ALUMINIUM AND THE NUCLEUS OF NERVE CELLS

SIR,—Birchall and Chappell[1] have reviewed in *The Lancet* neurochemical aspects of the interaction of aluminium (Al) with physiological ligands, emphasising the preference of this neurotoxin for association with oxygen donor groups, especially cytosolic phosphates. We would add to their argument the potential for Al to interact with nucleic acid polyphosphates. This is of neurotoxological interest because Al accumulates within affected neocortical nuclei in Alzheimer disease.[2]

The cell nucleus, with its phosphate-containing DNA and RNA, has the highest phosphate density—and thus the highest potential Al binding capacity—of any cellular organelle. Neuronal nuclei, with their large size, extensive euchromatisation, the faster digestion kinetics when exposed to nuclease, high transcriptional output, and extensive nuclear pore complex system, are especially susceptible to Al intoxication.

Al interacts strongly with chromatin and DNA and this association has harmful effects on nuclear metabolism. There is preferential binding of Al within the nucleus,[2-5] and associated with raised nuclear Al levels is decreased cell division and DNA synthesis,[6] and an increase in DNA replication errors and other effects at the chromosomal, DNA, and RNA levels* suggest Al-induced impairment of nucleic acid metabolism—and, ultimately, a deficit in the transmission of genetic information.

The small ionic radius and high positive charge density of Al may favour the translocation of this cation across endothelial, glial, or neuronal membrane barriers.[4,7-9] Concentrations of phosphate are 2 mmol/l in plasma, 10 mmol/l in the cytosol, and at least 50 mmol/l within the nucleus, so the nucleus provides a high affinity, high capacity sink which traps aluminium.

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1. Birchall JD, Chappell JS. Aluminium, chemical physiology, and Alzheimer's disease. *Lancet* 1988; ii: 1008–10.
2. Crapper Mclachlan DR, Quittkat S, Krishnan SS, Dalton AJ, DeBoni U. Intranuclear content in Alzheimer's disease, dialysis encephalopathy and experimental aluminium encephalopathy. *Acta Neuropathol (Berl)* 1980; 50: 19–24.
3. Crapper McLachlan DR, Karlik S, DeBoni U. Aluminium and other metals in senile dementia. In: Katzman R, Terry RD, Bick KL, eds. Alzheimer's disease: senile dementia and related disorders (*Aging* Vol vii). New York: Raven Press, 1978.
4. Wen GY, Wisniewski HM. Histochemical localization of aluminium in the rabbit CNS. *Acta Neuropathol* 1985; 68: 175–84.
5. Wedrychowski A, Schmidt WN, Hnilica LS. The in vivo cross linking of proteins and DNA by heavy metals. *J Biol Chem* 1986; 261: 3370–76.
6. Berlyne GM, Ben Ari J, Knoff E, Yagil R, Weinberger G, Donovitch DM. Aluminium toxicity in rats. *Lancet* 1972; i: 494–96.
7. Baks WA, Kastih AJ. Aluminium increases permeability of the blood brain barrier to labelled DSIP and β-endorphin: possible implications for senile and dialysis dementia. *Lancet* 1983; ii: 1227–29.
8. Banks WA, Abba J, Kastin J, Fasold MB. Differential effect of aluminium on the blood brain barrier transport of peptides, technetium and albumen. *J Pharmacol Exp Ther* 1988; 244: 579–85.
9. Forrester TM, Yokel RA. Comparative toxicity of intracerebroventricular and subcutaneous aluminium in the rabbit. *Neurotoxicology* 1985; 6: 71–80.

ALUMINIUM, HOT WATER TANKS, AND NEUROBIOLOGY

SIR,—Dr Martyn and colleagues (Jan 14, p 59) report a geographical relation between Alzheimer disease and aluminium (Al) in drinking water. Al levels in individual households may depend on the the condition of the house's hot water heater. Most glass-lined hot water heaters are made with a "sacrificial" anode rod of an active metal, such as Al or magnesium, which corrodes more easily than the steel tank if there is a chip or crack in the glass lining. The Al anode rod corrodes, through galvanic interaction with the steel of the tank of the hot water heater, and Al ions pass directly into the water supply. The steel wall in the tank is protected from rusting by the mild electric current generated by the corrosion of the Al. When the Al anode in a hot water heater is actively corroding Al levels higher than those in the local water supply may be released into the household water supply.

Even small amounts of Al compete effectively for Mg binding sites in biological systems. Al^{3+} initiates tubulin polymerisation with an association constant about 10^7 times that of Mg^{2+}, and calcium-ion induced depolymerisation of such Al^{3+} microtubules is greatly inhibited.[1] Mg^{2+} blocks the N-methyl-D-aspartate (NMDA) receptor channel in central nervous system neurons in a voltage-dependent manner[2,3] and there is thought to be an Mg binding site within the channel pore. The NMDA receptor complex provides a recognition site for the neurotransmitter glutamate that is coupled to a Ca^{2+} selective ion channel.[4,5] Since Al ions compete so strongly with Mg they may displace Mg ions from the Mg^{2+} binding site within the NMDA channel pore, resulting in disruption of the usual Mg^{2+} block of the NMDA-receptor-coupled ion channels and release of Ca^{2+} into the neuron. Ca^{2+} entry through NMDA-receptor-activiated channels is believed to cause striking increases in glutamate-induced cell death.[6]

The neurotoxic effects seen with Al intoxication may be mediated through disruption of Mg^{2+} block of NMDA receptors, resulting in uncontrolled activation of excitatory synapses or cell death from calcium influx. Such uncontrolled activation of excitatory synapses could lead to dementia.[7] Even small amounts of Al, by strong competition for Mg binding sites, may lead to unrestrained Ca influx at the NMDA receptor, followed by neuronal death and Alzheimer, or other neurodegenerative diseases.

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1. MacDonald TL, Humphreys WG, Martin RB. Promotion of tubulin assembly by aluminium ion in vitro. *Science* 1987; 236: 183–86.
2. Mayer ML, Westbrook GL, Guthrie PB. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. *Nature* 1984; 309: 261–63.
3. Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* 1984; 307: 462–65.
4. Mac Dermott AB, Mayer ML, Westbrook GL, Smith SJ, Barker JL. NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones. *Nature* 1986; 321: 519–22.
5. Reynolds IJ, Miller RJ. [³H] MK 801 binding to the N-methyl-D-aspartate receptor reveals drug interactions with the zinc and magnesium binding sites. *J Pharmacol Exp Ther* 1988; 247: 1025–31.
6. Hahn JS, Aizenman E, Lipton SA. Central mammalian neurons normally resistant to glutamate toxicity are made sensitive by elevated extracellular Ca^{2+}: Toxicity is blocked by the N-methyl-D-aspartate antagonist MK-801. *Proc Natl Acad Sci* (USA) 1988; 85: 6556–60.
7. Turnbull J. Speculations on disease states induced by excitatory amino acids. *Can J Neurol Sci* 1987; 14: 122–26.

*A fuller list of references in support of these (and other) statements is obtainable from *The Lancet*.

ALUMINIUM FROM A COFFEE POT

SIR,—Like Dr Martyn and colleagues (Jan 14, p 59) we are concerned about aluminium (Al) (and other substances) in drinking water and with the various ways Al enters our water.

One of us purchased an electrically heated pot for preparing instant coffee or tea ('Rival' model 407011). The salesperson told him that the heating chamber was ceramic but on examination it seemed to be made of Al.

We have compared the Al concentration of water heated in this new pot (A) with that in water from our regular coffee pot (B) ('Mr Coffee' model CM1Z), filtered with 'Mr Coffee' paper filters and unfiltered. Both results were compared with Al concentrations in tap drinking water filtered and unfiltered. Water in pot B is heated to about 88°C.

Duplicate water samples were collected and delivered to the laboratory without telling the technician their origin. Al was measured by atomic absorption, an excellent method for trace elements.[1]

Pot A contributed a significant amount of Al to the water. Al concentrations in μg/l (1 μg/l = 0·037 μmol/l) were: 22 in plain tap water; 11 in plain tap water run through a filter; 27·5 in tap water heated in pot B, no filter; 21 in tap water heated in pot B, with filter; and 1640 in tap water heated in pot A.

Groups such as the American Water Works Association, the US Environmental Protection Agency, and the World Health Organisation have suggested a water quality goal of about 50 μg/l (or

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