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Water Content of Aluminum, Dialysis Dementia, and Osteomalacia

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In the presence of normal renal function, a high concentration of aluminum in drinking water has been implicated as a factor in the etiology of a neurological syndrome in one specific geographical area. The role of aluminum as a toxic agent in other neurological disorders, where renal function is normal, is controversial.

Aluminum is absorbed from the gastrointestinal tract and is normally excreted by the kidneys in the urine. In patients with chronic renal failure, aluminum appears to be of proven toxicological importance. In these patients the accumulation of aluminum in tissues causes an encephalopathy (dialysis encephalopathy or dialysis dementia), a specific form of metabolic bone disease (osteomalacic dialysis osteodystrophy), and an anemia and also plays an etiological role in some of the other complications associated with end-stage chronic renal disease. A failure in the normal renal excretory mechanism accounts for the tissue accumulation in chronic renal failure. The majority of chronic renal failure patients who develop aluminum toxicity are on long-term treatment with either hemo- or peritoneal dialysis; some patients develop toxicity who are only on treatment with aluminum-containing phosphate-binding agents.

Aluminum in the dialysate appears to be the major source of the metal in chronic renal failure patients who develop aluminum toxicity. The aluminum content of the dialysate depends primarily on the content of the water with which it is prepared; there may be some contribution from the chemicals used in the concentrate which is added to the water. Some domestic tap-water supplies contain aluminum in high concentration, either naturally or because aluminum has been added as a flocculant in the purification process. Acid rain markedly increases the "natural" aluminum content of water.

The driving force for aluminum transfer during dialysis seems to be the effective concentration gradient between the dialysate aluminum and the free diffusible serum aluminum fraction. The transfer of aluminum from the dialysate across the dialyzing membrane appears to occur despite low concentrations of the metal in the dialysate. The species of aluminum in tap water and dialysate may significantly affect the dialysability of aluminum into the blood compartment and its subsequent deposition in tissues. The major portion, if not all, of aluminum in blood is tightly bound to serum proteins and an as yet unidentified lower molecular weight species.

Aluminum is the third most abundant element in the earth's crust and is the most abundant metal. Attention was first drawn to the potential role of aluminum as a toxic metal over 50 years ago. Aluminum cooking utensils were being introduced at that time, and these together with the aluminum present in city drinking-water and a variety of medicines were considered to represent a potential health hazard (*1*). In the intervening years, although the subject has been controversial, aluminum was not, until recently, recognized as a toxic metal. Aluminum was dismissed as a toxic metal in a comprehensive review in 1957 (*2*) and again as recently as 1974 (*3*). The only health hazard recognized, in those reviews, was that associated with industrial exposure and the inhalation of heavily aluminum-contaminated dust particles. The inhalation of dust heavily contaminated with aluminum, in an industrial environment, is a recognized cause of pulmonary fibrosis, usually an interstitial fibrosis of the upper lobes. Less commonly, aluminum exposure has been linked with a pulmonary granulomatosis.

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Aluminum Toxicity

Normal Renal Function

In patients with normal renal function, aluminum has recently been implicated as a factor in the etiology of the amyotrophic lateral sclerosis and Parkinsonism-dementia found in the indigenous (Chamorro) population of Guam (*4*). In brain tissue from two patients with the disease, an accumulation of aluminum was demonstrated within the nuclear region and perikaryal cytoplasm of neurofibrillary tangle-bearing hippocampal neurons (*4*). Soil and drinking water from areas in which there was a high incidence of these disorders had a high aluminum content with low concentrations of calcium and magnesium. There is some evidence to support the hypothesis that secondary hyperparathyroidism, provoked by the chronic environmental deficiency of cal-

cium and magnesium on Guam, may result in the increased intestinal absorption of aluminum, its subsequent deposition in the central nervous system and the high incidence of amyotrophic lateral sclerosis and Parkinsonism-dementia (*5*).

Aluminum has also been implicated as a neurotoxic agent in the pathogenesis of Alzheimer's disease. In brain tissue from patients with this disorder accumulations of aluminum have been identified within the nuclear region of a high percentage of neurons containing neurofibrillary tangles (*6,7*). In the same patients, adjacent normal appearing neurons were virtually free of detectable aluminum (*6*). The precise pathogenic role of aluminum in Alzheimer's disease is controversial and remains to be defined. It has been proposed that the accumulation of aluminum in brain tissue of patients with Alzheimer's disease may be a secondary phenomenon rather than an etiological agent (*8*). In this concept the accumulation of aluminum would represent a relatively nonspecific "marker" of neurons that are degenerating rather than be a specific etiological factor. In support of this concept is the fact that the aluminum concentrations are not elevated in specimens of serum and cerebrospinal fluid from patients with Alzheimer's disease.

Chronic Renal Failure

Although the toxicity of aluminum in the presence of normal renal function remains to be clearly defined it has been established, in the past decade, that aluminum has a toxic action in patients with impaired renal function. An increased serum aluminum concentration, and clinical manifestations of toxicity, may occur in patients with chronic renal failure who are on long-term treatment with either hemodialysis or peritoneal dialysis and may also occur in some patients who have not been dialyzed (*9*). The latter group of patients usually consists of children who are receiving oral treatment with aluminum hydroxide (*10,11*). Hyperaluminemia associated with toxic clinical sequelae may, however, also occur in adults who are not on dialysis treatment (*12*). In patients with chronic renal failure the clinical toxic phenomena associated with an increased body burden of aluminum include a specific encephalopathy (dialysis encephalopathy), a metabolic bone disease (osteomalacic dialysis osteodystrophy), and an anemia; aluminum may also be responsible for some of the other clinical features associated with end-stage renal disease (*9*). The importance of these aluminum-induced toxic phenomena in patients with chronic renal failure is that they can be prevented.

Hyperaluminemia

An increase in the serum aluminum concentration of some patients with end-stage chronic renal failure was first recorded by Berlyne and his colleagues in 1970 (*13*). They reported that in some chronic renal failure patients who were on oral treatment with either aluminum-cycle resins or aluminum hydroxide there was an increase in serum aluminum concentration; not all of these patients were on regular dialysis treatment. In these patients they proposed that the increased serum concentration was due to the intestinal absorption of aluminum with retention in serum because of a failure in the normal renal excretory mechanism for this metal. In some patients who were on regular dialysis treatment but were not taking oral aluminum-containing medications the serum aluminum values were also increased. In this group of patients they proposed that the hyperaluminemia was due to the fact that they had been "fortuitously exposed to a dialysate with a relatively high aluminum content" (*13*). Berlyne and his colleagues (*14*) subsequently reported that aluminum intoxication and hyperaluminemia could be produced in uremic and nonuremic rats after oral doses of aluminum-containing salts. In their experimental animals the clinical features of aluminum toxicity were associated with significant increases in the aluminum content not only of serum, but also in liver, heart, striated muscle, brain and bone tissues.

In 1971, Parsons and his colleagues (*15*) reported that there was an increased content of aluminum in some samples of bone from patients with end-stage chronic renal failure; all of their patients were on regular long-term dialysis treatment. In contrast, however, to the studies of Berlyne and his colleagues (*13*), they reported that in their patients there was no correlation between bone aluminum content and the amount of oral aluminum hydroxide that the patient had consumed. They did, however, observe that "on the whole" the longer the patient had been uremic and receiving dialysis treatment the higher was the bone content of aluminum. Parsons and his colleagues (*15*) did not speculate on the potential sources of the aluminum, their observations could have been interpreted as implicating the hemodialysis procedure itself. In support of this proposal are the earlier observations of Blomfield and her colleagues (*16*) who had reported that during hemodialysis both copper and zinc were actively taken up by blood, in the dialysis coil, from the hemodialysis fluid, even against a concentration gradient. There is now a substantial amount of evidence that, in patients with end-stage chronic renal failure—especially those managed by long-term intermittent hemodialysis—there is hyperaluminemia with accumulation of aluminum in various tissues. The excess in serum and tissue results from intestinal absorption of aluminum salts taken by mouth and also from the passage of aluminum across the dialysis membrane.

Sources of Aluminum

Oral

Aluminum salts are used extensively in the therapeutic management of the hyperphosphatemia which occurs in patients with chronic renal failure. In normal subjects, aluminum is absorbed from the gastrointes-

tinal tract; following oral doses of aluminum-containing salts in normal subjects there is a rise in serum concentration followed by an increase in the excretion of aluminum in the urine (*17*). In experimental rats the simultaneous administration of citrate has been reported to have a significant enhancing effect on the intestinal absorption of aluminum and its subsequent deposition in the cerebral cortex and bone (*18*). It could be proposed that the citrate facilitated the absorption of aluminum by the formation of a chelate complex. In patients with chronic renal failure a positive aluminum balance has been reported in some patients who were on hemodialysis treatment and who were taking oral aluminum-containing phosphate-binding gels (*19*).

Although the major source of aluminum in patients who develop toxicity is usually the dialysate, the intestinal absorption of the metal from phosphate-binding gels appears to have been the dominant factor in some patients (*10,20*). It is possible that individual aluminum absorption rates vary and that some patients may absorb excessive amounts from the intestinal tract after oral administration. It could be postulated that variations in the intestinal absorption rates of aluminum are due to variations in species. In patients with chronic renal failure it has been proposed that parathyroid hormone may contribute to the hyperaluminemia by increasing intestinal absorption and by influencing tissue distribution (*21*). The role of parathyroid hormone in the intestinal absorption of aluminum and the interrelationships between aluminum and calcium homeostasis remain to be defined.

Water

Aluminum is normally present in raw water; the concentrations are usually low in ground waters and are almost always high in surface waters (*22*). Acid rain markedly increases the "natural" aluminum content of water. The effects of acid rain, with specific regard to the metal content of water are controlled mainly by the buffering capability of geological factors in the area of precipitation. The geological factors include the nature of the bedrock, with regard to both basic minerals and acid-soluble toxic metals, together with the depth, texture, mineral and organic content of the overlying soil. Areas most susceptible to acid rain are those with shallow or no soil overlying granite or gneiss bedrock; this pattern is found in Scandinavia, eastern North America and parts of northern Britain (*23*). It is from these areas, with poorly buffered aquatic ecosystems, that the lethal effects of acid rain on animal and vegetable life have been reported. Fish and other forms of animals together with vegetable life have disappeared from the lake areas of Canada, eastern North America, Sweden, and Norway (*24*).

The acidification of lakes and streams by acid rain probably affects vegetable and some forms of animal life at pH values that are not directly harmful to fish; attention has, however, been mainly focussed on the latter. The lethal effects of acid rain on fish life are due not only to the acidification of their environment but also to the increased content of aluminum and other metals that are mobilized from the soil and rock in the water-shed area. The mobilization of aluminum by acid rain causes high concentrations of that metal in surface and ground waters (*25*). The toxicity of aluminum to fish is, however, dependent not only on its concentration but also on its species and the simultaneous pH of the aquatic environment (*26*). In a study of acidified lakes in the Adirondack region aluminum speciation was found to be highly variable with, as a consequence, a variation in the toxic effects of aluminum on fish (*27*). Driscoll and his colleagues (*27*) reported that aluminum in an organic species appeared to be virtually nontoxic to young fish, while the inorganic forms were lethal. In addition to the pH value and aluminum concentrations there is also evidence that the co-existent calcium concentration plays a significant role in the survival rate of fish (*28*). It is of importance to recognize that mercury, manganese, zinc, nickel, lead, and cadmium are also washed into lakes and streams as a consequence of acid precipitation. In this regard, concentrations of zinc and nickel which are toxic to aquatic life have been reported (*23*). The potential health hazards to man of acid rain-induced increases in pH, and the content of aluminum and other metals of surface and ground waters, with particular reference to species warrants evaluation.

Some domestic tap water contains aluminum in high concentration, either naturally or because aluminum has been added as a flocculant in the purification process. Aluminum salts are used as a flocculant to remove organic materials present in surface water that might affect either color or taste. Aluminum sulfate is the commonly used flocculant. In a recent national survey involving a random selection of 186 water utilities in the United States, the aluminum concentrations of finished waters were usually above the analytical detection limit of 14 μg/L (*22*). Miller and his colleagues (*22*) also reported that when aluminum was used in the purification process there was a 40 to 50% chance that the concentration of aluminum in the finished water would be increased above the original concentration in the raw water. In England the aluminum concentration of tap water varies considerably not only on a seasonal but also on a day-to-day basis (*29*). Parkinson and his colleagues (*29*) ascribed these variations to changes in weather conditions which affected the organic content of the water. In contrast to these findings, Miller et al. (*22*) reported that in their nationwide study of the United States there were no obvious seasonal patterns; other workers, however, in a localized study of lakes and streams in the northeastern United States reported the occurrence of seasonal variations in aluminum concentrations (*27*).

Dialysate

Aluminum in the dialysate appears to be the major source of the metal in those chronic renal failure patients

who develop aluminum toxicity. The driving force for aluminum transfer during hemodialysis seems to be the effective concentration gradient between the dialysate aluminum and the free diffusible serum aluminum fraction (*30*). The transfer of aluminum from the dialysate across the dialyzing membrane appears to occur despite low concentrations of the metal in the dialysate (*31,32*). The major portion, if not all, of aluminum in blood is tightly bound to serum proteins and an as-yet unidentified lower molecular weight species (*32*). The identification of the latter, which is nondialyzable, is of importance in the development of an understanding of the mechanisms involved in the tissue accumulation of aluminum and its consequent toxicity.

The aluminum content of the dialysate depends primarily on the content of the water with which it is prepared with some contribution from the chemicals used in the concentrate. The chemical state of the aluminum in the dialysate is of considerable importance because of the effects of organic and inorganic compounds and pH on speciation and thus dialysability. At a low and high pH, the majority of aluminum is in the ionic species. Gacek et al. (*33*) reported that because of the amphoteric nature of aluminum a highly water-insoluble aluminum hydroxide is formed at near neutral pH. A small change in pH, either to a more acid or alkaline value, can make a large difference in the amount of aluminum which is in the dialyzable form.

In patients with chronic renal failure the final pH value of the dialysate can be affected by the pH of the water used to make up the dialysate. The pH of the latter may vary between dialysis centers because of variations in tap-water pH; this factor may have played a role in the conflicting reports in the literature on aluminum transfer across the membrane during dialysis. Parkinson and his colleagues (*29*) reported that if the dialysate pH was carefully controlled to a value of approximately 7.0, the majority of the aluminum was in the colloidal form with a low dialyser clearance value. The transfer of aluminum during dialysis is dependent not only on the pH and aluminum concentration of the dialysis solution but also on the aluminum concentration of the serum, especially the ultrafiltrable fraction.

Dialysis Encephalopathy/Dementia

In 1972, Alfrey and his colleagues (*34*) reported the details of a progressive fatal neurological syndrome which occurred in some patients on long-term intermittent hemodialysis treatment for chronic renal failure. The first manifestation of the syndrome in this group of patients was a speech disorder, followed by the development of dementia, convulsions, and myoclonus; the syndrome terminated in death. In one kidney treatment center, dialysis encephalopathy was the major cause of death (*35*). Because of the similarities between the patients who developed the syndrome with regard to their clinical history, presentation, course and autopsy anatomical findings Alfrey and his colleagues (*34*) proposed that it was likely that the syndrome had a common etiological mechanism. They considered that the syndrome was the result of a metabolic encephalopathy and considered a number of possible factors, including toxins and the accumulation of heavy and trace metals; among the latter they specifically discussed the toxic effects of tin. Although they were unable to precisely define the cause of the metabolic encephalopathy and the associated neurological syndrome they concluded that trace metal abnormalities were common in patients with chronic renal failure on long-term dialysis treatment.

Alfrey and his colleagues (*36*) subsequently proposed that the syndrome called "dialysis encephalopathy" or "dialysis dementia," which occurs after three to seven years of dialysis treatment, may be due to aluminum intoxication. Their proposal was based on the findings of increased aluminum content in brain, muscle and bone tissues of affected patients; the brain gray-matter aluminum content was higher in all of their patients with the syndrome than in any of the controls or other uremics. It is now generally accepted that aluminum is the toxic etiological factor in the dialysis encephalopathy syndrome (*37–39*). The mechanism by which aluminum acts as a neurotoxin is not clearly defined. It has been proposed that aluminum acts as a neurotoxin by inhibition of dihydropteridine reductase (*40*). The inhibition of dihydropteridine reductase would reduce the brain content of tetrahydrobiopterin, tyrosine and neurotransmitters. The neurotoxicity of aluminum alternatively may involve alterations in the major postsynaptic enzymes of cholinergic neurotransmission (*41*). In support of this mechanism are the observations that aluminum inhibits choline transport in erythrocytes (*42*) and decreases choline acetyltransferase activity in nerve tissue (*43*). Aluminum has also been reported to inhibit cytosolic and mitochondrial hexokinase activities in rat brain and thus reduce carbohydrate utilization (*44*). The concentrations of aluminum used in these latter experiments were comparable to those found in the brains of patients who had died from dialysis encephalopathy.

In a recent epidemiological analysis of six dialysis centers, using a uniform clinical classification, 55 patients with dialysis encephalopathy were identified (*45*). Dialysis encephalopathy was the direct cause of death in most cases and the disease appeared to significantly shorten survival. The overall attack rate of dialysis encephalopathy was 4% and varied among the six centers from 2.2 to 14.7%; the difference in the rates was explained by variations to aluminum exposure in the dialysate water. The risk of developing encephalopathy was significantly related to cumulative aluminum exposure in the dialysis water. It is also now recognized that this neurological syndrome has a common etiology with osteomalacic dialysis osteodystrophy (*29,46*).

Osteomalacic Dialysis Osteodystrophy

Bone pain, as a consequence of metabolic bone disease, is a common symptom in patients with chronic

renal failure who are on a long-term intermittent hemodialysis treatment. The metabolic bone disease in these patients is progressive and should be called "dialysis osteodystrophy"—a term that distinguishes it, and some aspects of its pathogenesis, from renal osteodystrophy in the undialyzed patient. One of the major problems that has hampered studies into the etiology of dialysis osteodystrophy is that the reported incidence and rate of progression of its various components has varied not only between countries but also between dialysis centers within a country, despite apparently similar dialysis techniques. The characteristic of dialysis osteodystrophy and its various components is that it progresses or develops despite the maintenance of serum calcium and magnesium and their fractions at concentrations which in a healthy person would not interfere with bone mineralization. The osteomalacic component of dialysis osteodystrophy is a particular problem in that it is associated with a high incidence of fractures.

The type of osteomalacia that is caused by an excess of aluminum, as the etiological factor, is unresponsive to treatment with either vitamin D or its biologically active metabolites. This type of osteomalacia usually occurs in patients on dialysis treatment but it may also occur in nondialyzed patients (*12*). The mechanism for the disordered bone formation induced by an excess of aluminum remains to be clarified; it may involve a disturbance either in the formation of calcium apatite or in the bone mineralization process (*9,47*). Aluminum forms a complex with citrate that is a potent inhibitor of bone mineralization and the growth of calcium phosphate crystals *in vitro*. Thomas and Meyer (*47*) proposed that in patients with chronic renal failure the aluminum concentration exceeds that which is required for the formation of the aluminum-citrate complex and that the action of the complex as a crystal poison could account for the failure of bone mineralization. There is also some evidence from *in vitro* studies which suggest that aluminum may affect the activities of the bone enzymes acid and alkaline phosphatase and modify their response to parathyroid hormone and 1,25-dihydroxycholecalciferol (*48*).

Water Aluminum Content and Toxicity

In 1977, Platts and her colleagues (*49*) reported data on the prevalence of dialysis encephalopathy and spontaneous bone fractures in 202 patients who were on home hemodialysis for chronic renal failure. Noting the uneven geographical distribution of these complications they investigated the water supplies. The tap water used by patients who developed fractures or encephalopathy had concentrations of calcium and fluorine which were lower, while the concentrations of aluminum and manganese were higher, than those in the water of patients without these complications. The patients with multiple fractures had been dialyzed against water with higher aluminum and manganese content than those with a single fracture. Platts and her colleagues (*49*) did not incriminate oral aluminum hydroxide ingestion in the genesis of these complications because only some of the patients took the gel and even they did not take it consistently. Instead they concluded that "some contaminant in the water used for dialysis is very probably responsible for the development of dialysis encephalopathy and pathological fractures." Although they did not definitively incriminate aluminum as the toxic contaminant, they proposed that patients who were being dialyzed in areas with a high aluminum content in the tap water should be supplied with water deionizers.

The beneficial effect of using deionized water to prepare the dialysate was subsequently confirmed by other workers. Ward and his colleagues (*50*) reported that after one to four years of hemodialysis treatment, osteomalacia was evident in only 15% of a group of patients using dionized water compared with 70% of a group using softened, nondeionized water from the same source. They reported that in dialysis centers which used tap water with a high aluminum content there was a high incidence of both osteomalacia and dialysis encephalopathy. The close association between the occurrence of these two complications was consistent, in their opinion, with a common etiology. They also proposed that the evidence that aluminum absorption from the dialysate caused both osteomalacic dialysis osteodystrophy and dialysis encephalopathy was strong enough to justify the expense of treating tap water that had a high aluminum content prior to its use in the preparation of the dialysate. Ward and his colleagues (*50*) drew attention to their findings that water softeners removed only about one-half of the aluminum content of the tap water and did so unreliably; the process of deionization and particularly reverse osmosis were much more effective in removing aluminum from the water supply that they studied. In that particular water supply, however, most of the aluminum present was in the ionized form. They also noted that in other water supplies some of the aluminum is in the nonionic form and may pass through a deionizer, but change chemically when concentrate is added to the water during the preparation of the dialysate.

The critical role of the aluminum content of the tap water used to prepare the dialysate and the uneven geographical distribution of the development of osteomalacic dialysis osteodystrophy and dialysis osteodystrophy was clarified in a nationwide epidemiological survey in the United Kingdom (*51*). In that epidemiological survey, the data were derived from 1,293 patients in 18 dialysis centers; it was reported that there was a highly significant correlation between the aluminum content of water used to prepare dialysate and the incidence of osteomalacic dialysis osteodystrophy and dialysis encephalopathy (*51*). Parkinson and his colleagues (*51*) concluded that the adequate treatment of water, from the start of a patient on dialysis therapy, appeared to be essential to prevent the development of these syndromes. They also proposed from their epidemiol-

ogical survey findings that the "ideal or safe" aluminum dialysate content was probably below 50 μg/L and was more likely to be below 20 μg/L. Reverse osmosis is now the recommended method of water treatment since it provides water with a low aluminum content (< 10 μg/L) (*52*). It has also been recommended that the final aluminum concentration of the dialysate after dilution with treated water should be less than 15 μg/L and preferably less than 10 μg/L (*52*). The latter figure applies to dialysate fluids used for either hemodialysis or peritoneal dialysis. Reverse osmosis also provides water with a low content of other cations and eliminates organic contaminants which may contribute to the problems associated with hemodialysis. There may be between-batch differences in the aluminum concentration of dialysate concentrate and these variations need to be considered as a potential source of aluminum when monitoring programs are being established.

Conclusions

High concentrations of aluminum in water have been implicated as of etiological importance in some specific neurological disorders in patients with normal renal function. The precise role of aluminum in these disorders is, however, controversial.

In patients with end-stage chronic renal failure on dialysis treatment, either by hemo- or peritoneal-dialysis techniques, it has been established that aluminum accumulates in serum and tissues and exerts a toxic action. Aluminum accumulation, with toxicity, also occurs in some patients with chronic renal failure who are not on dialysis treatment but who are on oral therapy with aluminum-containing phosphate binding agents.

In normal subjects aluminum is absorbed from the gastrointestinal tract and is excreted by the kidney in the urine. A failure in the normal renal excretory mechanism accounts for the accumulation of aluminum in the blood and tissues of patients with chronic renal failure. The diet content of citrate appears to enhance the absorption rate of aluminum from the intestinal tract by an effect on species and specifically the formation of a chelate complex. The speciation effect of other dietary constituents on aluminum and the intestinal absorption rate of this metal requires further investigation, as does the use of alternative non-aluminum-containing phosphate binding therapeutic agents in patients with chronic renal failure.

Aluminum in the dialysate appears to be the major source of the metal in patients with chronic renal failure who develop aluminum toxicity. The aluminum content of the dialysate depends primarily on the content of the water with which it is prepared; there may be some contribution from the chemicals used in the concentrate which is added to the water to prepare the dialysate. Some domestic tap water supplies contain aluminum in high concentration, either naturally or because, more commonly, aluminum has been added as a flocculant in the purification process; in this regard the use of non-aluminum-containing flocculating agents warrants evaluation. Acid rain markedly increases the "natural" aluminum content of water.

The species of aluminum in water may affect the intestinal absorption rate in normal subjects and the rate of dialysis in patients with chronic renal failure. Aluminum species in water are complex; small variations in pH of the water can change aluminum from a highly insoluble colloidal form to much more water soluble species. Aluminum is amphoteric, and the insoluble form predominates at neutral pH, whereas a small change in pH to either a more acid or alkaline value can make a large difference in the amount of aluminum in the dialyzable form. The species of aluminum in water, the effect of pH and other variables, including metals, are potentially of considerable importance and require investigation.

In patients with chronic renal failure, the driving force for aluminum transfer during dialysis seems to be the effective concentration gradient between the dialysate aluminum and the free diffusible serum aluminum fraction. The transfer of aluminum from the dialysate across the dialyzing membrane appears to occur despite low concentrations of the metal in the dialysate. The species of aluminum in the final dialysate may significantly affect the dialyzability of aluminum into the blood compartment, and subsequent tissue deposition, and is a topic that warrants further study in patients with chronic renal failure.

The major portion, if not all, of aluminum in the blood compartment is tightly bound to serum proteins and an as yet unidentified lower molecular weight species. The identification of the latter may be of importance in the mechanisms of tissue accumulation and consequent toxicity of aluminum in patients with chronic renal failure. In these patients the increased tissue content of aluminum appears to be the major etiological factor in the development of the neurological syndrome termed either dialysis encephalopathy or dialysis dementia and the form of osteomalacia which is termed osteomalacic dialysis osteodystrophy.

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