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This Week's Citation Classic

Alfrey A C, LeGendre G R & Kaehny W D. The dialysis encephalopathy syndrome: possible aluminum intoxication. *N. Engl. J. Med.* 294:184-8, 1976.
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This report documented that brain aluminum levels were higher in dialyzed uremic patients dying of dialysis encephalopathy than in dialysis patients dying of other causes. It was the first hint that aluminum intoxication was responsible for this disease. [The *SCI*® indicates that this paper has been cited in over 320 publications since 1976.]

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"Upon my return to the University of Colorado Medical Center in late-1970, my staff and I began observing a unique neurological syndrome (dialysis encephalopathy) in uremic patients on chronic maintenance hemodialysis. This disease had distinctive features with all the patients presenting with speech disturbances. Death occurred some seven months later at which time patients were totally mute and unable to perform any purposeful movements. This illness was responsible for 50 percent of the deaths on our dialysis program and prevented any patient from living longer than six years.

"To watch our patients dying from such a devastating disease had a profound effect on the morale of our staff, as well as on the surviving patients and their families. We resolved to find its cause. When we first reported this syndrome, others felt it was unique to the Denver area, and one publication called it the 'Denver disease.' It soon became apparent, however, that it was occurring worldwide but with marked variations in frequency. For instance, it would occur in epidemic proportions in some units but was rarely, if ever, seen in other units. This, in association with the lack of anatomical changes in the brains of patients who had died of this disease, suggested that some environmental toxin, such as a trace element, might be responsible for the illness. Using an X-ray fluorescence method which measures all elements between the atomic numbers of 19 and 92, we could find no consistent differences in trace elements in brains of patients who had died of the disease. Because aluminum was known to be a neurotoxin, yet was too light to measure with this technique, we decided to develop a method to determine aluminum levels in biological samples. Over a period of three years, after attempting a variety of unsuccessful techniques, we finally developed a satisfactory flameless atomic absorption procedure to measure aluminum. When we applied this method to the brains of patients who had died of this neurological syndrome—as well as to the brains of dialysis patients who had died of other causes—it became immediately apparent that although brain aluminum was increased in all the patients studied, it was consistently higher in patients who had suffered from this neurological ailment. This finding was subsequently confirmed by other investigators.[1,2] In addition, large epidemiological studies showed that all units having frequent cases of this disease also had aluminum-contaminated dialysate, whereas units without this disease had dialysate free of aluminum. It was then found that the disease could virtually be eliminated from all involved units by dialyzing patients with aluminum-free dialysate.

"I believe this article is frequently cited because it documented the etiology of the first new disease described in dialysis patients and was instrumental in establishing water standards for the preparation of dialysate, making it possible to eradicate a disease which had been responsible for major mortality. Moreover, it opened up a new area of research into the role aluminum plays in the pathogenesis of a disabling bone disease of dialysis patients."[3]

1. **Cartier F, Allain P, Gary J, Chatel M, Menault F & Pecker S.** Encéphalopathie myoclonique progressive des dialysés. Rôle de l'eau utilisée pour l'hémodialyse. *Nouv. Presse Méd.* 7:97-102, 1978.
2. **McDermott J R, Smith A I, Ward M K, Parkinson I S & Kerr D N S.** Brain-aluminum concentration in dialysis encephalopathy. *Lancet* 1:901-3, 1978.
3. **Hodsman A B, Sherrard D J, Alfrey A C, Ott S, Brickman A S, Miller N L, Maloney N A & Coburn J W.** Bone aluminum and histomorphometric features of renal osteodystrophy. *J. Clin. Endocrinol. Metab.* 54:539-46, 1982.