NUTRITIONAL ASPECTS OF ALUMINIUM TOXICITY

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INTRODUCTION

Aluminium is a ubiquitous element, comprising approximately 8% of the earth's crust (Hem, 1986). It is commonly inhaled as well as ingested. Normal free-living adults will take in an average of 2–5 mg/d with food (Alfrey, 1983) and will drink in a variable additional

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quantity depending on how much Al naturally contaminates the water supply, how much alum is used in local water treatment, whether water is heated in Al utensils, and how much Al is leached from the soil by acid rain. This quantity ranges widely from less than 10 μg/l (Martyn *et al.* 1989) to as much as 6300 μg/l (Parkinson *et al.* 1979).

In one sense, problems associated with Al intake are not nutritional in nature since Al is not a nutrient *per se*. However, in another sense Al-related problems are pertinent to nutrition in that Al contaminates not only our food supply but also a variety of nutritional supplements used in the management of hospitalized patients. Furthermore, the body's ability to process ingested Al in a safe manner may depend on adequate mineral and trace-element nutrition.

Despite the quantity of this presumed non-essential trace element that people inhale and ingest daily, the respiratory system and gastrointestinal tract are felt to be relatively impermeable to Al (Alfrey, 1983). Normally, adults will maintain a serum concentration of Al less than 10 μg/l and excrete an average of 13 μg Al/24 h (Alfrey, 1983).

Nevertheless, when the barriers to Al entry to the blood are by-passed, as in patients with end-stage renal disease receiving haemodialysis therapy with Al-contaminated water (Platts *et al.* 1977) and total parenteral nutrition (TPN) therapy with Al as a contaminant of the protein source, casein hydrolysate (Klein *et al.* 1982*a*), considerable problems may occur. These include osteomalacia, low-turnover bone disease (Ott *et al.* 1982, 1983) and, in the case of patients with end-stage renal disease, an encephalopathy (Alfrey *et al.* 1976), anaemia (Short *et al.* 1980), myopathy (Pierides *et al.* 1980) and cardiac dysfunction (London *et al.* 1989).

Recently, Al has become the centre of controversy both in the scientific literature and in the lay media with regard to its role in the pathogenesis of a variety of other conditions. Specifically it has received most attention with regard to a possible aetiological role in Alzheimer's disease and other neurodegenerative diseases, such as the amyotrophic lateral sclerosis–Parkinsonism-dementia (ALS-PD) found in Guam (Perl *et al.* 1982) and as a significant contaminant of commercially prepared infant formulas (Sedman *et al.* 1985), which might predispose infants to unspecified toxic effects of Al. Receiving considerably less attention are the possibilities that Al may contribute to two conditions that complicate long-term TPN therapy in infants, especially premature infants. These are osteopenia and cholestatic liver disease.

The purpose of the present review is to examine these controversial areas in the light of what is currently known about Al intake, absorption, retention, excretion, tissue distribution, and mechanisms of toxicity. The present article will deal in sequence with the body's handling of Al in relation to the route of administration, experimental evidence from both in vivo and in vitro studies for the effects of Al on various tissues, and, finally, Al as an aetiological agent in various clinical disease states.

ALUMINIUM METABOLISM

This section will deal with the fate of Al in the body in relation to the route by which it enters.

There are two routes by which Al can enter the body: (1) orally or enterally, as a contaminant of food, nutritional supplements or medicines; (2) parenterally; the latter can be subdivided as follows: (*a*) intravascularly, as a contaminant of TPN solutions or medicines and, although currently less likely, haemodialysis water; (*b*) intraperitoneally, as a contaminant of fluids used in peritoneal dialysis; (*c*) subcutaneously, as a contaminant of hypoallergenic extracts precipitated with alum; (*d*) intramuscularly, as a contaminant of vaccines in which Al is used as an adjuvant. The most common route by far is that of

oral–enteral administration. The largest quantities of Al are taken in by this route. However, the most apparent toxicities of Al have been reported with the parenteral routes of administration.

ORAL–ENTERAL ADMINISTRATION

Absorption

Al is administered orally–enterally usually as an inadvertent contaminant of food or water, or deliberately as an Al-containing antacid compound for purposes of intestinal phosphate binding or gastric mucosal cytoprotection (DiJoseph *et al.* 1989).

Intestinal absorption of Al has not been accurately quantified and may be quite variable, depending on the form in which Al is found in the intestine. Although balance studies, which would reflect Al absorption, suggest that 200–300 mg/d is retained when 1–3 g Al/d is given (Clarkson *et al.* 1972; Gorsky *et al.* 1979), these results have been questioned inasmuch as body Al stores have been estimated by Alfrey *et al.* (1980) not to exceed 2–3 g, even in uraemic patients who chronically ingest Al-containing phosphate-binding gels. Furthermore, Greger & Baier (1983*a*), using lower quantities of Al, failed to demonstrate significant Al retention. To be sure, if normal adult subjects take in large doses of Al there will be some increased absorption. Thus, Kaehny *et al.* (1977) demonstrated that in normal subjects receiving 2·2 g Al/d in Al-containing antacids, urine Al rose from 16 to 275 μg/d. Similarly Gorsky *et al.* (1979) observed that urinary Al excretion rose from 65 to 280 μg/d in subjects given 1–3 g Al/d, and Recker *et al.* (1977) demonstrated an increase in urinary Al excretion from 86 to 495 μg/d when adult volunteers were given 3–8 g Al/d. In the study of Kaehny *et al.* (1977) plasma Al rose only minimally. In a more recent study, Weberg & Berstad (1986) estimated from changes in urinary Al excretion that Al absorption from antacids taken with water by normal volunteers was less than 0·1%, while Al absorption from antacids taken with citrate could be as high as 0·7%. Slanina *et al.* (1984, 1986) also demonstrated that citrate enhances intestinal Al absorption in animals and humans.

Other factors which may enhance Al absorption include acidic pH, leading Kaehny *et al.* (1977) to suggest that Al may be better absorbed in an acid environment, such as the stomach or proximal duodenum. Also, Nordal *et al.* (1988) found that serum Al concentrations were higher in Oslo-area residents in the autumn regardless of Al intake and renal function. They postulated an environmental factor that may increase Al absorption during that season.

Important but incompletely understood are the interactions of Al with other metals in the intestine. Greger & Baier (1983*b*) demonstrated that in 40-d balance studies of adult males consumption of 125 μg Al/d had no overall effect on retention of phosphorus, calcium, magnesium, iron, zinc or copper. However, the effects of ingestion of varying quantities of the previously mentioned metals on Al absorption in humans are not known.

Although both 1,25-dihydroxycholecalciferol (Long *et al.* 1980) and parathyroid hormone (Mayor *et al.* 1977, 1980) have been shown to increase tissue Al stores in the chicken and the rat, increasing tissue stores are not necessarily attributable to increased absorption. However, a recent study by Demontis *et al.* (1989) reports indirect evidence for 1-α hydroxyvitamin D_3 enhancing intestinal Al absorption in patients with end-stage renal disease. In contrast, other investigators have found that deficiencies of vitamin D or parathyroid hormone increase Al tissue accumulation (Lewis-Finch *et al.* 1986; Malluche *et al.* 1987). Studies by Ittel *et al.* (1987, 1988) found no effect of either parathyroid hormone or 1,25-dihydroxyvitamin D on Al absorption in uraemic rats, although they did find that Al excretion and serum Al were increased in vitamin-D-replete rats with normal renal function as compared with vitamin-D-deficient rats with normal renal function.

With regard to interaction between Al and other metals in the intestine, work by Wenk

& Stemmer (1983) and Carlisle & Curran (1987) suggests that giving rats diets low in Zn or silicon may increase brain Al content. In neither case is it clear whether Al absorption was increased or whether serum Al concentration or urine Al excretion was increased, although Wenk & Stemmer (1983) did find a slight increase in hepatic Al concentration.

Thus, the preponderance of evidence, especially from humans, indicates that the intestine is a significant barrier to Al absorption, although the interaction between Al and other elements may influence intestinal Al absorption in a manner that is incompletely understood.

Excretion

As implied in the preceding section, the major pathway of Al excretion is via the kidneys and not the bile or intestine (Kovalchik *et al.* 1978; Alfrey, 1983; Klein *et al.* 1982*a*, *b*, 1988, 1989*a*), regardless of route of administration. However, much of the information regarding Al excretion comes from studies of parenteral administration and should be viewed with that in mind.

Significant intestinal Al excretion was not detected in intestinal effluent of patients receiving chronic TPN therapy contaminated with Al (Klein *et al.* 1982*b*). Gorsky *et al.* (1979) found that in Al balance studies in men the majority of excreted Al was found in the stools. They suggested that biliary excretion was the most important means of Al removal from the body. However, this study did not distinguish between biliary excretion of Al and unabsorbed Al. The only findings suggesting that the biliary tract may be a significant route of Al excretion with oral administration come from Williams *et al.* (1986), who found that in patients given oral Al-containing antacid therapy following biliary tract surgery, biliary Al concentration exceeded urinary Al concentration. However, Al excretory rates in bile and urine were not determined.

In contrast it was recently found that in rats given intraduodenal Al in large quantities (100 mg/kg per d) for 2 weeks, biliary Al excretion was only 2–3% of urinary Al excretion (Klein *et al.* 1989*a*). These values corresponded to similar studies performed on rats following intravenous administration of Al (Klein *et al.* 1988). In dogs following intravenous administration of Al, biliary excretion of Al was negligible (Kovalchik *et al.* 1978), and in human adults receiving Al-contaminated TPN, Al excretion in small intestinal effluent was only 3·8 (SD 3·6)% of urinary Al excretion (Klein *et al.* 1982*b*).

Further studies were performed to determine whether the bile is a significant alternative route of Al excretion in Al-loaded rats who have undergone bilateral nephrectomy (G. L. Klein, T. C. Lee & A. C. Alfrey, unpublished results). Male Wistar rats were given high-dose Al (5 mg/kg per d) intravenously, or moderate-dose Al (1·5 mg/kg per d) intraperitoneally, for 5 d. At the end of this period all underwent common-bile-duct cannulation and bilateral nephrectomy. Bile was collected for 3 h and serum samples were obtained. Following these collections desferrioxamine (20 mg/kg) or an equivalent volume of saline (9 g sodium chloride/l) was given intravenously and the enterohepatic circulation reconstructed. A second laparotomy was performed 24 h later, the bile duct–duodenal anastomosis taken down, bile and serum collected, and the liver excised.

With high-dose Al, liver Al concentration reached 1264 (SD 160) mg/kg dry weight, while with moderate-dose Al liver Al concentration reached 94 (SD 34) mg/kg dry weight with normal levels being less than 1 mg/kg dry weight (Klein *et al.* 1988). Fig. 1 illustrates the significant rise in serum Al concentration 24 h after desferrioxamine chelation in comparison with the control groups given saline instead of desferrioxamine. However, as can be seen, biliary Al excretion did not increase following desferrioxamine administration.

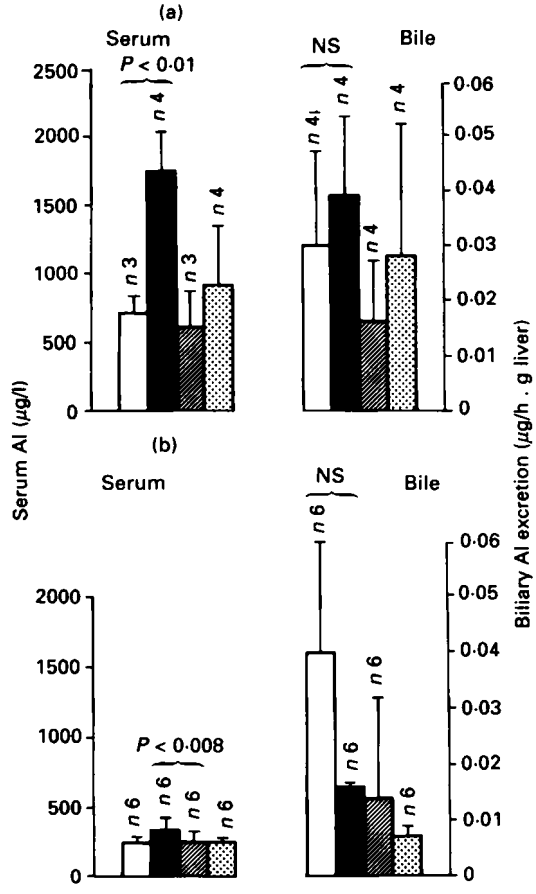

Fig. 1. Serum and biliary aluminium concentrations in nephrectomized rats given Al in (*a*) high doses (5 mg/kg per d intravenously) for 5 d or (*b*) moderate doses (1·5 mg/kg per d) intraperitoneally for 5 d. Values are mean concentrations before (□) and 24 h following (■) desferrioxamine (DFO) administration and before 24 h (▨) and following (▩) administration of a saline (9 g sodium chloride/l) control, and standard deviations represented by vertical bars. With high-dose Al, serum Al concentration post desferrioxamine was significantly greater than the predesferrioxamine concentration. With the moderate dose the rise in serum Al concentration from predesferrioxamine to 24 h post desferrioxamine significantly exceeded the rise in the controls. No significant differences in biliary Al excretion between desferrioxamine-treated rats and control rats were observed. NS, not significant.

Thus, it would seem that biliary excretion of Al even under conditions where the primary excretory route, the kidneys, are removed, is not significant.

Tissue accumulation

There is little evidence from the published literature that Al administered orally or enterally accumulates in tissue if renal function is normal. In one study in which Al-containing antacids were given over a long period of time to patients with end-stage liver disease, Al was reported to accumulate on the trabecular bone surface (Williams *et al.* 1986). Also, Recker *et al.* (1977) found increased bone Al in one patient with peptic ulcer disease and osteoporosis who had consumed large quantities of antacids. However, in other case reports in which patients consumed Al-containing antacids for prolonged time-

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periods, Al was not found in the bones by histochemical staining (Carmichael *et al.* 1984; Godsall *et al.* 1984), even though in both reports patients had evidence of osteomalacia. The cause of the osteomalacia turned out to be phosphate depletion. In addition, Alfrey (1980) and Alfrey *et al.* (1980) found that tissue Al levels are consistently low in patients with normal renal function.

Experimentally, Klein *et al.* (1989*a*) gave buffered aluminium citrate (100 mg elemental Al/kg) intraduodenally to rats daily for 14 d. Even though serum Al concentration and urinary Al excretion were significantly elevated compared with control rats, hepatic Al concentration was only minimally increased – less than 0·5% of what was achieved by intravenous administration of much lower doses of Al (Klein *et al.* 1988). Slanina *et al.* (1984) found slight but statistically significant increases in Al in bone and brain of rats tube-fed 100 mg aluminium citrate/kg for 4 weeks, but no change in bone or brain Al content in rats given aluminium hydroxide. However, if the rats were given $Al(OH)_3$ in conjunction with citric acid, bone and brain Al were increased (Slanina *et al.* 1985); these authors failed to find increases in bone or brain Al when rats were given acidic fruit soup prepared in Al-containing saucepans.

However, if renal function is impaired and Al cannot be excreted normally, tissue accumulation does occur. Andreoli *et al.* (1984) described significant bone Al accumulation in non-dialysed children with end-stage renal disease receiving Al-containing oral phosphate binders. Sedman *et al.* (1984) described Al accumulation in bone and suggested it may also accumulate in the brain in children with end-stage renal disease receiving oral phosphate binders containing aluminium hydroxide and sodium citrate. Salusky *et al.* (1984) showed that $Al(OH)_3$ given orally was associated with an increase in serum Al concentration. More recently, Kirschbaum & Schoolwerth (1989) described elevated Al in bone and brain in women with end-stage renal disease taking Al-containing antacids and Shohl's solution, which contains citrate.

Thus, there is little evidence at the present time to suggest that patients with normal renal function accumulate Al in tissues following oral or enteral Al ingestion; accumulation of Al appears to occur only when renal function is impaired.

PARENTERAL ADMINISTRATION

Intravascular administration

The main sources of Al contamination for intravascular administration are additives to TPN solutions, blood products prominently including albumin, some medicinals such as heparin, and, although much less common at present, water used in haemodialysis. Previous sources had included casein hydrolysate, the protein used in TPN solutions in several centres until 1981, when it was taken off the market (Klein *et al.* 1982*a*, *b*). A list of Al-contaminated products used for intravenous administration is given in Table 1.

There are two unique features of intravascular Al administration as compared with oral or enteral Al administration: the bypass of natural barriers to Al entry into the body and the accumulation of Al in tissues despite normal renal function.

Since the main route of Al excretion is renal, Al accumulation in tissues, especially bone, liver, spleen, brain and parathyroid gland, were first described in patients with end-stage renal disease receiving Al-contaminated water used in their haemodialysis therapy (Alfrey *et al.* 1976; Platts *et al.* 1977; Cann *et al.* 1979; Parkinson *et al.* 1979; Alfrey, 1980).

What was more surprising was the accumulation of Al in the tissues of patients with normal renal function. In adult patients receiving chronic TPN therapy renal function was either normal or minimally reduced (Klein *et al.* 1982*a*). Yet Al accumulation in bone and liver, as well as plasma, was substantial despite markedly elevated urinary Al excretion. In

Table 1. *Parenteral sources of aluminium contamination*

Source	Al (μg/l) Mean	SD	References
Casein hydrolysate (100 g/l)	2313	149	Klein *et al.* (1982*a*)
Crystalline amino acids (100 g/l)	26	20	Klein *et al.* (1982*a*)
Potassium phosphate (3 mmol/l)	16598	1801	Sedman *et al.* (1985)
Unspecified phosphate	3645	135	deVernejoul *et al.* (1985)
Potassium phosphate	2609		Koo *et al.* (1986*c*)
Potassium acid phosphate (136 g/l)	1882		McGraw *et al.* (1986)
Sodium phosphate (3 mmol/l)	5977		Sedman *et al.* (1985)
	2026		Koo *et al.* (1986*c*)
Calcium gluconate (100 g/l)	5056	335	Sedman *et al.* (1985)
	278	810	Koo *et al.* (1986*c*)
	3430		McGraw *et al.* (1986)
Calcium glucoheptonate	3645		Koo *et al.* (1986*c*)
Normal serum albumin (250 g/l)	1164	1218	Milliner *et al.* (1985)
	1822	2503	Sedman *et al.* (1985)
	1647		Koo *et al* (1986*c*)
Normal serum albumin (43 g/l)	324	162	Fell *et al.* (1986)
Plasmanate† (50 g/l)	235		Klein (unpublished results)*
Heparin (1000 u/ml)	684	761	Sedman *et al.* (1985)
Factor VIII	1386	2003	May *et al.* (1986)
Factor IX	495		May *et al.* (1986)
Trace metal solutions	972	108	deVernejoul *et al.* (1985)
	135		Koo *et al.* (1986*c*)
Multivitamin infusion	891		Koo *et al.* (1986*c*)

* Performed in the laboratory of Dr Nancy Alcock, Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, USA.

† Human plasma protein heated at 60° for 10 h (Cutter Biological, Elkhart, Indiana, USA).

fact, balance studies performed on patients receiving long-term treatment with TPN for a variety of severe gastrointestinal disorders revealed that 40–60% of the intravenously administered Al was retained (Klein *et al.* 1982*b*). Further investigation revealed that ultrafilterable Al was only 5% of total plasma Al. Therefore, approximately 95% of Al in plasma was bound to circulating plasma protein (Klein *et al.* 1982*b*), the majority of which is probably transferrin (Trapp, 1986; Martin *et al.* 1987). Thus, most circulating Al is bound to transferrin and not filtered through the renal glomeruli. This may be one explanation for the retention of Al by the body.

When casein hydrolysate was discovered to be the source of Al in TPN solutions, the TPN patients were admitted to the Clinical Research Centre at the UCLA Hospital and Al collection studies were peformed as the patients were switched from casein hydrolysate to crystalline amino acids as the protein source. Serum Al concentration and urinary Al excretion each fell by 50% within 48 h of discontinuation of the casein hydrolysate. However, over the next 3 months these levels remained substantially above normal (Klein *et al.* 1982*b*). In fact, 3 years after discontinuation of casein hydrolysate urine Al excretion and bone Al concentration were still significantly elevated (Vargas *et al.* 1988). These persistently elevated levels prompted the postulate that there were a rapidly exchangeable Al pool and one or more slowly-exchangeable Al pools (Klein *et al.* 1982*b*) in the body. The rapidly exchangeable pool or pools represented Al recently administered, while the slowly exchangeable pools represented tissue stores in equilibrium with plasma and urine. More recently, Sedman *et al.* (1985) studied premature infants given intravenous fluids acutely

with Al-containing additives and found that even after 1 d of Al loading there was a sharp rise in both serum Al concentration and urinary Al excretion. However, when the intravenous fluid administration was discontinued and the infants were nourished by standard commercially prepared formulas the plasma Al fell rapidly to normal while the urinary Al excretion continued to remain elevated. Thus, it would appear that blood Al concentration is more of an indicator of recent acute Al administration while urinary Al excretion and urinary Al:creatinine are more reflective of tissue Al stores.

Animal findings are substantially the same. Henry *et al.* (1984) gave Al intravenously on a daily basis for 3–5 weeks to dogs with normal renal function. They found substantial Al accumulation in bone, liver, spleen, kidney and parathyroid glands. Following one intravenous dose of 1 mg/kg, half-life of Al averaged 4·6 h with limited renal excretion of Al, only 10–20 % of administered Al excreted over 150 min following a dose. These findings suggest that Al is rapidly bound to plasma protein shortly after it enters the blood.

Intraperitoneal administration

Several studies, including Llach *et al.* (1986) and Salusky *et al.* (1988), found that patients with end-stage renal disease undergoing peritoneal dialysis rather than haemodialysis received relatively little Al from peritoneal dialysis fluid and bone Al accumulation was generally associated with oral intake of Al-containing phosphate-binding gels.

However, intraperitoneal administration of Al to rats (Chan *et al.* 1983) resulted in substantial Al accumulation in bone and liver in both uraemic and non-uraemic animals. This substantiated results obtained by Ellis *et al.* (1979) studying non-uraemic rats only. Therefore, intraperitoneal Al administration is another route by which Al can accumulate in tissue.

Subcutaneous administration

Much less information is available with regard to the fate of Al after subcutaneous administration. Yokel (1984) gave varying doses of aluminium lactate to rabbit does between the fourth and the twenty-ninth day post partum. Does receiving 800 μmol Al/kg per d (approximately 22 mg/kg per d) had a high milk Al concentration, 6 mg/l, by the fifteenth day post-natally and those receiving 11 or 22 mg/kg per d had substantial Al accumulation in bone, kidney and liver 5 weeks after the 25-d Al course was completed.

Glinert & Burnatowska-Hledin (1988) determined serum Al concentrations, 24-h urinary Al excretion and urinary Al:creatinine in six adult patients receiving alum-precipitated allergenic extracts and six control subjects receiving conventional aqueous allergenic extracts for 13–120 months. Subcutaneous injections were intermittent, once every 2–4 weeks, and alum-precipitated extracts were reported to range from 1·5 to 2·5 mg Al based on a maximum allowable Al content of 0·85 mg/5000 protein-N units. Serum Al concentration was not significantly different between subjects receiving alum-precipitated and aqueous allergenic extracts, while urinary Al excretion was slightly elevated at 67 μg/24 h and urinary Al:creatinine was threefold greater than control values and substantially higher than the ratio in normal children and adults studied previously (Sedman *et al.* 1985).

Thus, subcutaneous administration of Al appears to result in moderate tissue loading in rabbits and mild tissue loading in humans, as reflected by elevated urinary excretion of Al. The long-term consequences of this degree of tissue loading are unknown at present.

Intramuscular administration

Infants receiving routine periodic vaccinations against diphtheria, pertussis and tetanus are exposed to Al, which is contained in these vaccines as an adjuvant. May *et al.* (1986)

found that the Al concentration in these vaccines ranged from 34 to 505 μg/ml. Thus, an infant receiving 0·5 ml of a vaccine might receive as much as 250 μg Al intramuscularly. However, the tissue deposition and excretion of Al in these infants have not been studied.

Thus, findings presently available indicate that oral or enteral intake of Al is associated with tissue accumulation only in the case of inadequate renal function while parenteral intake by either the intravenous, intraperitoneal or subcutaneous routes may be associated with tissue accumulation regardless of renal function.

TISSUE EFFECTS OF ALUMINIUM: EXPERIMENTAL EVIDENCE

The effects of Al accumulation in various tissues have been studied. These tissues for which findings are available include bone, parathyroid glands, liver, kidney and brain. The results of these studies have considerable clinical significance in helping to evaluate the role of Al in the pathogenesis of a variety of disease states.

BONE AND PARATHYROID GLANDS

Experimental evidence indicates that Al administered parenterally can reduce bone formation, ultimately resulting in osteomalacia (Ellis *et al.* 1979; Robertson *et al.* 1983; Goodman, 1984; Goodman *et al.* 1984*a*, *b*; Sedman *et al.* 1987). The accumulation *per se* of Al at the mineralization front of bone may not be responsible for the toxic effect of Al; rather a deleterious effect on osteoblasts (Plachot *et al.* 1984; Lieberherr *et al.* 1987; Ott *et al.* 1987; Blair *et al.* 1989), their precursors (Simmons *et al.* 1991) or, alternatively, inhibitory effects on the production or action of parathyroid hormone (Cann *et al.* 1979; Morrissey *et al.* 1983; Henry *et al.* 1984; Bourdeau *et al.* 1987) or 1,25-dihydroxycholecalciferol (Henry & Norman, 1985; Klein *et al.* 1986) may be responsible for the bone abnormalities. In addition, Al may also contribute to the bone lesion by physically interfering with hydroxyapatite formation (Posner *et al.* 1986) or with calcium phosphate crystal formation (Meyer & Thomas, 1986). What is clear is that the lesion is reversible after Al administration is discontinued. Any or all of these factors may be operative in a clinical setting and it is uncertain at present which are most important and under what conditions. In addition, Al may be responsible for *de novo* bone formation (Smith, 1984; Galceran *et al.* 1987; Blair *et al.* 1989), their precursors (Simmons *et al.* 1991) or, alternatively, further study.

LIVER

Piglets given Al intravenously for 8 weeks had elevated serum concentrations of bile acids. Electron microprobe analysis confirmed Al localization to the lysosomes (Klein *et al.* 1987). No other ultrastructural changes were found. Al may also interfere with hepatic uptake or transport of bile acids when given in pharmacological doses (Klein *et al.* 1987, 1988). This may contribute to the cholestasis seen with even higher doses of Al given intravenously to rats (Klein *et al.* 1988). Furthermore, analysis of bile in rats given Al intravenously revealed decreased taurine conjugation of biliary bile acids that appeared to be inversely related to serum bile acid concentration and not related to bile flow (Klein *et al.* 1989*b*). In addition Bidlack *et al.* (1987) and Jeffery *et al.* (1987) found that intravenous Al administration to rats reduced microsomal cytochrome P450 and increased activity of non-activated glucuronyl transferase (EC 2.4.1.17), a microsomal membrane-bound enzyme, suggesting that Al may damage microsomal membranes, thus liberating more enzyme.

The pathophysiology of these effects of Al and their clinical relevance require further clarification.

KIDNEY

There is little information with regard to Al effects on the kidney. There is some evidence that Al in large enough doses is detrimental to overall kidney function (Henry *et al.* 1984). In rats with normal renal function Al given intraperitoneally failed to impair the rise in urinary cyclic AMP or phosphate excretion in response to intravenous administration of a bovine parathyroid hormone analogue (Klein *et al.* 1986).

Much of the information is contradictory with regard to the effects of Al on renal 25-hydroxycholecalciferol 1-hydroxylase (*EC* 1.14.13.13) activity, with some studies demonstrating inhibition (Henry & Norman, 1985), low serum levels of 1,25-dihydroxycholecalciferol (Goodman *et al.* 1984*b*; Vukičević *et al.* 1987) and others failing to demonstrate an effect of Al (Chan *et al.* 1983; Goodman *et al.* 1984*a*; Sedman *et al.* 1987). Some of the effects may be species- or dose-specific, or both. At this time no general conclusions can be drawn.

BRAIN

Although topical application of Al to the cerebral cortex of monkeys has been known to produce seizures since 1942 (Kopeloff *et al.* 1942), a variety of experimental evidence for Al neurotoxicity has accumulated over the past 25 years, some of which raises significant questions about the pathogenesis of neurodegenerative diseases in humans.

Ribak *et al.* (1979) not only confirmed that cerebral cortical application of alumina gel produced focal seizures, they also found that it reduced the number of synapses ultilizing γ-aminobutyric acid (GABA) as an inhibitory neurotransmitter. Also of interest with regard to the effect of Al on neurotransmitters was the finding of Siegel *et al.* (1982) that Al could bind to bovine brain calmodulin and alter its structure so that it could not bind Ca and participate in the second messenger system. Marquis & Black (1984) found that Al may inhibit bovine caudate acetylcholinesterase (*EC* 3.1.1.7) and that this effect may be modified by levels of tissue and cytoplasmic Ca.

Evidence for other Al effects on brain was obtained when Klatzo *et al.* (1965), Terry & Peña (1965) and Wisniewski *et al.* (1984) demonstrated that Al administration to rabbits produced a progressive encephalopathy with neurofibrillary degeneration that resembled, but differed in size and configuration from, that seen in human Alzheimer's disease. This same condition was subsequently reproduced by intracerebral injection of Al into cats (Crapper *et al.* 1980). Moreover, DeBoni *et al.* (1980) found that when human cortical cells were incubated with Al in vitro there was both decreased survival time and development of neurofibrillary tangles similar to those seen in rabbits and cats. Wisniewski *et al.* (1984) subsequently found that injection of Al into the cisterna magna of rabbits produced axonal swelling and dendritic thicknening.

In addition to the accumulation and deleterious effects following direct administration of Al into the central nervous system of susceptible species, Uemura (1984) has described brain Al accumulation with subcutaneous Al administration to rabbits. Moreover, Wenk & Stemmer (1983), measuring Al by flame atomic absorption spectroscopy, found an increase in Al in both brain (tenfold) and liver (33%) in rats consuming suboptimal amounts of Zn and supplemental dietary Al. Carlisle & Curran (1987) found that feeding rats low-Si diets with supplemental Al increased brain Al. Garruto *et al.* (1988) fed Al in conjunction with a low-Ca diet to juvenile cynomolgus monkeys for 4 years. No monkeys developed any clinical neurological impairment during that time. However, a variety of neuropathological changes were seen, including neurofibrillary tangles and phosphorylated neurofilaments, degeneration similar to that found in some human neurodegenerative

diseases, such as Parkinsonism-dementia and amyotrophic lateral sclerosis of Guam. There were no significant differences in pathology between monkeys given only a low-Ca diet and those given a low-Ca diet supplemented with Al. The pathological changes tended to be more severe in those receiving the low-Ca, Al-supplemented diet, but only six monkeys were studied.

Although many of the changes observed by Garruto *et al.* (1988) are also seen in the previously mentioned human neurodegenerative diseases, it is not clear whether these effects are due to Ca deficiency in the monkeys, Al-induced abnormalities in Ca metabolism in Al-susceptible species, or direct effects of Al. Yase (1988) also produced neurofibrillary tangles and other pathological changes by feeding rabbits Al, in addition to a low-Ca diet. However, a low-Ca diet without Al was not given.

Thus Al, even by the oral route of administration, may adversely affect the brain in some species. In addition, Al may produce neurological damage by itself, altering the permeability of the blood–brain barrier to various substances as suggested by Banks & Kasdan (1983). Whether these effects of orally ingested Al are relevant to humans and their diets is discussed in a later section on Al and neurodegenerative diseases in man (p. 130).

The uncertain nature of the interaction of Al and other minerals, such as Ca and Zn, which might result in increased Al in the brain, is especially puzzling. The gastrointestinal tract is such an efficient barrier to Al absorption that one would expect that for brain Al to be elevated there would be generalized tissue Al accumulation, as well as elevated serum Al concentration and urinary Al excretion. However, these features of Al loading have not been studied, with the one exception of the slight increase in liver Al found by Wenk & Stemmer (1983).

One intriguing possible explanation for brain Al accumulation is an olfactory pathway directly to the brain, which has been demonstrated by Perl & Good (1987) following the topical application of Al to the olfactory bulbs of rabbits, after which granulomas developed both at the olfactory bulb and in the cerebral cortex, with Al demonstrated by microprobe both in the pyriform cortex and in the olfactory bulb granulomas. Another possibility is that Al, primarily bound to transferrin in plasma, crosses into the central nervous system by means of the transferrin receptors on the endothelial lining of the blood–brain barrier, as speculated by Wills & Savory (1989).

In summary, Al administration directly to the central nervous system is associated with several pathological effects in some species, including neurofibrillary degeneration, phosphorylated neurofilaments, encephalopathy and possible alterations in neurotransmitter synthesis or activity. Some of these effects have been observed with oral or subcutaneous Al administration to susceptible species. How Al enters the brain and causes these changes in the light of its inefficient absorption and entry into the circulation and its apparent inability to accumulate in tissues remains to be clarified.

CLINICAL EVIDENCE FOR ALUMINIUM TOXICITY

Next to be examined is evidence for Al causation of discrete clinical entities, following which the likelihood of Al involvement in other clinical conditions will be assessed. Solid information is available regarding the involvement of Al in the pathogenesis of bone disease in patients with end-stage renal disease and those receiving long-term treatment with TPN. There is also strong evidence implicating Al in the pathogenesis of encephalopathy, including dementia, in patients with end-stage renal disease, as well as anaemia and myopathy.

The areas in which Al involvement has been suggested are in the pathogenesis of Alzheimer's disease and neurodegenerative diseases localized in Guam, the Kii Peninsula

of Japan, and western New Guinea, and the pathogenesis of osteopenic bone disease and cholestatic liver disease in the premature infant receiving therapy with TPN. In addition there has been recent controversy over the risks posed by the presence of substantial quantities of Al in a wide variety of infant formulas.

First, the conditions in which strong evidence of Al involvement exists will be discussed.

LOW-TURNOVER BONE DISEASE

In the late 1970s two distinctly different groups of patients were found to have an unusual painful and fracturing bone disease associated with decreased bone formation, and in some cases osteomalacia. Patients with end-stage renal disease were undergoing haemodialysis with Al-contaminated water (Platts *et al.* 1977; Parkinson *et al.* 1979) or receiving oral Al-containing phosphate-binding gels, or both (Bournerais *et al.* 1983; Andreoli *et al.* 1984). Patients receiving long-term therapy with TPN for a variety of intestinal diseases (Klein *et al.* 1980) inadvertently received Al as a contaminant of casein hydrolysate, the protein source in the TPN solutions (Klein *et al.* 1982*a*). Uraemic and TPN patients developed reduced bone formation and osteomalacia (Ott *et al.* 1982, 1983; deVernejoul *et al.* 1985) and both groups had substantial bone accumulation of Al (Hodsman *et al.* 1981; Klein *et al.* 1982*a*.

In both types of patients Al was located in the bone-osteoid surface either by histochemical staining with aurin tricarboxylic acid (Buchanan *et al.* 1981; Ott *et al.* 1982, 1983) or by electron-microprobe analysis (Cournot-Witmer *et al.* 1981). The stain was quantified by measuring the amount of surface taking up the stain. This measurement was found to correlate highly with quantitative bone Al, as determined by flameless atomic absorption spectroscopy, and in both groups of patients there was an inverse correlation between surface stainable Al and rate of bone formation (Ott *et al.* 1982, 1983).

Desferrioxamine treatment to chelate Al from bone of patients with end-stage renal disease and dialysis osteomalacia was found to improve this condition (Ott *et al.* 1986; Nebeker *et al.* 1987; Felsenfeld *et al.* 1989). Furthermore, substitution of crystalline amino acids for Al-containing casein hydrolysate in TPN patients also improved bone formation (Vargas *et al.* 1988). However, in this latter group of patients, although stainable Al at the mineralization front was greatly reduced, total bone Al concentration, as determined by flameless atomic absorption spectroscopy, was still abnormally elevated. Furthermore, these same investigators found an inverse relationship between plasma Al and bone formation rate, confirming an earlier report by deVernejoul *et al.* (1985). Thus, since plasma Al is likely to be more reflective of recent dosing with Al it is possible that decreased bone formation results from chronic repeated exposure to Al rather than to the direct effect of the total amount of Al that accumulates in bone. The Al accumulating at the mineralization front may reflect Al accumulation in and localized toxicity to osteoblasts, as has been suggested by some of the experimental evidence (Plachot *et al.* 1984; Lieberherr *et al.* 1987; Sedman *et al.* 1987) and formation of new bone on top of areas with Al accumulation may reflect Al egress from osteoblasts, as postulated by Ott *et al.* (1987) from their studies in rats.

With regard to effects of Al on other factors that may affect bone formation and mineralization, the findings have been equivocal. While serum concentrations of parathyroid hormone have been relatively reduced in dialysis osteomalacia (Hodsman *et al.* 1981; Andress *et al.* 1983; Kraut *et al.* 1983) and in the lower range of normal in adult TPN patients (Klein *et al.* 1981), secretion of parathyroid hormone was vigorous in TPN patients who were made hypocalcaemic (Klein *et al.* 1981, 1985*c*). Thus, as in experiments in vitro

and in vivo, any Al-induced suppression of parathyroid hormone secretion was overridden by a hypocalcaemic stimulus. However, Andress *et al.* (1985) have shown that parathyroidectomy in patients with end-stage renal disease may result in increased surface bone accumulation of Al from oral ingestion of Al-containing phosphate binders. Furthermore, Vargas *et al.* (1988) found an inverse correlation between stainable bone Al and serum levels of parathyroid hormone. Although these findings might suggest that parathyroid hormone may help to reduce bone Al accumulation, there is no evidence that total bone Al is altered. In fact Vukičević & Stavljenić (1989) reported that, after parathyroidectomy in rats, Al accumulated on inactive bone surfaces but total bone Al did not increase.

Clinical studies of the effects of Al on vitamin D metabolism have also been equivocal. Patients with end-stage renal disease generally have low serum levels of 1,25-dihydroxycholecalciferol as a result of their renal impairment. However, initial studies of adult patients receiving TPN therapy revealed that serum concentrations of 1,25-dihydroxycholecalciferol were low despite normal serum levels of the other major vitamin D metabolites (Klein *et al.* 1981; Shike *et al.* 1981). When adult patients were made hypocalcaemic and a vigorous parathyroid secretory response was elicited, serum concentrations of 1,25-dihydroxycholecalciferol failed to rise in response to this stimulus (Klein *et al.* 1981, 1985*c*). One patient who was followed after TPN therapy was transiently discontinued did not experience a rise in serum levels of 1,25-dihydroxycholecalciferol to normal until 8 weeks after discontinuation of TPN (Klein *et al.* 1981). Following resumption of TPN treatment, serum levels of 1,25-dihydroxycholecalciferol fell again. At 3 years after discontinuation of Al-containing casein hydrolysate the serum levels of 1,25-dihydroxycholecalciferol were normal or improved in patients studied initially (Vargas *et al.* 1988). Furthermore, studies of other groups of patients receiving TPN therapy with a low Al content failed to reveal low serum levels of 1,25-dihydroxycholecalciferol (Klein *et al.* 1985*b*; Shike *et al.* 1986). In addition, in uraemic patients Fanti *et al.* (1987) found that chelation of Al with desferrioxamine resulted in increased circulating levels of 1,25-dihydroxycholecalciferol. Thus, Al loading may affect vitamin D metabolism, but whether directly or indirectly is unknown.

DIALYSIS ENCEPHALOPATHY

The other major clinical condition associated with Al loading is dialysis encephalopathy, the clinical features of which are dyspraxia, hesitancy, dementia, myoclonus, seizures, hallucinations and progressive muteness and obtundation. Characteristic multifocal slow wave and spike activity were seen in bursts on electroencephalography. This syndrome was first described by Alfrey *et al.* (1972) and first attributed to Al by Alfrey *et al.* (1976), who found generalized Al loading in these patients. More dramatic still was the description by Bakir *et al.* (1986) of four patients with end-stage renal disease who developed acute encephalopathy leading to death within 1 month. All four were receiving $Al(OH)_3$ and Shohl's solution (citrate-containing) and it is postulated that the citrate led to enhanced Al absorption.

Histopathological studies initially failed to demonstrate features characteristic of this encephalopathy (Burks *et al.* 1976). However, more recent studies of brains from patients who died of dialysis encephalopathy suggest that there are also neurofibrillary tangles similar, although not identical, to those seen in other putative Al-associated neuropathies (Sabouraud *et al.* 1978; Brun & Dictor, 1981; Scholtz *et al.* 1987). Further evidence implicating Al as a cause of dialysis encephalopathy is neurological improvement with the

Al chelator desferrioxamine, provided treatment is begun early (Alfrey, 1986; Ackrill *et al.* 1986).

THE ROLE OF ALUMINIUM IN THE PATHOGENESIS OF OTHER CLINICAL DISORDERS

A series of clinical conditions will be discussed in which the role of Al is less well established. These are neurodegenerative disorders such as Alzheimer's disease and the neurodegenerative diseases of Guam, the Kii Peninsula of Japan, and western New Guinea, the osteopenic bone disease associated with TPN therapy in the small infant, cholestatic liver disease associated with TPN therapy in the small infant, and the possible risks posed to infants by Al contamination of commercially prepared infant formulas.

NEURODEGENERATIVE DISEASES

As mentioned earlier, brain concentrations of Al have been considerably lower than those in other organs, even in cases of dialysis encephalopathy. Al accumulation in the brain appears to be patchy (Perl *et al.* 1982) and concentrated primarily in grey matter (Alfrey *et al.* 1976). Recently, electron microprobe studies combined with immunocytochemical studies have detected similarities in the brain histopathology of patients with Alzheimer's disease and the ALS-PD of Guam, the Kii peninsula and western New Guinea. Perl & Brody (1980) and Perl *et al.* (1982), using electron microprobe techniques, have found Al in the brains of patients with Alzheimer's disease and ALS-PD of Guam, with a particularly prominent X-ray spectrum in the neurofibrillary tangles. Furthermore, Shankar *et al.* (1989) have demonstrated by immunocytochemical studies the antigenic similarity in the structure and configuration of the neurofibrillary tangles in the brains of patients with Alzheimer's disease and ALS-PD of Guam. Moreover, as mentioned previously, although previous studies of the histopathology of the brain in patients with dialysis encephalopathy failed to reveal neurofibrillary tangles (Burks *et al.* 1976), more recent studies have in fact found them. (Sabouraud *et al.* 1978; Brun & Dictor, 1981; Scholtz *et al.* 1987). Although the neurofibrillary tangles in dialysis dementia do not appear to be entirely the same as those in Alzheimer's disease, similar findings in three different disease entities, in addition to the experimental evidence previously cited, suggest that there may be an Al-associated histopathological signature in the brain in three different clinical dementias. Although this association is quite striking, how Al reaches the brain and what it does there still need to be better understood. It is not at all certain that Al entering the brain causes pathological changes to occur in all the conditions in which it is found. It cannot be ruled out that Al accumulation in the brain is secondary to the pathological changes that have already taken place.

The intestine is generally considered a barrier to Al absorption. Thus, in the case of patients with Alzheimer's disease and ALS-PD of Guam it is unclear as to how considerable amounts of Al could be absorbed and cause general Al loading in patients with apparent normal renal function. However, it is possible that factors which mediate intestinal Al absorption, such as intraluminal pH, high dietary citrate, unspecified season-related environmental factors, Zn or Ca deficiency and perhaps, though not likely, vitamin D sterols, combine in some way to enhance Al absorption.

Perl *et al.* (1982) suggest that in Guamanian patients with ALS-PD the low Ca content and high Al content of the water may create a hyperparathyroid state which would facilitate Al absorption and tissue deposition. However, other reports suggest that parathyroid hormone may at least protect against bone Al accumulation in patients with

renal failure (Andress *et al.* 1985) or with normal renal function (Vargas *et al.* 1988). Furthermore, if hyperparathyroidism facilitated Al deposition in tissue, especially in brain, why are there not more cases of dementia in patients with renal failure and secondary hyperparathyroidism who ingest large quantities of Al-containing phosphate binders?

In consideration of what Al might do when it reaches the brain, patients with dialysis encephalopathy are Al loaded from a parenteral source. However, adult TPN patients who received comparable quantities of Al over a similar time period failed to demonstrate any form of neuropathy (Klein *et al.* 1982*a*). Thus, even if Al were to cross the blood–brain barrier it is unclear that Al alone could directly produce clinical toxicity.

OSTEOPENIC BONE DISEASE

The premature infant requiring nutritional support with TPN therapy is a very complicated individual. Often the infant suffers from respiratory distress with consequent hypo-oxygenation of tissues in addition to infection, underdeveloped suck and swallowing abilities, and gastrointestinal disease. In addition, glomerular filtration rate is normally reduced until 34 weeks of gestation (Sedman *et al.* 1985).

Approximately 20% of the premature infants in the intensive care nursery at the Children's Hospital and Medical Center in Cincinnati develop rickets or fractures, or both. The majority of these infants receive TPN treatment and the peak incidence of severe bone disease was at approximately 2 months of age (Koo *et al.* 1986*a*). Many more develop 'osteopenia' on X-rays of the long bones.

Current thinking as to the pathogenesis of this condition favours inadequate provision of phosphate or Ca or both, in quantities to equal the *in utero* mineral accretion rate in the last trimester of pregnancy. While this may well be a very important part of the problem, various other factors may also play a role in modulating the phosphate and Ca requirements of these individuals. These would include initial exposure to gravitational force, which is beyond the scope of the present review, and exposure to Al. The reason for the Al exposure is that the TPN solutions are still contaminated with Al, particularly the Ca and phosphate salts, heparin and albumin. These observations were initially made by Sedman *et al.* (1985) as well as deVernejoul *et al.* (1985) and Milliner *et al.* (1985) (Table 1). TPN solutions prepared at medical centres around the United States have demonstrated a wide variation in Al content. Nonetheless the Al administered to premature infants averages 15–30 μg/kg per d – midway between the Al administered parenterally to Al-toxic adults receiving TPN (60 μg/kg per d) and that given to adults receiving TPN therapy without evidence of Al accumulation in tissue (1·5 μg/kg per d; Klein, 1990).

In premature infants receiving TPN with present levels of Al contamination and a developmentally appropriate decrease in glomerular filtration contributing to Al retention, Sedman *et al.* 1985) found that bone Al concentration was tenfold higher in infants fed intravenously for 3 weeks to 3 months than in non-parenterally treated infants. The elevated bone Al concentration was accompanied by elevation in both serum Al concentration and urinary Al excretion, indicating an increased tissue burden of Al. In addition, Koo *et al.* (1986*b*) found that on staining vertebral bone of infants with aurin tricarboxylic acid, as in adults, Al accumulates at the osteoid–mineralized bone interface.

Histomorphometric variables for low-formation bone disease are not at present as well established for infants as for adults. Thus, the determination of whether the Al that accumulates in the bones of these premature infants is actually causing disease is more difficult. However, anecdotal evidence suggests that present levels of Al contamination in infants is harmful to bone.

Recently an infant patient who had a demineralizing bone disease while receiving long-

term treatment with TPN was studied by Klein *et al.* (1989*c*). The infant maintained normal serum concentrations of Ca, P, Mg and vitamin D, most probably due to the continuous infusions of these nutrients in the TPN solution. Nonetheless, she did have mild hyperparathyroidism, which may have been responsible for at least some of the bone demineralization. However, provision of as much Ca and phosphate as could be mixed in the TPN solution without calcium phosphate precipitation and supplementation with vitamin D given intramuscularly failed to improve bone mineralization. Serum Al concentration and urine Al excretion were both markedly elevated and a trial of chelation therapy with desferrioxamine was begun. After only four doses the patient developed sustained hypocalcaemia despite the continuous infusion of Ca in the TPN solution, the lack of increased calciuria, probably due to the mild hyperparathyroidism, and the lack of affinity of desferrioxamine for Ca.

It appears possible that, with chelation of Al from the bones of this patient, Ca was taken up by bone. This would imply that Al in bone prevents bone Ca uptake. This is consistent with findings reported by Alfrey (1985), who gave ^{47}Ca to two uraemic patients. One of the patients had osteitis fibrosa and secondary hyperparathyroidism and demonstrated a high rate of ^{47}Ca incorporation into bone. The other patient had osteomalacia and presumed Al loading and demonstrated a low rate of ^{47}Ca incorporation into bone. Certainly this occurs in adults receiving TPN. Vargas *et al.* (1988) found a positive correlation between urinary excretion of Al and Ca, a finding consistent with Al in bone impairing bone Ca uptake and increasing the filtered load of Ca in the urine. Earlier studies by Klein *et al.* (1980, 1985*a*) demonstrated that hypercalciuria was a feature of the TPN-associated bone disease in adults and that this was primarily due to an increased filtered load of Ca.

Furthermore, in one patient (G. L. Klein & J. W. Coburn, unpublished results) urinary Ca excretion increased as the Ca content of the TPN solution increased, while the protein content of the TPN solution remained constant. Thus, although protein content may play a role in the hypercalciuria of TPN (Bengoa *et al.* 1983), the increased filtered load of Ca in conjunction with increased Ca administration suggests that the bones are not taking up Ca in Al-loaded patients.

Thus, an argument is made that Al may exacerbate osteopenic bone disease in premature infants receiving TPN therapy at least in part by blocking bone Ca uptake. The continued presence of Al in TPN solutions, its administration to infants at a rate exceeding known safe levels in adult patients, and its accumulation at the mineralization front of bone all bear a striking resemblance to its currently understood pattern of accumulation and action in adult TPN patients with Al-related bone disease.

CHOLESTATIC LIVER DISEASE OF TPN

Like the osteopenic bone disease, cholestatic liver disease is another complication of TPN therapy, especially in the young infant. This condition, which usually involves only mild localized periportal inflammation and bile stasis and occasionally fatty deposition may in certain cases progress to cirrhosis. Causes are felt to be multifactorial, including lack of intestinal stimulation and both the glucose and amino acid components of the TPN solution (Balistreri *et al.* 1986).

In adults and children who received long-term TPN therapy with casein hydrolysate as the protein source, liver Al concentration was elevated up to twentyfold normal values (Klein *et al.* 1982*b*, 1984). In infants receiving TPN therapy with crystalline amino acids instead of casein the liver Al concentration was five times greater than that in control patients (Klein *et al.* 1985*d*). All the TPN patients who received casein hydrolysate had histopathological evidence of liver dysfunction, as described previously.

However, in contrast to experimental evidence for bone and brain, Al appeared to cause

no distinctive histopathological change in the liver, except for one report of lysosomal distortion (Galle & Giudicelli, 1982). Therefore, it is not clear that Al is entirely responsible for pathological changes seen in the human livers. However, Al might contribute in some way to the cholestasis observed, since serum bile acid concentrations are elevated in infants receiving TPN (Balistreri *et al.* 1986) and in piglets and rats. Although there is currently no evidence suggesting that the quantities of Al in the liver actually contribute to cholestatic liver disease, Al may theoretically impair hepatocellular uptake of bile acids, thus contributing to cholestasis without contributing to the histopathological changes seen with TPN.

ARE THERE RISKS POSED BY ALUMINIUM IN INFANTS' FORMULAS?

The final subject to be considered is whether the Al that has been found to contaminate infant formulas poses a threat to the health of normal infants or either premature infants or term infants with impaired renal function.

Sedman *et al.* (1985) were the first investigators to detect Al in commercially prepared infant formulas. These findings have been confirmed by a number of groups, including Freundlich *et al.* (1985), McGraw *et al.* (1986), Koo *et al.* (1988), Semmerkrot *et al.* (1989) and Fisher *et al.* (1989). The specialized infant formulas, such as premature formula that is supplemented with energy up to 100 kJ (24 kcal)/30 ml and Ca and phosphate, formulas containing hydrolysed casein (Koo *et al.* 1988), and most of all soya-bean-based formulas, are all contaminated with Al to a greater degree than are standard infant formulas.

These reports have recently raised a great deal of concern in medical journals and in the lay press, as cited by Lawson *et al.* (1989), about the possible risks run by infants ingesting such formulas. Table 2 lists the formulas evaluated for Al content and published references for the citation.

At the time of writing, risks run by infants with normal renal function ingesting Al-contaminated formulas is theoretical as there have been no reports of Al toxicity in this population.

Almost certainly some of the Al is absorbed. Sedman *et al.* (1985) showed that the urinary Al:creatinine excretion in normal, growing term infants was sixfold greater than that in normal adults. This provides some evidence for absorption. However, serum Al concentration in these infants was normal. Serum Al concentration may not be as good an indicator of body burden of Al as urinary Al excretion or urinary Al:creatinine (Kaehny *et al.* 1977; Sedman *et al.* 1985). This is similar to the findings of Kaehny *et al.* (1977) in adult volunteers consuming larger doses of Al-containing antacids. Also, Litov *et al.* (1989) found normal serum Al concentrations in term infants consuming soya-bean-based formulas. However, urine Al was not measured. There is no published information to date suggesting that there is tissue Al loading in infants with normal renal function consuming infant formulas. Furthermore, experimental studies have confirmed that Al is poorly absorbed (Alfrey, 1983), and that even if sufficient amounts are absorbed so as to raise serum Al concentration and urinary Al excretion, there is no evidence that it accumulates in human tissue.

In cases of impaired renal function, Freundlich *et al.* (1985) attributed encephalopathy in two infants to Al accumulation in the brain. The only Al source received by either infant was milk formula. However, aspects of this study have been questioned by Koo *et al.* (1988) and by Sedman & Klein (1990), including the calculation that the brain Al concentration in one of the infants exceeded the total calculated Al intake. Thus, the culpability of formula Al in producing toxicity in patients with impaired renal function is uncertain and requires confirmation.

Table 2. *Aluminium content of infant formulas*

Formula	Al (μg/l) Mean	SD	References
Breast milk	9·9	6·9	Sedman *et al.* (1985)
	4		Freundlich *et al.* (1985)
	14		Koo *et al.* (1988)
	3		Semmerkrot *et al.* (1989)
Cow's-milk-based	266	192	Sedman *et al.* (1985)
formulas	173	56	Freundlich *et al.* (1985)
(84 kJ (20 kcal)/30 ml)			
	128	53	McGraw *et al.* (1986)
	154	111	Koo *et al.* (1988)
	113	55	Fisher *et al.* (1989)
	780		Semmerkrot *et al.* (1989)
	8*		
Cow's-milk-based	699	321	Sedman *et al.* (1985)
premature formulas	343		Freundlich *et al.* (1985)
(100 kJ (24 kcal)/30 ml)	407	164	Koo *et al.* (1988)
Soya-bean-based formulas	1478	103	Sedman *et al.* (1985)
(84 kJ (20 kcal)/30 ml)	330		McGraw *et al.* (1986)
	670	422	Koo *et al.* (1988)
	981	268	Fisher *et al.* (1989)
	1560		Semmerkrot *et al.* (1989)
	520*		
Commonly used specialized formulas			
Nutramigen	1204		Koo *et al.* (1988)
Pregestimil	729		Koo *et al.* (1988)

* Using standard and Al-free methods.

Furthermore, Salusky *et al.* (1990) followed uraemic infants consuming an Al-containing cow's milk-based formula for a mean period of 20 months. No increases were found in plasma Al concentration and bone biopsies failed to stain for the presence of Al. Thus, cow's-milk-based infant formulas appear to be safe for infants with renal failure.

Nonetheless, after having expressed doubt that the Al in infant formula is harmful, it should be noted that the Committee on Nutrition, American Academy of Pediatrics (1986) recommended that it would be prudent for premature infants and infants with impaired renal function not to be fed on soya-bean-based formulas as long as safer alternatives are available.

SUMMARY

In summary, Al, a metal with no known biological requirement, has been shown both clinically and experimentally to be toxic to bone and to the central nervous system and, experimentally at least, to the liver. Al is a contaminant of a number of substances given parenterally, most often intravenously.

The present review attempted to examine some of the more recent concerns with regard to Al toxicity and has concluded that patients at risk for Al toxicity include primarily infants with impaired renal function and those infants who are given Al as a contaminant of intravenous solutions which are provided with the aim of nutritional support. With regard to the likelihood that Al is a causative agent in Alzheimer's disease or the neurodegenerative diseases of the western Pacific, there are some consistencies between Al-

associated changes experimentally and some of the histopathological changes seen clinically. These suggest that Al may have a histopathological signature on the central nervous system. However, how Al reaches the brain and whether it can do so under the conditions that produce the previously mentioned neurodegenerative diseases must be explained. The action of Al in the brain under these circumstances also requires further study.

There is clear evidence for bone accumulation of Al in infants, especially premature infants, and an isolated experience with one case that suggests that Al may impair bone Ca uptake in infants receiving TPN therapy. There is some experimental evidence for an Al-associated cholestasis in various animal species, including pigs and rats, but no firm evidence yet that it might occur in humans. Finally, there are currently no findings to suggest that Al from infant formulas may have adverse effects on the health of infants even though there may be some increased Al absorption in comparison with the adult diet. In fact, existing findings suggest that cow's-milk-based formulas are safe for even uraemic infants (Salusky *et al.* 1990).

Much needs to be done to understand better the behaviour of this ubiquitous metal, and efforts need to be made to obtain a reduction of the Al content of intravenous fluids as well as infant formulas in order to minimize Al-associated toxicity.

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