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ALUMINUM METABOLISM

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ORAL EXPOSURE TO ALUMINUM

Diet and Water as Sources of Aluminum

The aluminum in the food supply comes from natural sources, water used in food preparation, food additives, and contamination by aluminum utensils and containers. Considering the average amounts of aluminum added by these sources and typical food patterns, Greger (55) estimated that most Americans consume 2–25 mg aluminum daily from food and water. Pennington & Jones (116) reported that the daily menu for 25- to 30-year-old males in the Total Diet Study by the Food & Drug Administration (FDA) contained 13.77 mg aluminum. Ellen et al (35), using duplicate portion techniques, reported that Dutch adults consume 0.60 to 33.3 mg aluminum per day.

Some aluminum is present naturally in most foods (Table 1) (52, 60, 116, 128, 136). Soil adhering to vegetables may be the source of some aluminum in certain fruits and vegetables. The aluminum content of soil is variable, but on average is estimated to be 7.1% (76). Even so, few foods, except "aluminum accumulators" such as herbs and tea leaves, naturally contain more than 5 μg

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Table 1 Estimated aluminum concentrations of selected foods

Foods	Aluminum concentration (μg/g)	Foods	Aluminum concentration (μg/g)
Animal products		Vegetables, fruits, and legumes	
Most meats cooked	0.2–1.2[a]	Common fruits (apples, bananas, oranges, peaches)	0.05–0.4[b,e]
Cheese, cheddar	0.2[b]	Common vegetables (cabbage, cauliflower, corn, cucumbers, tomatoes)	0.01–0.2[a,b]
Cheese, processed	297[c]		
Milk, whole	0.06[b]	Asparagus	4.4[d]
		Beans, green cooked	3.4[a]
Grains		Lettuce	0.6[d]
Biscuits, baking powder, refrigerated	16.3[b]	Peanut butter	5.8[b]
Bran, wheat	12.8[d]	Peas, green, cooked	3.4[a]
Bread, white	3.0[e]	Potatoes, unpeeled, baked	2.4[a]
Bread, whole wheat	5.4[e]	Spinach, cooked	25.2[d]
Corn chips	1.2[b]	Strawberries, fresh	2.2[b]
Cornbread, homemade	400[b]	Other	
Rice, cooked	1.7[a]	Baking powder	2300[e]
Herbs and spices		Beer, canned	0.7[b]
Basil	3082[e]	Cocoa	45[d]
Celery seed	465[e]	Cola, canned	0.1[b]
Cinnamon	82[e]	Cream substitute, powdered	139[b]
Oregano	600[e]	Pickles with Al additives	39.2[c]
Pepper, black	143[e]	Salt with additives	164[c]
Thyme	750[e]	Tea, steeped	4.3[c]

[a]Greger et al (60).
[b]Pennington & Jones (116).
[c]Greger (52).
[d]Schlettwein-Gsell & Mommsen-Straub (128).
[e]Sorenson et al (136).

Al/g food. The aluminum content of these "aluminum accumulators" can vary greatly with plant varieties and soil conditions, including pH (34, 71). For example, Eden (34) estimated that tea leaves contain 1000 μg Al/g, but some contain as much as 17,000 μg Al/g.

In general, the amount of aluminum naturally present in the diets of Americans is small (1–10 mg per day) (52). This reflects the limited use of most herbs and the insolubility of aluminum in tea leaves.

WATER Generally, water is not a major source of aluminum. The amount of aluminum in surface and groundwater is variable; 0.012 to 2.25 mg Al per liter have been reported in North American rivers (76). When the pH of water is 5, the amount of soluble aluminum in water tends to increase.

Aluminum-containing flocculants are used to clarify municipal water supplies. Miller et al (108) estimated that there was a 40–50% chance that aluminum coagulants increased the aluminum concentration of finished water above that naturally present in water. However, the median level (0.017 mg per liter) of aluminum in the finished water samples studied was very low (range 0.014–2.67 mg per liter). Thus, individuals consuming two liters of water daily would ingest less than 0.04 mg aluminum in water.

FOOD ADDITIVES Food additives are a major source of dietary aluminum in the United States, although aluminum-containing additives are present in only a limited number of foods (52, 115). In 1982 approximately four million pounds of aluminum were used in food additives in the United States (17).

The data compiled by the Committee on the GRAS List Survey-Phase III (18) indicated that individual usage of these aluminum-containing food additives varied greatly. About 5% of adults in the United States consumed more than 95 mg aluminum in food additives daily; 50% consumed 24 mg or less aluminum daily in food additives. The most commonly used aluminum-containing food additives are acidic sodium aluminum phosphate (leavening agent in baked goods); the basic form of sodium aluminum phosphate (emulsifying agent in processed cheese); aluminum sulphates (acidifying agents); bentonite (materials-handling aid); aluminum lakes of various food dyes and colors; and aluminum silicates (anti-caking agents) (52, 115).

Calculations based on industrial production figures may slightly overestimate aluminum intake from food additives (17, 18, 52). But estimates based on standardized menus such as those used in the Total Diet Study (116) tend to underestimate the usage of additives.

PACKAGING AND UTENSILS Several physicians have suggested that aluminum cooking utensils were a major source of aluminum in food (89, 143). Investigators have found that many foods accumulated statistically significant amounts of aluminum when cooked or stored in aluminum pans, trays or foil

as compared to similar batches of food processed in stainless steel containers. However, most foods accumulated less than 2 μg Al/g food during preparation and storage (60).

Low pH, long cooking periods, and the use of brand new pans or pressure cookers have all been found to result in greater aluminum accumulation by foods (60, 74, 113). Organic acids, including citric acid, fluoride, and copper in foods may also increase the solubilization of aluminum from pans and foil slightly (5, 35, 40, 125). However, it is doubtful that the use of aluminum utensils adds more than 2 mg aluminum to the diet of Americans daily.

INFANT FORMULAE Recently a number of investigators have become concerned about the aluminum content of infant formulae (85, 105, 130). The aluminum content of human or cow's milk is negligible (0.05 μg/ml) (85). Dabeka & McKenzie (21) reported that ready-to-use milk-based and soy-based formulae contained 0.01–0.36 and 0.40–6.4 μg Al/g, respectively. Thus 1–3-month-old infants consuming certain soy-based formulae could take in as much as 2.1 mg Al daily, whereas infants fed human or cow's milk would consume only 3 μg Al daily. A major source of the aluminum would be contamination in added calcium salts.

Pharmaceutical Products as Sources of Aluminum

The typical quantities of aluminum consumed in foods and beverages amount to less than 1% of the quantities that can be consumed in pharmaceutical products (90, 91). Lione (91) estimated that 126–728 mg and 840–5000 mg were possible daily doses of aluminum in buffered analgesics and antacids, respectively.

Calcium supplements, especially those based on oyster shells, have been reported to contain 0.2–0.6% aluminum (9). These products would be a minor source of pharmaceutical aluminum (12 mg per day).

Of special concern are parenterally delivered pharmaceuticals, because the protective barrier of the gut is bypassed. Several substances administered intravenously, including albumin (1,822 μg Al/g), calcium salts (5,056 μg Al/g), and phosphate salts (5,977–16,598 μg Al/g) have been reported to contain significant quantities of aluminum (129).

METABOLISM OF ALUMINUM

Absorption of Aluminum

Aluminum absorption has been very difficult to quantify. One reason is that no suitable radioisotopes of aluminum are available. Most aluminum isotopes (^{23}Al, ^{24}Al, ^{25}Al, ^{28}Al, ^{29}Al, and ^{30}Al) have half-lives of less than 10 minutes

(10). The only aluminum isotope with a biologically usable half-life is ^{26}Al (7.2×10^5 years), but it is too scarce and expensive to use in sufficient quantities for radiochemical detection (24).

A second reason is that collection and analysis of fecal samples do not provide data sensitive enough to monitor mineral, including aluminum, absorption when absorption is less than 1% (2, 53). When human subjects were fed pharmacological doses of aluminum (~1–3 g per day), fecal losses of aluminum were generally found to be less than aluminum intake (12, 15, 51, 121). The sensitivity of these measurements could be questioned because subjects in these balance studies appeared to absorb 100–600 mg Al per day but excreted at most only an additional 0.5 mg Al per day in urine. At that rate of excretion, aluminum levels in tissues would rapidly exceed any ever observed in autopsy tissues (2). Moreover, when subjects were fed 5–125 mg Al per day, aluminum losses in feces approximated dietary intake (12, 51, 57, 131, 141).

In response to this methodological quandary, Ganrot (49) suggested that urinary aluminum excretion could be assumed to equal aluminum absoprtion. Accordingly, he estimated that subjects in an earlier study (77) ingesting 2.2 g aluminum hydroxide absorbed 0.01% of the supplemental aluminum. On that basis, subjects ingesting a diet containing 5 mg aluminum daily absorbed 0.78% of the dietary aluminum and absorbed 0.094% of 120 mg of supplemental aluminum added to the diet as aluminum lactate (57).

However, the assumption that all absorbed aluminum is excreted in urine appears to be faulty because animals and humans accumulate aluminum in tissues with continued exposure (6, 47, 58, 59, 61, 68, 112, 113, 132, 133, 146). Moreover, it might be expected that the relative percentage of absorbed aluminum that is retained (not excreted in urine) could vary with kidney function, age, disease states, and/or perhaps other dietary factors.

Thus, Greger & Powers (62) hypothesized that an alternate way to estimate relative aluminum absorption was to compare tissue accumulation of aluminum in relation to dose in animals fed aluminum and in animals matched for age and weight and injected with aluminum. Using this methodology, they estimated that weanling Sprague Dawley rats fed 1–3 g Al as aluminum hydroxide per kilogram diet absorbed 0.011–0.036% of dietary aluminum. Percent apparent absorption of aluminum was less when higher concentrations of aluminum were fed.

Estimates of absorption based on urinary excretion of aluminum in the same rats tended to be slightly lower and ranged from 0.006 to 0.013% (62). Moreover, the relative effects of dietary treatments appeared to differ when aluminum absorption was estimated by the two different methods. Rats fed 3 g Al/kg diet excreted a higher percentage of oral aluminum intake than rats fed 1 g Al/kg diet.

Finally, Day et al (24) measured absorption of ^{26}Al in one adult human subject. The individual was fed 100 ng ^{26}Al with less than 1 μg of natural aluminum ^{27}Al in a sodium citrate solution. The ratios of $^{26}Al/^{27}Al$ in blood were measured in blood after 6, 12, and 18 hr. The investigators estimated that 1% of the tiny dose of aluminum was absorbed by this fasted subject.

In general, all these whole animal techniques indicate that aluminum absorption is very low (1%) and that the percent absorbed is sensitive to aluminum intake. Aluminum absorption was 10- to 100-fold greater when human or other animals were fed small amounts of aluminum (i.e. 5 mg per day for humans) rather than pharmaceutical doses of aluminum (i.e. 1–3 g per day for humans and 1–3 g/kg diet for rats).

MECHANISMS Although much has been published on intestinal absorption of aluminum, no clear, unified explanation has emerged. It is believed that intestinal absorption of aluminum includes both paracellular passage routes along enterocytes and through tight junctions by passive processes and transcelluar passage routes through the enterocyte, involving passive, facilitated, and active transport processes (147).

A number of investigators using in situ rat jejunal preparations (119), everted gut sacs (39), perfused duodenum (1, 16), and jejunal gut slices (118) have demonstrated that at least part of gut absorption of aluminum is due to active processes that are inhibited by dinitrophenol, sodium cyanide, vanadate, and/or the absence of glucose or sodium in the perfusate. Adler & Berlyne (1) using in vivo isolated duodenal segments estimated that about 23% of aluminum uptake was due to nonsaturable process and the rest was due to saturable (active) processes when aluminum was perfused as $AlCl_3$ at pH2.

At least part of the active absorption of aluminum may be due to processes shared with active absorption of calcium. Mayor et al (102, 103) found that parathyroid administration enhanced aluminum uptake by rats, but Ittel et al (75) noted that parathyroidectomy did not alter aluminum absorption in either normal or uremic animals. Adler & Berlyne (1) demonstrated that saturable absorption of aluminum was significantly less in vitamin D deficient rats than in normal rats.

Cochran et al (16) tried to assess the importance of calcium channels on aluminum absorption. They observed small but significant decreases in duodenal uptake of aluminum when verapamil, a calcium-channel blocking agent, was administered. Because the doses were high, the investigators only hypothesized that calcium channels might be an entry site for aluminum.

Interpretation of all of this work and comparisons among studies are difficult because the experimental conditions varied greatly. The relative importance of each absorptive process is dependent on the section of the intestine that is involved, concentrations of aluminum in gut and in blood, pH of the gut, speciation of aluminum, and other dietary factors (96, 114, 147).

Speciation of aluminum in water is complex and changes dramatically with pH (Figure 1) (95). For example, the concentration of free aluminum (Al^{+3}) in aluminum hydroxide solution is one thousand times greater at pH 4.2 than at pH 7.4 (2). Thus, it is not surprising that intestinal absorption of aluminum in in situ perfusion systems of the rat small intestine was found to be greater at pH4 than at pH7 (148). Similarly, it is logical to assume that aluminum absorption is apt to be greater in the proximal duodenum than in distal segments of the intestine because the lower pH of the proximal duodenum would result in more soluble aluminum. However, Beynon & Cassidy (7) could not demonstrate that patients with achlorhydria absorbed aluminum less efficiently than normal subjects.

DIETARY FACTORS AFFECTING ALUMINUM ABSORPTION The latter study demonstrates that although pH of the gut mileau is important in predicting the speciation and solubility of aluminum, the efficiency of aluminum absorption is also dependent on a variety of other factors. Two important dietary factors affecting absorption of aluminum are citrate and inorganic anions.

CITRIC ACID Several groups of clinicians observed increased aluminum absorption (as judged by serum and urine aluminum concentrations) among

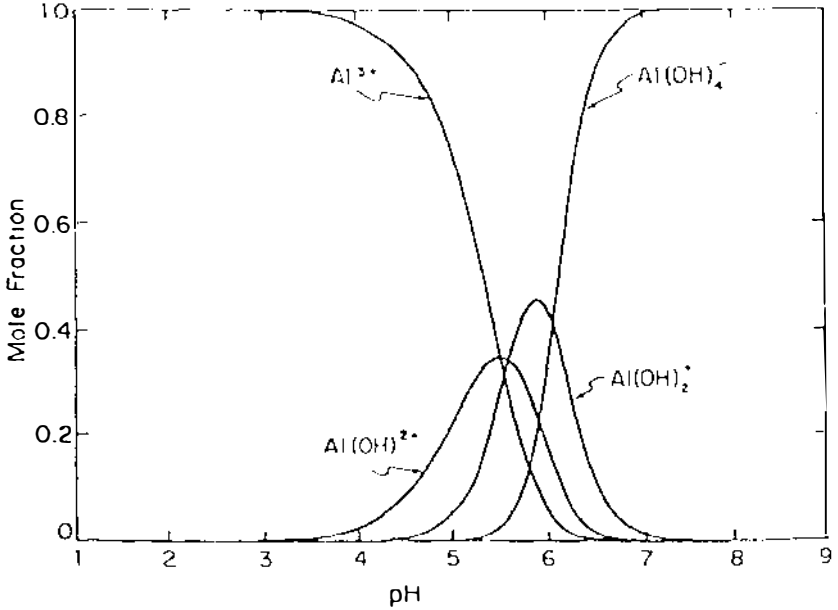

Figure 1 Distribution of soluble, mononuclear aluminum ion species in aqueous solution. At any pH the individual mole fraction sum to unity. Reprinted with permission from *Clinical Chemistry* (1986) 32(10):1798. Copyright American Association for Clinical Chemistry, Inc.

patients treated with both citrate-containing pharmaceuticals, such as Shohl's solution, and aluminum-containing pharmaceuticals (4, 80, 81, 111). Similarly, normal subjects were found to have higher serum aluminum concentrations when aluminum hydroxide was ingested with lemon juice (a source of citric acid) rather than water (134).

This led to real concern by physicians about the effect of citrate on aluminum toxicity (2, 69). But few investigators have reported the effect of chronic oral exposure to citrate on aluminum retention.

The practical significance of citrate on aluminum absorption varies in these studies. Slanina et al (132, 133) demonstrated elevated brain, blood and bone aluminum concentrations in rats treated daily by gavage with an aluminum citrate solution rather than aluminum hydroxide. Fulton and associates (46, 47) showed that the addition of citrate to drinking water containing aluminum hydroxide elevated bone and plasma aluminum concentrations in rabbits but increased only intestinal aluminum concentrations in rats.

Ecelbarger & Greger (31) found that ingestion of citrate (5–31 mmol added citrate per kilogram diet) increased aluminum retention in bones of rats fed 1 g Al/kg diet for ~28 days. Greger & Powers (62) noted that rats fed citrate (2.5 mol added citrate per kilogram diet) with aluminum excreted more aluminum in urine and had elevated tibia aluminum concentrations.

In general, animals chronically fed aluminum and citrate in diets (31, 62) retained more aluminum than animals given citrate with aluminum in drinking water (46, 47) but less aluminum than animals dosed with only citrate and aluminum by gavage (132, 133). The presence of other substances in the gut, as occurs when aluminum and citrate are added to feed and water, may have moderated the effect of citrate on aluminum absorption. Many of these substances (i.e. fluoride, phosphates, calcium) would not be important constituents in the gut lumen when aluminum and citrate were administered by gavage to fasted animals.

Citrate probably enhances aluminum absorption by several different mechanisms. (*a*) Citrate increases the solubility of aluminum in the gut. Martin (95) has shown that aluminum occurs as a neutral soluble complex in the presence of citrate at pH 2.5–5.5, a pH range in which aluminum is normally insoluble. Froment et al (44) demonstrated that solubility of aluminum in the presence of citrate did not totally explain the effect of citrate when they administered by gavage a variety of aluminum citrate mixtures to rats. Although citrate generally increased the amount of aluminum excreted in urine, the solubility of aluminum in these mixtures (38–91%) did not correlate with urinary aluminum (used in this study as an index of aluminum absorption).

(*b*) Citrate may chelate aluminum and transport aluminum into mucosal cells. Van der Voet et al (150) noted that dinitrophenol, an inhibitor of active

transport, decreased citrate enhanced aluminum absorption. If citrate-aluminum complexes are absorbed, it is logical to expect that aluminum absorption might be increased as the amount of citrate was increased. But Ecelbarger & Greger (31) observed that although the presence of citrate (5 to 31 mmol/kg diet) increased aluminum retention by rats, the response was not linear as the molar ratio of aluminum to citrate decreased from 1:3.7 to 1:1.2.

(*c*) Citrate has been demonstrated to open epithelial tight junctions in cultured cells, presumably by chelating calcium (98). Froment et al (45) demonstrated that aluminum citrate but not aluminum chloride increased the presence of ruthenium red, a low molecular weight surface marker, in the intercellular spaces of isolated intestinal loop preparations and induced prolonged significant reductions in transmural resistance.

Although the interaction of citrate and aluminum is practically important, the uniqueness of the interaction has been overstated. Domingo et al (27) observed that the addition of a variety of organic acids besides citric acid (including lactic acid, oxalic acid, and tartaric acid) to the drinking water of rats resulted in greater retention of aluminum in tissues. Moreover, citric acid has been found to increase the absorption of other minerals including calcium (66), lead (50), and zinc (73).

INORGANIC ANIONS A number of investigators have demonstrated that large oral doses of aluminum depress phosphorus absorption in humans (15, 26, 56, 93, 137), laboratory animals (112, 113), and livestock (122, 146). In fact, aluminum salts are used to treat hyperphosphatemia in renal patients because aluminum greatly reduces phosphorus absorption by forming insoluble complexes with phosphates in the gut (127).

Similarly, ingestion of large quantities of aluminum reduces fluoride absorption and retention in humans (56, 138) and livestock (64, 124). Accordingly, increasing phosphorus or fluoride intake should reduce aluminum absorption, *provided* that the molar quantities of phosphate or fluoride in the gut are significant in comparison to the molar quantities of aluminum. Typically that would not occur in regard to fluoride.

Potentially, silicates could also affect aluminum absorption (8). Exley et al (37) demonstrated that the addition of silicon to water reduced symptoms of aluminum toxicity in salmon fry. Birchall (8) hypothesized that silicon reduced the systemic absorption of aluminum by the salmon because above pH 6.6 silicates replace phosphates as primary complexors of aluminum in solution.

A few investigators have compared the biological effects of various aluminum salts. Although these investigators did not actually measure aluminum absorption, the studies provide insights on the interactions of anions with aluminum in the gut.

Storer & Nelson (140) observed that large oral doses of aluminum phosphate

were less toxic to chicks than equal doses of aluminum as chloride, sulfate, nitrate, and acetate salts. Similarly, Kaehny et al (77) found that subjects had a greater rise in serum and urine aluminum when they were given 2.2 g aluminum daily as aluminum hydroxide, aluminum carbonate, or dihydroxyaluminum aminoacetate rather than as aluminum phosphate. Yokel & McNamara (156) found that the increases in serum aluminum concentrations in rabbits after being fed similar doses of aluminum as aluminum borate, hydroxide, chloride, glycinate, sucralfate, and acetate were statistically similar but were significantly smaller than those increases in serum aluminum concentrations observed after doses of aluminum citrate or nitrate.

Greger et al (58) observed when moderate amounts of aluminum (200–300 mg Al/kg diet) were incorporated into diets of rats that aluminum accumulation in tissues was fairly similar whether the rats were fed aluminum hydroxide, aluminum phosphate, aluminum palmitate, or aluminum lactate. This suggests that the form of aluminum fed was less important when moderate quantities of aluminum were incorporated into diets rather than given in isolation because the speciation of aluminum in the gut was dependent on the total gut milieu (25).

Aluminum Distribution and Excretion

Ganrot (49) estimated that the total aluminum load for healthy individuals was 30 to 50 mg with about 50% present in skeleton and 25% in lungs. Skalsky & Carchman (131) in contrast suggested that the total body aluminum load is 0.3 g. Limited data suggest that, except for the lungs, bone generally has the highest concentrations of aluminum (5–10 mg Al/kg wet weight) (49, 145).

Generally, the concentrations of aluminum in soft tissues are much lower than in bone (i.e. 1 mg Al/kg wet weight) (49). Concentrations of aluminum in serum are even lower than in other tissues. Estimates of 1–5 μg Al/per liter are typical for samples drawn from fasted normal subjects when modern methods are used and contamination from anticoagulants and glassware is prevented (49, 86, 126).

ACCUMULATION OF ALUMINUM IN TISSUES WITH EXPOSURE AND AGING

Aluminum has been observed to accumulate in most tissues when large doses of aluminum were injected intentionally or were given through contaminated dialysis fluids (6, 20, 42, 154–157). Generally, aluminum accumulation was greater in spleen, liver, bone, and kidneys than in brain, other nervous tissues, muscle, heart, or lung. The sequence in which elevated aluminum concentrations appeared in tissues, and the actual accumulation of aluminum, varied with the aluminum salts administered (156). The species studied and the injection routine (i.e. intravenous, intraperitoneal, or subcutaneous and

repeated doses or single dose) appeared to affect tissue aluminum deposition. Greger & Powers (62) found that aluminum concentrations in tibias (r = 0.941), liver (r = 0.727), kidneys (r = 0.977), and sera (r = 0.863) were strongly correlated (p 0.0001) to injected (i.p.) aluminum loads when loads were varied from 0.01 to 94.5 μmol.

Oral ingestion of aluminum has most often been found to elevate bone, liver, and serum aluminum concentrations and to a lesser extent to elevate kidney aluminum concentrations (28, 48, 58, 59, 61, 62, 132, 133, 146). Brain aluminum concentrations have been measured less frequently and have often been found not to respond to dietary aluminum exposure. Greger & Powers (62) observed that tissue aluminum concentrations (tibia, r = 0.742; liver, r = 0.731; kidney, r = 0.265; sera, r = 0.678) were less tightly correlated with oral aluminum loads than with injected aluminum loads; rats were fed aluminum 0.01–3g Al/kg diet for 30 days.

In general, bone and liver aluminum concentrations are most often used as indices of aluminum exposure studies. Aluminum concentrations in these tissues are sensitive to oral and parenteral aluminum exposure and contamination is less of a problem than with serum.

Several groups of researchers believe that aluminum accumulates in the neurofibrillary tangles of individuals with Alzheimer's disease and amyotrophic lateral sclerosis with Parkinson's dementia in Guam (48, 117). Other investigators have been unable to demonstrate increased aluminum concentrations in brains of individuals with Alzheimer's disease but have demonstrated that brain aluminum concentrations increased with age (94, 104). Limited data indicate that aluminum accumulates in other tissues with age in humans (49), mice (100), *Drosophila* (101), and rats (32, 33).

Aluminum accumulation with age may reflect several factors. Even moderate reductions in kidney function in rats, as occurs with aging, have been correlated to increased aluminum accumulation in bone (32, 33). Although gut absorbtion of Ga-67 (an isotope sometimes used as a marker for aluminum) was low in rats of all ages, absorption was significantly greater in 18-month old rats than mature 5- or 8-month old rats (32).

The observed increases in aluminum concentrations with age in rodents have not been as large as predicted (32, 33, 100). This may reflect changes with age in tissue turnover or the exchangeability of aluminum in body pools. For example, a dose of desferrioxamine mobilized more than twice as much aluminum from tissues of 23-month old rats than from tissues of 8-month old rats, even though tissue aluminum concentrations of the 23-month old rats were generally only 30–50% greater than those of 8-month old rats (32).

PLASMA PROTEIN BINDING OF ALUMINUM Estimates of the percentage of aluminum in serum that is protein bound and nonfilterable in ultrafiltration

studies range from 0 to 98% (151). The percentage of plasma aluminum that is ultrafilterable has been found to be inversly related to plasma aluminum concentrations in normal human subjects and patients with chronic renal failure (120), in normal rabbits (156), and in rats (11, 92). Although much of this decrease in ultrafilterability was the result of increased protein binding of aluminum, the insolubility of aluminum at very high concentrations was also increased (92). Ultrafilterability of aluminum compounds, such as $AlCl_3$ and Al lactate, was also found to be greater at pH 5 and 9 than at pH 7 because of increased solubility (151).

The nonfilterable aluminum in plasma is bound to plasma proteins, predominantly transferrin and albumin, and to low molecular weight compounds, predominantly citrate (38, 97, 142). The relative importance of these factors as chelators of aluminum is debatable. The stability constants for transferrin binding to Al^{+3} ($\log K_1 = 12.9$, $\log K_2 = 12.3$) are many fold lower than for binding to Ga^{+3} ($\log K_1 = 20.3$, $\log K_2 = 19.3$) or Fe^{+3} ($\log K_1 = 22.7$, $\log K_2 = 22.1$) (97). But the binding of aluminum to albumin is even weaker than to transferrin. However, the large excess of albumin to transferrin in plasma and the ability of human serum albumin to bind about three aluminum ions per molecule are important (38). Accordingly, Fatemi et al (38) estimated that 60% of the aluminum in human plasma (at pH 7.4, with a concentration of 5 μM aluminum) would be bound to transferrin, 34% to albumin, and the remainder to citrate.

A variety of factors would affect the relative importance of these chelaters. Fatemi et al (38) estimated that the percentage of aluminum bound to transferrin would be reduced to 50% if the concentration of plasma aluminum was increased to 7.6 μM aluminum. The percentage of aluminum bound to transferrin would also be reduced by small shifts in pH from pH 7.4. The presence of other ions particularly of iron, calcium and magnesium, could be important because aluminum would have to compete with these ions for binding sites on transferrin, albumin, and citrate (65, 97). Moreover, the route of aluminum administration may affect the binding of aluminum in plasma. Orally administered manganese is distributed in body tissues as if it was bound to albumin (23), but manganese in serum is primarily bound to transferrin during the first four hours after dosing (22).

TRANSFERRIN AFFECTS ALUMINUM ACCUMULATION Although very little aluminum is generally found in the brain, transferrin provides a physiologic route of entry. Roskams & Connor (123) demonstrated that transferrin interacted with transferrin receptors similarly whether the transferrin was complexed with aluminum or iron. Morris et al (110) demonstrated that the distribution of aluminum in the brain cells of renal dialysis patients corresponded to the density of transferrin receptors in the brain. Finally, Fleming & Joshi (41)

reported that rats fed aluminum accumulated almost threefold more aluminum in the ferritin of their brains than did control rats.

Anemia is a common symptom of aluminum intoxication (29). Competition between iron and aluminum in the gut has been hypothesized (54). However, van der Voet & de Wolff (149) observed that the presence of Fe III in in situ perfusion systems did not affect the luminal disappearance or intestinal absorption of aluminum. The work of Cannata and associates (13, 14) suggests that the mechanism by which iron intake may affect aluminum absorption is mediated by transferrin and relates to nutritional status of iron, not iron intake per se. Cannata et al (13) observed that rats overloaded with iron by injections with iron dextran had lower concentrations of aluminum in serum and brain than did control rats, whereas rats depleted of iron by phlebotomy had higher concentrations of aluminum in serum and brain than did control rats. Similarly, serum aluminum concentrations of hemodialysis patients with high ferritin levels increased less after a dose of aluminum than those of patients with low or normal serum ferritin levels (14).

URINARY EXCRETION OF ALUMINUM As already noted, humans typically excrete little aluminum in urine, usually less than 100 μg per day (49). This primarily reflects the fact that little aluminum is absorbed. Thus when the protection of the gut was removed (as occurred when patients were infused with parenteral solutions contaminated with aluminum), subjects excreted 0.7 to 3.8 mg aluminum daily (83).

The accumulation of aluminum in tissues that occurs when humans and animals have high concentrations of aluminum in their scra reflccts the inability of the kidneys to rapidly excrete aluminum. Lote et al (92) observed that the fractional excretion of aluminum in urine by rats infused with insulin and 0, 25, or 800 μg aluminum was 12, 24, and 53%, respectively, in 4 hr. Several investigators have attributed this inefficiency in urinary excretion of aluminum to tubular reabsorbtion of filtered aluminum (11, 63). It is more likely that the inefficiency reflects the high plasma binding of aluminum, which prevents rapid filtration of plasma aluminum (92, 151). In any case, the elevation of plasma aluminum concentrations for several hours, theoretically at least, allows more transfer of aluminum to tissues.

EXCRETION IN BILE VS URINE The very small amounts of aluminum in urine have caused a number of researchers to search for an alternate route of aluminum excretion. Several groups in the 1920s and 1930s observed that dogs injected with aluminum excreted aluminum in the bile as well as in urine (36, 107, 144).

More recently, Gupta et al (63) found that rats excreted 60% of an intravenous dose of aluminum chloride in urine and 40% in feces. Yokel &

McNamara (157) found that rabbits infused for six hr with aluminum lactate had significant elevation in biliary excretion 4 hr, but not 12 hr, after completion of the infusion. Smeyers-Verbeke et al (135) noted that rats loaded with aluminum intraperitoneally continued to have elevated concentrations of aluminum in bile and urine for 200 days after the loading period.

However, the two most definitive studies indicate that bile is a fairly minor route of aluminum excretion, at least when aluminum is administered parenterally (84, 87). Kovalchik et al (87) found that dogs with their ureters ligated excreted more aluminum in their bile after dialysis with fluids that contained about 2.3 mg aluminum than did intact dogs. But biliary excretion of aluminum accounted for less than 0.1% of the total load of aluminum in both groups of dogs. Moreover, intact dogs excreted 27% of the aluminum load in urine. Similarly, Klein et al (84) found that rats infused with 5 mg aluminum/kg per day for 7 or 14 days excreted only 3 to 7% as much aluminum in bile as in urine.

In contrast, Williams et al (152) observed that patients ingesting aluminum containing antacids had greater concentrations of aluminum in their bile than in their urine 48 hr after the dose. It may be that excretion patterns of orally and parenterally administered aluminum differ as do excretion patterns of orally and parenterally administered manganese (23). The differences in volumes of urine and bile excretion, which were not reported (152), could also affect interpretation of data.

The aluminum salt administered may also affect bilary excretion of aluminum. Allain et al (3) found sixfold higher levels of aluminum in bile when rats were injected with aluminoxamine (the aluminum chelate of deferoxamine) than when they were injected with equal doses of aluminum as $Al(NO_3)_3$.

IS ALUMINUM ESSENTIAL?

Aluminum is the third most abundant element in the earth's crust. Horecker et al (72) in 1939 suggested that aluminum promoted the reaction between cytochrome C and succinic dehydrogenase in vitro. More recently, the activation of the purified guanine nucleotide binding the regulatory component of adenyl cyclase by fluoride was shown to require the presence of Al^{+3} (78, 139). The significance of these observations in vivo is not known. In fact, no conclusive evidence suggests that aluminum is essential for growth, reproduction, or survival of humans or animals (49, 145).

Kleber & Putt (82) reviewed articles in which the relationships between oral exposure to aluminum and the incidence of dental caries was considered. They concluded that aluminum was a cariostatic agent both by itself and in combination with fluoride.

TOXIC EFFECTS OF ALUMINUM

Aluminum is not a nutrient but it should be of interest to nutritionists for two main reasons. (*a*) Many of the toxic effects of aluminum are due to its interactions with nutrients, such as phosphorus, calcium, fluoride, magnesium, iron, and vitamin D (54). (*b*) It is well established that aluminum toxicity has been induced not only by infusion of aluminum-contaminated dialysate fluids and parenteral nutrition solutions but also by ingestion of aluminum-containing pharmaceutical products. A number of researchers also believe that high concentrations of aluminum in drinking water (30, 99) and even in food (43, 48, 117) resulted in toxic effects among sensitive individuals.

Thousands of papers and a number of reviews have been published on the toxic effects of aluminum (49, 53, 67, 88), especially as related to dialysis dementia and osteodystrophy and to Alzheimer's disease and amyotrophic lateral sclerosis with Parkinson's dementia in Guam (19, 70, 79, 106, 109, 153). Despite these massive efforts, the mechanism by which aluminum induces toxic effects and even the relationship of aluminum to a number of neurological and skeletal disorders remains debatable. This at least partially reflects our limited understanding of the metabolism of aluminum.

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Literature Cited

1. Adler, A. J., Berlyne, G. M. 1985. Duodenal aluminum absorption in the rat: Effect of vitamin D. *Am. J. Physiol.* 249:G209–13
2. Alfrey, A. C. 1988. Physiology of aluminum in man. See Ref. 50a, pp. 101–24
3. Allain, P., Leblondel, G., Mauras, Y. 1988. Effect of aluminum and deferoxamine on biliary iron elimination in the rat. *Proc. Soc. Exp. Biol. Med.* 188:471–73
4. Bakir, A. A., Hryhorczuk, D. O., Ahmed, S., Hessl, S. M., Levy, P. S., et al. 1989. Hyperaluminemia in renal failure: the influence of age and citrate intake. *Clin. Nephrol.* 31:40–44.
5. Baxter, M., Burrell, J. A., Massey, R. C. 1988. The effects of fluoride on the leaching of aluminum saucepans during cooking. *Food Addit. Contam.* 5:651–56
6. Berlyne, G. M., Ari, J. B., Knopf, E., Yagil, R., Weinberger, G., et al. 1972. Aluminum toxicity in rats. *Lancet* 1:564–68
7. Beynon, H., Cassidy, M. J. D. 1990. Gastrointestinal absorption of aluminum. *Nephron* 55:235–36
8. Birchall, J. D. 1992. The interrelationship between silicon and aluminum in the biological effects of aluminum. In *Aluminum Biology and Medicine, Ciba Found. Symp. 169*, pp. 50–61. Chichester: Wiley
9. Bourgoin, B. P. 1992. Alumino-silicate content in calcium supplements derived from various carbonate deposits. *Bull. Environ. Contam. Toxicol.* 48:803–8
10. Bureau of Radiological Health and Training Institute. 1970. *Radiological Health Handbook*, pp. 237–38. Rockville, Md: US Dept. Health, Educ. Welfare
11. Burnatowska-Hledin, M. A., Mayor, G. H., Lau, K. 1985. Renal handling

of aluminum in the rat: clearance and micropuncture studies. *Am. J. Physiol.* 249:F192–97

12. Cam, J. M., Luck, V. A., Eastwood, J. B., deWardener, H. E. 1976. The effect of aluminum hydroxide orally on calcium, phosphorus and aluminum metabolism in normal subjects. *Clin. Sci. Mol. Med.* 52:407–14
13. Cannata, J. B., Fernàndez-Soto, I., Fernàndez, M. J., Fernàndez-Martin, J., McGregor, S. J., et al. 1991. Role of iron metabolism in absorption and cellular uptake of aluminum. *Kidney Int.* 39:799–803.
14. Cannata, J. B., Suarez, C. S., Cuesta, V., Roza, R. R., Allende, M. T., et al. 1984. Gastrointestinal aluminum absorption: Is it modulated by the iron-absorptive mechanism? *Proc. Eur. Dialysis Transplant. Assoc.* 21: 354–59
15. Clarkson, E. M., Luck, V. A., Hynson, W. V., Bailey, R. R., Eastwood, J. B., et al. 1972. The effect of aluminum hydroxide on calcium, phosphorus and aluminum balances, the serum parathyroid hormone concentration and the aluminum content of bone in patients with chronic renal failure. *Clin. Sci.* 43:519–31
16. Cochran, M., Goddard, G., Ludwigson, N. 1990. Aluminum absorption by rat duodenum: further evidence of energy-dependent uptake. *Toxicol. Lett.* 51:287–94
17. Committee on Food Additives Survey Data. 1984. *Poundage Update of Food Chemicals 1982, PB 84-16214.* Washington, DC: Natl. Acad. Press
18. Committee on the GRAS List Survey-Phase III. 1979. *The 1977 Survey of Industry on the Use of Food Additives.* Washington, DC: Natl. Acad. Sci.
19. Committee on Nutrition. 1986. Aluminum toxicity in infants and children. *Pediatrics* 78:1150–54
20. Constantini, S., Giordana, R., Ioppola, A., Mantovani, A., Ballanti, P., et al. 1989. Distribution of aluminum following intraperitoneal injection of aluminum lactate in the rat. *Pharmacol. Toxicol.* 64:47–50
21. Dabeka, R. W., McKenzie, A. D. 1990. Aluminum levels in Canadian infant formulae and estimation of aluminum intakes from formulae by infants 0–3 months old. *Food Addit. Contam.* 7:275–82
22. Davidson, L., Lönnerdal, B., Sandström, B., Kunz, C., Keen, C. L. 1989. Identification of transferrin as the major plasma carrier protein for manganese introduced orally or intravenously or after in vitro addition to the rat. *J. Nutr.* 119:1461–64
23. Davis, C. D., Zech, L., Greger, J. 1993. Manganese metabolism in rats: An improved methodology for assessing gut endogenous losses. *Proc. Soc. Exp. Biol. Med.* 202:103–8
24. Day, J. P., Barker, J., Evans, L. J. A., Perks, J., Seabright, P. J., et al. 1991. Aluminum absorption studied by ^{26}Al tracer. *Lancet* 337:1345
25. Dayde, S., Filella, M., Berthon, G. 1990. Aluminum speciation studies in biological fluids, part 3. Quantitative investigation of aluminum-phosphate complexes and assignment of their potential significance in vivo. *J. Inorg. Biochem.* 38:241–59
26. Dent, C. E., Winter, C. 1974. Osteomalacia due to phosphate depletion from excessive aluminum hydroxide ingestion. *Br. Med. J.* 1:551–52
27. Domingo, J. L., Gomez, M., Llobet, J. M., Corbella, J. 1991. Influence of some dietary constituents on aluminum absorption and retention in rats. *Kidney Int.* 39:598–601
28. Donald, J. M., Golob, M. S., Gershwin, M. E., Koen, C. H. 1989. Neurobehavioral effects in offspring of mice given excess aluminum in diet during gestation and lactation. *Neurotoxicol./ Teratol.* 11:345–51
29. Drüeke, T. B., Lacour, B., Touam, M., Jucquel, J. P., Plaehot, J. J., et al. 1986. Effect of aluminum on hematopoiesis. *Kidney Int.* 29:S45–S48
30. Eastwood, J. B., Levin, G. E., Pazianas, M., Taylor, A. P., Denton, J., Freemont, A. J. 1990. Aluminum deposition in bone after contamination of drinking water supply. *Lancet* 336: 462–64
31. Ecelbarger, C. A., Greger, J. L. 1991. Dietary citrate and kidney function affect aluminum, zinc and iron utilization in rats. *J. Nutr.* 121:1755–62
32. Ecelbarger, C. A., Greger, J. L. 1991. Aluminum and Ga-67 metabolism in aging animals. *FASEB J.* 5:7408 (Abstr)
33. Ecelbarger, C. A., MacNeil, G., Greger, J. L. 1992. Effect of reduced kidney function and tissue turnover on aluminum accumulation and distribution in aging rats. *FASEB J.* 6:4136 (Abstr.)
34. Eden, T. 1976. *Tea,* pp. 8–15. London: Longman
35. Ellen, G., Egmond, E., Van Loon, J. W., Sahertian, E. T., Tolsma, K. 1990. Dietary intakes of some essential and nonessential trace elements, nitrate, nitrite and N-nitrosamines, by Dutch

adults: estimated via a 24-hour duplicate portion study. *Food Addit. Contam.* 7:207–21

36. Everleeth, D. F., Meyers, V. C. 1936. Studies on aluminum. II. Storage of intravenously injected aluminum in the dog. *J. Biol. Chem.* 113:467–71
37. Exley, C., Chappell, J. S., Birchall, J. D. 1991. A mechanism for acute aluminum toxicity in fish. *J. Theor. Biol.* 151:417–28
38. Fatemi, S. J. A., Kadir, F. H. A., Moore, G. R. 1991. Aluminum transport in blood serum. *Biochem. J.* 280: 527–32
39. Feinroth, M., Feinroth, M. V., Berlyne, G. M. 1982. Aluminum absorption in the rat everted gut sac. *Mineral Electrolyte Metab.* 8:29–35
40. Flaten, T. P., Odegard, M. 1989. Dietary aluminum and Alzheimer's disease—a reply. *Food Chem. Toxicol.* 27:496–98
41. Fleming, J., Joshi, G. 1987. Ferritin: Isolation of aluminum-ferritin complex from brain. *Proc. Natl. Acad. Sci. USA* 84:7866–70
42. Flendrig, J. A., Krvis, H., Dos, H. A. 1976. Aluminum and dialysis dementia. *Lancet* 1:1235
43. Freundlich, M., Abitbol, C., Zillervelo, G., Strauss, J., Faugere, M. C., et al. 1985. Infant formula as a cause of aluminum toxicity in neonatal uraemia. *Lancet* 2:527–29
44. Froment, D. H., Buddington, B., Miller, N. L., Alfrey, A. C. 1989. Effect of solubility on the gastrointestinal absorption of aluminum from various aluminum compounds in the rat. *J. Lab. Clin. Med.* 114:237–42
45. Froment, D. P., Molitoris, B. A., Buddington, B., Miller, N., Alfrey, A. C. 1989. Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate. *Kidney Int.* 36: 978–84
46. Fulton, B., Jaw, S., Jeffery, E. H. 1989. Bioavailability of aluminum from drinking water. *Fundam. Appl. Toxicol.* 12:144–50
47. Fulton, B., Jeffery, E. H. 1990. Absorption and retention of aluminum from drinking water. I. Effect of citrate and ascorbic acids on aluminum tissue levels in rabbits. *Fundam. Appl. Toxicol.* 14:788–96
48. Gajdusek, D. C. 1985. Hypothesis: Interference with anoxal transport of neurofilament as a common pathogenetic mechanism in certain diseases of the central nervous system. *N. Engl. J. Med.* 312:714–18
49. Ganrot, P. O. 1986. Metabolism and possible health effects of aluminum. *Environ. Health Perspect.* 65:363–441
50. Garber, B. T., Wei, E. 1974. Influence of dietary factors on the gastrointestinal absorption of lead. *Toxicol. Appl. Pharmacol.* 27:685–91

50a. Gitelman, H. J., ed. 1988. *Aluminum and Health: A Critical Review.* New York: Marcel Dekker

51. Gorsky, J. E., Dietz, A. A., Spencer, H., Osis, D. 1979. Metabolic balance of aluminum studied in six men. *Clin. Chem.* 25:1739–43
52. Greger, J. L. 1985. Aluminum content of the American diet. *Food Technol.* 9(5):73, 74, 76, 78–80
53. Greger, J. L. 1987. Aluminum and tin. *World Rev. Nutr. Diet.* 54:255–85
54. Greger, J. L. 1988. Aluminum in the dict and mincral mctabolism. In *Metal Ions in Biological Systems,* ed. H. Sigel, 24:199–215. New York: Marcel Dekker
55. Greger, J. L. 1992. Dietary and other sources of aluminum intake. See Ref. 8, pp. 26–35
56. Greger, J. L., Baier, M. J. 1983. Effect of dietary aluminum on mineral metabolism of adult males. *Am. J. Clin. Nutr.* 38:411–19
57. Greger, J. L., Baier, M. J. 1983. Excretion and retention of low or moderate levels of aluminum by human subjects. *Food Chem. Toxicol.* 21:473–77
58. Greger, J. L., Bula, E. N., Gum, E. T. 1985. Mineral metabolism of rats fed moderate levels of various aluminum compounds for short periods of time. *J. Nutr.* 115:1708–16
59. Greger, J. L., Donnaubauer, S. E. 1986. Retention of aluminum in the tissues of rats after the discontinuation of oral exposure to aluminum. *Food Chem. Toxicol.* 24:1331–34
60. Greger, J. L., Goetz, W., Sullivan, D. 1985. Aluminum levels in foods cooked and stored in aluminum pans, trays and foil. *J. Food Prot.* 48:772–77
61. Greger, J. L., Gum, E. T., Bula, E. N. 1986. Mineral metabolism of rats fed various levels of aluminum hydroxide. *Biol. Trace Element Res.* 9:67–77
62. Greger, J. L., Powers, C. F. 1992. Assessment of exposure to parenteral and oral aluminum with and without citrate using a desferrioxamine test in rats. *Toxicology.* 76:119–32
63. Gupta, S. K., Waters, D. H., Gwilt, P. 1987. Absorption and disposition of aluminum in the rat. *J. Pharm. Sci.* 75:586–89

64. Hahn, P. H. B., Guenter, W. 1986. Effect of dietary fluoride and aluminum on laying hen performance and fluoride concentration in blood, soft tissue, bone and egg. *Poultry Sci.* 65: 1343–49
65. Harris, W. R., Sheldon, J. 1990. Equilibrium constants for the binding of aluminum to human serum transferrin. *Inorg. Chem.* 29:119–24
66. Harvey, J. A., Zobitz, M. M., Pak, C. Y. C. 1988. Dose dependency of calcium absorption: a comparison of calcium carbonate and calcium citrate. *J. Bone Miner. Res.* 3:253–58
67. Haug, A. 1984. Molecular aspects of aluminum toxicity. *CRC Crit. Rev. Plant Sci.* 1:345–73
68. Herzog, P., Schmitt, K. F., Grendahl, T., van der Linden, J. Jr., Holtermuller, K. H. 1982. Evaluation of serum and urine electrolyte changes during therapy with magnesium-aluminum containing antacid: results of a prospective study. In *Antacids in the Eighties.* ed. F. Halter, pp. 123–35. Munchen: Urban & Schwarzenberg
69. Hewitt, C. D., Poole, C. L., Westervelt, F. B., Savory, J., Willis, M. R. 1988. Risks of simultaneous therapy with oral aluminum and citrate compounds. *Lancet* 2:849
70. Hewitt, C. D., Savory, J., Wills, M. R. 1990. Aspects of aluminum toxicity. *Clin. Lab. Med.* 10:403–22
71. Hopkins, H., Eisen, J. 1959. Mineral elements in fresh vegetables from different geographic areas. *Agric. Food Chem.* 7:633–38
72. Horecker, B. L., Stotz, E., Hogness, T. R. 1939. The promoting effect of aluminum, chromium and the rare earths in the succinic dehydrogenase-cytochrome system. *J. Biol. Chem.* 128:251–56
73. Hurley, L. S., Lönnerdal, B. 1982. Zinc binding in human milk: citrate versus picolinate. *Nutr. Rev.* 40:65–71
74. Inoue, T., Ishiwata, H., Yoshihara, K. 1988. Aluminum levels in food-simulating solvents and cooked in aluminum pans. *J. Agric. Food Chem.* 36:599–601
75. Ittel, T. H., Buddington, B., Miller, N. L., Alfrey, A. C. 1987. Enhanced gastrointestinal absorption of aluminum in uremic rats. *Kidney Int.* 32:821–26
76. Jones, K. C., Bennett, B. G. 1986. Exposure of man to environmental aluminum—an exposure commitment assessment. *Sci. Total Environ.* 52:65–82
77. Kaehny, W. D., Hegg, A. P., Alfrey, A. C. 1977. Gastrointestinal absorption of aluminum from aluminum-containing antacids. *N. Engl. J. Med.* 196:1389–90
78. Kahn, R. A. 1991. Fluroide is not an activator of the smaller (20–25 kDa) GTP-binding proteins. *J. Biol. Chem.* 266:15595–597.
79. King, S. W., Savory, J., Wills, M. R. 1981. The clinical biochemistry of aluminum. *CRC Crit. Rev. Clin. Lab. Sci.* 14:1–20
80. Kirschbaum, B. B., Schoolwerth, A. C. 1989. Acute aluminum toxicity associated with oral citrate and aluminum-containing antacids. *Am. J. Med. Sci.* 197:9–11
81. Kirschbaum, B. B., Schoolwerth, A. C. 1989. Hyperaluminemia associated with oral citrate and aluminum by dioxide. *Hum. Toxicol.* 8:45–47
82. Kleber, C. J., Putt, M. S. 1984. Aluminum and dental caries: A review of the literature. *Clin. Prev. Dent.* 6:14–25
83. Klein, G. L., Alfrey, A. C., Miller, N. L., Sherrard, D. J., Hazlet, T. K., et al. 1982. Aluminum loading during total parenteral nutrition. *Am. J. Clin. Nutr.* 35:1425–29
84. Klein, G. L., Heyman, M. B., Lee, T. C., Miller, N. L., Marathe, G., et al. 1988. Aluminum-associated hepatobiliary dysfunction in rats: Relationships to dosage and duration of exposure. *Pediatr. Res.* 23:275–78
85. Koo, W. W. K., Kaplan, L. A., Krug-Wispe, S. K. 1988. Aluminum contamination of infant formulas. *J. Parenter. Enteral Nutr.* 12:170–73
86. Kostyniak, P. J. 1983. An electrothermal atomic absorption method for aluminum analysis in plasma: Identification of source contamination in blood sampling procedures. *J. Anal. Toxicol.* 7:20–23
87. Kovalchik, M. T., Kaehny, W. P., Hegg, A. P., Jackson, J. T., Alfrey, A. C. 1978. Aluminum kinetics during hemodialysis. *J. Lab. Clin. Med.* 92: 712–20
88. Krueger, G. L., Morris, T. K., Suskind, R. R., Widner, E. M. 1984. The health effects of aluminum compounds in mammals. *CRC Crit. Rev. Toxicol.* 13:1–24
89. Levick, S. E. 1980. Dementia from aluminum pots. *N. Engl. J. Med.* 303: 164
90. Lione, A. 1983. The prophylactic reduction of aluminum intake. *Food Chem. Toxicol.* 21:103–9
91. Lione, A. 1985. Aluminum intake from non-prescription drugs and sucralfate. *Gen. Pharmacol.* 16:223–28

92. Lote, C. J., Wood, J. A., Saunders, H. C. 1992. Renal filtration, reabsorption and excretion of aluminum in the rat. *Clin. Sci.* 82:13–18
93. Lotz, M., Zisman, E., Bartter, F. C. 1968. Evidence for a phosphorus-depletion syndrome in man. *N. Engl. J. Med.* 278:409–15
94. Markesbery, W. R., Ehmann, W. D., Alauddin, M., Hossain, T. I. M. 1984. Brain trace element concentrations in aging. *Neurobiol. Aging* 5:19–28
95. Martin, R. B. 1986. The chemistry of aluminum as related to biology and medicine. *Clin. Chem.* 32:1797–1805
96. Martin, R. B. 1992. Aluminum speciation in biology. See Ref. 8, pp. 5–25
97. Martin, R. B., Savory, J., Brown, S., Bertholf, R. L., Wills, M. R. 1987. Transferrin binding of Al^{+3} and Fe^{+3}. *Clin. Chem.* 33:405–7
98. Martinez-Palomi, A., Mcza, I., Beaty, G., Cereijido, M. 1980. Experimental modulation of occluding junctions in a cultured transporting epitheliom. *J. Cell Biol.* 87:736-45
99. Martyn, C. N., Osmond, C., Edwardson, J. A., Barker, D. J. P., Harris, T. C., et al. 1989. Geographical relation between Alzheimer's disease and aluminum in drinking water. *Lancet* 1:59–62
100. Massie, H. R., Aiello, V. R., Tuttle, R. S. 1988. Aluminum in the organs and diet of ageing C57BL/6J mice. *Mech. Ageing Dev.* 45:145–56
101. Massie, H. R., Williams, T. R., Aiello, V. R. 1985. Excess dietary aluminum increases *Drosophila's* rate of aging. *Gerontology* 31:309–14
102. Mayor, G. H., Keiser, J. A., Makdoni, D., Ku, P. 1977. Aluminum absorption and distribution: Effect of parathyroid hormone. *Science* 197:1187–89
103. Mayor, G. H., Sprague, S. M., Hourani, M. R., Sanchez, T. V. 1980. Parathyroid hormone-mediated aluminum deposition and egress in the rat. *Kidney Int.* 17:40–44
104. McDermott, J. R., Smith, I., Iqbal, K., Wisniewski, H. M. 1979. Brain aluminum in aging and Alzheimer disease. *Neurology* 29:809–14
105. McGraw, M. E., Bishop, N., Jameson, R., Robinson, M. J., O'Hara, M., et al. 1986. Aluminum content of milk formulae and intravenous fluids used in infants. *Lancet* 1:157
106. McLachlan, D. R., Fraser, P. E., Dalton, A. J. 1992. Aluminum and the pathogenesis of Alzheimer's disease; a summary of evidence. See Ref. 8, pp. 87–108
107. Meyers, V. C., Morrison, D. B. 1928. The influence of the administration of aluminum upon the aluminum content of the tissues of the dog. *J. Biol. Chem.* 78:615–24
108. Miller, R. G., Kopfler, F. C., Kelty, K. C., Stober, J. A., Ulmer, N. S. 1984. The occurrence of aluminum in drinking water. *J. Am. Water Assoc.* 76:84–91
109. Monteagudo, F. S. E., Cassidy, M. J. D., Folb, P. I. 1989. Recent developments in aluminum toxicology. *Med. Toxicol.* 4:1–16
110. Morris, C. M., Candy, J. M., Oakley, A. E., Taylor, G. A., Mountfort, S., et al. 1989. Comparison of the regional distribution of transferrin receptors and aluminum in the forebrain of chronic renal dialysis patients. *J. Neurol. Sci.* 94:295–306
111. Nordal, K. P., Dahl, E., Sorbus, K., Berg, K. J., Thomassen, Y., et al. 1988. Gastrointestinal absorption and urinary excretion of aluminum in patients with predialysis chronic renal failure. *Pharmacol. Toxicol.* 63:351–54
112. Ondreička, R., Kortus, J., Ginter, E., Kortus, J. 1966. Chronic toxicity of aluminum in rats and mice and its effects on phosphorus metabolism. *Br. J. Ind. Med.* 23:305–12
113. Ondreička, R., Kortus, J., Ginter, E. 1971. Aluminum, its absorption, distribution and effects on phosphorus metabolism. In *Intestinal Absorption of Metal Ions, Trace Elements and Radionuclides,* ed. S. C. Skonyna, D. Waldron-Edward, pp. 293–305. Oxford: Permagon
114. Partridge, N. A., Regnier, F. E., White, J. L., Hem, S. L. 1989. Influence of dietary constituents on intestinal absorption of aluminum. *Kidney Int.* 35:1413–17
115. Pennington, J. A. T. 1987. Aluminum content of foods and diets. *Food Addit. Contam.* 5:161–232
116. Pennington, J. A. T., Jones, J. W. 1988. Dietary intake of aluminum. See Ref. 50a, pp. 67–100
117. Perl, D. P. 1985. Relationship of aluminum to Alzheimer's disease. *Environ. Health Perspect.* 63:149–53
118. Provan, S. D., Yokel, R. A. 1988. Influence of calcium on aluminum accumulation by the rat jejunal slice. *Res. Commun. Chem. Pathol. Pharmacol.* 59:79–92
119. Provan, S. P., Yokel, R. A. 1988. Aluminum uptake by the in situ rat

gut preparation. *J. Pharmacol. Expl. Ther.* 245:928–31
120. Rahman, H., Skillen, A. W., Channon, S. M., Ward, M. K., Kerr, D. N. S. 1985. Methods for studying the binding of aluminum by serum protein. *Clin. Chem.* 31:1969–73
121. Recker, R. R., Blotcky, A. J., Leffler, J. A., Rack, E. P. 1977. Evidence for aluminum absorption from the gastrointestinal tract and bone deposition by aluminum carbonate ingestion with normal renal function. *J. Lab. Clin. Med.* 90:810–15
122. Rosa, I. V., Henry, P. R., Ammerman, C. B. 1982. Interrelationships of dietary phosphorus, aluminum and iron on performance and tissue mineral composition in lambs. *J. Anim. Sci.* 55:1231–40
123. Roskams, A. J., Connor, J. R. 1990. Aluminum access to the brain: A role for transferrin and its receptor. *Proc. Natl. Acad. Sci. USA* 87:9024–27
124. Said, A. N., Slagsvold, P., Bergh, H., Laksesvela, B. 1977. High fluorine water to wether sheep maintained in pens: Aluminum chloride as a possible alleviator of fluorosis. *Nord. Vet. Med.* 29:172–80
125. Savory, J., Nicholson, J. R., Wills, M. R. 1987 Is aluminium leaching enhanced by fluoride? *Nature* 327:107–8
126. Savory, J., Wells, M. R. 1988. Analytical techniques for the analysis of aluminum. See Ref. 50a, pp. 1–24
127. Schaefer, K., vonHerrath, D., Erley, C. M. M. 1988. Treatment of uremic hyperphosphatemia—Is there still a need for aluminum salts? *Am. J. Nephrol.* 8:173–78
128. Schlettwein-Gsell, D., Mommsen-Straub, S. 1973. Spurenelemente in Lebensmitteln. XII. Aluminium. *Int. Z. Vitamin Ernaehrungsforsch.* 43:251–63
129. Sedman, A. B., Klein, G. L., Merritt, R. J., Miller, N. L., Weber, K. O., et al. 1985. Evidence of aluminum loading in infants receiving intravenous therapy. *N. Engl. J. Med.* 312:1337–43
130. Simmer, K., Fudge, a., Teubner, J., James, S. L. 1990. Aluminum concentrations in infant formulae. *J. Pediatr. Child Health* 26:9–11
131. Skalsky, H. L., Carchman, R. A. 1983. Pharmokinetics of aluminum: A review. *J. Am. Coll. Toxicol.* 2:405–23
132. Slanina, P., Falkeborn, Y. 1984. Aluminum concentrations in the brain and bone of rats fed citric acid, aluminum citrate or aluminum hydroxide. *Food Chem. Toxicol.* 33:391–97
133. Slanina, P., Frech, W., Berhardson, A., Cedergren, A., Mattsson, P. 1985. Influence of dietary factors on aluminum absorption and retention in the brain and bone of rats. *Acta Pharmacol. Toxicol.* 56:331–36
134. Slanina, P., Frech, W., Ekstrom, L. G., Loof, L., Slorach, S., Cedergren, A. 1986. Dietary citrate enhances absorption of aluminum in antacids. *Clin. Chem.* 32:539–41
135. Smeyers-Verbeke, J., Verbeelen, D., Massart, D. L. 1983. Investigation of the accumulation and excretion of Al in rats. In *Trace Element Analytical Chemistry in Medicine and Biology*, ed. P. Brätter, P. Schramel, 2:333–40. New York: de Gruyter
136. Sorenson, J. R. J., Campbell, I. R., Tepper, L. B., Longg, R. D. 1974. Aluminum in the environment and human health. *Environ. Health Perspect.* 8:3–95
137. Spencer, H., Kramer, L., Norris, C., Osis, P. 1982. Effect of small doses of aluminum-containing antacids on calcium and phosphorus metabolism. *Am. J. Clin. Nutr.* 36:32–40
138. Spencer, H., Kramer, L., Norris, C., Wiatrowski, E. 1981. Effect of aluminum hydroxide on plasma fluoride and fluoride excretion during a high fluoride intake in men. *Toxicol. Appl. Pharmacol.* 56:140–44
139. Sternweis, P. C., Gilman, A. G. 1982. Aluminum: A requirement for acitivation of the regulatory component of adenyl cyclase by fluoride. *Proc. Natl. Acad. Sci. USA* 79:4888–91
140. Storer, N. L., Nelson, T. S. 1968. The effect of various aluminum compounds on chick performance. *Poultry Sci.* 47:244–47
141. Tipton, I. H., Stewart, P. L., Martin, P. G. 1966. Trace elements in diets and excreta. *Health Phys.* 12:1683–89
142. Trapp, G. A. 1983. Plasma aluminum is bound to transferrin. *Life Sci.* 33:311–16
143. Trapp, G. A., Cannon, J. B. 1981. Aluminum pots as a source of dietary aluminum. *N. Engl. J. Med.* 304:172
144. Underhill, F. P., Peterman, R. I., Steel, S. L. 1929. Studies in the metabolism of aluminum. IV. The fate of intravenously injected aluminum. *Am. J. Physiol.* 90:52–61
145. Underwood, E. J. 1977. Aluminum. In *Trace Elements in Human and Animal Nutrition*, pp. 430–33. New York: Academic. 4th ed.
146. Valdivia, R., Ammerman, C. B., Henry, P. R., Feaster, J. P., Wilcox,

C. J. 1982. Effect of dietary aluminum and phosphorus on performance, phosphorus utilization and tissue mineral composition in sheep. *J. Anim. Sci.* 55:402–10

147. Van der Voet, G. B. 1992. Intestinal absorption of aluminum. See Ref. 8, pp. 109–17
148. Van der Voet, G. B., de Wolff, F. A. 1986. Intestinal absorption of aluminum in rats: Effect of intraluminal pH and aluminum concentration. *J. Appl. Toxicol.* 6:37–41
149. Van der Voet, G. B., de Wolff, F. A. 1987. The effect of di- and trivalent iron on the intestinal absorption of aluminum in rats. *Toxicol. Appl. Pharmacol.* 90:190–97
150. Van der Voet, G. B., van Ginkel, M. D., de Wolff, F. A. 1989. Intestinal absorption of aluminum in rats: Stimulation by citric acid and inhibition by dinitrophenol. *Toxicol. Appl. Pharmacol.* 99:90–97
151. Wilhelm, M., Jäger, D. E., Ohnesorge, F. K. 1990. Aluminum toxicokinetics. *Pharmacol. Toxicol.* 66:4–9
152. Williams, J. W., Vera, S. R., Peters, T. G., Luther, R. W., Bhattacharya, S., et al. 1986. Biliary excretion of aluminum in aluminum osteodystrophy with liver disease. *Ann. Intern. Med.* 104:782–85
153. Wisniewski, H. M., Wen, G. Y. 1992. Aluminum and Alzheimer's disease. See Ref. 8, pp. 142–54
154. Yokel, R. A. 1983. Persistent aluminum accumulation after prolonged systemic aluminum exposure. *Biol. Trace Element Res.* 5:467–74
155. Yokel, R. A. 1987. Toxicity of aluminum exposure to the neonatal and immature rabbit. *Fundam. Appl. Toxicol.* 9:795–806
156. Yokel, R. A., McNamara, P. J. 1988. Influence of renal impairment chemical form and serum protein binding in intravenous and oral aluminum kinetics in the rabbit. *Toxicol. Appl. Pharmacol.* 95:32–43
157. Yokel, R. A., McNamara, P. J. 1989. Elevated aluminum persists in serum and tissues of rabbits after a six-hour infusion. *Toxicol. Appl. Pharmacol.* 99:133–38