STATUS AND FUTURE CONCERNS OF CLINICAL AND ENVIRONMENTAL ALUMINUM TOXICOLOGY

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A wide range of toxic effects of aluminum (Al) have been demonstrated in plants and aquatic animals in nature, in experimental animals by several routes of exposure, and under different clinical conditions in humans. Aluminum toxicity is a major problem in agriculture, affecting perhaps as much as 40% of arable soils in the world. In fresh waters acidified by acid rain, Al toxicity has led to fish extinction. Aluminum is a very potent neurotoxicant. In humans with chronic renal failure on dialysis, Al causes encephalopathy, osteomalacia, and anemia. There are also reports of such effects in certain patient groups without renal failure. Subtle neurocognitive and psychomotor effects and electroencephalograph (EEG) abnormalities have been reported at plasma Al levels as low as 50 μg/L. Infants could be particularly susceptible to Al accumulation and toxicity, reduced renal function being one contributory cause. Recent reports clearly show that Al accumulation occurs in the tissues of workers with long-term occupational exposure to Al dusts or fumes, and also indicate that such exposure may cause subtle neurological effects. Increased efforts should be directed toward defining the full range of potentially harmful effects in humans. To this end, multidisciplinary collaborative research efforts are encouraged, involving scientists from many different specialities. Emphasis should be placed on increasing our understanding of the chemistry of Al in biological systems, and on determining the cellular and molecular mechanisms of Al toxicity.

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One hundred years has passed since the pioneering studies of Siem and Döllken on aluminum (Al) neurotoxicity in experimental animals (Döllken, 1897). Since then, a wealth of studies has clearly established Al as a potent neurotoxicant. In addition, a wide range of other toxic effects of the metal has been demonstrated in plants and aquatic animals in nature, in experimental animals by several routes of exposure, and under different clinical conditions in humans. The main focus in this article is on effects of Al that may be of clinical relevance to humans. However, human medicine can greatly benefit from the knowledge accumulated in other fields, in particular the environmental toxicology and chemistry of Al. Thus, it is vital to adopt a multidisciplinary perspective, starting by integrating the voluminous literature that exists in areas that at first glance may seem of little human relevance, like reductions in crop yields from soil Al and the effects of acid rain on fish and other aquatic animals. There is a great need for initiating serious collaborative efforts among scientists in toxicology, epidemiology, nephrology, nutrition, pediatrics, wildlife biology, environmental chemistry, forestry, and plant pathology, to name some relevant fields (Garruto, 1991). In this article, we discuss only to a limited degree related issues that are covered in the following articles in this issue. Recommendations for future research are summarized at the end of this article.

ENVIRONMENTAL ASPECTS AND ECOTOXICOLOGY

Aluminum toxicity in agricultural plants is a major problem that has been acknowledged at least since 1918 (Hartwell & Pember, 1918). Worldwide, it has been estimated that 40% of arable soils and perhaps as much as 70% of potential new lands that can be brought under cultivation are acidic enough to have an Al toxicity problem (World Food and Nutrition Study, 1977). The economic size of the problem has resulted in intensive research efforts. Consequently, although the majority of the studies have been descriptive rather than mechanistic, perhaps more is known about the toxic effects of Al in plants than in any other type of organism. However, the actual mechanism(s) at work in the field is still open to debate (Foy et al., 1978; Haug, 1984; Taylor, 1991; Delhaize & Ryan, 1995). It is obvious that part of the knowledge gained in the plant field is likely to be relevant to human situations.

In areas where fresh water has been acidified by acid rain, the main toxicant leading to fish extinction is aluminum (Schofield & Trojnar, 1980; Howells et al., 1990; Rosseland et al., 1990), which at more neutral pH values is leached very slowly from Al-containing minerals in the soils. The main target organ in mature fish is the gill. Death is due to disruption in iono- and osmoregulation and respiratory dysfunction. In a sense, the epithelium of the gill is analogous to the gastrointestinal epithelium in humans, so unraveling the nature of the bioactive forms of Al, the detailed mechanisms of intoxication, and the uptake into gill epithelial cells and further into the bloodstream of the fish may help us to understand the bioavailability and toxicokinetics of Al in humans (cf. Exley et al., 1996). For example, Exley and coworkers have proposed a two-step mechanism for acute Al toxicity in fish, whereby the initial binding of the metal to functional groups on the gill epithelial membrane is suggested to alter membrane permeability, allowing a secondary rapid intracellular accumulation of Al (Exley et al., 1991). Indeed, these workers also suggested that this might be a *general* mechanism for Al-induced accelerated cell death.

Regarding bioavailability, it is well documented in humans that concomitant intake of low-molecular-mass organic ligands like the common dietary constituents citrate and maltolate greatly enhances Al absorption. Therefore, citrate increases the potential for Al neurotoxicity (Molitoris et al., 1989). On the other hand, citrate complexation clearly *decreases* Al toxicity in plants (Ownby & Popham, 1989) and in fish (Driscoll et al., 1980; Lacroix et al., 1993), precisely because the mechanism of acute toxicity in plants and fish probably involves binding of Al to exterior cell membranes. Thus, in fish and plants it is quite possible that organic ligands reduce the *acute* toxicity of Al while at the same time increasing its uptake, thereby potentially increasing the risk of *systemic* toxic effects. Studies are needed on the uptake and tissue levels of Al in fish and the factors influencing this, like organic ligands and silicon (discussed later) in the water.

Because the lethal effects of aluminum in fish are so clearly linked to the gills, there has been little interest in determining the effects of Al intoxication on other organs of the fish, such as the nervous system or the bony structure. Preliminary studies have indicated that the central nervous system of fish from lakes affected by acid precipitation has some neuropathological changes similar to those found in experimental Al intoxication and in human neurodegenerative diseases. These changes include chromatolysis, perikaryal and neuritic inclusions, and plaque-like lesions that were strongly immunoreactive to antibodies against phosphorylated neurofilament and microtubule-associated protein tau (Flaten et al., 1993). In addition, strong focal histochemical staining for Al was observed in the olfactory epithelium, and in one fish, diffuse Al staining occurred inside the brain, in the olfactory glomeruli layer of the olfactory bulb, where axons from primary sensory neurons terminate and make synaptic connections with neuritic processes of secondary neurons. This is particularly interesting in light of the suggestion that environmental agents may predispose individuals to Alzheimer's disease through the olfactory neural pathways (Roberts, 1986). Experimentally, there is evidence of direct uptake of

Al via the nasal-olfactory pathway after intranasal application of Al salts in rabbits (Perl & Good, 1987). In fish and other vertebrates including humans, the olfactory organ is the only place where nerve cells are directly exposed to the environment. The olfactory uptake pathway for Al may be particularly relevant in fish from acid-rain lakes, because their olfactory receptor neurons are chronically exposed to up to several hundred micrograms of Al per liter of water, levels that when found occurring in the blood of humans with chronic renal failure cause dialysis encephalopathy. Further studies along these and other lines in fish, plants, and perhaps other natural models hold promise for helping us understand the cellular and molecular mechanisms of Al intoxication and bioavailability.

ALUMINUM TOXICITY IN HUMANS

The possible human toxicity of Al has been a matter of controversy for well over 100 years. Especially since the introduction of Al cookware and food containers, this debate has waxed and waned (Lunge & Schmid, 1892; Anonymous, 1913; Poe & Leberman, 1949; Levick, 1980; Müller et al., 1993). However, the first human conditions generally accepted to be causally related to Al exposure did not occur until the 1970s, shortly after the introduction of routine dialysis therapy in patients with chronic renal failure. Dialysis encephalopathy was perhaps the first iatrogenic disease recognized in this patient population (Alfrey et al., 1972, 1976; Alfrey, 1993). Later, fracturing osteomalacia (Platts et al., 1977; Ward et al., 1978) and a microcytic hypochromic anemia occurring despite adequate iron stores (Short et al., 1980) have been ascribed to Al exposure in dialysis patients.

There is little doubt that Al can cause encephalopathy, bone disease, and anemia in dialysis patients. This can result from introduction of Al directly into the bloodstream via high-Al dialysate or consumption of large oral doses of Al-containing phosphate binders. The lack of urine production, which is the major route for Al excretion, contributes to this problem. It would not be surprising, considering that Al is toxic in these patients, that other groups could be at risk depending on degree and route of exposure, metabolic disturbances, etc. Indeed, in the early 1980s, reports began to appear describing neuro- and osteotoxicity of Al in children with renal failure who were *not* on dialysis treatment (Nathan & Pedersen, 1980; Andreoli et al., 1984). Later reports that Shohl's solution and other sources of citrate greatly enhanced Al absorption and toxicity (Bakir et al., 1986; Molitoris et al., 1989) strongly suggested that most of these nondialyzed children developed Al toxicity through intake of citrate concomitant with Al-containing phosphate binders (Alfrey, 1993). Such observations highlight the need for clarifying the influence of speciation, other dietary and iatrogenic components, and particular disease states on Al absorption and toxicity. Among patients with renal failure, high-risk groups for Al accumulation and toxicity may include diabetics (Andress et al., 1987), patients with iron deficiency (Huang et al., 1992), and parathyroidectomized patients (Andress et al., 1985).

During the 1980s and 1990s, several reports appeared describing Al accumulation and toxicity in individuals *without* chronic renal failure. These include preterm infants, largely fed intravenously (Sedman et al., 1985; Bishop et al., 1989), patients on total parenteral nutrition (Klein et al., 1982; Klein & Coburn, 1994), patients with severe burns (Klein et al., 1994), patients receiving alum irrigation in the urinary bladder to prevent bleeding (Kavoussi et al., 1986; Murphy et al., 1992), and patients undergoing cranial bone reconstruction with Al-containing bone cement (Hantson et al., 1994; Renard et al., 1994). It is worth noting that all of these groups had iatrogenic exposure to Al. Judging from the nature and diversity of these different scenarios in which Al has been shown to accumulate and to have toxic effects, it is likely that other possibilities exist. Additionally, noniatrogenic sources may be creating unrecognized problems. Priority should be given to providing a full overview of the different drugs and clinical materials containing Al, which patient groups are at risk for iatrogenic Al loading, and under which conditions Al represents a health hazard. The dangers of Al-containing phosphate binders have long been realized and their use has been greatly reduced in renal failure patients. However, the fact that new exposure sources, for example, alum bladder-irrigating solutions and bone cement, continue to appear in the literature highlights the need for systematic thinking in this area, following the example of the studies of Al in parenteral solutions (Klein, 1995). The more complete knowledge we have for the iatrogenic setting, the better basis we have to judge whether different types of Al exposure are hazardous to the general population or to susceptible subgroups. Obviously, the current knowledge is too incomplete to perform meaningful quantitative risk assessments for most patient groups, not to speak about the general population. Consequently, it would be premature to recommend measures to protect the general population or susceptible subgroups against specific types of Al exposure.

Infants and Young Children

One susceptible subgroup could very well be infants, even term infants with normal renal function, partly due to their rapidly growing and immature brain and skeleton, and due to an immature blood–brain barrier. Preterm infants are generally recognized to be at risk for Al loading due to their immature kidney function. Full-term infants certainly have better kidney function than preterm neonates, but until they are 1–2 yr old they have lower glomerular filtration rates than adults (Engle, 1986). Furthermore, it is conceivable that infants have enhanced gastrointestinal absorption of Al due to an immature gastrointestinal tract, as is the case for lead (Ziegler et al., 1978), although one study in rabbits does not support this conjecture (Yokel & McNamara, 1985). Plasma concentrations of Al in full-term infants with normal renal function have been reported to increase severalfold after parenteral nutrition (Moreno et al., 1994), and even after prolonged oral intake of Al-containing antacids (Chedid et al., 1991; Tsou et al., 1991; Woodard-Knight et al., 1992). The results of Chedid, Woodard-Knight, et al. should be viewed with caution due to high Al levels in the plasma of control infants, but the highest value found by Tsou et al. among the 16 infants not on antacid therapy was only 10 µg Al/L. (The reference range for Al in the blood of healthy individuals is generally considered to be below 10 µg/L.) In this study, 3 infants (2–4 mo old) had plasma Al levels above 50 µg/L (cf. next paragraph) after oral intake of Al-containing antacids (Tsou et al., 1991). Although Tsou et al. stated that "there were no obvious signs of toxicity in our patients," biopsies were not done and the follow-up period was short, so that subtle symptoms or any long-term effects would not have been detected. In addition, there is considerable evidence from animal studies that developmental toxicity may be the most sensitive type of Al toxicity (Golub et al., 1996). Therefore, it is important to investigate further the toxicokinetics of Al in infants and young children, and in experimental animals of different ages, to help to identify if there are particular risk factors for Al loading in infants. Furthermore, detailed prospective studies are needed of possible effects of elevated Al exposure on cognition, behavior, motorics, delayed ossification, etc. in healthy children as well as in children with different degrees of renal failure. It seems prudent to add as a general recommendation that no child, with or without renal failure, should receive Al-containing antacids (Sedman, 1992).

Characterization of Clinical Effects and Pathology

There is a need for a better characterization of the spectrum of clinical effects associated with different Al blood levels or body burdens. Even within the category of overt dialysis encephalopathy, there seems to be two distinct types, one "classical," "subchronic" type, and one "acute" type, with quite different symptomatologies (Alfrey, 1993). The acute type occurs with greatly elevated plasma Al levels, usually >500 µg Al/L (typically when Al compounds are administered together with citrate), while the classical type has a more gradual onset of symptoms after prolonged periods with plasma levels usually in the range 100–200 µg Al/L. Earlier, 100 µg Al/L was considered a reasonable "limit" below which Al neurotoxicity was not likely to occur.

However, since the late 1980s some studies have indicated subtle neurocognitive and psychomotor effects and EEG abnormalities in dialysis patients well below this limit, at least down to 50 µg Al/L (Rovelli et al., 1988; Sprague et al., 1988; Altmann et al., 1989; Bolla et al., 1992).

Within the renal failure population, we need a better characterization of the pathology in bone and the hematopoietic system (cf. Jeffery et al., 1996) and particularly in the brain. This should encompass the entire spectrum from acute and classical dialysis encephalopathy to patients without clear clinical signs of neurotoxicity with mildly elevated blood Al concentrations who have been on dialysis for 10 yr and more. Emphasis should be placed on assessing possible variations in neuropathology from acute, extremely high-level exposure to long-term, low-level exposure. It is obvious that any pathology seen in the long-term, lower exposure group would be more relevant to the controversy of possible effects of Al in the general population than the pathology seen in overt encephalopathy. Two recent studies of long-term dialysis patients without dialysis encephalopathy showed a high frequency of amorphous amyloid plaques (but no neurofibrillary tangles) (Candy et al., 1992) and Alzheimer-like changes in protein tau processing (Harrington et al., 1994). Earlier, there have been anecdotal reports of Alzheimer neuropathology in dialysis encephalopathy (Brun & Dictor, 1981; Scholtz et al., 1987), although the general scarcity of such pathology has been widely used as an argument against Al playing a causal role in Alzheimer's disease (Wisniewski & Sturman, 1989). Indeed, the lowest serum Al level so far related to cognitive disturbances in dialysed patients (about 50 µg/L, discussed earlier) is still more than 5 times higher than Al levels in healthy individuals and Alzheimer patients.

Alzheimer's Disease

In a sense, the emphasis on the possible role of Al in Alzheimer's disease (cf. Savory et al., 1996) as an incentive for performing basic Al research has functioned as a double-edged sword. On one hand, there is sufficient evidence to warrant further study of the role of Al, 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. On the other hand, the vigorous debate has tended to force scientists and others into two "trenches," where the "nonbelievers" have tended to be skeptical towards Al as a human health hazard in general. This controversy has clouded the scientific open-mindedness and may be a factor behind the difficulties in obtaining governmental and industrial funding for health-related Al research. It is important that the scientific community recognize that Al is an important toxicant, based on the neurological and other effects in the renal patient population, in occupational (discussed next) and in other settings, and on the effects seen in plants, fish, and experimental animals. We should proceed to determine the extent and significance of this problem, beyond that already described, and to ascertain the role of Al in Alzheimer's disease.

Occupational Exposure

Another area where research efforts should be intensified is the occupational toxicity of aluminum. Before 1980, there were only 2 published case reports suggesting an association between Al exposure in the workplace and neurotoxicity (Spofforth, 1921; McLaughlin et al., 1962). The scarcity of overt cases among the large number of workers heavily exposed to Al provides an argument that Al neurotoxicity could at most be a very minor occupational problem. However, there is no doubt that Al accumulation occurs among occupationally exposed individuals. During the last decade a considerable number of studies reported cognitive changes and possible impairment and other neurological effects associated with occupational exposure to Al dusts or fumes (Rifat et al., 1990; Sjögren et al., 1990; White et al., 1992; Bast-Pettersen et al., 1994; McLachlan, 1995, gives further references). It should be emphasized that the effects attributed to Al were generally not robust, and that such studies have inherent difficulties due to diagnostic problems, a lack of agreement of which clinical criteria to use, and the possibility that the effects observed are due to other substances in the occupational environment. Taken together, however, these studies provide considerable evidence that long-term occupational exposure to Al by inhalation may cause harmful neurological effects. Partly because many companies keep records of the tasks of individual employees, the occupational setting offers unique opportunities for studies of neurotoxic effects of aluminum. Priority should be given to thorough behavioral and neurological assessments and to detailed neuropathological studies at autopsy of workers highly exposed to aluminum.

Toxicity Mechanisms, Toxicokinetics, and Chemistry in Biological Systems

Finally, a few areas of particular importance for understanding the clinical toxicity of Al warrant emphasis. These areas have been treated in more detail by other authors in this issue. First of all, intensive collaborative research efforts should be directed toward defining the toxic mechanisms of Al (cf. Strong et al., 1996; Savory et al., 1996; Jeffery et al., 1996). Numerous biochemical processes have been shown to be affected by aluminum (McLachlan et al., 1991; McLachlan, 1995), but there is no agreement on which of these mechanisms are relevant to real-life conditions. It seems fair to say that to date, much more research work has been devoted to describing the effects of the metal than to elucidating the underlying cellular and molecular mechanisms of toxicity, both in clinical and environmental toxicology.

A hindrance to further understanding of the mechanisms of Al toxicity has been the incomplete understanding of the chemistry of Al in biological systems (see Harris et al., 1996). For example, a common aspect across a variety of species is the ameliorating effects of silicon on Al toxicity (Birchall et al., 1989; Birchall, 1992; Hodson & Evans, 1995; Exley et al., 1996; Yokel et al., 1996). In an experiment in which 5 healthy volunteers drank orange juice containing ^{26}Al, Al absorption was reduced to 15% of that observed in the controls by 10^{-4} M silicon (Edwardson et al., 1993). Even without silicon, there was a greater than threefold difference in absorption between highest and lowest, suggesting that Al absorption may depend heavily on idiosyncratic factors, age, gastrointestinal disease, etc. Thus, to study whether a slow and insidious absorption of dietary Al may produce accumulation in vulnerable individuals, it is not sufficient to investigate total dietary intake. If little is known of the variability of dietary Al absorption in individuals, even less is known of the kinetics of Al handling in the kidney and the balance between excretion and reabsorption. Studies have indicated that in renal failure patients having undergone kidney transplantation, accumulated Al is excreted by the newly functioning kidney and is associated with and has its excretion enhanced by urinary silicon excretion (Bellia et al., 1994). Furthermore, the ingestion of silicic acid in water by healthy volunteers is rapidly followed by silicon excretion in urine coincident with enhanced Al excretion (Birchall et al., 1996). This indicates either that silicon (silicic acid) increases the filterable fraction of Al in the blood, or that it inhibits the fraction reabsorbed in the kidney tubules. Thus, in influencing gastrointestinal absorption and enhancing excretion, it is now clear that silicon is profoundly involved in Al homeostasis in humans. One likely mechanism behind such effects is that aqueous Al species interact with silicic acid to form hydroxyaluminosilicates, which are not absorbed across gastrointestinal membranes nor across the kidney tubular membrane (Birchall et al., 1996). Such hydroxyaluminosilicates may be formed in the tubular fluid where the silicon concentration reaches greater than 200 μM following the ingestion of a silicon-rich drink. It is perhaps by altering the handling of Al by the kidney that silicon influences the cellular and tissue distribution of Al, reducing its uptake into bone (Quartley et al., 1993) and brain (Carlisle & Curran, 1987) in rats. These effects of silicon require more detailed investigation and need to be taken into account in future epidemiological studies (Taylor et al., 1995).

The lack of a readily available radioactive isotope of Al has been a major obstacle toward elucidating the mechanisms of absorption, distribution, and excretion of the metal. The only relevant isotope is ^{26}Al, but its half-life is too long to be used with traditional radioassays. It was only about 1990 (Kobayashi et al., 1990; Meirav et al., 1991) that the technology of accelerator mass spectrometry was developed enough to be employed in metabolic studies of aluminum. Since then, a further handful of studies have been reported both in animals and in human volunteers (Day et al., 1991; Jouhanneau et al., 1993; Walker et al., 1994; Priest et al., 1995; Talbot et al., 1995; Walton et al., 1995). This technique is very expensive and labor intensive, but it is by far the most powerful tool currently available for such studies. It is advisable to utilize this research approach whenever possible to design studies at biologically relevant Al concentrations.

RECOMMENDATIONS

- Adopt a multidisciplinary perspective in Al research, involving collaborative research efforts among scientists from many different specialities.
- Determine the cellular and molecular mechanisms of Al toxicity, both for clinical and environmental effects, with emphasis on mechanistic features that are common for different biological effects.
- Studies in fish and plants should emphasize membrane effects, uptake of Al in roots, gills, and the olfactory system, and possible neuro- and osteotoxicity in fish.
- Provide a full overview of the different drugs and clinical materials containing Al.
- Define as completely as possible which patient groups are at risk for iatrogenic Al loading, and under which conditions Al represents a health hazard (e.g., concomitant citrate ingestion). The more complete knowledge we have for the iatrogenic setting, the better basis we have to judge whether different types of Al exposure are hazardous to the general population or to susceptible subgroups.
- Investigate the toxicokinetics of Al in infants and young children (term and preterm, with normal renal function and varying degrees of renal failure), and in newborn and young versus older animals.
- Perform detailed prospective studies of the possible effects (cognitive, behavioral, motor, delayed ossification, etc.) of elevated Al exposure in healthy children as well as in children with different degrees of renal failure and other pediatric patient groups.
- Provide a better characterization of the brain pathology in dialysis patients, encompassing the entire spectrum from acute and classical dialysis encephalopathy to patients without clear clinical signs of neurotoxicity, with emphasis on variations in neuropathology from acute, extremely high-level exposure to long-term, low-level exposure.

Compare pathology in series of long-term (>10 yr) dialysis patients to that of the age-matched general population.

- Conduct further studies on the absorption, metabolism and neurotoxic effects of Al in occupational settings.
- Perform thorough behavioral and neurological assessment, and detailed neuropathological studies at autopsy, of workers highly exposed to Al. Compare with similar studies in long-term dialysis patients and in the general population.
- Increase the understanding of the chemistry of Al in biological systems.
- Conduct further studies of Al toxicokinetics and homeostasis, including absorption in the gastrointestinal tract and the influence of silicon and other factors that determine this and the kinetics of its handling in the kidney, using, among other techniques, ^{26}Al and accelerator mass spectrometry.

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