that the same type of confounding factor could have operated in all these studies. Also, no good evidence exists for alternative hypotheses to explain the results [74].

A common critique of these epidemiological studies has been that they are unreliable because the diagnosis is unreliable. It is very difficult to diagnose AD correctly, especially without autopsy material, and many of the studies have not even used AD as the outcome variable, but dementia or cognitive impairment. However, it is difficult indeed to imagine how diagnostic errors should work in a systematic way to produce false positive results in all these studies. On the contrary, it is well known that diagnostic errors, and also misclassification in the exposure variable, usually work the opposite way in epidemiological studies. Such misclassification will most likely bias any true association towards the null value, thereby making it more difficult to demonstrate the association. So if the association between drinking water Al and AD is real, misclassification errors would reduce the magnitude of the association, and the real relative risks would be larger than those reported in the epidemiological studies. Thus, although all the individual epidemiological studies of Al in drinking water are more or less open to critique, the studies are remarkably consistent, particularly considering the difficulty in producing high-quality data for exposure and especially for the disease, and it would be irresponsible to completely disregard the possibility that Al in drinking water could represent a public health problem.

A fundamental difficulty in the interpretation of the epidemiological studies indicating increased risk of AD with increased Al concentrations in drinking water is that even at high concentrations (0.1–0.4 mg/l), drinking water only contributes a fraction of the total Al intake (see above). Even more striking, persons consuming antacids may ingest gram amounts of Al daily, and the epidemiological evidence reviewed above provides very little evidence that Al-containing antacids is a risk factor for AD, and thus constitutes considerable evidence against the notion that Al exposure in general could be an important causative factor in AD. However, Al is very poorly absorbed in the gastrointestinal tract; roughly in the order of 0.1% of the dietary intake is absorbed, depending on the chemical form of Al [18,52,70,75,76]. Hence it is certainly possible that the Al present in drinking water is more bioavailable than that present in food and medications, although there is little concrete evidence for this [40,76,77,90]. Intuitively, one could expect [77] that the actual speciation of Al in ingested food or water would be of minor importance for bioavailability, because in the acid environment of the stomach, low-solubility Al compounds would largely pass into solution and a complete re-speciation of Al could be expected to take place. However, the possibility cannot be excluded that certain species of Al could be stable enough to pass the gastrointestinal tract unchanged. In addition, the speciation of ingested Al may be much more important when the stomach is empty, because the pH is much higher and Al-binding food components [40] are not present. Indeed, after long-term fasting of rats, absorption of the ^{26}Al tracer isotope could be detected even after exposure to low Al concentrations [17,86,97], and fasting seems to lead to increased absorption of Al in rats [17].

The bioavailability and neurotoxic potency of Al is strongly dependent on the speciation. It is well established that citrate and other low-molecular-weight organic ligands strongly enhance gastrointestinal uptake of Al, and differences in lipophilicity, hydrophilicity, and hydrolytical stability are associated with remarkable

differences in the biological effects of different organic complexes of Al [14]. An especially interesting compound is Al maltolate [21], which is very stable to hydrolysis and seems to be an unusually potent neurotoxin [71]. It is perfectly conceivable that some natural waters may contain small amounts of organic Al complexes with properties similar to those of Al maltolate, stable enough to pass through the stomach and accumulate in brain and bone [95]. The total amount of Al in an Alzheimer brain is in the order of only 1 mg, and a continuous lifetime exposure to exceedingly small levels of Al compounds with a tendency to accumulate in the brain would be sufficient to produce this amount. In this light, it is very interesting that in the only epidemiological study employing data on Al speciation, the only Al species that was significantly associated with AD was the organic fraction of Al [39].

The evidence from dialysis encephalopathy (see Introduction) seems to indicate that massive Al exposure or high brain Al concentrations alone are not sufficient to cause full-blown AD neuropathology. The combined weight of the evidence seems to suggest that if Al does play an active role in AD, it more likely acts as a cofactor somewhere in the train of events leading from the initiation of the pathological cascade to the demented brain, somewhat akin to a promoter in the mechanism leading to cancer. Or, as McLachlan has phrased it [64]: "Al is probably not a root cause of AD but rather a cofactor in the molecular events driving the progression of the disease".

In conclusion, a real association between drinking water Al and AD cannot be dismissed from what we know today. However, there are too many inconsistencies in the epidemiological, toxicological, and mechanistical data to recommend public health measures such as lower, health-based limits for Al in drinking water. On the other hand, although there are many unanswered questions about the role of Al in AD aetiology and pathogenesis, and a causal link between Al and AD remains to be established, the combined evidence supporting such a link is certainly strong enough to warrant substantial research efforts, especially in light of the enormous public health impact of this devastating disease. Even if Al accumulation in the Alzheimer tangles and/or plaques should turn out to be only a passive effect, clarifying the mechanism behind this accumulation is likely to provide further insight into the basic pathological mechanisms of the disease. Priority research efforts should include clarification of the cellular and molecular mechanisms in Al toxicity and of the basic metabolism and kinetics of Al in the human body, and further epidemiological studies including diverse routes of Al exposure and also variables that are known or suspected to influence the individuals' susceptibility to AD, such as apolipoprotein E allele status and family history of the disease.

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