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Subacute aluminium intoxication in hemodialysis patients

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Subacute aluminum intoxication in hemodialysis patients

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in 1955

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Prof. Dr. A.E. Meinders
Prof. Dr. F.A.J. Muskiet (Rijksuniversiteit Groningen)

To the intoxicated patients

*de lijn die voedt en stoffen zuivert
de hoop die aan het leven hecht
het zijn de handen van ons allen
die maken wat niet is
en breken soms wat blijven moest*

*maar allen zijn wij aangelijnd
ongemerkt in andere hand
zo koesteren wij ons in zekerheid
een zekerheid van korte duur
die - God zij dank! - voor eeuwig lijkt*

Carel P. de Haseth

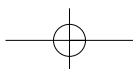
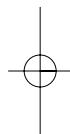
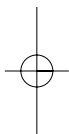
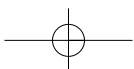
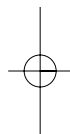
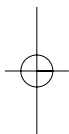


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CHAPTER I

General Introduction

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In 1996, in a small dialysis center (Diatel Curaçao), ten hemodialysis patients died of subacute aluminum encephalopathy, as a result of a unique set of circumstances. This was caused by a hitherto unknown source of aluminum exposure, namely aluminum that was released from the cement lining of a newly installed drinking water distribution pipe.¹⁻² The clinical, forensic and legal aspects of this tragic poisoning incident form the subject of this thesis.

Aluminum

In 1857, Charles Dickens became very interested in the discovery of a new metal that he believed would have an outstanding future, aluminum: *"Within the course of the last two years ... a treasure has been divined, unearthed and brought to light ... what do you think of a metal as white as silver, as unalterable as gold, as easily melted as copper, as tough as iron, which is malleable, ductile, and with the singular quality of being lighter than glass? Such a metal does exist and that in considerable quantities on the surface of the globe".*³

Aluminum is a ubiquitous metal in the natural and industrial environment and has been considered a harmless substance for a long time. After oxygen and silicon, aluminum is the third most abundant element in the earth's crust, of which it comprises about 8.2%.⁴ Aluminum has a great affinity for oxygen and therefore occurs only in the oxidized form, mainly as alumina (Al_2O_3). It is found in almost 300 different minerals, especially in complex compounds such as silicates like feldspars and micas, and is widely distributed in rocks, clay and soils including gems such as ruby, sapphire and turquoise, and minerals of industrial importance (alum, bauxite, cryolite, corundum and kaolin).⁵⁻⁶ Bauxite, the primary ore, is composed of impure oxides found in extensively weathered rocks in the tropics. As a highly charged and reactive element, aluminum is virtually always encountered in combined form.⁷⁻⁸ In fact, its ability to form strong chemical bonds initially frustrated man's attempts to obtain even the most minuscule of purified samples of the metal. This made it so rare that the Emperor Napoleon Bonaparte used aluminum plates and cutlery in 1858 to serve the King of Siam at a state banquet. Aluminum was then such a precious metal that "less important" guests had to eat from plates of pure gold. However, although aluminum was not isolated until 1825 by

Hans Christian Oersted from Denmark,³ alum (hydrated aluminum sulphate) had already been used for several thousand years by the Egyptians, Greek and Romans as a mordant in the dyeing process, in the preparation of hides, and since Roman times for the purification of water.^{5,9} In 1886 the Hall-Heroult process for the electrolyte separation of the metal finally yielded commercially feasible quantities of aluminum and transformed what was an exceedingly rare substance into a widely employed component of numerous industrial and household products.¹⁰

Despite the ubiquity of aluminum in the environment it is present only in trace amounts in living organisms and no biological function for the element has been described. In a paper by Von Döllken in 1897, reference was made to the earliest publication (by Orfila in 1814) discussing the potentially toxic effects of aluminum salts on animals, where behavioral changes and irritability were noted following parenteral administration. Von Döllken also commented on work performed by Siem in 1887 in which detailed animal studies found quite profound neurological changes following the parenteral administration of aluminum.^{11,12} It was first recognized as a human neurotoxin in 1886, in a Prussian army study of amputees whose wounds had been treated with alum to staunch bleeding.¹³ Although toxicity was reported periodically, not much attention was given to Spofforth, who in 1921 published the first description of the toxic effects of aluminum on man. He discussed the case of a 46-year-old metal worker who had been dipping red-hot metal articles into concentrated nitric acid using an aluminum holder and developed "loss of memory, tremor, jerking movements and impaired coordination".^{12,14} A publication, in 1928, by Ernest Ellsworth Smith referred to a study from 1880 in which feeding of aluminum containing baking powder to dogs led to an increase in organ aluminum, establishing the absorptive potential of the intestine for this element. He also covered several aspects of current concern namely aluminum in medicines, its absorption from the gastrointestinal tract, its presence in drinking water and its potential effects as a health hazard.^{5,15-17} In 1940, Kehoe and colleagues emphasized the need to establish normal aluminum values in man¹⁸ and in 1957, after reviewing 503 references, Campbell and coworkers concluded that aluminum presents a hazard in only a few special circumstances.¹⁹ The current interest in aluminum, however, began in the mid 1960s and early 1970s

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by developments in several areas of medical research and its applications. Aluminum was not considered to be a toxic element until the 1960's when a few reports appeared on the toxic effect of aluminum in humans²⁰ and animals.²¹ In 1970, Berlyne and coworkers drew the attention to the occurrence of hyperalumenemia in chronic renal failure due to the consumption of aluminum resins. Increased levels were found in nondialyzed patients with chronic renal failure either taking aluminum resins for hyperkalemia, or taking aluminum hydroxide for hyperphosphatemia.²² Although the statement of Berlyne appeared to be prophetic later, he was initially highly criticized when he claimed that aluminum salts should not be prescribed for patients with renal function impairment, and that these salts should be withdrawn from the market. In 1972, in a paper by Alfrey and his colleagues, the first account was given of an outbreak of encephalopathy in a dialysis center, which was called "dialysis dementia".²³ Unfortunately, numerous similar incidents followed, especially due to the use of aluminum salts by water companies that contaminated the water supply of dialysis centers,²⁴⁻³⁰ but also due to errors in design of hemodialysis equipment.³⁰⁻³²

In the face of abundant aluminum exposure and its demonstrated toxicity, living organisms have both active and passive mechanisms to prevent aluminum accumulation. In humans, this includes gut design that reduces absorption; internal chelation and excretion primarily through the kidney; sequestration in bone and binding by transferrin, the main blood metal shuttle protein, which reduces blood levels.^{33,34} Being especially vulnerable to the toxic effect of aluminum, the brain has lower aluminum levels than many other tissues due to partial exclusion by the blood brain barrier.³⁵ An active efflux mechanism for aluminum from the brain, probably as aluminum citrate is mediated by the monocarboxylate transporter,^{36,37} as well as removal by other mechanisms such as by small peptides.^{38,39} Nevertheless, while some aluminum that enters the brain is rapidly refluxed, another fraction is eliminated very slowly,^{36,37} causing severe encephalopathy after repetitive or continuous exposure.³⁰

Presently, wide ranges of toxic effects of aluminum to hundreds of cellular processes both in man, animals and plants have been demonstrated.

From a medical point of view, it seems remarkable to associate a single agent, especially one until recently considered to be completely harmless, with so many disease conditions.⁴⁰ Its wide range of toxic effects is largely attributed to its small ionic radius (0.54 Å)^{41,42} and its high oxidation potential (+1.706 V)^{42,43} causing it to bind in a biological environment, to almost any oxygen or nitrogen atom.⁴⁴ In addition, because aluminum is amphoteric, it can combine with both acids and bases to form respectively aluminum salts and aluminates.⁴¹⁻⁴⁵ The ability to be bound nonspecifically to so many different structures implies, for Al³⁺, a potential possibility to affect or interfere with almost any reaction in organisms.⁴⁴⁻⁴⁶ The possible effects of aluminum also have escaped attention because biological experiments tend to underestimate the effects as these may be far too slow in relation to the study design and many effects appear only after several decades of exposure. Numerous technical difficulties are also accountable for the relative lack of knowledge of aluminum-related effects in biological species.⁴⁵⁻⁴⁷ Using analytical methods that suffered from lack of sensitivity and major interference problems -which resulted in erroneous and inconsistent findings- hampered earlier studies predicated on the determination of aluminum in biological samples. With the development of electrothermal atomic absorption spectrometry (ETAAS) and other instrumental methods for the measurement and speciation of trace metals, these problems have been largely overcome.^{45,46} Nevertheless, due to the multifaceted interaction of aluminum with molecules found in biological systems at trace levels,⁴⁵ even today-after more than thirty years of intensive research- several aspects of aluminum metabolism and toxicity still remain to be elucidated.^{45,46}

Water production and distribution on Curaçao

Curaçao is a small island with a total area of 444 square kilometers (171 square miles), situated 40 nautical miles (74 km) off the north coast of Venezuela. Being just 12 degrees from the equator, Curaçao has a warm, dry (total annual rainfall averages only 570 mm or 22 inches) and sunny climate year round with an average temperature about 27°C (81°F) and together with the strong tradewinds (average velocity 7 meter/sec), a high degree of evaporation is observed.⁴⁷ Because Curaçao has no natural water resources its public drinking water supply depends totally on seawater desalination which was performed,

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until recently, by multistage flash distillation.^{48,49} The distillation process mimics the natural water cycle in that salt water is heated, producing water vapor that, in turn, is condensed to form fresh water. However, for this to be done economically in a desalination plant, the boiling point is altered by adjusting the atmospheric pressure on the water being boiled to produce the maximum amount of water vapor under controlled conditions. Of the more than 7,500 desalination plants in operation worldwide, 60% are located in the Middle East and 12% in the Americas, most of them located in the Caribbean and Florida.⁵⁰

Corrosiveness of the water on Curaçao

If iron water distribution mains are used, distilled water needs additional modification because very pure water is highly corrosive, resulting in rusting, leaks and reduced longevity of these mains. Among the water characteristics that most significantly influence the corrosion rate is the alkalinity. Alkalinity is composed mostly of carbonate and bicarbonate ions and is expressed as CaCO₃ mg/L. It provides water with buffering capacity to neutralize changes in pH. It also helps lay down a protective coating of metallic carbonate on the pipe wall and can help prevent the dissolution of calcium and metals from cement-lined pipe. The lower the alkalinity, the more corrosive the water will be.⁵¹⁻⁵³ Before 2001, until the fusion of the two companies, in Curaçao, the alkalinity of the drinking water was established in the delivery contract between the water company and the water distribution company. The alkalinity was low in the past,⁵³ but was increased substantially in June 2002 (Table 1).⁵⁴

Table 1. Alkalinity^a (mg CaCO₃/L) of the drinking water in Curaçao, 1996-2002

	Corrosive Water ^{b,1,2,4,5}	Before 1996 ¹	Water delivery contract ^c , 1979 ¹	Water delivery contract ^c , 2002 ⁵⁴	August 2002 ^d
Alkalinity, as CaCO₃ (mg/L)	< 60-75	25-40	< 60	> 50	45-63

^a The extent to which water can corrode the material used for water distribution depends on the characteristics of both the water and this material but there is no simple relationship of water characteristics defining the corrosiveness of water for these materials. For cement protection, water with a high alkalinity provides water with buffering capacity to neutralize changes in pH. It also helps to lay down a protective coating of metallic carbonate on the pipe wall and can help to prevent the dissolution of calcium and metals from cement-lined pipe by sealing the cement pores.⁵⁰⁻⁵²

^bThe alkalinity of the tap water was established in the water delivery contract between the water company and the water distribution company (or Aquaelectra after their fusion in 2001).

^cAquaelectra laboratory.

Generally, the effectiveness of the corrosion-prevention system has a direct bearing on the longevity of the pipeline and it significantly influences operational costs such as general maintenance, pumping energy, and capacity upgrades.⁵⁵ Corrosion is therefore one of the most important problems in the drinking water industry,⁵⁶ and consumes about 3-4 percent of the gross national product in developed countries.^{55,56} In Curaçao, the water utilities have an operational water loss of about 30%, partly due to corrosion problems, resulting in an energy loss of about 1403 TJ/year (thermal energy), which, in 1988, was almost the same amount as the total estimated energy consumption (1447 TJ/year) of the population.⁵⁷ This very high water loss is also reflected in the cost of drinking water (flat rate domestic water: 9.42 NaFl/m³ or 5.3 US \$/m³), which in Curaçao is by far the highest in the region.^{58,59}

In Saudi Arabia, very large desalination plants experienced similar corrosion problems in the past with soft water. By increasing the calcium carbonate level to concentrations above 60 mg/L, the corrosion rate was significantly reduced because a protective calcium layer was formed on the inner pipe wall. Thereafter, the calcium carbonate concentration could be reduced.⁵¹ In Curaçao, the adaptations made by the water company were insufficient and some iron water mains had to be replaced within 10 to 15 years,⁶⁰ in contrast with less corrosive drinking water conditions in other countries where cemented pipes may have an asset life of 100 years or more.⁶¹ This prompted the water distribution company to install water pipes with a cement layer to protect the iron pipe from corrosion and increase the longevity of the water mains.⁵²

Worldwide, cement coatings have been used for over 100 years by the water industry and these generally provide considerable protection to embedded ferrous materials against the corrosive effects of soil and water.⁶¹ Cement mortar pipes, however, cannot be used under all conditions, as its appropriateness is not only related to the cement composition but also to the characteristics of the water to be transported.^{1,51-53,61} In Curaçao the cement lining dissolved partially due to the softness of the distributed water. Consequently, components of cement leached into the water supply of the dialysis center resulting in moderately higher calcium concentrations and excessively high aluminum concentrations for a prolonged period of time.^{1,2,30,52}

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Renal disease and dialysis facilities on Curaçao

In 1981, Curaçao had 147.388 inhabitants, a number that decreased to 130.067 in 2001. In the United States⁶² and in some European Countries,⁶²⁻⁶⁵ men from African descent are among the fastest growing racial minority groups with end stage renal disease (ESRD). Recently, as an example, African-Americans comprised approximately 31% of the ESRD population in the United States,⁶² resulting in a three to five times greater incidence amongst subjects of African-Caribbean origin compared with Caucasians in the United Kingdom.⁶³ Likewise, as can be expected, the high prevalence of end-stage renal disease in Curaçao is above 1 per 1000, since 85% of the population is of (mixed) African origin.⁶⁶ In 1992, with the aid of the Dutch Kidney Foundation, a dialysis unit (Diatel Curaçao) with eight units was opened as the eleven dialysis units in the local hospital, did not suffice to take care of the increasing number of patients with ESRD.

Legislation

Curaçao is the largest island of a federation called the Netherlands Antilles. This federation, which is constituted by the islands of Curaçao, Bonaire, St. Maarten, Saba and St. Eustatius, is an autonomous part of the Kingdom of the Netherlands. With respect to the Netherlands Antilles, the fundamental laws are enacted in the "Staatsregeling" and "Eilandsregeling Nederlandse Antillen". Each of the islands of the Netherlands Antilles is autonomous in a distinctive manner. Matters of common interest to the islands, such as jurisdiction, police etc., are administered by the Central Government of the Netherlands Antilles. Deputies of the Executive Body of the Island Council (Bestuurscollege) regulate matters of local concern.⁶⁷ During the four years following the aluminum intoxication, a criminal prosecution was conducted to evaluate if the physicians in charge of the dialysis program had been criminally negligent. Since the local law -which was to be amended the following year-,⁶⁸ did not permit the prosecution of board members of legal entities like foundations,⁶⁹ neither the water utilities, nor the board members of Diatel were prosecuted.

Aim

The general aim of this thesis is to address 1) the sequence of events regarding the actual poisoning incident, including the new clinical and pathogenetic insights of subacute aluminum-intoxication, 2) the causes of the incident related to the water management, and 3) the forensic and legal consequences.

In **chapter II**, the impact is rendered of the use of water distribution pipes with inner cement linings, on the quality of tap water.

In **chapter III**, the outbreak of subacute aluminum encephalopathy in a dialysis center is described.

In **chapter IV**, the post-mortem toxicological findings in subacute aluminumencephalopathy are presented.

In **chapter V**, the literature on symptomatology, the sources of aluminum exposure and pathogenic mechanisms of aluminum intoxications is reviewed. Also a treatment schedule to treat hemodialysis patients with aluminum intoxication is shown.

In **chapter VI**, the judicial implications of the subacute aluminum intoxication outbreak are discussed.

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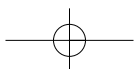
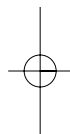
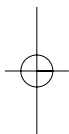
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General Introduction



CHAPTER II

Cement-Mortar Pipes as a source of aluminum

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Abstract

In 1996 in Curaçao, acute aluminum (Al) intoxication sickened patients in a dialysis center that used tap water to prepare dialysate. The mortality rate was 32 percent. A new factory-lined cement-mortar water distribution pipe had recently been installed. It is known that substantial amounts of barium, cadmium, and chromium can leach from cement-mortar linings. This article shows that high concentrations of Al can leach from cement mortars for at least two years in soft aggressive water. The newly installed pipe, cement containing four times as much Al as usual, corrosive water, the high pH and temperature of the water, long residence time and perhaps the use of the corrosion inhibitor polyphosphate may have promoted this leaching. Certification of cements used to line water pipes is warranted. Central water treatment plants must distribute noncorrosive water, especially plants that use membrane desalination or other reverse osmosis or nanofiltration processes. Dialysis centers should be promptly informed of any impending change in water treatment that might increase the Al content of tap water and also of any accidental pollution of the water distributed. Dialysis centers should always practice extended purification of tap water used for dialysate. Although Al as a risk factor for Alzheimer's disease in the general population is still debated, there is no doubt that Al causes dialysis encephalopathy.

Introduction

Aluminum (Al), a ubiquitous metal in the natural and industrial environment and has long been considered a harmless substance. It may be a natural or an added ingredient in food and drinking water. In past decades, it has been suggested that Al in drinking water plays a role in Alzheimer's disease. Al concentrations < 100-200 µg/L in drinking water do appear to be an important risk for the normal population.¹⁻³ A different situation exists with regard to the role of Al in dialysis encephalopathy in hemodialysis patients. That Al causes this neurological disorder is beyond dispute.⁴⁻⁶ Early epidemics of Al intoxication in dialysis centers were largely due to contamination of hemodialysis fluid made with tap water. The geographical distribution of these incidents correlated with locally high concentrations of Al in tap water, mainly from the use of Al salts as a flocculant during water treatment.^{5,7} To arrest these epidemics, many dialysis centers began to purify their tap water with combinations of filtration, carbon adsorption, deionization, and reverse osmosis (RO) tailored to the individual water supply.^{4-6,8,9}

Even so, some dialysis centers still use drinking water for hemodialysis without special treatment.^{8,9} In these cases the dialysis centers and home dialysis patients rely on a constant, acceptable quality of drinking water from the public supply. To protect such hemodialysis patients, some countries require drinking water companies to inform the public health authorities if the Al content in drinking water has exceeded 30 µg/L in the finished water entering the distribution system.¹⁰ It has been generally assumed that the Al concentration does not increase during distribution.^{11,12}

This article describes for the first time an outbreak of acute Al intoxication in a dialysis center because of Al contamination of drinking water during distribution. The possible origin and consequences of this source of contamination are discussed.

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The intoxication episode was unexpected

The water supply had been reliable

With the support of the Dutch Kidney Foundation, a dialysis center with eight stations (Diatel Curaçao) was opened in Willemstad, Curaçao, in 1992. The water used for dialysis was obtained from the local drinking water company. The water company produced drinking water from desalinating seawater, which has a very low metal content (Al concentration < 5 µg/L). Because this water had been used for dialysis without purification for > 26 years in the local hospital, further water treatment in the dialysis center was judged to be unnecessary.

On occasion, network flow conditions in the water mains caused low water pressure that prevented normal dialysis at the center. The drinking water company remedied the pressure problem by changing the distribution to the dialysis unit, as part of a larger project for rebuilding the distribution network. On Mar. 21, 1996, the drinking water company laid a cement-mortar water distribution pipe; water began to flow to the dialysis center through this new pipe on May 21, 1996.

Dialysis patients became ill

The first signs of illness among the dialysis patients were noted on June 15, 1996; patients suffered nausea, vomiting and hypercalcemia. These illnesses were attributed to a higher-than-usual calcium (Ca) content in the tap water (on June 24, 1996, hardness as CaCO₃ was 43 mg/L). On June 29, 1996, after the insufficient success of medical intervention, the dialysis center was temporarily closed. Thereafter, patients were dialyzed in the hospital using tap water further treated with RO and later, after installation of an RO unit, in the reopened dialysis center. At first the patients seemed to do well, but after a clinical silent period of days to weeks, nine of the twenty-eight intoxicated patients (32 percent) died with symptoms of acute Al intoxication.

The nature of the disease was difficult to trace in the beginning because it was thought that only the calcium content of the water had changed. Later, clinical symptoms such as seizures and coma pointed to acute Al intoxication. The first analysis of Al concentrations in the tap water was obtained July 3, 1996, about six weeks after the pipe was put in use. The value,

650 µg/L, was about 40 times as high as the usual value. Experts from the Netherlands (International Water Consultancy, Keuringsinstituut voor Waterleiding Artikelen, and Netherlands Organization for Applied Scientific Research) concluded that both calcium and Al had leached from the cement mortar of the newly installed water distribution pipe.

Water is distributed through iron pipes

New cement-mortar pipe had been installed

The distribution mains consisted mainly of ductile-iron pipes. Corrosion and red water problems led to the use of cement-coated pipes to protect the iron in a region that supplied the dialysis center and a small shopping area. The pipes connecting the water mains and the dialysis unit were 2,200-m- (7,200-ft-) long ductile-iron pipes with a cement-mortar lining. Two pipes from different companies were used. One pipe was 1,700 m. (5,580 ft) long and had a diameter of 200 mm (8 in.). The other pipe was 500 m. (1,640 ft) and had a diameter of 150 mm (6 in.). The water flow was 27.5 m³/d (7,266 gpd) providing a low velocity of about 0.01-0.04 m/s (0.03 – 0.13 ft/s). Moreover, periods of suspended flow were likely after office hours. On the basis of the flow rate, a residence time of the water in each segment was calculated: it was two days in the 200 mm-(8in.-) diameter pipe and 0.32 days in the 150-mm- (6-in.-) diameter pipe. The total residence time of the drinking water in the cement-coated pipes therefore is estimated as 2.3 days. Periods of suspended flow are likely after office hours.

In July 1996, after the intoxication of the patients and installation of a RO unit, the persistent extremely high Al concentration in the tap water became apparent. In response, the original 2,200 m (7,200 ft) of the cemented pipe was reduced to 1,000 m (3,280 ft) Aug. 1, 1996, by changing the influent water point of the water mains.

Both new pipes placed in the distribution network were lined with cement mortar at the factory, by a rotary centrifugal process, and neither had an asphaltic seal coat applied to the lining. The cement type was very similar to blast furnace cement and had a high sulfate resistance.* The cement used in the distribution network had a higher Al

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content than blast furnace cement, pozzolanic metallurgical cement, or portland cement, but a lower content than high alumina cement (Tabel 1).

Table 1. Composition of cement types commonly used in cement-lined pipe and composition of cement described in this report

Parameter	Blast Furnace cement	Pozzolanic Metallurgical cement	High- Alumina Cement	Portland Cement	Cement composition in this case
SiO ₂ , %	27	29	3.5	21	18
CaO, %	48	44	38	65	55
Free CaO, %	0.5	1.5	0.5	2.5	ND**
Al ₂ O ₃ , %	13	13	36	5	18.7
Fe ₂ O ₃ , %	1.5	3	18	2.5	3.5
SO ₃ , %	3.8	2.2	0.1	1.9	ND
Na ₂ O, %	0.4	0.3	0.1	0.1	ND
K ₂ O, %	0.8	0.7-1.7	0.05	0.8	ND
MgO, %	2.8	3	0.4	0.5	4.3
Density, g/cm ³	2.9	2.8	3.2	3.1	ND
Specific surface, cm ² /g	3,350-3,450	3.650	2,750	3,870	ND

**ND-not determined

Drinking water is flash distilled seawater

The water used in the dialysis fluid was obtained from the local drinking water supply, which was then filtered but not further purified. At the water plant, seawater was treated with multistage flash distillation in a desalination plant. The distilled water was filtered through coal and conditioned by marble filtration. Fluoride was added and ultraviolet light disinfection was applied. Chlorine was not routinely applied. Polyphosphate was added as a corrosion inhibitor at a dosage of 1 µg/l of the chemical product. The water entering the mains was aggressive, soft, and of low alkalinity (maximum Langelier Index [LI] between -0.5 and -1.5, hardness as CaCO₃ 15-20 mg/L, and pH 8.5 to 9.5).

Al and Ca were high in tap water

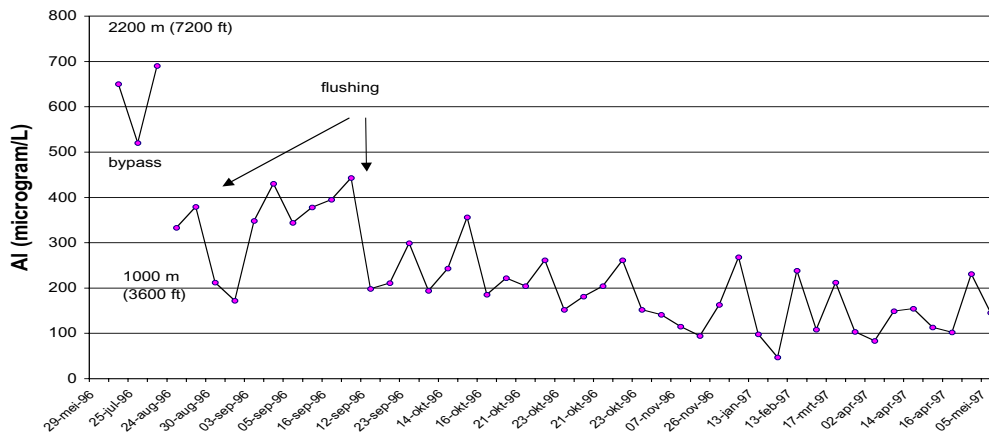
Tap water was sampled many times for testing according to association for the Advancement of Medical Instrumentation (AAMI) standards.¹³ The samples were placed in pyrolytical tubes and shipped overnight for analysis.† Al analysis was performed by inductively coupled plasma-atomic emission spectroscopy. Water quality parameters were measured by the local water company and a laboratory in Holland.‡

* Netherlands Organization for Applied Scientific Research, The Netherlands

† Spectra Laboratories, Fremont Calif.

‡ International Water Consultancy

Figure 1. Aluminum in tap-water July 1996-May 1997



Water constituents and parameters important in dialysis were measured in 1994, 1996, 1997 and 1998 (Table 2), and the Al concentration in the tap water from July 1996 to March 1998 was plotted (Figures 1 and 2). In 1994 the Al concentration in the tap water entering the dialysis unit was 16 µg/L.

In 1996 AL was first measured after the new cement-mortar pipe had been in use for six weeks. The Al concentrations ranged from 550 to 690 µg/L for more than 2 months after the pipe was put in use. After the original 2,200-m (7,200-ft) was reduced to a length of 1,000-m (3,280-ft) Aug. 1, 1996, the Al concentrations dropped to a maximum of 443 µg/L. Flushing the pipe several times temporarily lowered of the Al concentration. More than two years after the pipe was put into use, Al still leached to concentrations above 100 µg/l (Figures 1-3). Initially, other water parameters changed as well: pH increased from 8.5 to 9.1, total hardness as CaCO₃ from 15 to 43 mg/L, alkalinity from 18 to 32 mg/L (as CaCO₃) and L1 from -0.5 to +0.4. Ca concentrations as Ca²⁺ in the tap water ranged from 16.3 to 18.1 mg/L, only slightly higher than the concentration of 15 mg/L at the water plant. Water quality tests on July 30, 1996, found other components of cement as well, especially silicon (22 µg/L), molybdenum (17 µg/L) and strontium (2600 µg/L).

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Table 2. Composition of tap water at Diatel Curaçao –January 1994-August 1998

Constituents and parameters	January 1994	July 1996	August 1996	November 1996	February 1996	April 1997	May 1997
Sodium, mg/L	22.98	14.48	14.29	16.82	19.72	23.04	34.1
Potassium, mg/L	2.350	1.999	1.917	1.205	<1.000	1.726	2.445
Aluminum, µg/L	0.016	0.650	0.401	0.099	0.103	0.149	0.231
Calcium, mg/L	10.79	18.1	14.43	15.46	19.84	16.04	16.55
Copper, mg/L	0.003	<0.005	0.016	0.013	0.068	0.020	0.012
Magnesium, mg/L	4.618	1.665	2.082	2.541	4.545	3.377	4.601
Selenium, mg/L	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Zinc mg/L	0.184	0.062	0.093	0.081	0.207	0.063	0.054
Chromium, mg/L	<0.005	0.007	0.006	<0.005	0.007	0.005	0.012
Lead, mg/L	<0.001	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002
Arsenic, mg/L	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002
Mercury, mg/L	<0.0002	<0.0002	<0.0002	<0.0002	<0.0002	<0.0002	<0.0002
Cadmium, mg/L	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Fluoride, mg/L	0.18	0.50	0.40	0.64	0.38	0.72	0.71
Nitrate(N), mg/L	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Sulfate, mg/L	5.1	4.1	3.9	3.70	4.8	5.5	8.5
PH	7.5	8	8.1	7.9	8.2	8.0	8.4
Resistivity, meg Ohms	0.005	0.006	0.006	0.005	0.004	0.004	0.003
Silver, mg/L	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	0.003
Barium, mg/L	0.003	0.004	0.003	<0.001	0.002	0.001	0.002

Discussion

Cement is not inert

Several factors promote leaching of Al

Ferrous-metal water distribution pipe can corrode by electrochemical action, which leads to scaling, leaks and tuberculation. Lining the pipe interior with cement mortar protects the metal from corrosion by providing a coating of electrochemically inert material between the metal and water. Although cement-mortar lining successfully protects against electrochemical corrosion, water can leach cementitious materials from this lining for as long as four years. Extended contact time under low-flow conditions can increase pH, alkalinity and concentrations of leached components such as calcium.¹⁴ In addition, recent laboratory studies showed that substantial amounts of barium, cadmium, and chromium can leach from cement-mortar linings.¹⁵ Reports of these studies did not mention substantial leaching of Al. Water that is low in pH and alkalinity and that contains little calcium appears to be the most corrosive to cement-mortar linings.¹⁴⁻¹⁹

Cement composition influences leaching

Corrosion rates are influenced by cement mortar composition, the

Table 2. Composition of tap water at Diatel Curaçao –January 1994-August 1998, Continued

Constituents and parameters	August 1997	September 1997	November 1997	February 1998	April 1998	June 1998	August 1998
Sodium, mg/L	8.013	7.596	11.32	10.24	23.34	12.37	7.364
Potassium, mg/L	<1.000	1.725	<1.000	<1.000	1.92	1.808	1.377
Aluminum, µg/L	0.090	0.090	0.064	0.088	0.090	0.103	0.070
Calcium, mg/L	25.42	23.16	29.10	18.95	22.88	17.87	16.56
Copper, mg/L	0.070	0.057	0.161	0.079	0.051	0.032	0.055
Magnesium, mg/L	1.246	1.872	1.759	2.382	4.213	2.562	1.895
Selenium, mg/L	<0.05	<0.05	<0.05	<0.05	<0.002	<0.002	<0.005
Zinc mg/L	0.162	0.091	0.179	0.092	0.055	0.069	0.071
Chromium, mg/L	<0.005	0.009	0.009	0.006	<0.005	<0.005	<0.005
Lead, mg/L	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002
Arsenic, mg/L	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002	<0.002
Mercury, mg/L	<0.0002	<0.0002	<0.0002	<0.0002	<0.0002	<0.0002	<0.0002
Cadmium, mg/L	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Fluoride, mg/L	0.47	0.42	<0.10	0.12	<0.10	<0.10	0.67
Nitrate(N), mg/L	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2
Sulfate, mg/L	1.7	1.9	2.5	2.4	5.4	2.9	1.8
PH	7.9	8.0	7.9	8.2	8.0	7.3	8.0
Resistivity, meg Ohms	0.005	0.005	0.005	0.006	0.003	0.006	0.007
Silver, mg/L	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003	<0.003
Barium, mg/L	0.002	0.002	0.002	0.001	0.001	<0.001	<0.001

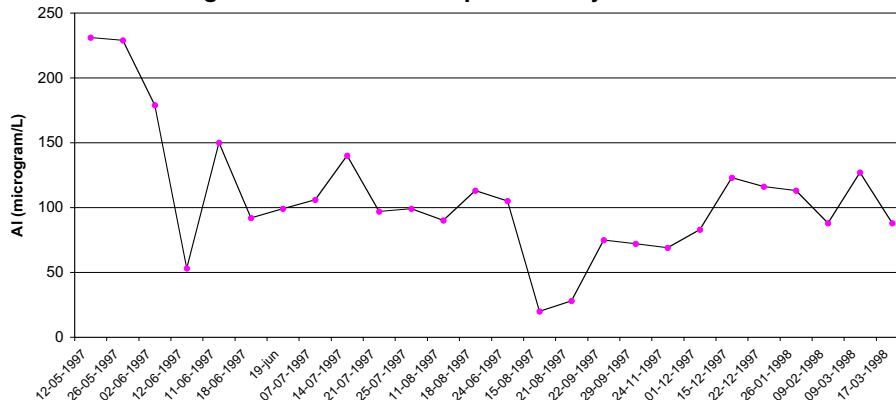
method of lining, and by protective coatings.¹⁴⁻¹⁹ Generally the concrete used for water treatment plant pipes, water tanks, and filters is made of portland cement, whereas cement mortar linings may be portland cement, high alumina cement, blast furnace cement or super-sulfated cement. The use of high-alumina cement and acrylic resins additives greatly increases corrosion resistance of the mortars, but the setting behavior of high-alumina cement differs from that of any other type of cement. The compounds formed are not the same, the nature of the process depends on the temperature, and the reactions lead to an excess of Al hydroxide.¹⁶ More than 100 compounds and phases important to the chemistry of portland related cements have been described,²⁰ and because of the possibility of solid solution, probably many more exist.

Solution of Al compounds in cement poorly understood

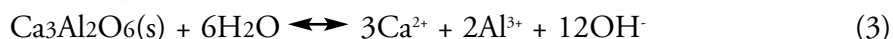
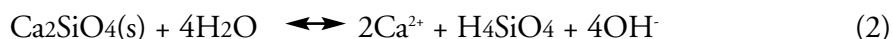
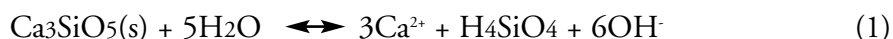
Understanding of the thermodynamic solubility in water of the major compounds in cement lags far behind the understanding of minerals and synthetic compounds important to drinking water chemistry. At present, only some qualitative generalizations can be made. Three of the predominant crystalline phases in cement are tricalcium silicate (nominally Ca_3SiO_5),

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Figure 2. Aluminum in tap-water May-March 1998



dicalcium silicate (nominally Ca_2SiO_4), and tricalcium aluminate ($\text{Ca}_3\text{Al}_2\text{O}_6$). Possible dissolution reactions may be represented as follows:¹⁶



Cement-lined pipes in Holland studied

After the tragedy in Curaçao, studies in 1996 investigated the leaching of Al from cement-mortar water pipes in Holland.²¹ Samples were taken from water in cemented pipes and asbestos cement-pipes at 20 locations. Locations that favored the leaching of Al were chosen: new, small-diameter pipes, low flow and soft water. Al concentrations in these samples never exceeded 11 µg/L at any location. Investigators concluded that home hemodialysis might be safe with this water, but because higher concentrations cannot be excluded in new pipes, they advised testing for pH and Al shortly after new cemented pipes are installed.

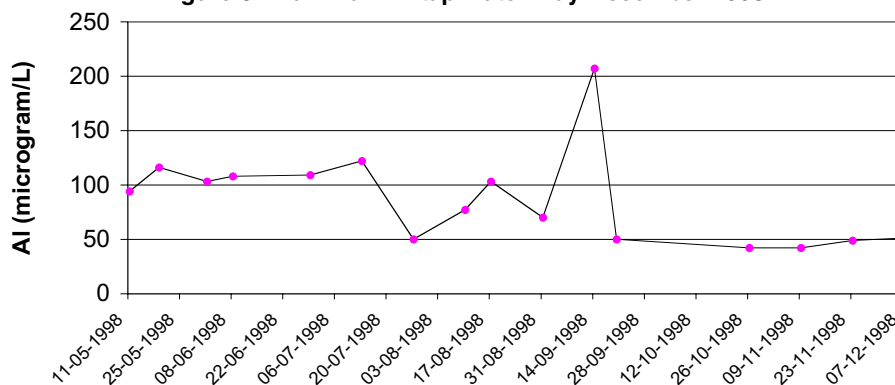
In Holland the recommended cement types are portland cement and portland cement with high resistance against sulphates.²² To use other types of cement, the water supplier must prove the appropriateness of the pipe. In 1999, however, no laws apply and no certification of the toxicological aspects of pipe has been implemented.

Two types of cement investigated

A set of studies investigated ordinary portland cement (OPC) mortar lining and a blast furnace slag (GGBFS) cement mortar containing 65 percent GGBFS and 25 percent OPC applied in situ and in the factory.^{18, 19} The extent and duration of pH increase appeared to depend primarily on the alkalinity of

the water. The pH increased in water from all pipes (except one) containing in situ linings; water carried by the one exception was hard. Only in low-alkalinity water did Al concentration increase after passing through cement-mortar pipes. Al concentrations above the (EC) Directive²³ maximum admissible concentration of 200 µg/L were found for a prolonged period, one to two months, low-alkalinity water (about 10 mg/L CaCO₃).¹⁸ After long contact times (up to 13.30 h) in cement-mortar pipes that had been exposed for 40 days to a typical soft water, water was sampled and analyzed for Al. Al concentrations were as much as 380 µg/L (GGBFS in situ linings) and 450 µg/L (OPC in situ linings). Factory-applied linings leached less Al into the water than did in situ linings. It was suggested that under conditions of low flow and long retention times, should determine which cement type should

Figure 3. Aluminum in tap-water May-December 1998



be used. In situ linings of OPC should not be used if the supply water has an alkalinity < 55 mg/L; in situ linings of GGBFS should not be used if the supply water has an alkalinity < 35 mg/L.¹⁸ Factory-applied cement linings could be used when the water supply alkalinity is > 25 mg/L CaCO₃.¹⁹

Water quality influences leaching

High pH

Aside from high Al content of the cement linings, mobilization of Al from the cement may have been promoted by the high pH of the water, which increases Al solubility. Al in water forms numerous complexes with inorganic and organic ligands, as well as polynuclear intermediates and Al trihydroxide colloidal precipitates under neutralizing conditions. The solubility and speciation of inorganic Al depend strongly on pH, whereas the solubility of organically complexed Al correlates with the concentration of dissolved organic matter. In distilled water with low concentrations

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of dissolved organic compounds such as humic and fulvic acids, the dependence of dissolved Al on pH resembles on a logarithmic scale a parabola with a sharp solubility minimum near pH 6.5 (figure 4). In water more acid than pH 5, Al^{3+} exists as an octahedral hexahydrate, $\text{Al}(\text{H}_2\text{O})_6^{3+}$, usually abbreviated as Al^{3+} and referred to as free Al. As a solution becomes less acidic, $\text{Al}(\text{H}_2\text{O})_6^{3+}$ undergoes successive deprotonations to yield $\text{Al}(\text{OH})^{2+}$, $\text{Al}(\text{OH})_2^+$, and soluble $\text{Al}(\text{OH})_3$, and the number of water molecules with a decreases but is variable. At $\text{pH} > 6.2$ tetrahedral aluminate, $\text{Al}(\text{OH})_4^-$, is the primary soluble Al(III) species.²⁴ Al concentrations in the water will be related to pH and to Al hydroxide solubility equilibria. In addition to complexing with the hydroxide ion, the Al ion will also form complexes with inorganic ligands such as fluoride (F^-), sulphate (SO_4^{2-}) and silicate (HSiO_4^{3-}).^{25,26}

The pH has a pronounced effect on the corrosion of cement-mortar linings. An EC directive for drinking water states that an appropriate pH range is 6.5-8.5, but for extremely soft water it should be 9.5 (EC 1980).²³ In Germany,

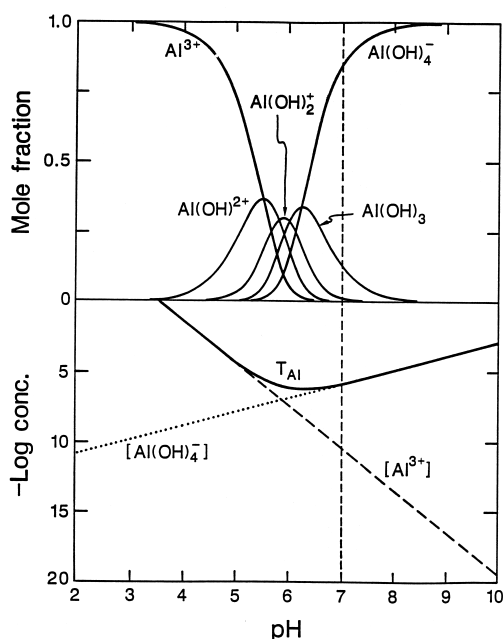


Figure 4. Aluminum hydrolysis²⁴

Al^{3+} hydrolysis. Upper half: mole fraction of soluble species as a function of pH. Lower half: negative logarithm of molar concentration in saturated solutions for the free ion, $[\text{Al}^{3+}]$, straight dashed line; and the sum over all species present, T_{Al} , curved solid line. The straight dotted line represents the concentration of the aluminate ion, $[\text{Al}(\text{OH})_4^-]$.

Source: Elsevier Science Publishing Co. Inc.

Denmark, and some parts of France, authorities require that drinking water be calcifying to protect against corrosion. The German national regulation states that if the calcium carbonate saturation index is < 0 , the pH must be adjusted to 7.8-8.0. This regulation is intended to protect cement materials and to avoid releasing metals into drinking water.²³ The West German Standard W342 (DVGW 1978) identifies the type of water for which cement-mortar lining is appropriate. Water should have a total carbonic acid concentration of $< 0.25 \text{ mol/m}^3$ (about 11 mg/L) as CO_2 and a calcium concentration of $> 0.02 \text{ mol/m}^3$ (about 1 mg/L) as Ca^{2+} . Calcium leaching increases as the concentration of dissolved carbon dioxide increases.²⁷

Polyphosphate

Polyphosphate may reduce tuberculation of iron and steel and provide a smooth pipe interior.^{16,17} On the other hand, at low dosages it may increase iron and steel corrosion, and it may attack and soften cement linings. Polyphosphates can form strong aqueous chelates or complexes with Ca^{2+} and Al^{3+} , which are major components of cement, as well as with other potentially protective ions such as Zn^{2+} , Fe^{3+} , or Mn^{2+} . These complexes may increase the solubility of the cement-mortar pipe under many conditions.

The chemical reactions that protect cement rely upon the sealing of the porosity, most notably by calcium carbonate deposited between the cement grains. If these voids are not sealed, then free lime will leach out, and pH increase will rise. At the very least, CaCO_3 deposits are not forming to protect the cement. Continuing leaching will ultimately deteriorate the cement surface in contact with water, and in time the lining will soften. Thus, chemicals that inhibit the formation of these CaCO_3 , either by sequestering the Ca (polyphosphates) or by retarding crystal growth (orthophosphates and polyphosphates), will be detrimental to some degree.²⁸

Al is widespread in drinking water

Al occurs naturally

Al is the most abundant metallic element in nature (8 percent of the earth's crust) and the third most abundant element of all elements. Despite the ubiquity of Al in the environment and its present in living organisms (in small amounts), no biological function for the element has been found, and it is considered a non-essential element.

Al in drinking water originates mainly from two sources. Al can be found naturally in ground water or surface water sources, and Al sulfate can be used in water treatment processes as a coagulant.^{3,7} In most cases, Al concentrations in drinking water are monitored only at the treatment plant and mainly when Al-based coagulants are used. It is assumed that the Al concentrations will not increase during distribution.^{11,12}

Few drinking water companies routinely monitor Al concentration at the tap. Our findings however, prove that leaching from cement coatings can substantially raise Al concentrations during distribution.

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Al can pose a health hazard

Gastrointestinal absorption

The potential harm from exposure to Al depends not only on the dosage but also the percentage of the dose that is absorbed and retained. The gut is a very effective protective barrier: only 0.04 – 1 percent of oral doses of Al appears to be retained.²⁹ Even so, very high concentrations of Al in drinking water may be harmful. On July 6, 1988, 20 metric tons of Al sulphate was deposited into a water tank that fed into the tap water supply of the Lowermoor area of North Cornwall, England. People (12,000 residents and 8,000 tourists) were exposed for three days. The water tasted unpleasant because of its acidity and Al content up to 620 mg/L; it also contained abnormally high amounts of copper, lead and zinc that dissolved from the water pipes. Consumers noted an unpleasant taste and reported acute symptoms such as mouth ulceration, joint pain, gastrointestinal disturbance, skin rashes, fatigue, nausea, vomiting, itching and sore eyes.^{30, 31} Nevertheless, the initial toxicological assessment concluded that the limited exposure would not cause acute or chronic disease.³⁰ Two years later, however, 400 of the 20,000 persons exposed to the contaminated water had illnesses that they attributed to the incident.³¹ Bone Al concentrations remained elevated at six to seven months, but not at 19 months after the accident in at least two individuals.^{31,32} Thus, substantial Al can be deposited in the bodies of normal individuals after a short exposure to highly contaminated water.

Alzheimer's disease

For many years a link between Al intake and Alzheimer's disease has been proposed. The evidence for this link is derived to a large extent from ecological studies that compared rates of the disease in populations that were supplied with water containing various amounts of Al. However, only a handful of major epidemiological studies have addressed this possible association. Because of methodological difficulties the results of these studies have been inconclusive.³

Regulations mainly consider aesthetics

Because few countries set standards for Al in drinking water, Al is not

routinely investigated. The main objections to high concentration of Al in drinking water are currently based on aesthetic aspects, and attention is focused on the concentrations at the treatment plant. No attention is given to the possibility that Al concentrations might rise during distribution.

World Health Organization

The World Health Organization (WHO) publishes no health-based guideline value for Al, but it has stated that further studies were needed to elucidate the role, if any, of Al in Alzheimer's disease.³³ A concentration of Al of 200 µg/L in drinking water provided a compromise between the practical use of Al salts in water treatment and discoloration of distributed water. A recent International Program on Chemical Safety Project document of WHO guidelines for chemical substances in drinking water quoted the 1997 Environmental Health Criteria monograph: "The positive relationship between Al in drinking water and Alzheimer's Disease, demonstrated in several studies, cannot be totally dismissed. However, strong reservations about inferring a casual relationship are warranted in view of failure of these studies to account for demonstrated confounding factors and for total Al intake from all sources. Taken together, the relative risks for Alzheimer's disease from exposure to Al in drinking water above 100 µg/L as determined in these studies are low. Such imprecise predictions may, however, be useful in making decisions about the need to control exposures in the general population".¹

United States

The US Environmental Protection Agency (USEPA) has established a secondary maximum contaminant level (SMCL) range of 50-200 mg for Al.³⁴ Utilities are encouraged to meet an Al concentration of 50 µg/L when possible, but differing water quality and treatment situations necessitate a flexible approach. On this basis USEPA established an SMCL range rather than a specific number. Each state primacy agency is responsible for setting the precise concentration for each system, on a case-by-case basis.

Europe

The European Union defines a maximum Al concentration of 30 µg/L in water used for hemodialysis and states that drinking water companies should

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warn health authorities if this concentration is exceeded. In turn, authorities responsible for water distribution shall inform all dialysis units, if possible in advance, of any important change in the treatment of water that might increase the Al concentration in the water distributed, and also of any accidental pollution of the water distributed. The possibility of replacing of Al salts in the treatment of water should be studied.¹⁰ The European Economic Community Standard has a guide concentration of 50 µg/L and a maximum admissible concentration of 200 µg/L Al in drinking water.²³

Table 3. Maximum recommended concentrations of inorganic substance in water* used to prepare the dialysate¹³

Contaminant	Concentration-mg/L
Calcium	2 (0.1 mEq/l)
Magnesium	4 (0.3 mEq/l)
Sodium	70 (3.0 mEq/l)
Potassium	8 (0.2 mEq/l)
Fluoride	0.2
Chlorine (free)	0.5
Chloramine	0.1
Nitrate (N)	2
Sulfate	100.0
Copper, Barium, Zinc	each 0.1
Aluminum	0.01
Arsenic, Lead, Silver	each 0.005
Cadmium	0.001
Chromium	0.014
Selenium	0.09
Mercury	0.0002

*To prepare dialysis fluid (dialysate), (purified) tap water is mixed by the dialysis machine with a bicarbonate concentrate and an "acid" component containing calcium, magnesium and other compounds

Excess Al in dialysate is harmful

Standards exist for hemodialysis water

The maximum recommended concentrations for inorganic substances include toxic substances described in the dialysis literature and non-toxic substances normally included in the dialysate (Table 3).

These concentrations are based on the lowest toxic concentrations reported in the dialysis literature with an appropriate margin of safety. These recommendations³⁴ have been adopted by AAMI.¹³

Dialysis encephalopathy continues to be a threat

Two types of dialysis encephalopathy can be distinguished. The classical type with encephalopathy and bone fractures is a slowly progressive disease that takes months to many years to develop; the Al concentration in the dialysate is typically < 600-1000 µg/L. Acute Al intoxication with seizures, myoclonic jerks, and a high mortality rate within weeks develops when the Al concentration in the water used for dialysis is much higher. In the past, most outbreaks of Al intoxication were caused by residual Al in drinking water treated with Al salts by water companies.⁴⁻⁶ Such incidents have been reported by centers with and without on-site water purification.

Al encephalopathy in a dialysis center with on-site water purification

Probably because most water companies try to meet the WHO guideline of 200 µg/L Al in finished water, outbreaks of acute encephalopathy because of extremely high Al concentrations (> 600-1000 µg/L) in the dialysate are rare. The only report (other than this one) of an outbreak of acute Al encephalopathy occurred in a dialysis center in Portugal using RO.³⁶⁻³⁸ Scarce rainfall in the south of Portugal in 1992 depleted water sources and markedly increased the concentration of suspended particles. Huge amounts of alum were used to reduce turbidity, an action not reported to municipal authorities. The severely contaminated water obstructed the RO membranes of a water purification installation in a dialysis center.^{36,37}

The efficiency of the RO membranes relies on two rejection mechanisms: a mechanical sieving filter with 200-D pores and an electrostatic repulsive mechanism. Ionized Al is rejected very efficiently (by 99 percent) by the RO membranes. However, most Al is present as a colloid, and colloids foul RO membranes. Fouling causes Al to accumulate at the membrane, masks the electrostatic repulsion mechanism, and leads to increased Al breakthrough. In these circumstances, the RO membrane may reject as little as 30-50 percent.³⁷ Consequently, RO membranes and cartridge filters had to be replaced frequently. During these interventions, which took place over a period of several days, insufficient treated water was sent directly to the dialysis machines and to patients. Eighteen of 71 (25.3 percent) patients died of severe encephalopathy. Patients' mean serum concentrations of Al were 505 + 255 µg/L (normal < 60 µg/L). Al concentrations up to 2,200 µg/L were measured in water used to prepare the dialysate.³⁷

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Al encephalopathy in centers without on-site water purification

In countries where water companies use Al components to treat water, many outbreaks of classical Al intoxication have been reported in dialysis centers using tap water to prepare the dialysate.^{4,6} The cumulative risk of death because of dialysis dementia in patients whose water supply had a mean Al concentration > 200 µg/L was much greater (27.9 percent deaths in the first 40 months) than the risk in patients whose mean water Al content was < 200 µg/L (2.1 percent deaths in the first 40 months). The relation between the mean Al concentration in the dialysate and time to death is given by this formula:⁴ the time in months from the first symptoms of dialysis dementia to death equals $65 - 0.081 \times (\text{mean Al concentration } [\mu\text{g/L}] \text{ in dialysis water})$. According to this equation the patients in the case reported here had been exposed to Al concentrations in the tap water of at least 800 µg/L.

Although most dialysis centers now have sophisticated water treatment devices, there might still be dialysis centers or home dialysis treatments without reverse osmosis, some do not (and home dialysis patients may not). Of 173 dialysis units in Germany in 1989 and 1990, pure tap water was still used without purification in 10 percent of university and 7 percent of community hospitals.⁹ In addition, dialysis centers commonly bypass membranes that do not function properly, and then they use only deionization for water treatment. Because deionization removes Al less efficiently, high Al concentrations in tap water may persist in the treated water. It can be argued that dialysis centers should be fully responsible for the water used for dialysis, but in practice they rely on a constantly acceptable drinking water supply combined with extended water purification.

Conclusions

Water passing through cement-mortar pipes can leach substantial amounts of barium, cadmium, chromium for the first 14-18 days of water stagnation and increase pH, alkalinity and calcium for up to four years.^{14,15} Another less well known effect, described in this article, can be the leaching Al into tap water to unacceptably high concentrations for more than 2 years. In the instance described, leaching may have been promoted by newly placed

pipes, high alumina cement-mortar (an Al content four times as high as usual), aggressive water, low-flow regimes, high water temperature, and perhaps the use of polyphosphate corrosion inhibitors.

To ensure public safety, a given cement type should be appropriate for a given water source. In addition, certification of cemented pipes used for drinking water distribution is warranted. Bleaching of compounds from the pipe not only poses possible health risks but may also reduce the durability of the pipe. In the worst case, such water used for dialysis without further purification can produce devastating outcomes.

Dialysis centers should always be prepared for unsuspected variations in tap water composition and always practice extended purification of tap water used for dialysis. Cooperation between drinking water companies and dialysis centers remains a prerequisite. Water utilities should notify dialysis centers when changes in water quality are expected. In particular, dialysis centers be warned if the Al concentration in drinking water may exceed 30 µg/L, as when water utilities first begin to use Al flocculants. The centers should also be informed if the concentration of Al exceeds the relatively high concentration of 200 µg/L. When cemented drinking water distribution pipes are put into service, tap water should be tested for Al, and dialysis centers should be warned if Al concentrations are > 30 µg/L.

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Michael Schock of the USEPA discussed the effects of various water treatment processes on the corrosion of distribution system materials and commented on a draft of this article.

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Cement-Mortar Pipes as a source of aluminum

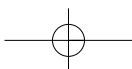
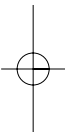
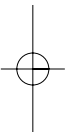
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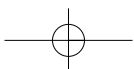
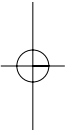
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Cement-Mortar Pipes as a source of aluminum





CHAPTER III

Acute aluminum encephalopathy in a dialysis center caused by a cement mortar water distribution pipe

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Abstract

Background. *In Curaçao, distilled seawater from the water plant was used without further purification for hemodialysis for several decades. A new distribution pipe supplying water to a dialysis center on the island was installed in May 1996. To protect it from corrosion, this pipe was lined on the inside with a cement mortar. Because of the aggressiveness of the distilled water, calcium and aluminum (Al) leached from the cement mortar into the water used to prepare dialysate. This caused a possible hard water syndrome and definite acute Al intoxication.*

Methods. *We reviewed clinical details and outcome at follow-up, and arranged laboratory and toxicological studies of serum and hemodialysis water.*

Results. *Of the 27 patients who had a similar exposure (~60 hours) to the contaminated dialysate, 10 died from acute Al encephalopathy, whereas 17 patients had no or only minor symptoms and survived. The nonsurvivors were older (64 ± 3 years vs. 52 ± 2 years, $P < 0.01$) and had a lower body weight (57.5 ± 5.9 kg vs. 86.5 ± 4.1 kg, $P < 0.01$) and lower serum albumin concentrations (33 ± 1 vs. 36 ± 1 g/L, $P < 0.01$). Anuria tended to be more common in the nonsurvivors (8 out of 10 vs. 8 out of 17, $P > 0.05$). Serum Al concentrations, available in seven nonsurvivors, were significantly higher than in the survivors (808 ± 127 vs. 255 ± 25 μ g/L, $P < 0.01$).*

Conclusions. *The water distribution pipe was lined with a cement mortar that was probably inappropriate for transporting drinking water. Water distribution facilities as well as the dialysis community should be aware of the possibility of Al leaching from cemented water distribution pipes. Similar Al loads appear to induce a more severe intoxication in malnourished, older patients with smaller Al distribution volumes and anuria.*

Key words: hemodialysis, calcium, aluminum intoxication, nephrotoxicity, hard water syndrome, dialysate preparation.

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Introduction

Hemodialysis patients are very susceptible to changes in the composition of water used to produce dialysate. Their blood is brought in close contact with hundreds of liters of dialysate every week, and contaminants present in the water may diffuse across the dialysis membrane and cause intoxications. Therefore, guidelines for the composition of water used to generate dialysate are very strict.^{1,2} To reach this standard, most dialysis centers use more or less elaborate water purification systems, consisting of combinations of water softeners, activated carbon filters, deionizers, and reverse osmosis (RO).³⁻⁶

We report the combination of an acute aluminum (Al) intoxication and a possible hard water syndrome in a small dialysis unit on the island of Curaçao that traditionally used untreated tap water for dialysate production. The intoxication was caused by a newly installed drinking water conduit pipe leading to the dialysis center. This ductile iron pipe had an inner cement mortar lining from which Al and calcium (Ca) leached into the water used to prepare the dialysate. Although the patients had a similar exposure time to the contaminated dialysate, 10 patients became critically ill and died, whereas 17 had no or relatively mild symptoms and survived. A subgroup analysis was performed in an attempt to explain these interindividual differences.

Methods

Dialysis center and water supply

Curaçao is a small island with 160,000 inhabitants. Approximately 90% of the population is of Afro-Caribbean origin. The prevalence of end-stage renal

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disease is 800 per million, which is among the highest in the world. Because of the large number of patients, a separate dialysis unit (Diatel Curaçao) with eight stations was opened in 1992 in addition to the hospital dialysis facility. On Curaçao, drinking water is produced by distillation of seawater. This expensive water treatment system produces very pure water (low ionic content, Al < 5 mg/L, Ca < 5 µg/L), which is of even better quality than produced by RO.⁶ Before distribution, however, Ca and fluoride are added to the water supply in a low concentration. On Curaçao, as well as on other small Antillean islands, the municipal water supply has been used for more than two decades for dialysis without further purification. Because the local hospital intended to begin a high-flux dialysis program, for which ultrapure water is needed, an RO unit was installed in this institution in 1993. Because Diatel did not have a water storage tank and occasionally had insufficient water pressure for dialysis, installation of a spare water tank together with a RO unit for sterilization of the water was scheduled for August 1996. To solve the water pressure problem, the Water Company replaced a distribution pipe to the area of the center over a length of 2200 m. Water supply through this pipe started on May 21, 1996, after flushing the entire pipe. This cast iron pipe had an inner cement mortar lining to protect it from corrosion. The hospital received water supply via a different conduit pipe than Diatel.

At the time of replacement of the new conduit pipe, 29 patients were dialyzed in the dialysis unit. Patients were dialyzed three times per week during 3.5 to 4.5 hours using hollow fiber kidneys (Fresenius®, F6 and F8) and Braun® or Fresenius® dialysis machines. Untreated tap water was used to manufacture dialysate after passage through three particulate filters (25, 10, and 5 mm, respectively). The intended Ca content of the dialysate was 1.75 mmol/L. Because none of the patients used Al-containing phosphate binders and the Al content of tap water on Curaçao has traditionally been low, no regular serum Al determinations were made.

Epidemiology

The epidemiology of the intoxication on Curaçao was retrospectively

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analyzed by systematically reviewing dialysis and hospital charts and relevant laboratory sheets and correspondence. The day on which the new water distribution pipe was put into use (May 21, 1996) was designated "day 0" of the intoxication; all subsequent events, shown in Figure 1, were related to this starting date.

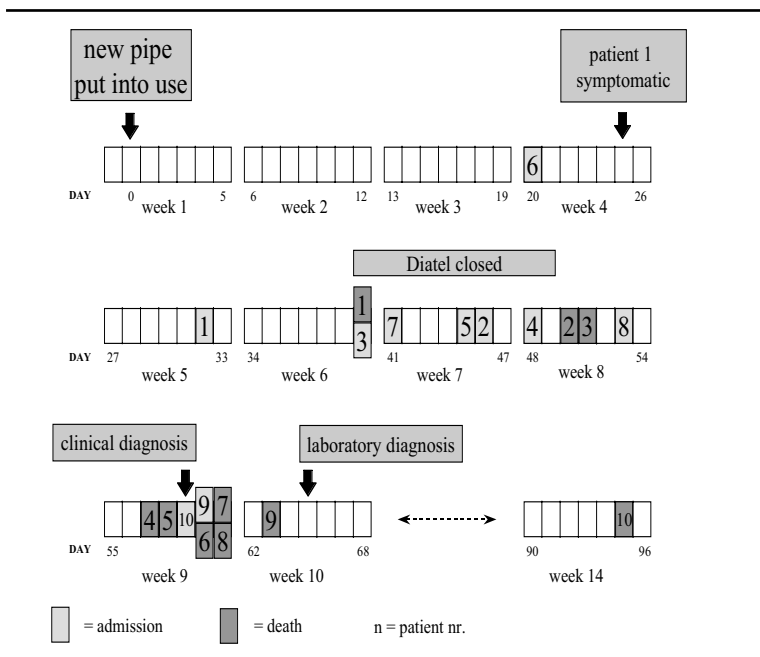


Fig 1. Emergence of the acute aluminum intoxication.

Day '0' (May 21, 1996) is the first day on which water was delivered to Diatel Curaçao through the new cemented water distribution pipe. On day '5' of week 9, the clinical diagnosis of 'acute aluminum intoxication' was made, on day '4' of week 10 this diagnosis was confirmed by a serum aluminum assay.

Symbols are:
 □ = admission;
 ■ = death;
 N = patient number.

Serum aluminum: Sampling and assay

In 6 of the 10 patients who died (Table 1, patients 3 through 5 and 7 through 9), serum samples taken during admission in the third week of July 1996 (week 9 of the intoxication) were stored in the freezer in regular glass tubes. Samples of three healthy control subjects were obtained in the same tubes and processed in the same way as these patient samples. In three patients, no serum samples had been stored (patients 1, 2, and 6). In one patient (patient 10), who also eventually died, a serum sample for Al determination was obtained while he was still alive. This was done using the appropriate tubes mentioned later in this article. This was also the case for all the samples of the survivors obtained in the fourth week of July 1996

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(week 10 of the intoxication). In these patients, serum samples were collected using Al-free polypropylene and polystyrene tubes prerinsed with 1 N HNO₃ to avoid Al contamination. All samples were sent by express mail to the Toxicology Laboratory (Leiden University Medical Center, Leiden, The Netherlands). The Al levels were analyzed with an atomic absorption spectrometer (Perkin Elmer 3030; Perkin Elmer, Norwalk, CT, USA) with a transversal Zeeman background correction system, using a graphite furnace (HGA 600) and pyrolytically coated graphite tubes. A calibration range was used between 0 and 200 µg/L (within-day precision was 13.8 and 6.1%, between-day precision was 22 and 8% for standard solutions 20 and 100 µg/L, respectively). For levels >200 µg/L, the calibration range was adapted between 200 and 1000 µg/L.⁷

Other analytical methods

Intact parathyroid hormone (PTH) concentrations were measured by radio immunoassay (Elisa-PTH; CisBio Int., Gif-sur-Yvette, France). Concentrations of Ca, alkaline phosphatase, ferritin, albumin, and mean cellular erythrocyte volume (MCV) were measured by standard laboratory methods.

Subgroup analysis

Two surviving patients with low serum Al levels (< 60 µg/L) caused by a very short duration of exposure to the contaminated dialysate were excluded from this analysis. The remaining 27 patients were divided in two groups: survivors (N = 17) and nonsurvivors (N = 10). Both groups were compared with respect to the following characteristics: age, sex, body weight, presence of diabetes mellitus, diuresis, duration of exposure to contaminated dialysate, PTH status, severity of hypercalcemia, and initial serum Al concentration.

Statistical analysis

Data are expressed as mean ± SEM. The statistical significance of differences between mean values in the two groups was tested by Student's t-test for unpaired samples or the Mann-Whitney ranks sum test when appropriate.

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Fisher's exact test was used to test the difference of two proportions. Differences were considered to be of statistical significance at a P value of < 0.05 .

Results

Epidemiology

The first day with regular dialysis sessions using water delivered through the new distribution pipe (May 21, 1996, day 0) was uneventful, but on the second and third days, several dialysis machines had transient conductivity alarms, possibly because of small air bubbles in the water mains. Extra flushing of the tap water solved this problem. The conductivity of the dialysate, measured by an external conductivity meter, was normal. The first patient (patient 6) was admitted to the hospital for a bleeding duodenal ulcer on June 10, 1996 (day 20; Fig. 1). On admission, she was slightly disoriented and developed seizures three weeks later (day 43) from which she died six weeks after admission (day 60). She may have been the first patient to become symptomatic because of Al intoxication, but it is also possible that she died of uremic encephalopathy with convulsions because dialysis was stopped two weeks prior to her death, and she had the shortest exposure time to the contaminated dialysate of all patients dying during the intoxication. The first patient (patient 1) without apparent underlying disease became symptomatic (myoclonus of jaw musculature) on June 15, 1996 (day 25). She was admitted to the hospital on June 22, 1996, because of hypercalcemia, nausea, vomiting, and confusion. She developed unexplained seizures and died on June 30, 1996 (day 40). On June 19, 1996 (day 29), seven patients had minor complaints of nausea and vomiting. Postdialysis hypercalcemia was observed in 25 of the 27 patients. The diagnosis "hard water syndrome" was made, and the use of Ca carbonate and vitamin D preparations was stopped. There was initial amelioration of the symptoms, but as the improvement was incomplete, the dialysis unit was closed on June 30, 1996 (day 40). All patients were referred to the hospital for dialysis where the symptoms of nausea, vomiting, as well as the hypercalcemia disappeared after a single dialysis with low Ca dialysate (1.50 mmol/L). From week 7 onward, transfusion-dependent microcytic anemia became evident (lowest MCV

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value: 70 ± 2 fL, N = 16). After installation of a RO system, including a deionizer, dialysis was resumed at the Diatel unit on July 10, 1996.

Unexpectedly, another eight patients (patients 2 through 5 and 7 through 10) had to be admitted to the hospital because of severe neurological symptoms (disorientation, myoclonus, convulsions and coma, N = 7) or unexplained sepsis (N = 2) with a delay of days to three weeks after the last dialysis with contaminated water (Fig. 1). Attempts to treat myoclonic jerks or seizures with intravenous diphantoin or diazepam were unsuccessful. The clinical diagnosis of acute Al intoxication was made on July 19, 1996 (day 59). Some days prior to this, the local toxicology laboratory reported a very high serum Al level in one patient using a semiquantitative method. Because the blood sample had not been processed correctly, the validity of this report was doubted initially, and blood samples were sent to the toxicology laboratory. When the diagnosis of "acute Al intoxication" was established by the results from this laboratory, on July 25, 1996 (day 65), nine patients had died (Fig. 1). A 10th patient, who was comatose, was transferred to a hospital in Florida (Florida Hospital, Orlando, FL, USA). Daily high-flux dialysis treatment combined with desferrioxamine administration was unsuccessful, and he died on August 24, 1996 (day 95). Seventeen patients who had elevated serum Al concentrations but were clinically asymptomatic were treated with intravenous desferrioxamine and high-flux dialysis according to the protocol suggested by Barata et al.⁸ For logistical reasons, especially the inability to provide high-flux dialysis to all patients on short notice, these patients were transferred to six different hospitals in the Netherlands. Two patients, who in retrospect had been exposed to contaminated dialysate only briefly, did not need further treatment.

Calcium and aluminum content of tap water

Water supplied through the new pipe was first used for dialysis on May 21, 1996. On June 20, 1996 (day 30), the Ca-carbonate concentration of tap water delivered to the dialysis unit was 43 mg/L (17.2 mg/L or 0.45 mmol/L as Ca²⁺), which is above the standard of 2 mg/L advised by the Association for the Advancement of Medical Instrumentation.² In the past,

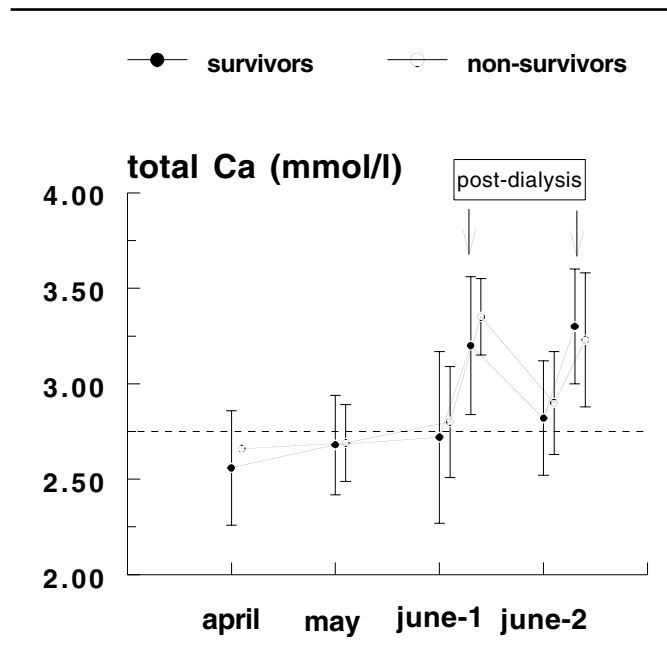
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the Ca-carbonate concentration had been 15 to 20 mg/L (6.0 to 8.0 mg/L or 0.16 to 0.21 mmol/L Ca²⁺). A sample of tap water obtained on July 3, 1996 (day 43), after the closing of Diatel was sent for analysis to Spectra Laboratories (Fremont, CA, USA). The results became available in August 1996. The Al content was excessively high (650 µg/L, normal below 10 µg/L), and the Ca²⁺ concentration was moderately elevated (18.1 mg/L, 0.47 mmol/L).

Serum calcium concentrations

In the two months prior to the intoxication, the mean predialysis total Ca concentration was 2.59 ± 0.05 mmol/L (April 1996) and 2.68 ± 0.05 mmol/L (May 1996). On two occasions in June 1996, when a hard water syndrome was suspected, Ca concentrations were determined before and after dialysis. The mean predialysis and postdialysis Ca concentrations were 2.75 ± 0.06 and 3.25 ± 0.06 mmol/L, respectively. The interdialytic drop was to 2.84 ± 0.05 mmol/L, with an increase to 3.27 ± 0.06 mmol/L after the next dialysis. The mean serum Ca concentrations in the survivors and nonsurvivors did not differ (Fig. 2).

Fig 2. Total serum Ca concentration in survivors (●) and nonsurvivors (○) of the Al intoxication. Data are presented as mean ± SEM. Post-dialysis calcium concentrations were not available at the time of routine sampling in April and May 1996. In June, samples were obtained both before and after two subsequent dialysis sessions taking place in week 5 & 6. The dotted line indicates the upper level of the normal range for our laboratory.



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Table 1. Characteristics of non-survivors and survivors

Patient number	Age years	Serum [Al] ^b µg/L	sex	Weight kg	Exposure hours	Diuresis mL/day	PTH pg/mL	Albumin g/L
Non-survivors (N = 10)								
1	61	-	f	66	52	0	28	35
2	79	-	f	33	51	0	105	32
3	54	1189	m	85.5	68	150	52	34
4	64	725	f	52.5	52	0	22	35
5 ^a	51	894	f	40	68	0	72	30
6	69	-	f	39.5	39	2000	-	28
7 ^a	62	1275	m	62	60	0	8	34
8 ^a	63	359	f	47	68	0	325	36
9 ^a	74	517	f	86	64	0	32	32
10	65	696	m	64	68	0	480	35
Mean	64	808	-	57.5	59	-	125	33
SEM	3	127	-	5.9	3	-	55	1
Survivors (N = 17)								
11	64	490	m	57	68	0	710	40
12	57	395	m	65	59.5	0	80	39
13	50	321	f	87	68	0	21	34
14	44	319	m	97	62	0	630	39
15	49	318	m	57	66	200	50	36
16	23	315	f	104	68	0	97	39
17	66	303	f	78.5	64	60	280	34
18	57	301	f	90	68	350	170	37
19	50	248	f	57.5	64	1000	65	36
20	56	207	f	103	68	0	82	36
21	50	205	m	104	60	2	700	37
22	57	187	f	101	64	50	1200	32
23	57	182	f	95	62.5	1100	100	30
24	41	166	m	91.5	68	0	3	-
25	60	132	m	97.5	67	1200	270	39
26	41	116	m	93.2	60	200	680	38
27	56	113	f	91.5	67	1400	99	33
Mean	52 ^c	255 ^c	-	86.5 ^c	65	-	308	36 ^d
SEM	2	25	-	4.1	1	-	84	1

^a patients in whom post mortem examination was performed^b [Al]: serum aluminum concentration^c $P < 0.01$ ^d $P < 0.05$, survivors vs. non-survivors***Serum aluminum concentrations***

The serum Al concentrations obtained in seven of the nonsurvivors were invariably very high (mean 808 ± 127 µg/L, range 359 to 1189 µg/L; Table 1). Seventeen of the surviving patients had clearly elevated serum Al concentrations (mean 255 ± 25 µg/L, range 113 to 490 µg/L). The average value obtained approximately one week later, when the surviving patients had been transferred to the Netherlands, was virtually the same as before the initiation of desferrioxamine treatment (248 ± 20 µg/L, $P > 0.05$). One patient, who had been exposed only briefly (5 hours) to the contaminated dialysate, had a serum Al concentration of 50 µg/L (normal < 60 µg/L). The serum Al concentration of another patient was 16 µg/L

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several weeks later. She also had a short exposure time to the contaminated dialysate because she went to Holland on June 3, 1996, shortly after installation and flushing of the new water pipe. The serum Al concentrations in three healthy controls were all below 10 µg/L (**Methods** section).

Subgroup analysis

The patients who survived the dialysis with contaminated dialysate were significantly younger than those who died (Table 1). The average body weight in the nonsurvivors was almost 30 kg below that of the survivors. Serum albumin was slightly but significantly lower in the nonsurvivors. The proportion of patients suffering from diabetes mellitus tended to be greater in the nonsurvivors than in the survivors (60 vs. 16%, $P = 0.11$), as was the proportion being anuric (80 vs. 47%, $P = 0.12$). It is noteworthy that the duration of exposure to the contaminated dialysate was even somewhat longer in the group of survivors. This was because two of the nonsurvivors (patients 1 and 6) were admitted to the hospital relatively early and consequently had a shorter exposure time. Survivors tended to have higher serum PTH concentrations (survivors, 308 ± 84 pg/mL; nonsurvivors, 125 ± 55 pg/mL, normal, 11 to 62 pg/mL).

Discussion

We report a unique set of circumstances leading to a probable hard water syndrome followed by an epidemic of acute Al encephalopathy in a dialysis unit (Diatel) on the island of Curaçao. Traditionally, municipal water had been used without extended purification for the production of dialysate because the distributed distilled seawater was very pure and its ionic content low. Because of complaints of low water pressure in the dialysis center, the water distribution company replaced an old iron water distribution pipe by a new cement-coated pipe. Three of the predominant crystalline phases of the cement matrix are tricalcium silicate (nominally Ca_3SiO_5), dicalcium silicate (nominally Ca_2SiO_4), and tricalcium aluminate ($\text{Ca}_3\text{Al}_2\text{O}_6$). Possible dissolution reactions may be represented by $\text{Ca}_3\text{SiO}_5 + 5\text{H}_2\text{O} \rightleftharpoons 3\text{Ca}^{2+} + \text{H}_4\text{SiO}_4 + 6\text{OH}^-$, $\text{Ca}_2\text{SiO}_4 + 4\text{H}_2\text{O} \rightleftharpoons 2\text{Ca}^{2+} + \text{H}_4\text{SiO}_4 + 4\text{OH}^-$, and $\text{Ca}_3\text{Al}_2\text{O}_6 + 6\text{H}_2\text{O} \rightleftharpoons 3\text{Ca}^{2+} + 2\text{Al}^{3+} + 12\text{OH}^-$. The purity of the water with a relatively low Ca concentration enhanced the leaching

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of Ca and Al from the cement coating into the water used to prepare dialysate.

Approximately four weeks after the new water distribution pipe had been put into use, a tentative diagnosis of a "hard water syndrome" was made. This syndrome is characterized by dialysis-related nausea and vomiting, weakness, and lethargy and is caused by hypercalcemia caused by elevated Ca concentrations in the dialysate.¹⁰ Leaching of Ca from the new pipe was suspected, and the patients were transferred to a hospital dialysis unit using water softening and RO for water preparation and a low-Ca dialysate. This effectively ended exposure to the contaminated dialysate; the symptomatic patients improved, and the hypercalcemia disappeared. In retrospect, the Al intoxication may have contributed to the development of hypercalcemia because Al can decrease the incorporation of Ca into the bone by inhibiting bone formation.¹¹ Additional Ca from the dialysis fluid and therapy with vitamin D and Ca added to the severity of the hypercalcemia.

Unexpectedly, with a delay of days to weeks after ending exposure to the dialysate supposed to be contaminated only with Ca, 10 patients developed severe and progressive neurological symptoms and all died. Because all serum Ca levels already normalized, it became obvious that another contaminant had to be responsible for the delayed neurotoxicity. A lag time causing "acute" Al neurotoxicity has been observed in animal studies¹² as it seems likely that several steps are necessary in the process leading to Al encephalopathy and that each step causes a delay in time before symptoms can occur.¹³ The actual diagnosis of Al intoxication was later confirmed by very toxic serum Al concentrations and elevated brain Al levels that were four to eight times higher than normal. Acute Al intoxication is characterized by a neurological syndrome, including seizures, myoclonus, obtundation, and coma. Bone disease and dialysis dementia, features of classic chronic Al toxicity, are usually absent,¹⁴ but microcytic anemia can occur.⁸ Sporadic cases have been reported after intake of Al-containing phosphate binders alone¹⁵ and in combination with citrate-containing drugs,¹⁶ during treatment with desferrioxamine for chronic Al overload¹⁷ and following intravesical Al infusion for hemorrhagic cystitis in renal patients.¹⁸ Epidemic forms of acute Al intoxication have been described following the use of water for dialysis, which was severely contaminated with Al.^{8, 19}

In our center, the contamination of water used to prepare dialysate was caused by installation of a new cast iron water distribution pipe supplying water

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to the dialysis facility. Water distribution pipes are commonly coated on the inside with cement mortar to protect them from corrosion by the electrochemical action of water. These coatings can adversely affect the water quality because its constituents may leach from the cement matrix into the water increasing both its Ca content and pH.²⁰ Unfortunately, it was unknown to the local water distribution company and to the water industry in general that not only Ca, but also Al can leach from these cement mortars and cause excessively high water Al concentrations. Conditions that enhance Al leaching include low water alkalinity and hardness, relatively high water temperatures, and low or intermittent water flow. Unfortunately, all of these factors coincided in the situation, especially because Diatel was located at the dead end of a water main, resulting in the highest Al concentrations on the island. The pipe was partially bypassed by the water company (from 2200 to 1000 meters), but the Al leaching continued for at least two years.²¹ Kidney patients with chronic renal failure—not on dialysis—living in the small distribution area were told not to consume the water because of the risk for developing Al intoxication. Elsewhere on Curaçao, where the same pipe was used, higher water flow conditions prevented Al concentrations to increase to very high levels.

In a number of European countries (for example, Germany, Denmark, and some parts of France), the authorities require that drinking water should be calcifying because of the pronounced effect on the corrosion of cement-mortar linings. This regulation is intended to protect cement materials and to reduce water quality deterioration, especially with regard to metal release.²² If the water on Curaçao had been pretreated by the water company according to these regulations, Al leaching from the cement coating would probably have been less. Nevertheless, a crucial factor in the tragedy seems to be the deviant cement composition of the water distribution pipe with an Al content that was four times higher than usual,²¹ because Al leaching was not shown in similar circumstances and the use of different cement pipes. After the tragedy in Diatel, a study was performed in Holland to see whether the same problem existed there as well. Samples were taken on 20 locations with (standard) cemented pipes and asbestos cement pipes. Locations with "worst case scenarios" favoring the leaching of Al were chosen, defined as low flow, soft water, new pipes, and small diameter. The Al levels in the tap water in Holland never reached levels above 11 µg/L at any location,²³ while the Al level in our case was 690 µg/L two

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months after the installation of the pipe. Cement linings with a high Al content are therefore probably inappropriate to distribute drinking water.

Although all patients were exposed to the contaminated dialysate for a similar period of time, 17 patients survived the Al intoxication with only minor symptoms, whereas 10 patients died from severe neurotoxicity. The nonsurvivors were the older population with a low body weight and lower serum albumin concentrations and a greater proportion of them had diabetes mellitus. This suggests that the general state of health was an important determinant of the chance of survival. In a review of 15 studies in animals and humans, an extremely narrow margin of safety between normal and toxic levels of Al in brain tissue seems to exist, with greater susceptibility in the older population.²⁴ More importantly, however, the serum Al concentrations were considerably higher in the nonsurvivors. This suggests that a similar Al load also caused higher Al concentrations at the tissue level in the low body weight patients, possibly because they had smaller distribution volumes. In addition, anuria was more common in the nonsurvivors, which is relevant because the main natural route of Al removal from the body is via the kidneys, and residual renal function protects against Al toxicity.²⁵

Although this is the first report of intoxication in dialysis patients caused by a water distribution pipe, it is not the first account of an intoxication linked to the water industry. In a recent and equally treacherous acute Al intoxication reported from Portugal, large amounts of Al sulfate had been used as a flocculating agent in the process of manufacturing drinking water. This was necessary because the concentration of suspended particles was excessive due to a long period of drought in the area. This severely contaminated water caused RO membrane fouling over several months of time, which might have decreased the ability to reject Al to as low as 30 to 50%, but in addition, the RO membranes were also temporarily bypassed several times for filter exchange and RO maintenance.²⁶ This resulted in an acute Al intoxication, causing the death of 25 of 71 dialysis patients.^{8,26,27} Both the intoxications on Curaçao and in Portugal underscore that dialysis centers should establish a good working relationship with the local drinking water production and distribution companies, as this may increase their awareness of the specific needs and problems of the dialysis community.

The catastrophe on Curaçao clearly demonstrates that physicians in

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charge of a dialysis unit cannot rely on the quality of the water produced by the water plant, no matter how excellent the specifications may be in terms of appropriateness for hemodialysis when water leaves the plant. The hard lesson was learned that the composition of the water could change unexpectedly and erratically in the water distribution system, making it absolutely unsuitable for preparation of dialysate upon its arrival in the dialysis unit without further water treatment. Therefore, dialysis centers should use extended purification procedures, including RO, at all times. In this respect, it is of note that dialysis without water preparation by RO was common practice until recently.²⁸ Nephrologists, who are responsible for the dialysate quality, often lack formal training in water safety and purification procedures. They therefore tend to rely unconditionally on the municipal water supply and the water purification system in their unit. That this is not always justified has been shown by several recent serious accidents with Al,^{8,19} chloramine,²⁹ fluoride,³⁰ copper,³¹ hydrogen peroxide,³² sodium azide,³³ and microcystins.³⁴

In summary, our sad experience shows that the use of extended water purification systems is imperative in hemodialysis. Furthermore, our experience and that of others indicate that continuous monitoring of the water before and after water treatment seems necessary as well and that dialysis centers should establish a good working relationship with local water production and distribution authorities. Finally, water purification procedures and water quality control perhaps deserve more attention in the training of nephrologists.

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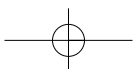
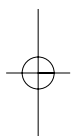
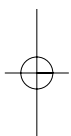
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CHAPTER IV

Subacute fatal aluminum poisoning in dialyzed patients: post-mortem toxicological findings

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Abstract

The population of Curaçao, Netherlands Antilles (133,000) shows a very high prevalence of end-stage renal disease (approx. 1 per 1000). These patients are often treated chronically with haemodialysis. As the drinking water on the island is prepared by distillation of sea water, the haemodialysis fluid used to be prepared with tap water without further treatment.

In 1996, 7 of the 27 patients of one of the dialysis centers on the island presented with nausea, vomiting, and hypercalcaemia in a short time span, which was initially diagnosed as 'hard water syndrome'. In spite of treatment with low-calcium dialysate, microcytic anaemia and neurological symptoms developed. Ten patients died of convulsions, sepsis, and coma. As aluminum (Al) intoxication was suspected, Al in serum (ALS) was measured. Ante mortem ALS was 808 µg/L (n=7; range 359-1189); in the survivors ALS was 255 µg/L (n=17; range 113-490). Normal ALS is < 10 µg/L, and < 50 µg/L in asymptomatic dialysed patients.

The court requested post-mortem toxicological analysis of four patients. Al concentrations in liver, bone, and cerebral cortex were significantly increased as compared with background levels. Al intoxication was, therefore, considered to be the most likely cause of death in these patients.

Investigations of the tap water supply revealed that a few weeks before the onset of the symptoms, a water conduit pipe to the dialysis unit had been replaced, which was lined with Al-rich cement mortar. These ions leached into the distilled water and caused both Ca- and Al-intoxication through uptake from the dialysate into the patients' circulation. The symptoms of the latter were initially not recognized as they were masked by the symptoms of hypercalcaemia.

Key words: Aluminum; Poisoning; Subacute; Haemodialysis; Post-mortem; Metals; Toxicity
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Introduction

The prevalence of end-stage renal disease amongst the population of the Caribbean island Curaçao is one of the highest in the world: approximately 1 per 1,000. This is due to the fact that 90% of the population totaling 133,000 is of Afro-Caribbean origin with a very high incidence of diabetes and hypertension, both being a possible cause of renal insufficiency. About 140 patients with end-stage renal disease are chronically treated in the two haemodialysis centers on the island. As other sources of drinking water are extremely scarce, tap water is produced by distillation of sea water. For consumption, the distilled water is supplemented with small amounts of calcium and fluoride. Water quality used to be sufficient for the preparation of dialysate without further treatment. No incidents due to water contamination have been reported in the course of two decades.

At the onset of the incident reported here, 27 patients were treated with chronic intermittent haemodialysis in the Diatel Curaçao unit. From 10th June 1996 onwards, some patients started to present with nausea, vomiting, and hypercalcemia. These symptoms are consistent with the 'hard water syndrome' which may occur in patients treated with a high-calcium dialysate. This was confirmed by the observation of postdialysis hypercalcaemia (up to 3.50 mmol/L), and by a very high calcium concentration (17.2 mg/L) in tap water, considerably exceeding the generally accepted maximum of 2 mg/L for dialysate. The source of this high calcium concentration was a new cast-iron water distribution pipe, which was internally protected against corrosion by application of a cement mortar lining from which calcium leached into the tap water.¹ As the laboratory observations confirmed the clinical diagnosis of calcium intoxication, other possible sources of poisoning were not considered. A more detailed description of the clinical symptomatology has been published elsewhere.²

In spite of discontinuation of oral calcium carbonate and vitamin D

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preparations, the symptoms did not cease in some patients, which led to the closing of the unit and the referral of the patients to other centers. When aluminum intoxication was suspected and confirmed in serum samples sent to the LUMC Toxicology Laboratory in The Netherlands, 6 weeks after the first signs of 'hard water disease', 10 patients had died from seizures, sepsis, and coma. The 17 survivors, all showing increased serum aluminum levels, were transferred to haemodialysis centers in The Netherlands, and treated with desferrioxamine infusion and high-flux dialysis according to Barata et al.³ After installation of reversed-osmosis equipment for water treatment, the dialysis unit in Curaçao was re-opened, and the 17 survivors were repatriated.

The Court of the Netherlands Antilles then started a judicial investigation into this case as to whether the medical staff of Diatel could be held responsible for the death of these 10 patients, and requested the LUMC Toxicology Laboratory to perform the post-mortem toxicological investigation. The results of this forensic study are presented here.

Material and Methods

From 7 of the 10 patients who died, serum samples had been collected during admission shortly (approx. 1 week) before death. Blood for AIS assay was also sampled from the 17 survivors, and sent by express mail to the LUMC Toxicology Laboratory in The Netherlands. All blood and serum were collected and stored in Al-free polypropylene and polystyrene tubes prerinsed with 1 M HNO₃ to avoid contamination.

Tissue samples (liver, bone, and cerebral cortex) were obtained at autopsy in Curaçao of four patients, under strict Al-free conditions. The instruments were thoroughly washed and rinsed with Al-free distilled water, and the (Al-containing) talcum was washed from the surgical gloves used when taking the samples. The samples were kept frozen at -20°C during storage and mailing to The Netherlands.

Al in serum was analyzed with electrothermal atomic absorption spectrometry (EAAS; Perkin-Elmer 3030; Perkin-Elmer, Nordwalk, CT, USA) with a transversal Zeeman background correction system, using a graphite furnace (HGA 600) and pyrolytically coated graphite tubes. A calibration range was

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used between 0 and 200 µg/L; for standard solutions 20 and 100 µg/L the within-day precision was 13.8 and 6.1 %, and the between-day precision 22 and 8%. For levels > 200 µg/L, the calibration range was adapted between 200 and 1000 µg/L.⁴

Al in tissues was analyzed likewise, with a procedure developed earlier in this laboratory.⁵ Tissue samples were digested in 1 mL of a mixture of 65% HNO₃ + 96% H₂SO₄ (4+1, v/v) and gradual heating to 105 °C before EAAS analysis.

Calcium and aluminum in tap water were determined by Spectra Laboratories (Fremont, CA, USA).

Results

The serum of 7 deceased patients, collected before death, contained a very high Al concentration: 808 ± 127 µg/L (mean ± S.E.M., n = 7, range 359 - 1275). In the survivors, this value was 255 ± 25 µg/L (mean ± S.E.M., n = 17, range 113 - 490), significantly lower than that of the non-survivors (P < 0.01).

The results of the post-mortem analysis are presented in Table I, in which the tissue levels of Al are compared with the concentrations in serum obtained when the patients were still alive. In these serum samples, other ions were measured with standard clinical chemical methods. These ions were: Fe,

Table 1. Post-mortem analysis of liver, bone and brain aluminum in four patients

Patient	Serum (µg/L)	Liver (µg/g)	Bone (µg/g) ^a	Cerebral cortex (µg/g) ^b
A	517	43.0	21.9	1.09
B	696	32.7	88.7	1.40
C	1275	51.7	7.54	1.12
D	894	4.70	77.0	1.78
Reference values ^{5,6,8}	< 10	< 2	< 2	0.14 - 0.22

^a Collected from a femoral shaft

^b Collected from the gyrus temporalis inferior and superior

Mg, Ca, V, Si, Pb, and Hg, none of them being outside the normal range. It should be noted that at the time of blood collection for Al analysis the hypercalcaemia had been normalized.

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From Table 1 it is clear that the Al concentrations in liver, bone and cerebral cortex are extremely high in comparison to the reference values which were taken from D'Haese et al.⁶ and Van Ginkel et al.⁵

Analysis of tap water -sampled at the time of closure of the unit-showed a calcium concentration of 18.1 mg/L and an aluminum concentration of 650 µg/L. These concentrations, which are far too high for dialysate, were shown to be caused by release from the cement mortar with which a newly installed water piping system was lined.¹

Discussion

The case history presented here confirms that exposure of dialysed patients to dialysate contaminated with Al may lead to systemic intoxication, as was reported as early as 1976.⁷ The sources of Al were either extracorporeal exposure to contaminated water, or high-dose oral aluminum hydroxide prescribed to bind dietary phosphate. Most cases of Al intoxication in dialysed patients that have been reported, however, are of the chronic type, showing a gradually developing cerebral impairment, starting with speech disturbances, motor apraxia, and twitching, slowly deteriorating into myoclonic jerks, seizures, and global dementia.⁸ Together with normochromic mycrocytic anaemia and Vitamin D-resistant osteomalacia, these symptoms of chronic Al intoxication in long-term dialysed patients are generally well-known to nephrologists involved in chronic intermittent haemodialysis. In this case, sudden exposure to an extremely high Al concentration in the dialysate took place, so that the normal onset of 'dialysis encephalopathy' was bypassed. In addition, the symptoms that were observed approximately 3 weeks after installation of the new water supply system were consistent with another well-known side effect of haemodialysis, the 'hard water syndrome'. Hypercalcaemia was confirmed in all patients, and an extremely high calcium concentration in the tap water (17.2 mg/L, preferred value < 2 mg/L) provided an explanation for this diagnosis. These observations masked the underlying Al intoxication, which was suspected only after the hypercalcaemia was normalized without clinical improvement of the patients. Then, serum analysis showed very high ALS values in all patients. Analysis of the tap water at that time revealed an Al content of 650 µg/L, which should be below 10 µg/L.

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Comparison of the serum levels of aluminum (ALS) from seven of the 10 deceased patients, collected ante mortem, with the ALS in the group survivors (n=17) indicates that the ALS level -which is generally accepted as an indicator for the total body burden of Al³⁺- may have a predictive value for the outcome of Al poisoning.

Conclusion

A sudden rise of aluminum (Al) concentrations in dialysis fluid may lead to considerable systemic uptake of Al by patients dialyzed with this fluid. The dramatic neurological symptoms that result from this heavy exposure differ from the slowly developing, better known 'dialysis encephalopathy'. The subacute Al intoxication presented here initially resembled 'hard water syndrome' in dialysis patients. This observation, supported by both hypercalcaemia and a high calcium concentration in tap water, masked the underlying Al intoxication. Only when serum Ca was normalized and neurological symptoms (convulsions, myoclonias) were observed, Al intoxication was suspected.

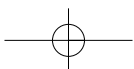
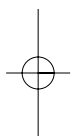
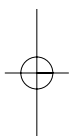
In the report to the court it was explained that the death of the four patients of whom autopsy was performed was most probably the result of serious subacute aluminum poisoning, due to contamination of the water with which the dialysate was produced.

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Subacute fatal aluminum poisoning in dialyzed patients: post-mortem toxicological findings.



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Acute Aluminum Intoxication

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Abstract

Despite the abundance of Aluminum (Al) in nature, it has no known biological function in humans. On the contrary, wide ranges of toxic effects of Al to hundreds of cellular processes both in man and animals have been demonstrated in plants and aquatic animals in nature, experimental animals by several routes of exposure, and under different clinical conditions in humans. Manifestations of Al toxicity that are encountered vary substantially, with major differences arising due to different sources and varying intensity of the Al burden in combination with differences in individual susceptibility. Al neurotoxicity occurs only under extreme conditions and the conditions are the worst in acute Al encephalopathy where myoclonic jerks, convulsions and a high mortality rate are the major manifestations. Especially hemodialysis patients are at risk when the dialysate is contaminated with high Al concentration, but also the use of Al in bladder irrigation and the use of Al containing cement in otosurgery have been related to acute Al encephalopathy. Therefore, every effort should be undertaken to limit the use of compounds containing Al in medicine.

Key words: Aluminum, Intoxication Acute, Hemodialysis

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1. Introduction

Aluminum (Al) is present in small amounts in mammalian tissues but it has no recognized physiological role. On the contrary, wide ranges of toxic effects of Al have been demonstrated in plants and aquatic animals, in experimental animals by several routes of exposure, and under different clinical conditions in humans. Its neurotoxic effect on living organisms is beyond any doubt and Al has been shown to interfere with a variety of cellular metabolic processes in the nervous as well as several other systems. About eight percent of the earth's crust consists of Al (w/w) and despite its abundance its toxicity remained disputed until the discovery of Al - related diseases in renal patients. This is due to the fact that the bioavailability of Al is very low after oral ingestion and even lower after inhalation.¹⁻⁴ These protection barriers are bypassed during hemodialysis and during this treatment, trace elements can cross the artificial kidney and enter the blood of the patients. Due to the fact that patients are exposed to some 400 liters of water on a weekly basis, patients can be exposed parenterally to huge amounts of the toxic element and evidence of Al as a neurotoxic trace metal was established in the early 1970s after many years of uncertainty. Al neurotoxicity was initially described in 1886⁵ and rediscovered in 1921⁷ and 1937.⁶ Animal studies showed that local administration or application of Al to the brain caused animals to develop a seizure disorder.⁶ In 1921 a possible single case of industrial poisoning with Al was reported⁷ but it lasted until 1962 before the second case with industrial-related Al encephalopathy was described. In this case speech difficulties, seizures and pulmonary fibrosis was associated with the inhalation of Al-containing dust in an Al plant⁸ and in 1975 a similar case of neurotoxicity was described in association with increased brain Al concentration.⁹ These were the first reports to suggest that Al neurotoxicity could occur in humans. In 1972 a new distinct neurological disease, dialysis encephalopathy, dialysis dementia, or chronic Al encephalopathy with speech disturbances, personality changes, seizures and myoclonus was described in dialysis patients¹⁰ and numerous similar reports followed thereafter.¹¹⁻⁴⁶ Subsequently, it was found that certain species of animals, cats and rabbits developed neurofibrillary tangles following exposure to Al,⁴⁷⁻⁵⁶ which

prompted the suggestion that Al was a possible cause of Alzheimer's disease. However, this theory was disputed because not all patients with Alzheimer's have high brain levels of Al and the senile plaques that are common in Alzheimer's disease are not seen in experimental Al toxicity.⁵⁷ Another reason for disregarding a role for Al in Alzheimer's disease has been the fact that the incidences of cognitive impairment and Alzheimer's disease are not increased in renal patients with high s-Al levels. Nevertheless, these patients cannot be compared with the general population, because dialysis patients have a reduced longevity and may be protected by other compounds like silicon.⁵⁸⁻⁶¹

It remains remarkable that, after the discovery of chronic Al encephalopathy and numerous reports of patients suffering from this syndrome, fourteen years passed before the first publication on acute Al neurotoxicity appeared.⁶² Acute Al encephalopathy is a devastating, often fatal disease that is the result of iatrogenic exposure to Al. Unfortunately, in spite of efforts to avoid Al exposure as much as possible, recently new sources of serious exposure have been added to the growing list of sources of Al exposure. In contrast to a fascinating history and abundant literature, many uncertainties about Al toxicity still exist. Clinical data in humans on acute Al neurotoxicity are very limited and we will, therefore, compare our experience in one of the two documented outbreaks in dialysis centers, with that of the literature.

2. Case report

2.1. Course of events and clinical symptomatology

In Curacao, the major island of the Netherlands Antilles with a population of 130.000 inhabitants, distilled seawater from the water plant was used without further purification for hemodialysis for several decades. Unfortunately, two months before the planned installation of a water treatment system including a reverse osmosis (RO) in the dialysis center Diatel, a new distribution pipe supplying water to a dialysis center on the island was installed in 1996. To protect it from corrosion, this pipe was lined on the inside with a cement mortar. Because of the aggressiveness of the distilled water, calcium and Al leached from the cement mortar into the water used to prepare dialysate. At the time of replacement of the new

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conduit pipe, 29 patients were dialyzed in the dialysis unit. Patients were dialyzed three times per week during 3.5 to 4.5 hours using hollow fiber kidneys (Fresenius®, F6 and F8). Untreated tap water was used to manufacture dialysate after passage through three particulate filters (25, 10, and 5 mm, respectively). The intended Ca content of the dialysate was 1.75 mmol/L. None of the patients used Al containing phosphate binders. After the installation of the new water distribution pipe, the patients were exposed to the contaminated water from May 21, 1996, until June 29, 1996. This caused a possible hard water syndrome and definite acute Al intoxication in 27 patients and led to the death of 10 patients.

In the third week of June 1996, 7 of 27 patients had minor symptoms of nausea, vomiting and post-dialysis hypercalcemia. On June 20, 1996, the Ca-carbonate concentration of tap water delivered to the dialysis unit was 43 mg/L (17.2 mg/L or 0.45 mmol/L as Ca²⁺), which is above the standard of 2 mg/L advised by the Association for the Advancement of Medical Instrumentation.⁶³ In the past, the Ca-carbonate concentration had been 15 to 20 mg/L (6.0 to 8.0 mg/L or 0.16 to 0.21 mmol/L Ca²⁺). At that time the diagnosis "hard water syndrome"⁶⁴ was made, due to leaching of calcium from the water distribution pipe. The use of Ca-carbonate and vitamin D preparations was stopped and although there was initial amelioration of the symptoms in almost all patients, the improvement was incomplete whereafter the dialysis unit was closed on June 30, 1996. All patients were referred to the hospital for dialysis where the symptoms of nausea, vomiting, as well as the hypercalcemia disappeared after a single dialysis with low Ca dialysate (1.50 mmol/L). After installation of a RO system, including a deionizer, dialysis was resumed at the Diatel unit on July 10, 1996. Although the patients were dialyzed on ultra pure water, either in Diatel after the installation of the RO on July 10, 1996, or in the local hospital, before the manifestation of serious symptoms, after a lag time of several days to weeks several patients had severe neurotoxic symptoms. Eight patients (Table 1, patients 2 through 5 and 7 through 10) had to be admitted to the hospital because of severe neurological symptoms (disorientation, myoclonus, convulsions and coma, n = 7) or unexplained sepsis (n = 2) with a delay of days to three weeks after the last dialysis with contaminated water (Fig. 1). Attempts to treat myoclonic jerks or seizures with intravenous phenytoin or diazepam were unsuccessful.

*Acute Aluminum Intoxication***Table 1. Characteristics of non-survivors and survivors**

Patient No.	Age (years)	[Al] ^s (μg/ml)	sex	Weight (kg)	Exposure (h)	Diuresis (mL/day)	PTH (pg/mL)	Albumin (g/L)	pt ^e		Treatment (weeks)
									E ^f	D ^g	
Non-survivors (n = 10)											
1	61	-	f	66	52	0	28	35	4	9	-
2	79	-	f	33	51	0	105	32	7	12	-
3	54	1189	m	85.5	68	150	52	34	2	12	-
4	64	725	f	52.5	52	0	22	35	15	18	-
5 ^a	51	894	f	40	68	0	72	30	7	20	-
6	69	-	f	39.5	39	2000	-	28	7	22	-
7 ^a	62	1275	m	62	60	0	8	34	5	23	-
8 ^a	63	359	f	47	68	0	325	36	14	23	-
9 ^a	74	517	f	86	64	0	32	32	21	24	-
10	65	696	m	64	68	0	480	35	21	30	-
Mean	64	808	-	57.5	59	-	125	33			
SEM	3	127	-	5.9	3	-	55	1			
Survivors (n = 17)											
11	64	490	m	57	68	0	710	40	-	-	75
12	57	395	m	65	59.5	0	80	39	-	-	91
13	50	321	f	87	68	0	21	34	-	-	16
14	44	319	m	97	62	0	630	39	-	-	13
15	49	318	m	57	66	200	50	36	-	-	24
16	23	315	f	104	68	0	97	39	-	-	8
17	66	303	f	78.5	64	60	280	34	-	-	18
18	57	301	f	90	68	350	170	37	-	-	5
19	50	248	f	57.5	64	1000	65	36	-	-	13
20	56	207	f	103	68	0	82	36	-	-	16
21	50	205	m	104	60	2	700	37	-	-	82
22	57	187	f	101	64	50	1200	32	-	-	16
23	57	182	f	95	62.5	1100	100	30	-	-	9
24	41	166	m	91.5	68	0	3	-	-	-	18
25	60	132	m	97.5	67	1200	270	39	-	-	4
26	41	116	m	93.2	60	200	680	38	-	-	11
27	56	113	f	91.5	67	1400	99	33	-	-	4
Mean	52 ^c	255 ^c	-	86.5 ^c	65	-	308	36 ^d			
SEM	2	25	-	4.1	1	-	84	1			

^a Patients in whom post mortem examination was performed.^b [Al]^s: serum aluminum concentration.^c $P < 0.01$ ^d $P < 0.05$, survivors vs. non-survivors.^e pt E/D Delay in time in days after end of exposure to Al, the onset of encephalopathy (E^f), and death (D^g).
With permission Blackwell Sciences. Adapted.

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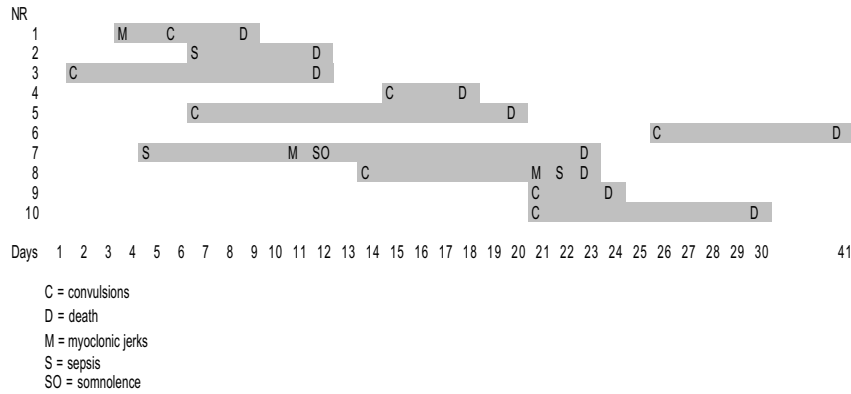


Figure 1. Days between the onset of severe symptoms after the end of exposure to aluminum contaminated dialysate.

When the diagnosis of "acute Al intoxication" was established on July 25, 1996, nine patients had died. The 10th patient, who was comatose, was transferred to a hospital in Florida (Florida Hospital, Orlando, FL, USA). Daily high-flux dialysis treatment combined with desferrioxamine administration was unsuccessful, and he died on August 24, 1996. Of the 27 patients who had a similar exposure (~60 hours) to the contaminated dialysate, 10 died from acute Al encephalopathy, whereas 17 patients had no or only minor symptoms and survived. The first Al tests in the water supply were performed the first week of July 1996, and values of 550 to 690 µg/L were observed. The water company flushed the pipe several times, but because the values remained above 500 µg/L, 1000 m of the initial 2200 m pipe was bypassed. Nevertheless, although the Al level at the water plant was below 5 µg/L, the Al levels at the tap water in Diatel remained high (up to 443 mg/L several months after the bypass), and above 100 µg/L for more than two years.¹⁸

Of the 29 patients, two patients had been dialyzed for less than a week (one at the end of May, and one at the end of June 1996) on the contaminated water, had a s-Al levels of 16 µg/L and 50 µg/L (< 60 mg/L normally seen in dialysis patients without symptoms) and were therefore excluded from further evaluation. Table 1 shows the characteristics of non-survivors and survivors. It is not certain if patient No. 6 did or did not develop acute Al encephalopathy, because of the 27 patients she probably had the lowest Al burden. The patient with a diabetic nephropathy had been on hemodialysis for only two months and had a considerable residual kidney

function with normal diuresis. Compared with the other patients she was exposed for the shortest period (39 h vs. 59-65 h) because she was admitted twice to the hospital for a bleeding duodenal ulcer and hypercalcemia. Hypercalcemia was due to a combination of factors consisting of the use of a calcium phosphate binder, vitamin D, a higher than usual calcium content of the water supply, the availability of calcium in the dialysate and the Al contamination. The calcium level normalized after she had been dialyzed in the hospital with a low-calcium dialysate. The patient nevertheless developed convulsions and twitching of her hands that might have been a sign of Al neurotoxicity, especially because the EEG, performed two weeks before the start of convulsions showed, in retrospect, signs of Al encephalopathy (Table 2). These symptoms however, could also be due to a metabolic or uremic disorder because she had skipped some dialysis sessions. These twitchings were also absent in the other patients. After a one weeks of hospital admission dialysis treatment was stopped because of worsening of the general condition with anorexia and she died 22 days after the end of exposure to the contaminated dialysate (Fig. 1). No blood samples had been available for Al testing.

2.2. EEG

Table 2 shows the EEG recordings before treatment in 12 patients (patient Nos. 1, 3, 4, 6, 7, 10-13, 20, 23, 25) and five patients after treatment (patient Nos. 11, 12, 15, 20, 25). The abnormalities in the EEG recordings of the patients who died were the most severe and consisted of an abnormal ground pattern, some periods of slower high voltage activity, bilateral synchronous with some frontal intermittent recurrent delta activity, sometimes followed by short periods of suppression. After termination of desferrioxamine therapy an EEG was performed in five patients (patient Nos. 11, 12, 15, 20 and 25). Minor non-specific signs possibly related to Al encephalopathy were found after therapy in two patients (Nos. 11 and 25). Slightly abnormal EEG became normal in two patients (patient Nos. 12 and 20). In patient No. 15 with a normal EEG after therapy no EEG had been obtained before therapy.

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Table 2. EEG before and after therapy, serum aluminum levels and duration of treatment

No. ^b	s-AI	R/ weeks	Initial EEG	EEG survivors, after therapy
1	-	-	Abnormal ground pattern. Delta activity with a maximum bilateral frontoparietal and also bilateral synchronous spikes and triphasic waves.	
2	-	-	ND ^c	
3	1189	-	Abnormal ground pattern. More or less continuous slow to very slow peak waves.	
4	725	-	Normal ground pattern. Left central sharp theta waves (middle high)	
5	894	-	ND	
6	-	-	Some periods of slower high voltage activity, bilateral synchronous with some frontal intermittent recurrent delta activity	
7	1275	-	Abnormal ground pattern. Diffuse abnormal EEG	
8	359	-	ND	
9	517	-	ND	
10	696	-	Abnormal ground pattern. More or less continuous high voltage delta waves followed by short periods of suppression	
11	490	75	Multifocal theta, bilateral frontotemporal, followed by asymmetrical waves with a mitigated epileptiform aspect	Left temporal slow theta and delta waves of middle high to high
12	395	91	Minor abnormality. Intermittent right temporal some theta activity	Normal
13	321	16	Some signs of aluminum encephalopathy	ND
14	319	13	ND	ND
15	318	24	ND	Normal
16	315	8	ND	ND
17	303	18	ND	ND
18	301	5	ND	ND
19	248	13	ND	ND
20	207	16	Scattered some delta/theta activity temporobasal and dorsum of the brain.	Normal
21	205	82	ND	ND
22	187	16	ND	ND
23	182	9	Diffuse hypofunctional abnormal. Not typical of aluminum encephalopathy	ND
24	166	18	ND	ND
25	132	4	Scattered multifocal, frontotemporal irregular and irritable.	Left frontoparietal slow waves
26	116	11	ND	ND
27	113	4	ND	ND

^aIn all patients who had a EEG recording had inconsistent signs of a metabolic encephalopathy. The abnormalities in the EEG recordings of the patients who died were the most severe and consisted of an abnormal ground pattern, some periods of slower high voltage activity, bilateral synchronous with some frontal intermittent recurrent delta activity, sometimes followed by short periods of suppression. After termination of desferrioxamine therapy an EEG was performed in five patients (patient Nos. 11, 12, 15, 20 and 25). Minor non-specific signs possibly related to aluminum encephalopathy were found after therapy in two patients (Nos. 11 and 25). Slightly abnormal EEG became normal in two patients (patient Nos. 12 and 20). In patient No. 15 with a normal EEG after therapy, no EEG had been obtained before therapy.

^bpatient number, see Table 1

^cND not done

2.3. Pathology (Table 3)

Post-mortem examination was done in four of the 10 patients (Patients Nos. 5, 7-9). Brain Al contents of cerebral cortex of these four patients were 0.93 to 1.81 $\mu\text{g/g}$ dry weight (normal 0.14-0.22 $\mu\text{g/g}$; values in patients with chronic Al encephalopathy 0.4-3 $\mu\text{g/g}$).⁶⁵ On light-microscopic evaluation of gyrus frontalis superior and inferior, hippocampus, nucleus lentiformis and insula, capsula interna and caudatus, thalamus, nucleus dentatus cerebelli, brainstem, and pons, non-specific changes of some fibrohyalin thickening of the wall of the blood vessels and brain edema were noted.

In patient No. 9, additional Al staining was performed and positive coloring was found centrally in calcifying areas in the plexus chorioidea of the hippocampus and in the wall of the vessels with mineralization in globus pallidus. No Al staining was found in the epithelium of the plexus chorioidea, corpora amyloacea, endothelium, neurons or glia cells. In Bodian silver staining scattered neurofibrillary tangles with tau protein were found in the hippocampus, similar to other studies.^{47-51,53,55-57,66} Iron (Perls) and calcium (Alizarine) staining showed the same pattern of staining as in Al.

2.4. Predisposing factors

When the ten nonsurvivors are compared as a group, they were older (64 ± 3 years vs. 52 ± 2 years, $P < 0.01$), had a lower body weight (57.5 ± 5.9 kg vs. 86.5 ± 4.1 kg, $P < 0.01$) and lower serum albumin concentrations (33 ± 1 vs. 36 ± 1 g/L, $P < 0.01$) as a parameter for the feeding state of the patients. Anuria tended to be more common in the non-survivors (8 out of 10 vs. 8 out of 17, $P > 0.05$). S-Al concentrations, available in seven non-survivors, were significantly higher than in the survivors (808 ± 127 vs. 255 ± 25 mg/L, $P < 0.01$).

The 17 patients who survived dialysis with contaminated dialysate were significantly younger than those who died (Table 1) and the average body weight in the non-survivors was almost 30 kg below that of the survivors.¹⁷ Diabetes mellitus was more frequent in the non-survivors than in the survivors (60 vs. 16%, $P = 0.11$), as was the proportion being anuric (80 vs. 47%, $P = 0.12$). Survivors tended to have higher serum PTH concentrations (survivors, 308 ± 84 pg/mL; non-survivors, 125 ± 55 pg/mL, normal, 11 to 62 pg/mL). Shortly after the intoxication, the mean corpuscular volume in the patients was low (70.25 ± 6.22 , normal 81-99 fL) in seventeen patients.

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Table 3. Postmortem Al in serum, brain, bone and liver in patients Nos. 5, 7-9^a

Patient No	Normal values	Chronic Al encephalopathy in dialysis patients	5	7	8	9
Serum Al µg/L	< 10 µg/L ^{23,129}	> 100 µg/L ²⁰	894	1275	696	517
	(40-60 µg/l in dialysis patients) ^{23,129}					
Brain						
Hippocampus	< 0.4 µg/g dry weight ⁶⁵	0.4-3.7 ⁶⁵	NA ^b	1.14	1.3	1.03
Gyrus temporalis inferior	< 0.4 µg/g dry weight ⁶⁵	0.4-3.7 ⁶⁵	1.75	1.04	1.4	0.93
Gyrus Frontalis Superior	< 0.4 µg/g dry weight ⁶⁵	0.4-3.7 ⁶⁵	1.81	1.19	1.51	1.3
Liver	< 2 µg/g ¹²⁹	> 30 µg/g ⁴²	4.7	51.7	32.7	43
Bone	< 2 µg/g ^{23,129}	50.8 ± 29.5 µg/g ¹⁹⁷	77	7.54	88.7	21.9

^aAl levels in serum, liver and bone are much higher than in the brain, which shows the effectiveness of the blood brain barrier and the storage capacity of liver and bones. Nevertheless, severe neurological symptoms are due to an extremely narrow margin of safety between normal and toxic levels of Al in brain tissue and the lethal concentrations exceed the normal level by only a factor 8-10 in literature studies³¹ and a factor 3-4 in this study. Epilepsy and myoclonic jerks are prominent signs of neurological dysfunction due to Al encephalopathy. The grey matter of the brain is vulnerable to Al-induced pathologic changes and dysfunction of the hippocampus often manifests as epilepsy. Myoclonus is often associated with abnormally increased excitability of cortical structures.²⁷⁴ The gyrus temporalis inferior and gyrus frontalis superior are related to speech disorders and dyscalculia as can be seen in chronic Al encephalopathy and Alzheimer's disease.²⁷⁵

2.5. Detoxification Treatment and Follow-Up of the Survivors

The 17 surviving patients had elevated s-Al concentrations but were fairly asymptomatic and had to be treated with intravenous desferrioxamine (DFO) and high-flux dialysis according to the treatment schedule of Table 4. For logistic reasons, especially the inability to provide high-flux dialysis to all patients on short notice, these patients were transferred to six different hospitals in the Netherlands. In the initial treatment week no serious side effects were observed. In the second week one patient had a short period with myoclonic jerks during dialysis. In the weeks following the treatment only minor neurological or ophthalmologic symptoms were observed, expressed by slight headache (n = 3), and blurred vision (n = 1). None of the patients had serious side effects of the treatment with desferrioxamine. One patient had an allergic reaction expressed by generalized itching during infusion of DFO, but when DFO was infused the next session after

steroid infusion, no symptoms were recorded. One patient had painful localized swellings on both legs, diagnosed as erythema nodosum. This is not a known side effect of desferrioxamine. The lesions disappeared rapidly with steroid treatment. One patient had an infection of a dialysis shunt (Goretex graft).

A large variation of the duration of the detoxification was noted (Table 1). Only five patients could be treated less than 10 weeks, while twelve other patients had to be treated up to 91 weeks. The treatment was discontinued in patients in whom both s-Al and the increment of s-Al after desferrioxamine treatment was below 50 µg/L at two successive occasions). The treatment duration was significantly related to the residual diuresis as all patients with a residual diuresis of a liter/day or more could be treated for less than two months (Fig. 2). Other studies have also established the protective capacity of an even minimal functioning kidney.^{30,67} None of the patients died during treatment with desferrioxamine, and six patients (patient Nos. 11-13, 22, 25, 26) died more than one year after termination of the desferrioxamine treatment, due to causes unrelated to the Al intoxication. As of November 2001, more than five years after the intoxication episode, 12 of the 17 surviving patients (patient Nos. 11,12, 14, 16-24) are still alive and none of the patients developed any clinical signs of Al toxicity, like speech disturbances, cognitive defects, bone fractures or dementia-like symptoms.

2.6. Discussion

An unique set of circumstances was responsible for symptoms resembling hard water syndrome⁶⁴ followed by an epidemic of acute Al encephalopathy in a dialysis unit (Diatel) on the island of Curaçao. A tragic coincidence was that the intoxication happened about two months before the planned installation of a water treatment system with deionization and reverse osmosis (RO). Traditionally, municipal water had been used for more than two decades without extended purification for the production of dialysate. The pure (Al < 5 µg/L), distilled drinking water, which is one of the purest drinking water sources worldwide,⁶⁸ was in fact indirectly responsible for the fatal outcome. The water entering the mains was aggressive, soft and the alkalinity low (maximum Langelier Index [LI] between -0.5 and -1.5, hardness as CaCO₃ is 15-20 mg/L, pH 8.5 to 9.5).¹⁸ The water utilities did not condition the water to make it less corrosive but installed

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Table 4. Practical approach with desferrioxamine (DFO) treatment of severe aluminum intoxication in hemodialysis patients, using Monday as the starting day.

Therapy	Aluminum levels > 300 µg/l, or post DFO administration > 300 µg/L. Four times a week dialysis.		Aluminum levels < 300 µg/l, or post DFO administration < 300 µg/l. Three times a week dialysis.	
	DFO administration 5 mg/kg, 5 hours before dialysis (1 h infusion time)	High flux dialysis of at least four hours, F 80 or similar	DFO administration 5 mg/kg at the last hour of dialysis (1 h infusion time)	High flux dialysis of at least four hours, F 80 or similar
Day 1 Monday	Yes	Yes, four hours after termination of infusion	Yes	Yes
Tuesday	No	Yes, preferably 20 hours after termination of last dialysis session (within 72 hours)	No	No
Wednesday	No	No	Yes	Yes
Thursday	Yes	Yes, four hours after termination of infusion	No	
Friday	No	Yes, preferably 20 hours after termination of last dialysis session	No	Yes
Saturday	No	No	No	No
Sunday	No	No	No	No

other pipes with a "protective" cement coating.¹⁸ Water distribution pipes are commonly coated on the inside with cement mortar to protect them from corrosion by the electrochemical action of water. Although cement-mortar linings have been successful in protecting iron pipes against electrochemical corrosive effects, recent research indicates that water can leach cementitious materials from this lining up to four years. Adverse effects of these coatings on the water quality are generally an increase of calcium and pH,⁶⁹ but recent reports did not mention the possibility of Al contamination into drinking water from cement linings.¹⁸ The water distribution company had replaced the water distribution pipe to help the dialysis center with the low water pressure problem, but had been unaware of the fact that these pipes are inappropriate for the local water conditions. Conditions that enhance Al leaching include low water alkalinity and hardness, relatively high water temperatures, and low or intermittent water flow. Unfortunately, all of these factors coincided in this situation, especially because Diatel was located at the dead end of a water main, resulting in the highest Al concentrations on the island. The Al level rose from about 16 µg/L to at least

up to 690 µg/L. Clearly, no one, not even the water industry in particular had ever been aware of the possibility of Al contamination during distribution, as this had never happened before in dialysis history.¹⁸

2.7. Legal consequences

The incident caused a flood of media coverage and a criminal investigation followed with the help of the local and Dutch Health Inspectorate. Thereafter, the prosecutor dismissed the case and held that the intoxication was caused by a unique and complex set of circumstances that not only involved the physicians, but also external consultants for the dialysis center, the local Water Authorities and the government. After an appeal of family members of some of the patients that died, the court reopened the case and after a preliminary judicial inquiry the physicians were initially convicted, but acquitted at the Court of Appeal.

3. Symptoms and Diagnostics of Al Intoxication Syndromes

There are wide variations in the clinical manifestations and degrees of expression of toxicity as patients are exposed to Al. In renal disease Al accumulation in tissues and its resulting toxicity is mainly due to poor elimination, since the kidney normally excretes the metal. There is no simple relationship between the amount of Al to which the patient is exposed and the occurrence of the clinical manifestations of the disease; apparently there is considerable interindividual difference in sensibility since the symptoms developed in some patients but not in other equally exposed patients. Some of the variations in the clinical features in Al toxicity in the past most likely occurred because of differences in both the rapidity and magnitude of Al loading. Therefore the manifestations of Al toxicity that are encountered vary substantially, with major differences arising due to different sources and varying intensity of the Al burden.

3.1. Definitions of Al Intoxications

In the past several clinical patterns have been described. The most important recognized clinical patterns or types of Al toxicity include two types of encephalopathy. Firstly, the "classical" dialysis dementia sometimes

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referred to as "dialysis encephalopathy syndrome (DES)" or dementia dialytica^{24,28,37,42,70-74} and secondly, the "acute" or "subacute" Al encephalopathy.⁴¹ There are also two types of bone disease –either osteomalacia with bone fractures and proximal myopathy or aplastic bone disease.^{41,75,76} There is quite some confusion in the definitions of Al toxicity in the literature. Because there seems to be an obligatory lag phase of at least several days to weeks for symptoms to occur, "acute" Al encephalopathy, defined as a direct result of a single overdose, probably does not exist. Because of the long lag phase of several months to years necessary to develop the "chronic" dialysis encephalopathy and also because "acute" Al encephalopathy has an abrupt, sudden onset of symptoms one can understand why the term "acute" is used instead of the more descriptive "subacute". The descriptions "dialysis dementia"^{37,42,46,73,74} and "dialysis encephalopathy"^{33-36,38,40,41,78} are also unfortunate because true dementia is rare in Al encephalopathy⁷³ and non-dialyzed patients can also develop these symptoms.⁷⁸ There are also many dialysis-related encephalopathy syndromes unrelated to Al. As an example, the disequilibrium syndrome and sodium disturbances can also produce seizures.⁷⁹ In addition to this, some publications on "acute Al intoxication"^{17,80} refer to the predominant neurological symptoms, while other publications only described gastrointestinal symptoms.^{20,81,82}

To avoid this confusion it is necessary to separate acute Al intoxication into "acute Al gastroenteropathy" and "acute Al encephalopathy". Chronic Al gastroenteropathy as such probably does not exist, because patients will terminate the oral exposure because of complaints.

3.2. Acute Al Gastroenteropathy

Gastroenterological symptoms due to Al toxicity have been described as massive gastrointestinal intoxication and as peritoneal dialysis fluid contamination with Al.⁸¹⁻⁸³

3.2.1. Oral exposure

The potential negative effects of exposure to Al do not only reflect the dose, but also the percentage of the dose that is absorbed and retained. The effectiveness

of the gut as a protective barrier is illustrated by the observation that only 0.04 – 1 % of oral doses of Al appears to be retained.^{1-4,59,84-87} However, very high concentrations of Al in drinking water may have health consequences. Drinking water plants commonly use Al sulfate as a flocculent. Unfortunately, human errors can increase human exposure to excessive amounts. On July 6, 1988, twenty metric tons of Al sulfate were accidentally emptied into the treated water reservoir at Lowermoor Water Treatment Works that supplied the Camelford area of North Cornwall, UK. Twelve thousand residents and 8000 tourists were exposed for 3 days and when the error was detected corrective measures were started. The water tasted unpleasant because of its acidity and Al content up to 620 mg/L; it also contained abnormally high amounts of copper, lead and zinc dissolved from water pipes. Consumers noted an unpleasant taste and reported a variety of acute symptoms such as mouth ulceration, joint pain, gastrointestinal disturbance, skin rashes, fatigue, nausea and vomiting, itching and sore eyes.^{82,88,89} Nevertheless, initial toxicological assessment was that the limited exposure would not cause acute or chronic disease.⁸² Two years later, however, of the 20,000 persons exposed to the contaminated water 400 people had illnesses that were attributed to the incident.⁸⁸ Bone Al concentrations remained elevated for 6 to 7 months, but were absent at follow-up 19 months after the accident in at least two affected individuals.^{88,89} In one study some patients demonstrated poor short-term memory and concentration disturbances, which were regarded as a possible organic brain dysfunction due to the accident in one study.²⁰ Thus, Al absorption and deposition in the body can be significant when normal individuals are exposed to highly contaminated water, even when exposure is short. This may seem remarkable, considering the fact that Al-related bone disease in dialysis patients disappears after kidney transplantation and the rate of removal of Al from bone seems to be independent of graft function and bone turnover.^{90,91} One would expect that healthy kidneys should be able to eliminate Al in these circumstances. However, it has been demonstrated by special Al staining that Al-induced argyrophilic degradation products remain in the cellular cytoplasm in unchanged fashion up to 10 years after renal transplantation, when the renal Al excretion was normalized.⁹²

3.2.2. Peritoneal Membrane

Another route of exposure resulting in gastrointestinal symptoms

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have been in peritoneal dialysis. In three of the centers supplied with contaminated peritoneal fluid in Paris, Glasgow and Edinburgh regular monitoring of the s-Al disclosed unexpected high Al levels. In 14 of 19 patients plasma Al levels exceeded 470 µg/L; four patients had symptoms of nausea, vomiting, cramp like abdominal pain and general malaise which appeared within three days of first using the contaminated fluid. The cause of the syndrome was recognized before irreparable harm was done, and all patients eventually recovered. Al concentrations in the affected batches ranged from 613-1440 µg/L. Within a month time, s-Al rose to peaks of 267-1440 µg/L.^{81,83} The mechanism of these symptoms is unknown; they seem to be due to a direct irritation of the bowel wall. We are unaware of any studies on neurotoxic damage to the autonomic nerves of the bowel due to AL.

3.3. Hemodialysis. Clinical Symptoms of Acute Al Encephalopathy and Chronic Al Encephalopathy (also Referred to as Classical "Dialysis Dementia")

Hemodialysis patients are very susceptible to changes in the composition of water used to produce dialysate, as the effective barrier of the gut is bypassed during this treatment. Patients are exposed to about 120 L of water during each dialysis treatment and contaminants present in the water may diffuse across the dialysis membrane and cause intoxications.⁶³

Slow, relatively "low exposure" accumulation of Al over a period of years can lead to a number of clinical manifestations, some of which seem to be "bypassed" in acute Al encephalopathy due to extremely high exposure to Al. Al encephalopathy is a clinical syndrome and, as can be seen in Table 5, there are similarities and differences in the neurological symptoms of acute and chronic Al encephalopathy. In chronic Al encephalopathy, microcytic anemia^{41,93, 95-98} and EEG changes⁹⁹⁻¹⁰⁴ can precede clinical symptoms.¹⁰⁵ It is unknown if these symptoms can also precede the clinical symptoms of acute encephalopathy. In contrast to acute Al encephalopathy, where speech disturbances are absent, speech disorders are an important presenting clinical sign of neurotoxicity in chronic Al encephalopathy. The neurological basis of the speech apraxia is obscure but it appears to have elements of dysarthria and dysphasia.^{33,73} The initial episodic nature of the condition suggests that it

may be due to a transient toxic state as often occurs after dialysis with contaminated dialysate, but it might as well be part of a complex seizure state.³³ The neuropil spongiosis of the upper layers of the temporal cortex was thought to be relevant to the language disorder.¹⁰³ In addition to communication disturbances, cognition disturbances, fracturing osteomalacia and/or myopathy can also be the presenting clinical symptoms in chronic Al encephalopathy, while these symptoms are absent in the acute form. Disturbed handwriting (dysgraphia) has been noted in some cases of the chronic encephalopathy, but not the acute form of Al encephalopathy. Changes in handwriting can be evaluated retrospectively in many cases, because patients in dialysis centers tend to note some of their dialysis parameters in the dialysis chart themselves. It should be stressed that many of these symptoms like relapsing speech and language abnormalities, clouding of consciousness, grimacing, tremor and asterixis, muscle jerks and seizures are common to numerous metabolic encephalopathies unrelated to Al.^{22,79,104}

Patients with acute and chronic Al encephalopathy can demonstrate unilateral or bilateral myoclonic jerks of the extremities for several months in the chronic form and days to weeks in the acute form, followed by convulsions and coma even when the exposure is terminated. It seems as if brain pathology reaches a point of no return, which results in frequent epileptic insults and inevitably leads to coma and death, either due to superimposed infections like aspiration pneumonia, or pulmonary edema due to cardiac toxicity. Recovery is exceptional in severe cases. In the past, reports showed that the early stages of chronic Al encephalopathy progressed to death, mainly because the most important source of Al, namely the dialysis fluid contamination was not recognized as such and the exposure continued for months to years.^{10-17, 19-42}

Fluctuation of neurological symptoms can be seen in relation to dialysis in chronic Al encephalopathy, sometimes provoked by dialysis sessions due to additional exposure with contaminated dialysate superimposed to chronic Al intoxication.^{28,29}

One of the most confusing features of Al encephalopathy is the lag phase between exposure and clinical symptoms and the subsequent rapid course of the disease. The delay can be months to years in the classical form

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Table 5. Clinical features of acute and chronic aluminum encephalopathy and gastroenteropathy

Aluminum encephalopathy	
	<p>Acute aluminum encephalopathy <small>1,7,23,30,44,45,62,80,131,150,154,158</small></p> <p>Classical or chronic aluminum encephalopathy <small>10,15-19,26,28,32,35,39-42,77,127,197,200,273</small></p>
Etiology	<p>1. Ingestion of Al with citrate by kidney patients</p> <p>2. Dialysate water > 600-1000 µg/L</p> <p>3. Marked rise in plasma Al with desferrioxamine treatment</p> <p>4. Haemorrhagic cystitis bladder treatment with Alum</p> <p>5. Al-containing biomaterial in otosurgery</p>
Onset	Abrupt, sudden within weeks. Between seizures apparently symptom free. Microcytic anemia and EEG changes might precede neurotoxicity.
Clinical features	<p>I. Neurotoxicity</p> <p>a. Communication disturbances None or minimally</p> <p>b. Cognition disturbances None or minimally. Coma and death in a high percentage of cases.</p> <p>c. Movement disorder (90-100%) Seizures 90% Myoclonic jerks 30%</p> <p>II. Muskuloskeletal symptoms Absent</p> <p>III. Other symptoms</p> <p>a. Possibly increased susceptibility to infections</p> <p>b. Possibly cardiotoxicity leading to sudden death</p>
	<p>1. Months - years of parenteral or oral Al exposure</p> <p>2. Dialysate water 50-1000 µg/l</p> <p>Insidious, gradual with impressive fluctuations in severity of symptoms. Microcytic anemia and EEG changes might precede neurotoxicity.</p> <p>I. Neurotoxicity</p> <p>a. Communication disturbances (87%) Speech disorder often the presenting symptom: slowing of speech, stuttering, stammering, misarticulation</p> <p>b. Cognition disturbances (66 %) Concentration difficulty, disorientation, personality changes, hallucinations, dysgraphia. Coma and death in advanced cases.</p> <p>c. Movement disorder (without intervention 63-93%) Motor apraxia, Myoclonic jerks, Seizures</p> <p>II. Muskuloskeletal symptoms</p> <p>a. Fracturing osteomalacia and/or myopathy with progressive skeletal pain, proximal muscle weakness 67%, sometimes arthritis</p> <p>b. Adynamic bone disease</p> <p>III. Other symptoms</p> <p>a. Possibly increased susceptibility to infections</p> <p>b. Possibly cardiotoxicity leading to sudden death</p>

<p>Laboratory findings</p>	<p>In epidemic cases when related to water contaminated dialysate: Al in water used for dialysis > 600-1000 µg/l</p> <p>Plasma Al usually > 500-1000 µg/l (epidemic cases)</p> <p>Microcytic anemia (almost always)</p> <p>Hypercalcemia (depends on concomitant use of vit D, calcium preparations and calcium level in the dialysate)</p> <p>EEG changes probably in all patients (multifocal burst of slow [delta] and spike activity)</p> <p>Cerebrospinal fluid aluminum level relatively low (< 10 µg/l)</p> <p>Bone aluminum level ~ 85 times higher than controls</p> <p>Non-specific histological changes brain</p> <p>Brain aluminum level 0.93 – 1.81 µg/g dry weight (>20 times higher than normal)</p>	<p>In epidemic cases when related to water contaminated dialysate: Al in water used for dialysis > 50 µg/l</p> <p>Plasma Al usually 100-350 µg/l</p> <p>Microcytic anemia (frequent)</p> <p>Hypercalcemia (depends on concomitant use of vit D, calcium preparations and calcium level in the dialysate)</p> <p>EEG changes preceding any clinical signs 4-6 months (multifocal burst of slow [delta] and spike activity) 100 %</p> <p>Cerebrospinal fluid aluminum level unknown</p> <p>Bone aluminum level ~ 85 times higher than controls</p> <p>Non-specific histological changes brain</p> <p>Brain aluminum level 0.4 – 3.7 µg/g dry weight (10 times higher than normal)</p>
<p>Treatment</p>	<p>Seizures and myoclonic jerks do not or hardly respond on benzodiazepines.</p> <p>Severe cases probably do not respond to desferrioxamine. The less symptoms, the better the outcome with early desferrioxamine treatment.</p>	<p>Benzodiazepines can be very effective in treating myoclonic jerks and seizures in the early stages.</p> <p>In early stage reversible with desferrioxamine</p>

Aluminum gastroenteropathy

Acute aluminum gastroenteropathy

Chronic aluminum gastroenteropathy

1. Oral exposure:^{7,20,82,88,89} unpleasant taste, mouth ulceration, joint pain, gastrointestinal disturbance, skin rashes, fatigue, nausea and vomiting, itching and sore eyes.
2. Peritoneal exposure:^{81,83} nausea, vomiting, cramp like abdominal pain and general malaise within days.

probably nonexistent

Other agents involved, could have contributed to, or could have been responsible for the symptoms^{20,82,88,89}

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and several weeks in the acute form. Because patients are generally symptom-free or demonstrate minor symptoms like microcytic anemia, physicians are unaware of the exposure until the development of severe symptoms. Until recently it was not known that a relatively short dialysis related exposure time to Al could be fatal.

Myocardial dysfunction may arise from Al loading, but this is not substantiated as yet. Al levels have been found markedly increased in the heart in patients with chronic dialysis encephalopathy.¹⁵ It is presumed that sudden cardiac death may practically be due to Al cardiotoxicity.^{27,106} At pathology evaluation patients Nos. 7-9 showed signs of pulmonary edema. Al is also present in the synovial fluid and arthritis-like symptoms have been reported in patients with Al bone disease, possibly due to an inflammatory effect on the synovial cells.^{107,108} We did not see signs of arthritis shortly after the intoxication, but after several months of treatment with desferrioxamine, three patients developed a possible transient synovitis with hydrops in the knee joints.

Although Al bone disease can occur in any patient intoxicated by Al, the risk is greater in diabetics. This may be related to a lower than normal bone formation rate, an abnormality that has been demonstrated in type 1 diabetics prior to the onset of clinical renal disease.^{109,110} The risk for developing acute Al encephalopathy also seems to be increased in diabetic patients; this might be related to a decreased storage capacity of the bones.¹⁷

3.4. Diagnostic Parameters

3.4.1. *S-Al levels*

It should be stressed that testing of Al in body fluids can be easily disturbed by contamination, due to the ubiquity of Al. Especially talcum in medical gloves, and glass tubes are known to be responsible for falsely elevated values. Protocols have been developed to avoid Al contamination and Al-free polypropylene and polystyrene tubes prerinsed with 1 N HNO₃ are used for this purpose.¹¹¹ In patients with Al exposure through Al containing biomaterial in otosurgery, s-Al levels can be below 300 µg/L.¹¹²⁻¹¹⁶ In all other intoxications resulting in acute Al encephalopathy

s-Al levels are invariably well above 300-500 µg/L.

3.4.2. Other serum determinants

Especially in Al bone disease hypercalcemia, suppressed PTH levels, and normal or slightly elevated alkaline phosphates have been reported. Hypercalcemia may develop in some hemodialysis patients with acute Al encephalopathy when they are simultaneously exposed to oral calcium and vitamin D preparations in combination with the available calcium from the dialysate.¹⁷ It is not known whether PTH levels and serum alkaline levels change during acute Al encephalopathy.

3.4.3. Liquor

Al levels in the cerebrospinal fluid are not always helpful for the diagnosis because even at very low levels (below 10 µg/L) neurotoxic effects can be present.^{23,80,99}

3.4.4. Microcytic anemia

Among dialysis patients, a microcytic anemia most commonly arises due to iron deficiency but Al toxicity should be suspected in all cases where iron deficiency is unlikely. Probably most patients with acute and chronic Al intoxication develop microcytic anemia.^{93,95-98,105}

3.4.5. EEG

Almost all patients with acute or chronic Al encephalopathy showed EEG alterations. These were characterized by multifocal bursts of slow (delta) and spike activity. Background rhythms between bursts were relatively normal in patients with chronic Al encephalopathy, in contrast to uremia and other metabolic encephalopathies where there is general slowing of the rhythmic cycle.^{33,99-102,105,118}

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4. Sources of Al Exposure Leading to Acute and Chronic Al Intoxication

4.1. Contamination of the Dialysate

4.1.1. Al Contamination at Drinking Water Plants

4.1.1.1. Al Use in the Drinking Water Industry

Since at least the Roman times, alums and the related $\text{Al}_2(\text{SO}_4)_3$ have been added to drinking water to improve the appearance and it is still the most widely used coagulant for turbid water to precipitate organic matter, because the process is cheap and practical in its use. The coagulants commonly used by water system plants are alum, poly-Al chloride, ferric salt and polymer.^{119,120} In the process residual Al levels are generally low. The Environmental Protection Agency encourages utilities to meet a level of 50 $\mu\text{g}/\text{L}$ Al where possible, but believes that "varying water quality and treatment situations" necessitate a flexible approach.¹²¹ Therefore, and also because no health-based guideline value for Al was recommended by the World Health Organization (WHO),¹²²⁻¹²⁴ large variations in Al concentrations in drinking water can be found due to variations in source water and water Al levels as high as 1600-2700 $\mu\text{g}/\text{L}$ have been reported.¹¹⁹ Features of Al toxicity can affect a high percentage of dialysis patients using such water for dialysate preparation because of inadequate water purification procedures,^{10,16,17,19,23-26,37,38,46} or when water purification procedures insufficiently protect the patients.^{28,30,39,44} Table 6 gives a review of the literature on dialysate contaminations with Al, the reported serum levels (when available) and the outcome of the patients. These data clearly demonstrate that there is an exceptional variation of the severity of symptoms, which hardly seem to correlate with neurotoxicity or serum levels. This is in part due to the fact that reported Al levels in municipal drinking water were evaluated retrospectively and that these levels can vary substantially from month to month.

4.1.1.2. Relatively Low Al Levels (50-75 mg/L) in Water Used for Preparation of Dialysate

A large discrepancy between dialysate and s-Al levels are found at the lower end of the spectrum, as there is no linear relationship between Al concentrations in water used to prepare the dialysate and s-Al concentrations.

Al is transferred against the concentration gradient, because it binds a non-dialyzable plasma constituent, mainly transferrin. With Al dialysate-water levels of 50-75 µg/L, the plasma Al level can rise by 50% to 70% during a single hemodialysis procedure. The body load of Al may thus progressively be increased in a rate of at least 20.5 µg/min, or about 6 mg/dialysis.³² The transport in the opposite direction can presumably occur when the plasma protein binding sites are saturated with Al, but the amounts transferred are rather small.⁴² Such observations have urged dialysis facilities to keep the dialysate Al level below 5 to 10 µg/L.

4.1.1.3. High Levels of Al (> 75-200 mg/L) in Water Used for Preparation of Dialysate

Davison et al. found that the cumulative risk of death due to dialysis dementia in patients whose water supply had a mean Al concentration > 200 µg/L was significantly greater (27.9% deaths in the first 40 months) than the risk in patients whose mean water Al content was < 200 µg/L (2.1% deaths in the first 490 months). The relation between the mean Al concentration in the dialysate and time to death was given in the formula:²⁴ The time in months from the first symptoms of dialysis dementia to death = $65 - 0.081 \times [\text{mean Al concentration } (\mu\text{g/L}) \text{ in dialysis water}]$.

It may be postulated that the severity of exposure to Al determines the pattern of morbidity. Normally, Al in plasma is bound and transported by transferrin. However, when plasma Al levels are > 500 to 600 µg/L, transferrin's capacity for binding Al is exceeded, and Al probably exists in plasma in combination with citrate or as a hydroxide in association with phosphate. Thus, acute severe exposure may be more likely to produce the neurological disorder and increased sensitivity to flicker, whereas chronic moderate exposure may manifest primarily as bone disease and the other less dramatic symptoms.^{27,125-128} In any case, considering the fact that there have been only two reports of outbreaks of acute Al encephalopathy in dialysis centers,^{17,43-45} and s-Al levels of 1200 µg/L⁴⁴ to 1700 µg/L (Table 1) have been reported (Table 6), acute Al encephalopathy due to water contamination probably only develops when Al level in the tap water is well above 1000 µg/L.

There are several possible reasons why some patients remain relatively symptom-free while others develop serious neurological symptoms in cases with

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Table 6. Dialysis water contaminations in dialysis centers. Comparison of serum and dialysate aluminum levels in patients without reported symptoms^a and patients with classical^b and acute aluminum encephalopathy

Location	Reported Al level in dialysis water ($\mu\text{g/L}$) [*]	Serum AL level ($\mu\text{g/L}$)	Time between intoxication and death or Encephalopathy	Death	Chronic Al encephalopathy	N=
Belgium ⁴⁴	62	154 \pm 70 ^a		none	none	NR
Egypt ⁴⁴	85	119 \pm 99 ^a		none	none	NR
Paraguay ⁴⁴	98	83 \pm 43 ^a		none	none	NR
Denver, USA ¹⁶	150-350		4-6 year			
Cork, Ireland ³⁴	70-450	147-423 ^b	22-93 months	5	14	NR
Newcastle, UK ³⁵						NR
Manchester, UK ^{12,127}	300-1200 6-109	NR ^b 84 ^a	< 2 year	10 none	NR NR	NR
Manchester, UK ^{37,198}	200-1000	NR ^b	3-40 months	NR	8	34
United Kingdom ^{13,14}	\leq 702 \leq 80 20-60	\leq 756 ^b \leq 300 ^b \leq 165 ^b	NR	none none none	NR NR NR	NR NR NR
Minneapolis, UK ¹⁹	160-1630	NR ^b	NR	20/22		NR
Trent region, UK ^{36,198}	\leq 480	NR ^b	4 years	NR	11	202
Scotland ^{26,27}	400 \pm 33.3 \geq 1000	NR ^b NR ^b	NR 3 months on home dialysis	NR 1	none NR	NR NR
Eindhoven, The Netherlands ^{28,29}	800-1000	NR ^b	Years	NR	8	NR
Portugal ^{23,30,44,45,80}	2200	104-1257 ^c	Weeks	25	None	71
USA ³⁹	up to 262 (in dialysate 81-8400)*	N=64, ^b 100-642 ^b	2 years	1	8	64
Curaçao ¹⁷ [table 1]	690	118- 1700 ^c	Weeks	9 or 10	None	27

*calculated retrospectively.

N= total exposed patients

Table 6. Due to insufficient data and retrospective studies, it is impossible to have a proper evaluation of the aluminum levels in the water used for dialysis, the serum levels in patients and their outcome, from the available literature. Water aluminum values can vary substantially over a short period, and some water companies may either be reluctant to release their data, or did not test aluminum on a frequent basis. There have been only two outbreaks of acute encephalopathy: one in Portugal, and one described in this article, on Curaçao, with similar symptomatology and a mortality rate above 30%. Al levels in the water used for dialysis was > 650 $\mu\text{g/L}$ in both studies.^{17,23,30,44,45,80} In several other studies Al levels in the water used to prepare the dialysate were > 1000 $\mu\text{g/L}$, and retrospectively calculated concentrations up to 8400 $\mu\text{g/L}$ were reported, but remarkably the patients no clinical symptoms were reported in these cases. Because acute aluminum encephalopathy has been extremely rare and patients seem to tolerate extremely high serum levels (above 1000 $\mu\text{g/L}$) before acute aluminum encephalopathy develops, it seems likely that levels of the water used for dialysis probably need to be at least > 1000-1500 $\mu\text{g/L}$ before acute aluminum encephalopathy will develop.

apparent similar exposure.

- With concomitant use of Al-containing drugs a parenteral exposure is superimposed on chronic exposure.
- The hours of dialysis treatment with subsequent Al loading can vary substantially, as well as the "effectivity" of dialysis due to flow differences, artificial kidney characteristics, etc.
- Large individual differences may protect patients from neurotoxicity. Large

body stores for Al (bone, spleen, liver) and volumes of distribution differ among patients. Reduced storage capacity in liver failure or osteoporosis might account for large differences. High PTH levels,²⁹⁻¹³² high iron stores⁷⁹ and high silicon^{58,59} levels may also protect patients partly due to influences on the bodily distribution of Al. Some reports have demonstrated large differences in silicon levels between patients and silicon levels can differ 100-fold in both cerebrospinal fluid and serum compared to subjects with normal renal function.^{20,23,58} The protective effect of silicon against Al toxicity may be either by affecting the bioavailability of Al^{20,23,59} or reversing the Al-induced conformational changes of neurofibrillary tangles.^{51,55,60,61} A residual diuresis protects against Al toxicity, as it will be excreted in these patients⁶⁷ (Fig. 2, see page 136).

4.1.1.4. Al Contamination During Drinking Water Distribution

Only one case reported an increase of Al during drinking water distribution (also discussed in this article), because Al leached from the cement lining of a water distribution pipe.^{17,18}

4.1.1.5. Al Contamination by Hemodialysis Equipment

- a. In one case, fatal Al toxicity occurred in a dialysis unit in Eindhoven, the Netherlands, due to the release of Al into water from an electrical anode used to protect a boiler from corrosion.²⁸
- b. Several reports have related the use of Redy cartridges in hemodialysis with Al exposure. Al oxide is present in the Redy cartridge and due to the increased solubility of Al in alkaline solution, Al can be released from the Redy cartridge and cross a dialyser membrane.^{76,132-135} The risk for Al intoxication is even higher when citrate anticoagulation is used in combination with Redy dialysis. Infusion of citrate into the arterial line, followed by infusion of calcium into the venous line, has been used for regional anticoagulation during hemodialysis of patients with bleeding diatheses or heparin-induced antiplatelet antibodies. These patients are often hospitalised in intensive care units where the use of a sorbent regeneration dialysis system is convenient.^{134,135}

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- c. An outbreak of Al intoxication in hemodialysis patients due to an Al pump was reported in 1991. In a dialysis centre in Pennsylvania bicarbonate-based dialysate passed through one of two electric pumps. The electric pumps used to deliver acid concentrate used in bicarbonate dialysis had an Al casing, casing cover, and impeller. Elevated levels of Al were found in acid concentrate after passing through a pump.³⁹
- d. Eight patients undergoing acetate-free biofiltration suffered aluminum intoxication. The source of this outbreak was parenteral exposition to high concentrations of aluminum in sodium bicarbonate solutions. At the peak of intoxication serum aluminum determination revealed an average value of $147.3 \pm 21 \mu\text{g/l}$. Aluminum levels in bicarbonate solutions were $400 \mu\text{g/L}$.⁹⁶

These outbreaks demonstrates why it is essential to ensure that all fluid pathways, storage tanks, central delivery systems, and pumps are compatible with low pH fluids before converting from acetate to bicarbonate dialysis.

4.2. Desferrioxamine (DFO) Administration

Patients with a substantial Al burden can be detoxified with desferrioxamine. In some cases where high dosages were used patients may suffer seizures and myoclonia a few hours after administering the chelator. It is argued by Ackrill et al. that the rise in plasma Al levels cannot explain the rapid neurological deterioration since it begins within hours of administering DFO, whereas peak al levels only occur 24-48 hours following DFO infusion.¹¹ It has been suggested that desferrioxamine has a direct neurotoxic effect on the brain. Another hypothesis suggests that after Al alters the permeability of the blood brain, and allows the aluminioxamine complex with a relatively low molecular weight of 583 Daltons to cross the blood brain barrier more readily than naturally circulating Al, that is largely bound to serum transferrin and albumin, especially because the DFO-Al complex is lipophilic.¹³⁶ A recent study however, makes it more likely that unchelated desferrioxamine passes the blood-brain barrier and chelates the Al present in the brain to convert it to aluminioxamine causing acute neurological symptoms in the already damaged brain.⁸⁰

4.3. Gastrointestinal Exposure

4.3.1. Oral phosphate binders

Because of poor phosphate removal with dialysis, the use of Al or calcium phosphate binders has been required for lowering serum phosphate levels in uremic patients. A prospective, controlled study of pediatric patients demonstrated that a presumed "safe" dose of Al gels leads to Al accumulation and the current opinion is that there is no safe dose of Al in chronic renal failure that is also large enough to control the plasma phosphate concentration. The dietary intake of phosphate is higher in North America than in many European and Asian countries, and the amount of Al hydroxide prescribed in dialysis patients had been high in these countries, resulting in a considerable number of patients suffering from Al-related bone disease.¹³⁷⁻¹⁴³ Close correlations have been observed between s-Al levels and the amount of Al-containing gels ingested in both children and adults undergoing dialysis. In children with renal failure, the ingestion of doses of Al hydroxide containing more Al than 75 mg/kg per day was associated with plasma levels of Al above 100 µg/L, and features of Al bone toxicity were common.^{78,137,143-145} In uremic patients life-threatening Al encephalopathy has been observed when Al hydroxide has been administered with sodium citrate¹⁴⁶ or calcium citrate.²⁸ Non-dialyzed uremic patients showing Al encephalopathy had received the combination of oral Al with citrate compounds.¹⁴⁶ Citrate is known to enhance the passage of Al over the intestinal wall and the blood-brain barrier and to contribute to the development of toxicity.^{3,147} Uremic patients prescribed medications containing citrate (calcium citrate, Shohl's solution) or Alka-Seltzer, along with those medications containing Al (Basaljel, Amphogel, Carafate) are particularly prone to Al accumulation.¹⁴⁸

4.4. Bladder Irrigation With Al Sulfate

Al toxicity also has been reported from intravesical bladder irrigation with Al sulfate (alum). Alum is an astringent and controls bladder hemorrhage. In the past it was regarded to have a non-significant systemic absorption, but probably a breach of endothelial integrity secondary to hemorrhagic cystitis

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allows Al to leach across the vesical mucosa, contributing to significant tissue loading. As the intact renal function is essential for a rapid disposal of a parenteral Al load, most reported instances of encephalopathy after alum irrigation have occurred in patients with compromised renal function. Manifestations of encephalopathy appeared after continuous irrigation with 1% alum for at least 2 days and are associated with elevated s-Al concentrations. Patients are treated with alum with up to 30 liters of irrigant over a 24 h period.¹⁴⁹ Probably most cases involve acute Al encephalopathy with serum levels of 135 to 436 $\mu\text{g/L}$ and a high mortality.¹⁴⁹⁻¹⁵⁵ The symptoms are similar to that of acute Al encephalopathy in dialysis patients with convulsions and coma but interestingly, the lag phase of 2 to 8 days,¹⁵⁰ is much shorter than reported in hemodialysis outbreaks of acute Al encephalopathy. This is possibly related to both the rapidity and magnitude of Al loading, causing large body stores for Al (bone, spleen, liver) to be partially bypassed.

Some authors claim to have had patients with Al neurotoxicity symptoms when the highest s-Al concentration was 17 to 22 $\mu\text{g/L}$.^{156,157} It seems very unlikely that these patients indeed suffered from Al encephalopathy because the patients did not had typical symptoms and s-Al levels below 100 $\mu\text{g/L}$ are generally considered unlikely to cause encephalopathy in hemodialysis patients.²⁰ In these cases several other complicated metabolic abnormalities, in retrospect, were probably responsible for the neurological symptoms.¹⁵⁰ Nevertheless, alum should not be employed as a bladder irrigant, especially not in patients with acute or chronic renal failure.

4.5. Al Containing Biomaterial (Cement) in Otosurgery

Ionomeric cements are used routinely in otosurgery, especially in maxillofacial or skull bone-cementoplasty by an Al-containing biomaterial and canal reconstructions where the proximity to the facial nerve is evident. Cement, however, is not inert, and Al is an important constituent of cement. The literature contains reports of diffusion of Al ions, which can reach toxic levels in tissue fluid and adjacent bone as the cement hardens. During setting and hardening, the hybrid bone substitute ionomeric cement achieves a stable and durable bond with the apatite of the adjacent bone without interpository soft tissue. A close contact between an Al-containing cement and

the cerebrospinal fluid results in the release of Al ions, which may reach critical levels as high as 3000 µg/L.^{23,128} This has resulted in a fatal (sub)acute Al encephalopathy in some patients without renal failure. After a latent phase up to six weeks, patients suffered loss of consciousness, myoclonic jerks, and persistent grand mal seizures.¹⁵⁸⁻¹⁶⁰ A direct toxic effect on peripheral nerve transmission has been reported when ionomeric cements were introduced into near-nerve anatomic locations, mainly the facial nerve, following surgical reconstruction of the posterior ear canal with ionomeric cement. Paralysis developed in some cases postoperatively within two to three weeks.¹¹⁵ Except in cases where individual peripheral nerves adjacent to the biomaterial showed signs of dysfunction, symptoms of post-otosurgery Al encephalopathy are quite similar to acute Al encephalopathy with other exposure routes. They include convulsions and myoclonus of the extremities but also stupor, and mutism. In some patients there was no clinical improvement after the biomaterial was removed. Because of these cases the use of one of these cement compounds (Ionocem) was stopped in France by order of the Direction Générale de la Santé in 1994. It was suggested that all patients operated on with these products should have serum and cerebral fluid Al analysis and electroencephalograms and the biomaterial should be removed when abnormal values were noted.¹¹²

4.6. Peritoneal Dialysis and Acute Al Gastroenteropathy

Acute Al gastroenteropathy with symptoms of nausea, vomiting, cramp-like abdominal pain and general malaise can follow after accidental Al contamination of the peritoneal dialysis fluid.^{81,161} It seems as if Al has a direct toxic effect on the outer epithelium of the gastrointestinal tract.

4.7. Other Sources of Al Exposure not Related to Acute Al Intoxications

4.7.1. Parenteral Nutrition and Oral Milk Based Formula in Children

Pediatric patients are particularly at risk for Al neurotoxicity. The development of the brain occurs in the first year of life. High permeability of the immature blood-brain barrier to Al, the increased uptake of Al via a relatively poorly developed gastrointestinal tract, immature formation and

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function of the kidneys and high Al to body ratios probably all contribute to the Al toxicity.^{144,145,162-165} Children not on dialysis were intoxicated by Al-containing phosphate binders and developed encephalopathy.^{78,162,164,166,167}

A study of newborn and premature infants found that the intake from milk and formulas for preterm infants is about 0.03 mg Al/day.^{168,169} Several cases were reported to develop neurological symptoms with elevated Al tissue levels receiving no dialysis and no Al-containing phosphate binders, but Al-containing milk based formula.^{165,170} The Al content of breast milk is very small (about 20 µg/L), and formulas based on cow's milk contain about ten times as much Al. The highest amount of Al has been reported from soya-based formulas for lactose intolerance (200 µg/L to 1000 µg/L), but its toxicity risk is unknown.^{171,172}

In preterm infants, prolonged intravenous feeding with solutions containing Al is associated with impaired neurological development. These studies have methodological problems that may influence the results, but nevertheless acute Al encephalopathy with seizures and myoclonia has not been reported. Low dose of Al, present in parenteral nutrition formula, can produce marked portal inflammation correlating with the duration of exposure and the amount of Al accumulated in the liver.¹⁷³ As a result of the concern about Al in total parenteral nutrition solutions, the United States Food and Drug Administration now requires that Al concentrations be less than 25 µg/L in large volume parenteral drug products.¹⁷⁴

4.7.2. *Drinking water*

In recent study the relative bioavailability of Al naturally present in food and in alum-treated drinking water (ATW) were determined using 29 healthy volunteers, who drank, during two-day periods, ATW or pure water, with and without citrate, while on a controlled diet. Only 1-2 percent of the daily intake of Al came from ATW and only 0.3 to 0.4 percent of the Al in ATW was absorbed by the body, which was the same percentage that absorbed from food. It was estimated that drinking 1.6 L/d of ATW containing 140 µg/L Al would contribute only 0.4-1.1 percent of the lifetime body burden of Al.² However, although Al is very poorly absorbed in the gastrointestinal tract, and the possibility that some Al fractions present in drinking water may be particularly bioavailable cannot be dismissed at present, especially when exposure starts

from childhood.⁶¹ In addition, oral administration of ²⁶Al to rats resulted in higher brain ²⁶Al concentrations.¹⁷⁶ Nevertheless, recent reports on the risk of Al levels below 100-200 µg/L in drinking water do not indicate an important risk for the normal population.^{122-124,175}

4.7.3. Inhalatory Exposure

Most of the Al absorbed from the respiratory tract accumulates in the lungs. Pulmonary lesions have been described in employees of Al processing or manufacturing industries and encephalopathy after Al inhalation have been reported. Al is widely distributed and has many industrial uses, and toxicity from occupational exposure is assumed to be extremely rare.^{2,177} Nevertheless, a recent study investigating adverse effects on the central nervous system of Al welders found an Al-exposure-related increase in blood and urine Al concentrations, deficits in neuropsychological test performance and mild diffuse EEG abnormalities. Therefore the potential for Al-induced neurotoxicity in those occupationally exposed to Al-fumes may be greater than previously suspected.¹⁷⁷

Aerosol antiperspirants can be absorbed systematically via the lungs and airways and through the nasal-olfactory route. There is as yet insufficient information available to determine the possibility of Al accumulation in the brain.¹⁷⁸

4.7.4. Dermal Exposure

Blepharopigmentation with Al-silicate has been introduced during the last decade as a technique for creating a permanent line along the eyelid margin, thus simulating a cosmetic eyeliner. Patients can have a delayed hypersensitivity granulomatous reaction.¹⁷⁹

Dermal perspirants. In a preliminary study the dermal absorption of Al from antiperspirants have been estimated to be 0.03-4 µg/L, or 0.012% in one study. The clinical significance is unknown.¹⁸⁰

Vaccines adjuvants: the purpose of a vaccine adjuvant is to enhance the immune response of the vaccine. An adjuvant vaccine will tend to have a higher, earlier, and longer-lasting immune response than a non-adjuvant vaccine. Until recently, the only vaccine adjuvants approved for human use were Al salts generally referred to as alum. Commonly used Al-adjuvant vaccines

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include: diphtheria, tetanus, hepatitis, lyme, rabies and anthrax.¹⁸¹ Known side effects from Al adjuvants include short-term effects such as swelling, inflammation and granulomas¹⁸² but recently there has been a controversial finding that macrophagic myofasciitis is associated with Al-containing adjuvants.^{168,182} Although the dissolution of the Al adjuvants can take 4 to 18 months, according to animal studies, probably very little Al is incorporated into the brains.¹⁶⁸

4.7.5. *Intranasal Absorption*

There are no data that could be used to estimate Al bioavailability following intranasal exposure to indicate whether this represents a significant route of exposure,⁴ but toxicity through this route has not been reported.

4.7.6. *Low, or Absent Toxicity of Other Sources of Al Exposure in Humans in Normal Circumstances*

Commercially, Al salts are added to foods, such as frozen strawberries, maraschino cherries, and pickles, to improve their appearance. Al³⁺ salts are often added to processed, grain products, salt, cheeses and beer.¹⁸³ Plants can accumulate Al³⁺ especially in acidic soils, and evidently detoxify the Al³⁺ by possessing basic fluids or organic chelators. Especially tea is known to store Al³⁺ in cell vacuoles in older leaves separate from metabolically active parts of the plant. As much as 3% of Al³⁺ can be found in older tealeaves, while only 0.01% in younger ones, a 300-fold difference. Commercial teas yield up to 100 ppm Al³⁺ in a drink, but much higher Al concentrations can be found in certain species of leaves.^{184,185} Adding milk to form the insoluble phosphate can reduce gastrointestinal absorption of Al from tea but by addition of lemon substantial amounts of an Al citrate complex will be absorbed. Numerous other food substances were described as a possible –most likely harmless- sources of Al, like small amounts of dissolved Al from cookware, fruit juices, coffee and baking powder.^{186,187} Some foods contain large amounts of Al as a result of processing. Levels of up to 4 mg have been reported to be present in one serving of food.¹⁸⁶ Although the major source of Al in drugs remains the use of Al hydroxide phosphate binders in renal patients, some common oral pharmaceutical products can contain high amounts of Al, such

as calcium supplements (12 mg/day), buffered aspirin (10-20 mg/tablet), and Al-containing antacids (50 mg/tablet).^{140,188} Much effort is being taken to reduce the Al content of the above products or to switch to alternative products, which contain less Al.²⁰

5. Pathogenetic Mechanisms of Aluminum Intoxications

5.1. Speciation, Biokinetics and Metabolism

5.1.1. Al speciation

Despite several decades of clinical experience and animal study, the pathophysiology of brain encephalopathy is far from understood. One of the main reasons for the complexity of the research on Al is the difficult interaction with molecules found in biological systems. In most natural systems, a small fraction of Al is found as the simple Al^{3+} aqua ion. Thus Al absorption, excretion, tissue retention, and deposition will all depend on the properties of the Al^{3+} complexes formed with biological ligands. Unfortunately, the search for an accurate description of Al complexation equilibria and kinetics has been consistently frustrated by the tendency of both free Al^{3+} ion and simple Al complexes to hydrolyze at or below neutral pH.

An important issue in the toxicity of Al is the solubility and speciation of inorganic Al, which are strongly pH dependent, whereas the solubility of organically complexed Al is correlated with the level of dissolved organic matter. In aqueous circumstances with low concentrations of dissolved organic compounds, the dependence of dissolved Al on pH resembles on a logarithmic scale a parabola with a sharp solubility minimum at around pH 6.5. In water more acid than pH 5, Al^{3+} exists as an octahedral hexahydrate, $\text{Al}(\text{H}_2\text{O})_6^{3+}$, usually abbreviated as Al^{3+} and referred to as free Al. As a solution becomes less acidic, $\text{Al}(\text{H}_2\text{O})_6^{3+}$ undergoes successive deprotonations to yield $\text{Al}(\text{OH})^{2+}$, $\text{Al}(\text{OH})_2^+$ and soluble $\text{Al}(\text{OH})_3$, with a decreasing and variable number of water molecules. At pH > 6.2 tetrahedral aluminate, $\text{Al}(\text{OH})_4^-$, is the primary soluble Al^{3+} species. The Al levels in the water will be related to the pH conditions with Al hydroxide solubility equilibria but in addition to the hydroxide ion, the Al ion will also form complexes with inorganic ligands such as fluoride (F^-),

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sulphate (SO_4^{2-}) and silicate (HSiO_4^{3-}). Therefore, the actual chemical species of Al is strongly predisposing for the availability of Al for intestinal uptake as well as its metabolic behavior and toxicity.¹⁸⁹⁻¹⁹³ The mixed Al(ligand) - hydroxide complexes are the rule, rather than the exception, - and hydroxo-bridged polynuclear complexes are common.¹⁹³ Metal hydrophilic species show different neurotoxic properties indicating the ability of Al^{3+} , when diversely coordinated, to produce different biological effects.¹²⁹ Two main Al^{3+} species are recognized in aqueous solutions: the hexahydrate Al^{3+} at $\text{pH} < 5.5$ and the tetrahedral aluminate at $\text{pH} > 6.2$. In blood plasma, citrate is the main small molecule carrier and transferrin the main protein carrier of Al^{3+} . In fluids where the concentrations of these two ligands are low, nucleoside di- and triphosphates become Al^{3+} binders. Under these conditions Al^{3+} easily displaces Mg^{2+} from nucleotides. When all three classes of ligands are at low concentrations, catecholamines become likely Al^{3+} binders. In biological systems Al^{3+} will associate with oxygen donor ligands, at least some of which should be anionic to counter the $3+$ charge of the cation. Carboxylate and phosphate groups, nucleotides, and polynucleotides meet this description. Double-helical DNA binds Al^{3+} weakly. Al^{3+} forms weak complexes with amines and sulhydryl ligands. With multidentate amino-carboxylate ligands such as EDTA, Al^{3+} forms strong complexes. Al^{3+} in the cell nucleus probably binds to nucleotides or phosphorylated proteins.¹⁹⁰

5.1.2. Biokinetics

5.1.2.1. Absorption and Excretion

In man, without excessive exposure to Al and a normal renal function, the total body burden of Al is 30 to 35 mg, and the intake of Al in foods is 2 to 3 mg/day, with only a small percentage absorbed.^{15,129} The lungs contain the largest amount of Al because dust is trapped in pulmonary macrophages and its concentration increases slowly with age. After the lungs the highest concentration of Al is found in the liver, bone, spleen, myocardium and parathyroid cells and their concentration is 1 to 4 mg/kg dry weight. In these subjects bone and muscle account for about 40% of total body Al and the lungs for 12%.^{129,194} Because trace metals are indestructible, chronic accumulation of the element

will occur in patients with end-stage renal failure, because the major elimination route, i.e., the kidney is absent. This results in a much higher Al burden, ranging between 220 and 1600 mg. In these patients also a different distribution is observed with bone and liver as the major storage sites with comparable Al concentrations.¹²⁹ Most ingested Al is eliminated in the stool within several days and the Al bioavailability from food is ~ 0.1%. The remaining Al, which enters the blood via the intestinal system, is then eliminated in urine. Daily urinary Al excretion has been estimated to be 4-12 µg.⁴ About 85% of the intravenously injected Al and gallium citrates is normally removed in two weeks. The amount of Al that is not eliminated in the urine is then retained in the body by deposition in tissue and removed very slowly. An estimated terminal $t_{1/2}$ in one human being who received intravenous ²⁶Al was 7 years.^{194,195}

For many years, there has been some controversy about the quantitation of intestinal absorption of Al. Because of the lack of a suitable isotope and a sensitive technique of analysis, in the past Al have been studied indirectly using analogs such as ⁶⁷Ga ($t_{1/2}$ = 78 h). Recently, with the development of accelerator mass spectrometry (AMS), it has become possible to use the artificially produced radionuclide of Al, Al 26 (²⁶Al), ($t_{1/2}$ = 7.16 x 10⁵ years).⁸⁴ With this technique, literature data on fractional gastrointestinal absorption still varied between 0.04 and 1%.^{59,87} The fractional intestinal absorption of trace oral doses of Al hydroxide is at least 0.1% (compared with the previous estimate of 0.01% using large ²⁷Al oral loads). Absorption of Al citrate given alone is significantly greater (0.7%) and is further increased to 5% by the accompanying sodium citrate, consistent with an enhancing effect of added citrate upon mucosal Al permeability. Al maltolate absorption approximates that of Al hydroxide (0.1%).^{129,194} Although no single explanation of the exact mechanism of gastrointestinal absorption has emerged, it is believed that intestinal absorption of Al includes both paracellular pathways along enterocytes and through tight junctions by passive processes as well as transcellular pathways through the enterocytes involving both active and passive processes.¹ In normal subjects there is little or no increase of tissue Al content (except in the lungs) with aging; this suggest that the body is in neutral balance. The factors that affect the absorption of Al include uremia, dietary factors such as citrate, a low gastric pH, fasting, and also a lesser effect on absorption has been reported from lactate, parathyroid hormone and vitamin D. When Al enters the body, the kidney is

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the major organ for excretion and in renal failure there will be a widespread deposition in extracerebral organ systems of patients with Al overload and the bone and liver serve as the major storage organs.¹⁹⁴ Sequestration of Al in bone and liver protects the brain from Al toxicity.^{195,196} This is supported by the fact that conditions associated with a negative calcium balance, such as immobilization, surgery, cortocosteroid therapy, and hypophosphatemia, may precipitate the onset of the disease.¹⁹⁷ In the presence of high PTH levels there will be an increased bone uptake of Al.^{198,199} On the other hand, Al also influences the parathyroid negatively and lowers the parat hormone secretion, which reduces bone turnover.²⁰⁰ An open compartmental model for describing Al biokinetics after p.o. administration of ²⁶Al has been presented in one study, with a central compartment consisting of transferrin- and citrate-bound Al in blood plasma and interstitial fluid, and three peripheral compartments for organs, muscles and bones and the gastrointestinal tract. The rate constants describing the transport of Al are normalized to an estimated plasma volume and do not depend on the size of the individual.²⁰¹ Other routes of absorption (inhalatory, dermal and intranasal) are discussed above.

5.1.2.2 Distribution

5.1.2.2.1 Metabolism

Citrate: Since it occurs to the extent of about 0.1 nM in the blood plasma, citrate becomes the pre-eminent small molecule plasma binder of a metal ion like Al³⁺ that prefers oxygen donor ligands. Citrate complexation of Al³⁺ in the upper gastrointestinal tract with a pH of 2 - 5, may form a zero-charged complex that may pass through membranes. Sodium citrate as well as calcium citrate may cause a 100-fold enhancement of gastrointestinal Al absorption. The adsorption of Al from Al(OH)₃-based antacid rises substantially upon intake of citrate, and therefore these antacids should not be taken with citrus fruit or juices.¹⁹⁰

Protein binding: Although transferrin is generally acknowledged to be the serum protein binder of Al, also other proteins such as albumin, albindin²⁰⁵ and de novo synthesized proteins⁷² have been suggested as potential s-Al binders. The common albumin and globulin proteins of the plasma bind metal

ions such as Al^{3+} only weakly and non-specifically. With a pair of sites that avidly binds Fe^{2+} , transferrin stands as the leading plasma protein for Al^{3+} binding and carrier in the plasma.¹⁹⁰ The cerebrospinal fluid lacks any transferrin and contains only about 2 μM citrate. The transport of Al by transferrin favors the delivery of Al to cells with numerous transferrin receptors, such as hepatocytes and red blood cells precursors.²³

Catecholamines: By binding to the catechol of catecholamines, trace amounts of Al^{3+} may possibly disrupt many neurochemical processes.¹⁹⁰

5.1.2.3. Nucleotides and Organic Phosphates

Al behaves as an extremely potent genotoxic agent and specific genetic sub-compartments are selectively targeted. Numerous molecular genetic mechanisms have been described, involving Al neurotoxicity towards neuronal and glial cell nuclei and brain specific gene transcription. In spite of a considerable body of scientific evidence the precise pathophysiology remains unclear. One emerging hypothesis is that Al is strongly attracted to the phosphates of nucleic acids (and nucleotide triphosphates) especially rich in adenine (A) and thymine (T) residues, so brain RNA and DNA sequences containing a high molar percentage of A + T nucleotides may be particularly at risk for the deleterious effects of Al. In particular, the high content of intranuclear phosphate (approaching 60 mM), the normally decondensed or extensive euchromatization characteristic of neocortical neuronal nuclei, their intrinsically high rate of transcriptional output and their generation of complex RNA message populations required for normal brain cell function may specifically target neutral cells for many of Al's genotoxic effects.⁶⁶ In experimental Al neurotoxicity studies, especially when acute high dose of Al were applied, Al targets numerous cytoplasmic and nuclear structures. For example, a single stereotactic injection of 100 $\mu\text{g}/\text{L}$ of a 1 per cent Al lactate solution into rabbit cerebral ventricles results within 3 hours, in decreased levels of RNA messages encoding the key cytoskeletal components alpha-tubulin, beta-actin and the light chain of the neuron-specific neurofilament protein.^{66,204} This observation would be in accordance with, though not explain, the development of neurofibrillary pathology as observed in experimental Al intoxications and in Alzheimer's disease.

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Another interesting speculation is that Al is able to exchange other key cations like iron, magnesium and zinc from binding sites necessary for normal molecular genetic function of transcription factor proteins and thereby play an ancillary role for further disrupting gene transcription mechanisms.⁶⁶ After calcium and iron, zinc is the third most abundant trace element in the mammalian brain, and has been receiving a lot of attention lately because of its potential role in the development of human neuropathology.^{188,206,207} Excessive synaptic zinc release and postsynaptic zinc accumulation may contribute to neuronal loss associated with certain acute brain injury conditions including transient global ischemia and epilepsy. In the normal brain, zinc is thought to provide highly specialized neuromodulatory, neuroprotective and neurosecretory functions and is intimately involved with structural, regulatory and enzymatic proteins that provide these functions.¹⁸⁸ Bioinformatics analysis of newly sequenced human DNA from the human genome project suggests that up to 1 percent of total human coding DNA, or up to 1000 genes, encoding zinc-requiring transcription factors^{207,208} and therefore Al has the potential to interact with many important zinc-containing elements of the brain's gene expression system.⁶⁶

5.2. Neuropathological Mechanisms

The published descriptions of the neuropathologic changes of chronic Al encephalopathy in the past have been remarkably brief, absent or non-specific, and no data at all are available from the neuropathologic changes in acute Al encephalopathy in humans. In the brain significant Al content was observed in the hippocampus, the occipito-parietal cortex, the cerebellum, and the striatum. This topographic distribution correlated with the clinical defects in higher cortical functions, including aphasia. Spongy changes consisting of vacuoles in the neuropil and inside nerve cell bodies were found and the vacuoles were located mainly in dendrites and astrocytic processes. Thus, Al encephalopathy is a disease of neurons and astrocytes of the cerebral cortex.^{103,209-211} None of these abnormalities found post-mortem were sufficient to account for the patients' neurological conditions.^{25,211} In animal studies most pronounced changes in the brain were observed in the hippocampus.²¹²

The development of a new silver-staining technique by Reusche allowed

the visualization of characteristic patterns and distinct morphological changes of chronic Al encephalopathy in humans. Central nervous tissue (CNS) and peripheral organs of 50 autopsy cases with chronic renal failure (CRF) and dialysis treatment were evaluated for Al-containing argyrophilic inclusions using the Howell and Black method modified by Reusche.^{51,195,213} Al encephalopathy morphology is characterized by lysosome-derived intracytoplasmic, Al-containing, pathognomonic, argyrophilic inclusions in choroid plexus epithelia, cortical glia and neurons. The most sensitive structure for CNS deposits is choroid epithelia, followed by glial cells and neurons. Autonomic ganglia, heart, ovary/testis, parathyroid, adrenal, and pituitary demonstrated reliably peripheral deposits.^{213,214} Glial cells presented massive silver-stained deposits, which were restricted to the gray matter. Finally, neurons revealed numerous fine-granular black inclusions, scattered throughout the cytoplasm. Brainstem nuclei were primarily affected, but neurons within cortex, subcortical gray matter and spinal cord were also involved to various degrees; inclusions were not evident in the nucleus dentatus and the oliva inferior. Vessel-related deposits were found frequently. By electron microscopy the cytoplasm of neurons was filled either with large amounts of small electron-dense granules, or with lipofuscin granules, containing numerous irregular, non-membrane-bound inclusions. Massive electron-dense depositions were seen in the cytoplasm of choroidal epithelia and in proximity to nuclei of cortical astro- and oligodendroglia. These deposits remain for many years and even after renal transplantation, with termination of drug-related Al intake and normalized renal Al excretion, the Al-induced argyrophilic degradation products remained in the cellular cytoplasm in unchanged fashion up to ten years.⁹²

Many investigators have also observed neurofibrillary degeneration changes that were regarded to be similar to neurofibrillary tangles in Alzheimer's disease and the hallmark of the experimental encephalopathy induced by Al in rabbits, cats and ferrets is neurofibrillary tangle.^{50,60,70,215} Al-induced tangles are due to the accumulation of 10 nm neurofilaments in the body and processes (axon and dendrites) of neurons.⁴⁸⁻⁵⁰ Neurofilaments begin to accumulate a few hours after intracisternal injection of Al.²¹ The diffuse distribution of neurofibrillary pathology suggests that nearly all nerve cell populations are prone to the toxic action of Al, the most vulnerable being neurons of the anterior horns of the spinal cord, of the reticular formation

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and of the basal forebrain, the Purkinje cell system and the pyramidal neurons of the cerebral cortex. These studies have supported the theory concerning Al as an etiological agent for cerebral changes in Alzheimer's disease.⁷⁰ Recently, however, skepticism has developed about the similarity of these neurofibrillary tangles in Al encephalopathy and Alzheimer's disease. In a study using a new silver staining technique, the described neuronal changes and, in particular, alterations of choroidal epithelium and glia were demonstrated to be completely different from characteristic plaques and tangles in senile dementia of Alzheimer type.^{51,92} This assumption is also supported by the fact that neurofibrillary deposits are detected in the proximal end of the axon only one day after experimental administration of Al, while it takes several weeks before neurofibrillary degeneration is seen near the nucleus. During this latency period the neurons show progressive loss of excitability. Therefore cell damage is conceivably not caused by the presence of fibrillary deposits, per se, but by the loss of the normal functions of neurotubules and neurofilaments.³¹

5.3. Theories of Pathophysiology of Aluminum Encephalopathy

5.3.1. Blood-Brain Barrier (BBB)

The brain is defended by a continuous layer of cell membranes, the blood-brain barrier (BBB), which not only hinders the entry of large molecular mass substances into the central nerve system, but additionally regulates all the exchanges of nutrients, hormones, toxins and therapeutic agents that enter the CNS from the blood (to see a diagram visit <http://www.sfn.org/briefings/blood-brain.html>).²¹⁶⁻²¹⁸ When Al enters the systemic circulation it binds to transferrin, the predominant Al species in plasma, and results in a rapid entering of the brain. It has been suggested that Al can alter the BBB permeability and alter the flux of molecules and ions into and out of the brain,²¹⁷ but others state that Al uptake into the brain is not dependant upon alterations to BBB permeability.²¹⁸⁻²²⁰ This brain Al entry could be mediated by transferrin-receptor-mediated endocytosis and is enhanced when Al binds to citrate (TfR-ME) (Fig. 3).^{4,221,222} Al can penetrate into the extracellular space of the brain frontal

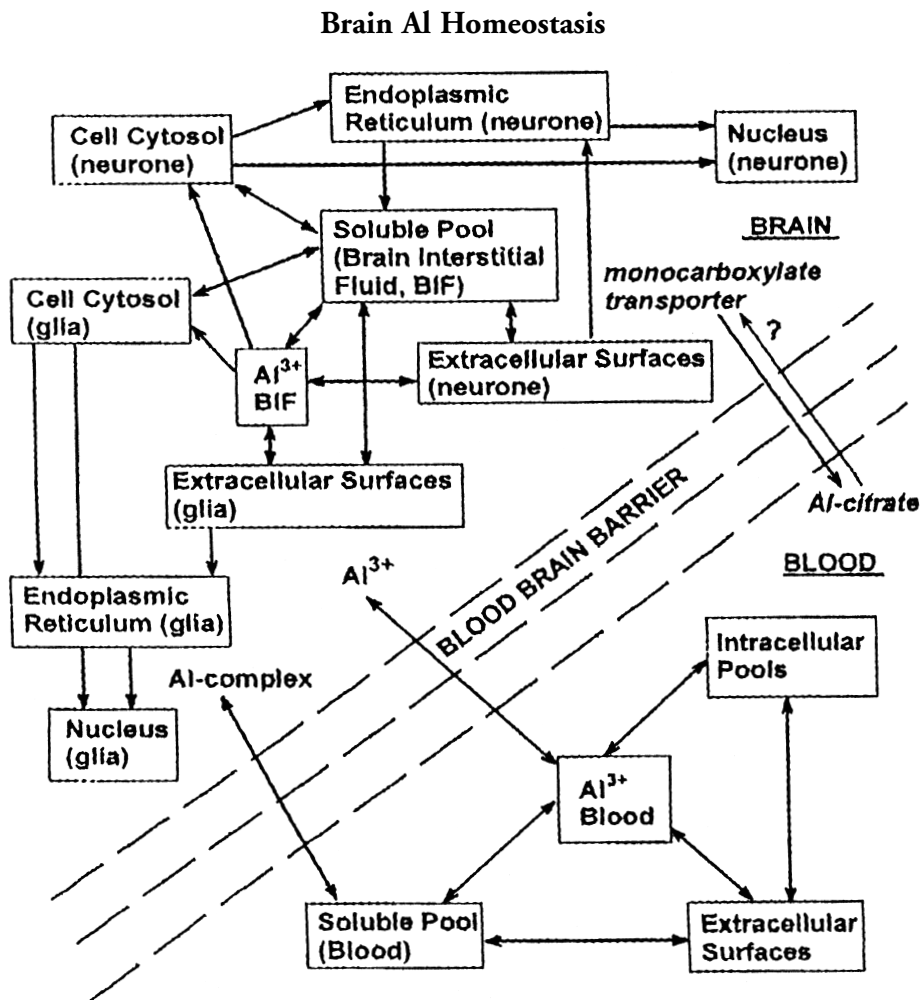


Fig 3. The dynamic partitioning of aluminum in the brain results in three (extracellular, surface associated and intracellular) significant sources of biologically available aluminum. In the blood, aluminum is bound by proteins, such as transferrin, and a number of lower molecular weight ligands which could include small peptides, nucleotides, nucleic acids, citrate, phosphate and silicic acid. In BIF, aluminum is bound by some of the lower molecular weight ligands found in blood as well as neurotransmitters such as glutamate and GABA. Aluminum is associated with the phosphate headgroups of lipids which act as sites for the nucleation and aggregation of aluminum. Intracellular aluminum may be found bound to ATP or in endoplasmic reticulum and Golgi in close proximity to the nucleus. Aluminum may also be found in nuclear chromatin. There is continuous exchange of aluminum between intracellular and extracellular compartments and the predominant exchange pathway will change in tandem with changes in brain physiology.

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cortex and ventral hippocampus within 20 minutes.²¹⁷ Although some Al that enters the brain is rapidly refluxed, it is suggested that a fraction enters brain compartments within 24 h from which it is only very slowly eliminated.²²³ The $t_{1/2}$ of ^{26}Al in rat brain was > 100 days following intravenous ^{26}Al transferrin dosing.²²²⁻²²⁴ Although neurotoxicity may be the most striking form of Al-related toxicity, the brain (and also blood) in fact contains the lowest levels of Al overload.^{31,38,151,225-227} Transferrin receptors are expressed on blood vessels, large neurons in the cortex, striatum and hippocampus as well as oligodendrocytes and astrocytes²²⁸ but in the cerebrospinal fluid Al will preferentially bind to citrate due to the fact that the molar concentration of citrate in cerebrospinal fluid is up to 900-fold higher than that of transferrin.^{23,218}

5.3.2. Brain Al Homeostasis and Cellular Mechanisms

Al has been found in glia (mainly astrocytes, oligodendrocytes and microglia)²²⁹ and in the perinuclear endoplasmic reticulum of neurons.^{230,231} Disruption of glial cell function by Al results in the accumulation of unwanted, probably cytotoxic debris and modulation of synaptic transmission and neurone-glia signaling.²³² Al^{3+} binds almost 10^7 more strongly to ATP^{4-} than does Mg^{2+} ¹⁸⁹ and forms a stable complex, which is more stable than a complex with Mg.²³³ Mg^{2+} is associated with phosphate groups and Al^{3+} can compete with Mg^{2+} for the phosphate sites. In the brain ATP acts upon extracellular inotropic (P2X) and metabotropic (P2Y) receptors to optimize the activities of neurotransmitters including glutamate, gamma-aminobutyric acid (GABA) and acetylcholine.²³⁴⁻²³⁶ It was also suggested that a disturbance of neurotransmitter metabolism in the brain as a result of Al inhibition of dihydropteridine reductase is responsible for the neurotoxicity.²²⁰ To date, 14 different P2 receptors have been identified in the brain. Some of them might be released as a complex with Mg, and in these cases Al will be intracellular in competition to form Al-ATP instead of Mg-ATP. Al-ATP might act upon muscarinic receptors to potentiate the negative feedback controlling the release of acetylcholine into the synaptic cleft, causing deficits in neurotransmitter stimulation.^{237,238} Another mechanism, which might explain the neurotoxic and other actions of Al, is the interaction with calmodulin.

One of the most abundant and versatile Ca^{2+} -binding proteins, calmodulin regulates a large number of cellular processes and target proteins in response to Ca^{2+} signaling. Calmodulin is found in all eukaryotic cells. It couples the intracellular Ca^{2+} signal to many essential cellular events by binding and regulating activities of more than 40 different proteins and enzymes in a Ca^{2+} -dependent manner.²⁰⁷ The calmodulin-calcium complex modulates a number of different enzymes and cellular processes.^{239,240} The N-methyl-D-aspartate (NMDA) receptor mediates synaptic transmission and plasticity in the central nervous system (CNS) and is regulated by tyrosine phosphorylation. Al inhibits Ca-dependent inactivation of NMDA receptor channels.²⁴¹ It was suggested that the inhibition of the Ca-dependent inactivation of NMDA channels by Al could occur through the stabilization of the post-synaptic regulatory protein that might be possibly a sub-unit of a P2 receptor²³⁸ (Fig. 3). Block of the channel of N-methyl-D-aspartate (NMDA) receptors by external Mg^{2+} has broad implications for the many physiological and pathological processes that depend on NMDA receptor activation²⁴¹ and it seems likely that these effects are even more severe with external Al^{3+} . Lipid peroxidation and the production of superoxide radicals have also been reported as a possible mechanism of Al toxicity.²⁴²

5.3.3. Al and Neurotransmission

Cognitive impairments due to Al may in part be the result of the alteration of the function of GABA receptors due to cognitive impairment through disruption of inhibitory circuits.²⁴³ Al lowers the excitability of the nerve cells of hippocampus, which can result in convulsions. Synaptic currents were normal in animal studies, but the possibility to activate the spike discharge was less effective. The abnormal excitability of such neurons in vitro is probably related to abnormal lengthening of the depolarizing after-potential, with reduced post-discharge depolarization,⁴⁷ and to reduce electronic length of the cell as well.²⁴⁴ Another typical feature of Al encephalopathy is the progression of the disease with an increasing number of clinical epileptogenic features until coma and death ensues. This might be related to a increasing loss of neurons. Neuropathological studies show a decreased number of tangle-bearing neurons and severe nerve cell loss, especially in anterior horns

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and hippocampus, and behavior studies reminiscent of temporal lobe epilepsy, may be due to the atrophy of the hippocampus.^{21,22}

5.3.4. *Delayed Neurotoxicity*

Cellular and molecular mechanisms of neurotoxicity are also influenced by the fact that neurons are postmitotic and do not divide. Thus, the capacity for replacement of damaged cells does not exist in the nervous system, whereas most other organ systems have a well-established capacity for regeneration. Many neurotoxins can cause encephalopathy and an important concept in neurotoxicology is the delayed manifestation of symptoms sometimes up to years after the exposure started. Several agents show a lag time between exposure and neurotoxicity. Examples are organophosphate chemical warfare agents,²⁴⁵ bismuth intoxications²⁴⁶ and methylmercury intoxication²⁴⁷ with a lag phase of weeks to months. One of the longest delays in time between exposure and neurotoxicity however, seems to be in the case of Al encephalopathy, where it can take several years to develop. In one case report a 14-year old boy was described who sustained a skull wound as a result of a hand-grenade explosion. This resulted in implementation of a fragment of metallic Al into the left occipital brain. Fifteen years later, at age 29, he developed seizures, mental disturbances and language difficulty. After a gradual deterioration he died at age 34 in status epilepticus.²⁴⁸ Similar observations on delayed neurotoxicity in acute Al encephalopathy have been made in animal studies. Mice and rats seem to be very resistant to the effects of Al, but rabbits are particularly sensitive to Al neurotoxicity and develop severe neurological changes, especially if the metal is administered directly into the central nervous system. Rabbits injected intracerebrally or into the cisterna magna with Al chloride developed quadriplegia and generalized epileptic seizures within seven to 20 days after an incubation period during which they seemed completely normal except for the EEG. Most animals died after a few days of seizures by the 15th day of injection.^{52,53} It seems very obvious that several steps are necessary in the process leading to Al encephalopathy and that each step causes a delay in time before symptoms can occur. It could be postulated that, in the final analysis, no one of these mechanisms will emerge as the mechanism but that Al neurotoxicity is due to many, if not all, of them acting synergistically.²⁴⁹

5.4. Pathological Mechanisms of Bone Disease

Much clinical and experimental experience has been obtained about the manifestation of bone diseases, especially in renal patients. Many patients with Al-induced bone disease remain asymptomatic. There are two distinct forms of Al done disease. The most severe form is osteomalacia, with recurrent fractures and resistance to vitamin D therapy. This disease is characterized by an increase of osteoid due to a mineralization defect induced by Al that is localized at a critical site in the bone, i.e., the osteoid calcification front.²⁵⁰ The adynamic bone disease is another form of Al-related bone disease, characterized by a reduced bone turnover.⁹⁷ Al can have a direct negative effect on the bone by deposition at the mineralization front, causing a defective calcification. This is due to the influence of Al on calcium-phosphorus precipitation, crystal formation and crystal growth.²⁵¹ There might also be a toxic effect on the proliferation of osteoblasts and on mature osteoblasts with a time- and dose- dependent effect on osteoblast growth and function.¹⁴³

Al also suppresses PTH secretion and maybe as well as the PTH synthesis, which results in reduced bone formation and increases Al accumulation in the bone.²⁵² Other studies have found that:

- (1) human parathyroid gland/parathyroid cells exhibit transferrin receptors;
- (2) Al- transferrin complex is taken up by the parathyroid gland in a dose dependent manner; and
- (3) uptake of Al by transferrin receptor-mediated endocytosis reduces the secretion of PTH but not its synthesis.

These in vitro findings allow us to suggest that transferrin receptor-mediated uptake of Al might, besides other factors such as vitamin D, high calcium dialysate or CaCO₃ intake, play a role in the development of hypoparathyroidism associated with Al bone disease. The exact mechanism by which Al-transferrin suppresses iPTH secretion remains to be elucidated.²⁵³ Hyperparathyroidism may afford the bone some protection against the toxic effects of Al.¹⁷

5.5. Microcytic anemia

Most patients with Al intoxication develop an erythropoietin-resistant microcytic anemia in the absence of iron deficiency, and this may be a useful

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early indication of Al toxicity.^{41,93,254,255} The chemical similarity between Fe^{3+} and Al^{3+} suggest that both elements will have similar metabolic effects, suggesting that iron and Al compete during erythropoiesis, resulting from a reversible block in heme synthesis due either to a defect in porphyrin synthesis or to impaired iron utilization. It was also suggested that the main mechanisms for Al toxicity in the erythropoietic system are the interference of Al in the uptake and utilization of iron and an interaction of Al with cellular membrane components, affecting not only their structures but also their functions.²⁵⁶

6. Treatment of AL Intoxications

6.1. Prevention and Management Al Intoxication

Because Al toxicity is a serious iatrogen complication, any preventive measures to avoid exposure to Al are incumbent. Unfortunately, with the current treatment practices, there continues to be a risk that patients receive excessive amounts of Al orally or parenterally. If Al compounds cannot be avoided in patients with renal failure, routine Al tests performed every 3-4 months in serum will identify persons at greatest risk (s-Al levels > 100 to 150 $\mu\text{g/L}$) for chronic Al intoxication. Ideally, any patient with s-Al higher than 40 to 50 mg/L should discontinue Al gels and use other substitutes. These patients should also be warned not to ingest these compounds with liquids containing citrate, for example, fruit juices.

Hemodialysis patients in dialysis centers or on home hemodialysis generally will be protected from Al intoxications by the combination of deionization and RO devices. Nevertheless, one should realize that the composition of the dialysate is a combination of "normal" drinking water according to WHO guidelines and extended water purification. Drinking water conditions can change unexpectedly and erratically at the water plant as well as in the water distribution system, making it absolutely unsuitable for preparation of dialysate upon its arrival in the dialysis unit without optimal further water treatment. Especially Al concentrations in the water supply in regions that use Al salts for purification can vary from day to day and it is impossible to monitor the water Al levels frequently enough to detect periodic but dangerous increments in Al levels.

Physicians in charge of dialysis centres should be aware of the fact that they are solely responsible for the water quality of the dialysate⁶³ and that the conditions of the water treatment system can change, especially due to Al compounds in the water supply. Membrane fouling in reverse osmosis (RO) systems is inevitable in many systems and effectively anticipating, compensating for and counteracting the fouling phenomena is necessary. While overall flux performances will decline for all membrane systems, the actual time between cleanings will vary, depending upon membrane type, system design and feed water quality. Reverse osmosis is an effective means of removing a wide spectrum of contaminants, including particles, inorganic substances, organic chemicals with molecular weight greater than 300, bacteria and endotoxins. An important exception to this general rule relates to Al, which, because of its amphoteric nature, may be present as a non-ionized species. In such circumstances, deionisation with mixed bed units may be ineffective for Al removal and reverse osmosis may be superior to deionisation. Other factors, especially scalants, can also reduce the quality of the RO membranes. The two most common scalants are calcium carbonate and calcium sulfate. Sharply pointed scale crystals may come into contact and cut the membrane, causing irreversible damage. Well-known fouling particles besides bacteria are Al, iron and silica.²⁵⁹ Although in a review in the 1980s 92% of reported dialysis dementia cases were dialyzed with either unprocessed or softened water, still 6% of dialysis dementia patients were treated with water prepared by either deionisation or reverse osmosis until the 1990s.⁴⁶ Even dialysis centres with sophisticated water treatment devices may be faced with episodes of serous Al intoxication, due to the use of Al salt coagulants in potable water treatment. The scarce rainfall in the South of Portugal in 1992 resulted in a subsequent decrease in the level of water sources, resulting in high concentrations of suspended particles, which, in turn, necessitated the addition of huge amounts of alum. This action was not reported to the municipal authorities. In a dialysis centre in Portugal using a RO, the passage of this severely contaminated water through the water purification installation of a hemodialysis centre resulted in the obstruction of the RO membranes.^{30,43-45} The efficiency of the RO membranes relies on two rejection mechanisms: a mechanical sieving filter with 200 Dalton pores and an electrostatic repulsive mechanism. The ionized Al fraction is rejected very efficiently (up to 99%) by the RO membranes. However, for the bulk Al, present as a colloid, the RO membranes get fouled.

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Membrane fouling *does* enhance the accumulation of concentration at the membrane level and masks the electrostatic repulsion mechanism. This is matched with an increased Al breakthrough. In these circumstances, it has been found that the ability of the RO to reject Al may become as low as 30% to 50%. Consequently, RO membranes and cartridge filters had to be replaced frequently. During these interventions, which took place over a period of several days, insufficiently treated water was sent directly to the dialysis machines and to the patients involved. In this case both ways of exposure probably contributed to acute Al intoxication and all together 18 of 71 (25.3%) patients died of severe encephalopathy.^{30,43,44} Al levels up to 2,200 µg/L were measured in water used for preparation of the dialysate.⁴⁵ Most RO units, however, make use of continuous conductivity monitoring of the purified water. A low conductivity represents a low amount of dissolved ions, which means that the membranes are functioning well. Nevertheless, in some cases one series of RO membranes may be insufficient which makes two RO membranes in line necessary.²⁶⁰

It should be stressed that regular monitoring of the Al levels in serum and dialysate at the normal frequency of one to three times a year,⁶² might give a false sense of reassurance when the results are normal, as serious exposure might be unnoticed between these testing intervals and serious irreversible neurological damage can develop within weeks. Additional safety precautions can result from a good cooperation between drinking water companies and dialysis centres. Water utilities should notify dialysis centres when situations with important changes in water quality are expected. In particular, dialysis centres should be warned when the Al concentration in drinking water can exceed 30 µg/L. This implies that the dialysis centres should be informed when water utilities change the practice of flocculation to the use of Al flocculants. The centres should also be informed if the concentration of Al exceeds the relatively high level of 200 µg/L, above the WHO standards. In addition, when cemented drinking water distribution pipes are put into service, Al levels should be tested in the tap water and dialysis centres should be warned when Al levels are above 30 µg/L.¹⁸

6.2. Treatment

At the start of therapy one should identify and eliminate the source or sources of the Al. Up to date, desferrioxamine is the hallmark of therapy

for Al intoxication.²⁶⁰⁻²⁷³

6.3. Desferrioxamine (DFO)

Desferrioxamine (DFO) is a trihydroaminic acid obtained from isolates of *Streptomyces pilosus*. Since 1963 it has been clinically used as an iron-chelating agent in patients with iron overload.²⁶¹ DFO effectively chelates trivalent ions such as iron and Al, producing respectively ferrioxamine and aluminoxamine.^{12,30,260-269} DFO displays rather complicated physicochemical characteristics. Unchelated DFO is a straight-chained lipophilic molecule that can penetrate plasma membranes and undergo metabolic breakdown. In contact with Al, it twines itself around the metal to form stable hydrophilic complexes.^{260,261} Since 1980 it is also used in the diagnosis and treatment of Al overload in dialysis patients.¹¹ DFO treatment has a number of side effects such as digestive dysfunction, skin rashes, neutropenia, hypotension, auditory impairment, cataract, visual impairment, retinal changes similar to those seen in retinitis pigmentosa and life-threatening infections with non-siderophore-producing germs, especially mucormycosis with a fatality rate of 86%. This increased susceptibility to mucormycosis, especially the *Rhizopus* species, is due to the by-product of DFO therapy, ferrioxamine. Ferrioxamine can promote the growth and pathogenicity of specific *Rhizopus* species with receptors for ferrioxamine.²⁶² In addition, exacerbation of Al encephalopathy is an important side effect, which limits high doses of this chelating agent in Al intoxications. The exacerbation of the Al encephalopathy might also be the result of redistribution of Al mobilized by DFO into the brain when very high plasma Al levels in excess of 500 µg/L occur.⁷⁴ It has also been speculated that the Al chelated compound, that is, aluminoxamine, by its ability to cross the blood-brain barrier might precipitate or exacerbate Al-related encephalopathy.^{80,219} On the other hand, DFO itself might be a possible causative agent of these neurotoxic effects as the neurotoxicity is dose-dependent and it is also observed in patients with normal renal function.^{266,267} Chelation of Al with DFO has been very useful in the treatment of Al encephalopathy, but the best mode of administration, optimum dose, and duration of treatment are not clearly established. The current practice is to administer DFO once per

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week; it can be given intramuscularly the evening prior to dialysis, or several hours before dialysis so that sustained ferroxamine levels are present in the plasma for the shortest possible time before being removed. Removal of Al from Al intoxicated patients is difficult due to its large volume of distribution, high protein binding, and poor dialyzability.²⁶⁸ The Al chelation by DFO is less dose-dependent compared to iron chelation. Apparently there exists a readily available pool of Al, which can be chelated by relatively low doses of DFO, while a deeper pool is more difficult to reach even with higher doses of the chelating agent.²⁶⁹

6.4. Treatment with DFO in Hemodialysis Patients

The optimal dose of DFO for long-term chelation is uncertain, although toxicity appears to be reduced at lower doses. In the search for an optimal dose one should consider the following aspects.

- 1) Side effects of treatment with DFO
 - a. The potential side effects are, at least in part, dose- and duration-related. With the high doses used in the past, varying between 30 and 80 mg/kg, serious side effects have been reported even after a single dose of the chelator. These include hypotension, exacerbation of Al-related encephalopathy, retinal and auditory neurotoxicity, rash and fatal bacterial and fungal infections. Of 89 patients receiving nightly subcutaneous DFO for transfusion-dependent thalassemia major, 13 presented with visual loss or deafness of acute onset or both. Detailed ophthalmologic, audiologic, and evoked-potential studies uncovered abnormalities caused by neurotoxicity in 27 more. Four patients with visual loss had optic neuropathy, with a marked decrease in acuity, loss of color vision, and delayed visual evoked potentials. Five asymptomatic patients had changes in the pigment of the retinal epithelium. The hearing loss was characterized by a high-frequency sensorineural deficit, which necessitated hearing aids in six patients. When desferroxamine was stopped, recovery of vision was complete in two patients and partial in two, and in 22 patients with abnormal audiograms, reversal of the hearing deficit was complete in four and partial in one.²⁶⁴
 - b. High DFO treatment dosage requires the need of regular follow-up

(at least every three months). Thus; patients treated with DFO should be referred to ophthalmology and otorhinolaryngology for baseline and follow-up examinations.²⁶⁴

- c. The dosage and interval of DFO treatment should be adjusted to keep peak s-Al levels below 400-500 mg/L, to avoid exacerbation of neurological symptoms.²⁶⁵
- d. Low dose DFO (5 mg/kg) has been recommended at the Consensus Conference on diagnosis and treatment of Al overload in end stage renal failure in 1992 in Paris.³⁰
- e. DFO infusion can cause hypotension. This can be reduced by slowing the infusion rate to one hour, and treated by temporarily stopping the infusion, and administration of a volume expander if required.³⁰
- f. A dosage of 5 mg/kg DFO can differentiate between patients with Al-related bone disease; increased risk for Al toxicity and Al overload. A serum increment after DFO of more 50 mg/L or more had a sensitivity of 91% and a specificity of 95% in the detection of Al overload, thus suitable to detect patients at an increased risk.³⁰

2) Techniques of treatment with DFO:

- a. The removal of aluminoxamine using conventional dialyzers is modest. However, it can be increased substantially when used in combination with a charcoal hemoperfusion column (ALUCART) or by replacing the conventional dialyzers by high flux polysulphone dialyzers. With the latter devices up to 80% of both the total aluminoxamine and ferrioxamine can be extracted from the body during a single dialysis session. The presence of DFO and the use of a charcoal column (ALUCART) in combination with a conventional dialyzer may markedly increase the extraction of Al during dialysis.²⁷³
- b. Treatment of Al overload using a cartridge with immobilized DFO is efficient and safe and eliminates the potential toxicity of DFO treatment. Although this seems to be the treatment of choice in severely intoxicated patients, this device is not readily available and may be expensive.²⁷³
- c. The high polysulfone F-80 dialyzer effects a much greater removal of the DFO- chelated complexes, than conventional dialyzers.²⁷²

Timing of DFO treatment and monitoring of Al levels: Administering a

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- 3) test dose of DFO and measuring the increment of serum or plasma Al may estimate the body burden of Al. Patients with Al levels above 300 $\mu\text{g/L}$ at any time are at increased risk for neurotoxicity during the treatment. The treatment schedule should be adjusted in these patients.
 - a. High-risk patients (peak s-Al levels 300-500 $\mu\text{g/L}$). Peak aluminoxamine levels occur several hours after administration of DFO and there is no decline of serum aluminoxamine levels during the inter dialytic period. Unchelated DFO is no longer detectable 6 h (i.e., 3 half lives) after administration.²⁷⁴ Especially patients with high Al levels ($> 300\text{-}500 \mu\text{g/L}$) are at risk for developing neurotoxicity symptoms during these first 6 hours. Therefore dialysis should cover these hours in these patients and DFO should be administered i.m. 5 hours prior to a dialysis session with a high flux dialyzer and side effects of DFO infusion will then be minimal.³⁰

Low risk patients (s-Al level $< 300 \mu\text{g/L}$). Patients with s-Al levels below 300 $\mu\text{g/L}$ are at lower risk of neurotoxicity and the chelator can be given safely during the last hour of a dialysis session at the start of which a serum sample is taken for Al determination. A second serum sample is taken at the start of the next dialysis session.
 - b.
- 4) Practical considerations concerning DFO treatment in hemodialysis patients: the treatment schedules not only should avoid complications, but they also should accommodate the patients and dialysis staff as much as possible and therefore fit into the regular dialysis sessions. Considering this, as an example dialysis should not be necessary during the weekends, high Al levels should be avoided during the weekends, and i.m. injections the day before dialysis should be given only when strictly necessary.
- 5) Duration of treatment:

The optimal duration of treatment is not clearly established. In any case one should want to reduce the s-Al levels below normal values (60 $\mu\text{g/L}$) in dialysis patients, without increment of Al levels above 50 $\mu\text{g/L}$ at two successive occasions after low dose DFO treatment. This will lead to treatment schedules for over a year in some patients, especially those

without residual diuresis. On the other hand, Al intoxication is an iatrogenic disorder and maybe therefore one should consider treating patients until their Al burdens have reached the levels before the intoxication (approximately below 20 µg/L) especially when the Al intoxication is due to accidental poisoning (see Table 4).

Considering all the above-mentioned facts, a treatment schedule was developed by W.H. Boer (University of Utrecht, The Netherlands), K. Berend (Diatel Curaçao) after consultation of M.E. de Broe (University of Antwerpen, Belgium). In our experience and that of Barata et al.³⁰, the dose of 5 mg/kg once or twice a week seems safe enough for long-term treatment and further decrease of this dosage seems unnecessary, although half this dosage may have similar efficacy.²⁶⁵

7. Conclusions

Al is a very potent neurotoxicant, with a wide variety of pathological, neurochemical, and behavioral consequences of Al exposure. There is no single unifying mechanism that can explain the wide ranges of toxic effects of Al and hundreds of cellular processes both in man and animals have been demonstrated in plants and aquatic animals in nature, experimental animals by several routes of exposure, and under different clinical conditions in humans.

Acute Al toxicity is an iatrogenic pathology that has an asymptomatic phase, whereafter severe epileptic manifestations like myoclonus and seizures result in coma and a high mortality. Especially hemodialysis patients are at risk when the dialysate is contaminated with high Al. The use of Al in bladder irrigation can lead to acute Al encephalopathy in patients with reduced kidney function. Not only kidney patients are at risk for acute Al encephalopathy, also the use of cement in otosurgery has been related to acute Al encephalopathy. Therefore, every effort should be undertaken to limit the use of compounds containing Al in patients. Unfortunately, despite widespread agreement on this point, the abolishment of Al in medicine has only partially been put in practice. Understanding the trends and basics of materials science should help the clinician to avoid unnecessary exposure. However, while Al has no biological function in mankind, it is the most abundant metal in the earth's crust and the widespread occurrence of Al, both in the environment, foodstuffs and medicine, makes it virtually impossible for man to avoid exposure. Up to date, despite an

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abundance of literature and almost forty years of research, many questions remain unresolved and several aspects of the Al metabolism, as well as the mechanisms of toxicity at the bone and brain level remain to be elucidated.

8. Recommendations for Further Study

1. Adopt a multidisciplinary perspective in Al research, involving collaborative research efforts among scientists from many different specialties.
2. Provide a full overview of the different drugs, clinical materials containing Al.
3. Determine Al concentrations in parenteral fluids that are safe for infants and children and enforce these standards.
4. Provide a better characterization of the brain pathology in dialysis patients, encompassing the entire spectrum from acute and chronic Al encephalopathy in patients with and without clinical signs of neurotoxicity, with emphasis on variations in neuropathology from acute, extremely high- level exposure to long-term, low- level exposure. All existing pathology material should be reevaluated for this purpose.
5. Cement linings of drinking water distribution pipes should be reevaluated for their possible toxicological properties.

Fig 2. Mean duration of desferrioxamine treatment (weeks) and residual diuresis in seventeen patients with aluminum intoxication

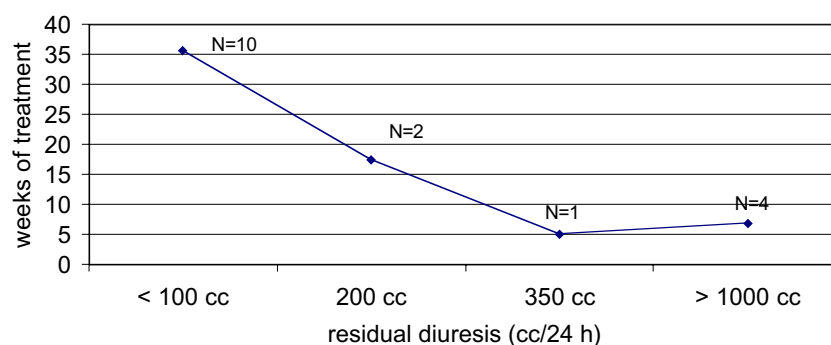


Figure 2. The treatment duration with desferrioxamine was related to the residual diuresis as all patients with a residual diuresis of a liter/day or more could be treated less than two months, while the patients with a residual diuresis less than 200 cc/24 h had to be treated up to 91 weeks (table 1). Even minimally functioning kidneys can protect patient from aluminum toxicity.
see page 107

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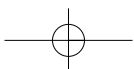
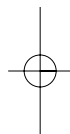
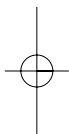
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CHAPTER VI

Prosecution after an outbreak of subacute aluminum intoxication in a hemodialysis center

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Legal Medicine, in press

CHAPTER VI

Abstract

Background. *Criminal prosecution of physicians for the death of patients has been extraordinarily rare, but there seems to be a rising trend. This case report describes the medical and judicial implications of criminal prosecution of two doctors of a hemodialysis clinic in the Netherlands Antilles that had to stand trial over the death of ten dialysis patients. The patients died of subacute aluminum intoxication when aluminum leached from the cement lining of a newly installed water distribution pipe into the water supply of the dialysis center that did not make use of a water treatment system (WTS).*

Material and methods. *Data of the case history of the dialysis patients, the criminal prosecution, preliminary judicial inquiry, the defense arguments and verdicts were reviewed.*

Results. *The prosecutor first decided to dismiss the case, but after an appeal by the families, the Court of Appeal decided to pursue prosecution for gross negligence. It held that the dialysis center should have used a WTS and also held that the dialysis staff insufficiently reacted on extra alarms on the dialysis machines the two days after the new water distribution pipe was put in use. From June 6, 1998 until January 1999 a preliminary judicial inquiry was performed in The Netherlands and on Curaçao. After a cross-examination of thirteen court-appointed experts by the prosecutor and the investigative judge, the prosecutor charged the two physicians of gross negligence and manslaughter for not testing the composition of the water after the construction at the water distribution network. A prison sentence with probation of six months was demanded. The District Court disagreed on all issues with the prosecutor, but nevertheless held the medical director of Diatel guilty for performing hemodialysis without a WTS. In May 2000, the Court of Appeal held that it was not allowed to rule on the omission to install a WTS because this issue was not included in the charge and overturned the conviction.*

Conclusions. *Medical personnel in charge of potentially dangerous procedures should be prepared for unexpected changes in the quality of their treatment. Because court-appointed experts might have an extraordinary role in the decision making process, guidelines should be prepared to assure the quality of their testimony.*

Key words: Aluminum intoxication hemodialysis prosecution expert witness

Introduction

Criminal prosecution of physicians for the deaths of patients are extraordinarily rare,¹ but its occurrence continues to rise.²⁻⁵ The vast majority of doctors will not deliberately expose patients to serious risks, but when it appears as if a physician's medical acts, or negligence, result in the death of a patient, the public expects that some action will be taken against the physician. Some people believe that prosecution is essentially necessary due to the ineffectiveness of the current disciplinary mechanisms within the health care profession.³ For the medical practitioner, prosecution will be one of the most distressing experiences in his medical career, not only because the judicial process may last several years, but primarily because it touches upon the foundation of medical ethics. In most cases, expert evidence information is decisively important in a rapidly growing percentage of decisions throughout civil and criminal law. This is also because expert witnesses are in a very privileged position as they may give their opinion as evidence, unlike other witnesses who can only give evidence of facts.⁶⁻⁹ This report describes the prosecution of the two physicians of a the hemodialysis center Diatel in the Netherlands Antilles, after an outbreak of acute aluminum (Al) intoxication when Al leached from the cement lining of a newly installed drinking water distribution pipe.^{10,11}

Materials and Methods

The dialysis center

Patients on maintenance hemodialysis are parenterally exposed to 20-30,000 liters of water annually. To ensure the water quality, water treatment systems WTS with reverse osmosis (RO) filters are used in most countries since the early 1980's, but some dialysis centers continued using untreated tap water long after.¹² In Curaçao, an island of the Netherlands Antilles, public city water is produced by distillation of seawater. This tapwater had been used for hemodialysis since 1971 in the local hospital. In 1993 the hospital installed a WTS in the dialysis unit but remained using tapwater for hemodialysis in the intensive care unit. In 1992, a non-profit dialysis center Diatel was opened with the financial and technical support of the Dutch Kidney Foundation. Initially

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it was decided not to install a WTS, but because of water pressure problems a WTS with a booster pump and storage tank was scheduled to be installed in August 1996. Table 1 shows the water analysis of 1994 and 1996, compared with several dialysis standards,¹³⁻¹⁵ toxicity levels¹⁴ and the WHO drinking water guidelines.¹⁶ Four of the tested chemicals were above American standards in

Table 1. Water^b analysis in 1994 and 1996, compared with several dialysis¹³⁻¹⁵ and drinking water standards¹⁶.

	Tapwater ^b analysis January, 1994	Tapwater ^b analysis September, 1994	Tapwater ^b analysis July, 1996	A.A.M.I. hemodialysis water ^b standards ¹³	Water; ^b lowest toxicity level ¹⁴	EC Directive, water ^{b15}	WHO drinking water guideline ¹⁶
Sodium, mg/L	22.98		14.48	70	300		
Aluminum, µg/L	16		650	10	60	30	200
Calcium, mg/L	10.79	8.4	18.1	2	88 ^a		
Copper, mg/L	0.003		< 0.005	0.1	0.49		
Magnesium, mg/L	4.618	5.1	1.665	4	88 ^a		
Zinc, mg/L	0.184		0.062	0.1	0.2		
Fluoride, mg/L	0.18		0.5	0.2	1		
Nitrate(N), mg/L	<0.2		< 0.2	2	21		
Sulfate, mg/L	5.1		4.1	100	200		

^aThe sum of the Calcium and Magnesium levels should be below 88 mg/l.¹⁴

^b To prepare dialysis fluid, (purified) tap water is mixed by the dialysis machine with a bicarbonate concentrate and an "acid" component, containing calcium, magnesium and other compounds.

1994,¹³ but below toxic levels¹⁴ and below the European Union (EU) guideline for Al (see table 1).¹⁵ To prepare dialysis fluid, water is mixed by the dialysis machine with a bicarbonate concentrate and an "acid" component, containing calcium, magnesium and other compounds. The first 3.5 years with 9600 dialysis treatments were uneventful and the mortality low (one local patient and one tourist had died). In May 1996, the water distribution company tried to assist Diatel with the low water pressure and connected the water supply of the dialysis center to an earlier installed new water distribution pipe after flushing of the entire pipe. The interruption of the water supply lasted a few hours and dialysis was performed without incident that afternoon. During the following two days however, six of the eight dialysis machines produced repeatedly intermittent conductivity alarms for seconds to minutes. This is an indication of technical

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problems or a change of electrical conductivity that reflects the total concentration of the dissolved ions of the dialysis solution.^{13,17,18} Because an external conductivity meter demonstrated normal values of the dialysate the technician focused on technical defects and changed water tubes because of suspected air leakage and thereafter the frequency of the alarms reduced to normal proportions.

The patients

Dialysis continued for several weeks but at the end of June 1996, the dialysis center had to be closed when some patients suffered from symptomatic post dialysis hypercalcemia resulting from calcium that leached from the cement layer into the water supply. The patients recovered temporarily after transfer to the dialysis unit of the hospital but days to weeks later 10 of the 27 patients developed sepsis, convulsions, coma and myoclonic jerks of the extremities and died. The court requested post-mortem toxicological analysis of four patients. Aluminum concentrations in serum, liver, bone, and cerebral cortex were significantly increased as compared with background levels. The serum aluminum level of the non-survivors was 359-1275 µg/l (mean 808 µg/l) and that of the survivors 113-490 µg/l (mean 255 µg/l) [<60 µg/l normally seen in dialysis patients without symptoms]. Aluminum intoxication was, therefore, considered to be the most likely cause of death in these patients.^{19,20} The 17 survivors were transferred to The Netherlands and were successfully detoxified, by using the chelator desferrioxamine.²⁰

The water distribution pipe

Subsequent evaluation demonstrated that a very high Al content of the cement coating of the newly installed water distribution pipe in combination with aggressive water in a low flow situation was responsible for the prolonged high Al levels that intoxicated the patients during dialysis treatment.¹⁰

Results*The prosecution.*

Curaçao is part of The Kingdom of The Netherlands and most judges

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and prosecutors work on a short time contract from The Netherlands. The penal system is quite similar to that in The Netherlands. On April 9, 1997, after an extensive investigation with the aid of The Netherlands Health Inspectorate, Water Authorities from The Netherlands and the Pan American Health Organization, the prosecutor decided to dismiss the case. He concluded that it was not criminally negligent to dialyze without a WTS because: a) the water quality was generally considered to be good; b) consultants considered a WTS to be superfluous; c) there had been extensive consultation with experts from The Netherlands and the USA; d) several nephrologists had visited Diatel without advising the purchase of a WTS; e) since 1993 the purchase of a WTS was considered and eventually ordered in November 1995; f) the installation of the WTS was delayed for constructional reasons; g) there was no legislation concerning dialysis treatments; h) there was no control by the Health Inspectorate; i) the dialysis unit in the hospital acquired a WTS in 1993, not because of problems with the water quality, but to introduce a special (high flux dialysis) treatment for which a WTS is necessary and; j) the intensive care unit in the hospital still performed dialysis without a WTS in 1996.

On January 27, 1998, after an appeal of the family, the Court of Appeal decided to pursue prosecution. It held that it was a severe omission a) to dialyze without a WTS because A.A.M.I. standards¹³ were not met before (table 1); b) that no water tests were performed after the interruption of the water supply and c) that no water quality guarantees were obtained from the Water Company after the new water distribution pipe was installed. Some patients also requested the prosecution of board members of the water utilities but neither the water utilities, nor the board members of Diatel could be prosecuted, because at that time no legal provision was in force to allow this.

Expert witness testimony during the preliminary judicial inquiry

From June 6, 1998, until January 1999, a preliminary judicial inquiry was performed in The Netherlands and Curaçao. Expert assistance was appointed by the investigative judge and consisted of two water experts, two dialysis

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Table 2. Points of contention. Verdict summaries of the Court of Appeal after it decided to pursue prosecution, the charge and allegations of wrongdoing of the prosecutor after the preliminary judicial inquiry (June 6, 1998 - January 1999), the defense arguments and the summary of the verdict report of the District Court.

Ruling of the Court of Appeal, before the preliminary judicial inquiry.	Charge and allegations of wrongdoing by the prosecutor	Arguments of the defense	Ruling of the District Court (November 1999)
To dialyze without a WTS ^b is a severe omission because certain dialysis standards for water ¹³ were not met before in 1994.	The WTS ^b was not an element of the charge, as the prosecutor did not find it criminally negligent that dialysis was performed on tapwater.	<ol style="list-style-type: none"> 1. At the opening of the dialysis center dialysis had been performed on tap water for 26 years on the island and the staff was advised by consultants not to install a WTS^b. 2. The contaminations of 1994 were within safe limits. 3. A WTS is not always capable to prevent Al intoxications.²¹⁻²⁵ 	Contamination could occur at any time since a chemical contamination already had occurred in 1994 (table 2).
Water tests should have been performed after the interruption of the water supply, when extra alarms were noted on the dialysis machines.	The dialysis staff did not react properly on the extra alarms and should have tested the water as it may have been a sign of improper water quality.	<ol style="list-style-type: none"> 1. It is impossible to neglect or overrule these "conductivity" alarms because dialysis machines automatically interrupt dialysis treatment until the conductivity problem has been solved.^{17,18} 2. Aluminum could not have caused the conductivity alarms because these levels were very low compared with the concentration of the other standard ions in the dialysate (Table 1). 3. The extra conductivity alarms were probably due to air bubbles that deregulated the internal conductivity cells of the dialysis machines. 4. There was no reason to test the chemical composition of the water when the external conductivity meter demonstrates normal values. 5. Aluminum is not a normal component of distilled water, but even if it were tested, certainly no higher levels would have been found early after the water interruption because the entire pipe had been flushed after installation. 	Agreed with the defense.
Water quality guarantees should have been obtained from the Water Company after the new water distribution pipe was installed.	Idem.	<ol style="list-style-type: none"> 1. The water utility was notified that dialysis was performed without extended water purification. 2. It was unknown by the water utilities that a substantial change of water quality could occur during distribution. 	Agreed with the defense.
	Prison sentence on probation of 6 months was demanded.		Prison sentence on probation of 6 months demanded and (maximum) penalty of 10,000 NAF (6,500 US \$).

^a On April 9, 1997 the prosecutor decided to dismiss the case. On January 27, 1998, after an appeal of the family, the Court of Appeal decided to pursue prosecution.

^bWTS water treatment system.

technicians and nine medical and nursing experts from four universities and three dialysis clinics. During the questioning of the experts, the prosecutor, the investigating judge and the defense attorney were present. Table 3 shows some important expert witness statements that were regarded as erroneous by the defense.

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Table 3. Important expert witness statements that were regarded as erroneous by the defense

- 1 **Testimony:** "You ask me if I am aware that the European Community (EC) directive requires that a water treatment system (WTS) is installed and that aluminum levels should be below 10 µg/l; my answer is yes. "If I had seen the water analysis of 1994, I would definitely have advised to install a WTS"; "the EC Directive norm for aluminum in the water used for dialysis is since the eighties 10 µg/l".*
- Defense:** The EU does not require a WTS and the EC Directive aluminum norm is 30 µg/l.¹⁵
- 2 **Testimony:** "A Reverse Osmosis^a (RO) excludes a Al intoxication"; "The calamity in Portugal was due to bypass of the RO". ‡
- Defense:** A RO does not exclude a Al intoxication.²¹⁻²⁵ If the Al present is weakly ionized, reverse osmosis rejection rates may be decreased to as low as 30-50%^{21,23} and double RO systems in line may be necessary.²² Possibly it was not the bypass of the RO, but membrane fouling that was the major contributing factor of the intoxication in Portugal.²³
- 3 **Testimony:** "If alarms are pushed away, that is a mistake. You can overrule almost every alarm on a dialysis machine"; "It is possible to push away alarms and continue to dialyze". "It is possible to turn off the alarm without solving the problem". "If the alarm is pushed away, the pump continues to roll and there will be an exchange between blood and dialysate". "To push away alarms can be life threatening". ‡
- Defense:** It is impossible to "push away" or to "overrule" a conductivity alarm. Dialysate conductivity monitoring is especially developed to guarantee safety in case of mix-up of concentrates.^{13,17,18} Audible and visible alarms interrupt delivery of dialysate to the hemodialyzer and prevent blood in the hemodialyzer from reaching the patient.^{13,17,18}
- 4 **Testimony:** "You can change the sensitivity of a conductivity alarm. If you go too far you create a time bomb". ‡
- Defense:** Upper and lower conductivity alarm limits are set at ± 5% of the expected conductivity. Limits cannot be set beyond a certain level fixed at the factory.^{17,18}
- 5 **Testimony:** "Symptoms of an acute Al intoxication are especially speech problems"; "Every nephrologist should know the symptoms of an acute Al intoxication"; "The symptoms of an acute Al intoxication and hypercalcemia are quite similar but after a few days the difference should become obvious". ‡
- Defense:** Speech problems are not a sign of acute Al intoxication.^{11,25} The symptoms of hypercalcemia are not similar and Al intoxication has a symptom free interval of several days to weeks.^{11,25}

RO = Reverse Osmosis (RO filters are nowadays part of in a WTS in dialysis centers)

* Testimony acquired by police officers.

‡ Testimony acquired by the prosecutor and the investigative judge.

The charge

In October 1999, the prosecutor charged both physicians for manslaughter of at least eight patients and held it gross negligence that the water was not tested after the water interruption or in the two days of the extra alarms on the dialysis machines. It was not regarded criminally negligent to dialyze without a WTS. A prison sentence on probation of 6 months was demanded.

The defense

The defense disagreed with the allegations of the charge and some statements of the expert witnesses (table 3) and provided publications to the court on water quality issues,¹³⁻¹⁶ alarms on dialysis machines,^{17,18} water treatment systems²¹⁻²⁴ and symptoms of aluminum intoxication (table 1-3).^{12,25}

Court rulings

After a court hearing and a deliberation of 10 h on 18 and 25 October 1999, the District Court disagreed with the prosecutor on all issues, but nevertheless held the medical director guilty for performing dialysis without a WTS, although the use of a WTS was not an element of the charge. The Court held that contamination could occur at any time since a chemical contamination already had occurred in 1994 (see table 1). The medical director was sentenced to the maximum financial penalty of 10,000 Antillean guilders (approximately 6,500 US dollars). The other physician was acquitted because he was not involved in the purchase of the WTS.

In May 2000, the Court of Appeal gave a final decision. Since the indictment of the prosecutor did not include the omission to install a WTS the court held that it was unable to address this element. As it sustained the other issues of the first ruling, both defendants were acquitted.

Discussion

The intoxication

Trust is a dangerous companion in medicine. More than two decades tap water was relied upon to be sufficiently pure for dialysis because its quality is one of the best in the world.²⁶ After a seemingly unimportant interruption of the water supply, the Al level increased unexpectedly more than 40 times (table 1) which resulted in the death of ten dialysis patients, a flood of media coverage in Curaçao and The Netherlands, the resignation of the Minister of Health and prosecution of two physicians. The tragedy is that the good initial water

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quality in fact was indirectly responsible for the fatal outcome. Pure, low calcium water is corrosive for iron water pipes and therefore other pipes with a "protective" cement coating were installed. At that time however, it was not known that the Al content of the cement layer was four times higher than common and that the purity of the water enhanced the leaching of Ca and Al. Clearly, no one had been aware of the possibility of an Al contamination during distribution, as this had never happened before in dialysis history.^{10,11,20} Nevertheless, hemodialysis is a potentially dangerous therapy and according to the law, everyone who is under control of anything whatever, which, in the absence of precaution or care, may endanger human life, has the duty to take reasonable precautions against and to use reasonable care to avoid such danger.²⁷ The failure to take precautions had been the result from the lack of awareness on the part of the physicians and external consultants that any precautions were required because it was believed that the Water Authorities would take all relevant measures involved in the water supply. This is in fact an excuse of ignorance or negligence but when several patients die, the public opinion and that of the Court can easily rise to the level of gross negligence, which then justifies prosecution.

This case shows that although the quality of the water delivered by the factory may be constant, it can change suddenly during distribution and the physician in charge of dialysis treatments will be held responsible for the consequences. The intoxication was caused by a unique and complex set of circumstances that not only involved the physicians, but also external consultants, the board of Diatel, the local Water Authorities, the cement industry and the water distribution industry but the local law²⁸ -which was amended the following year-²⁹ did not permit the prosecution of board members of legal entities like foundations.

Expert witness testimony

In the criminal process that lasted almost 4 years, police officers, the prosecutor and the investigating judge questioned 18 different court-appointed experts in The Netherlands and on Curaçao. Although the defense had proposed most experts in the preliminary judicial inquiry, they did

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not testify on behalf of the defendants. Neither the defendants nor an expert on behalf of the defendants were invited to attend these cross-examinations; that does not comply with article 6 Section 1 and 3 of the European Convention on Human Rights.³⁰ Therefore, several errors in expert witness testimony could not be corrected before these statements were produced as evidence (table 3). The case mainly focused on three technical issues discussed during the preliminary judicial inquiry with the expert witnesses

Firstly, the question if the water quality had been good enough to dialyze without a WTS. In 1994 the aluminum level in the water supply had been below the below the European Community (EC) standard,¹⁵ but one of the experts erroneously testified to police officers that the dialysis clinic breached this standard (tables 1 and 3). This error in testimony was an important reason for the Court of Appeal to pursue prosecution after family members appealed the decision not to prosecute.

Secondly, the question of whether the dialysis staff had reacted sufficiently on the numerous "conductivity" alarms of the dialysis machines the 2 days following the water interruption. Hemodialysis machines monitor continuously the total concentration of ions in the solution by a built-in conductivity meter and visual and audible alarms alert the dialysis staff if the conductivity is beyond certain levels. This serves as a "watchdog" to protect the patients as dialysis machines automatically go into 'bypass' so that the blood stream will not be exposed to the dialysate.^{13,17,18} The extra alarms were, in retrospect, probably due to air bubbles from the water mains that deregulated the conductivity meters repeatedly for seconds to minutes. It seems unlikely that high concentrations of solutes like Al or Ca can activate the conductivity meters intermittently for such a short time period. The prosecutor, however, regarded these conductivity alarms as a sign of improper water and implicated that dialysis should have been stopped until the water quality was ensured. The prosecutor probably based his opinion on some expert's statements, implicating that bypassing the audible alarm may be hazardous (table 3). Even after the Magistrate of the District Court held that it is impossible to neglect conductivity alarms and continue dialysis, the prosecutor sustained this theory before the Court of Appeal.

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And thirdly, the question whether a WTS would have prevented the AI intoxication. Some medical experts testified that a WTS is always sufficient to prevent AI intoxications (table 3) and because the judge at the District Court neglected evidence that proved the contrary²¹⁻²⁵ he ruled that a WTS sufficiently protects patients and convicted the physician involved in the purchase of the WTS for this matter, as he did not install this WTS.

In an attempt to counterbalance the errors in testimony, counter expert reports had been presented at trial. These documents however, were found to be inadmissible by the District Court, because if it is to be used, the defense has to disclose expert opinion reports to the prosecutor, before trial. Although the Court of Appeal accepted the validity of the counter expertise reports, it remained difficult to convince the judges and the prosecutor at trial of the errors in the testimonies. No experts were called to trial because the defense was unable to find experts that could cover all issues sufficiently. This meant a heavy burden of proof to the defendants who made no use of their right to remain silent and had to discuss the errors in expert witness testimony in court.

Unlike a charge of malpractice, a criminal charge must be proved beyond a reasonable doubt.^{1,8} Because the judge at the District Court disagreed on all issues of the charge with the prosecutor, "reasonable doubt" was established and therefore the defendants should have been acquitted. The Court of Appeal indeed held that it was not allowed to rule on the installation of a WTS because this was not included in the charge.

Worldwide, legal institutions in civil and criminal trials have difficulty in differentiating adequately between reliable and unreliable expert evidence.^{6-9,31-33} In this case, the expert witness testimony was obtained in the absence of the defendants or an expert on behalf of the defendants. In such cross-examinations it is not easy to avoid errors. Oral statements require quick judgments, which may obscure a more complex truth especially when only possible culpable evidence is presented and opinions are not required to be supported by peer-reviewed publications. Experts, who are not trained in giving evidence, can easily underperform because of the unusual and stressful circumstances. Because few

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qualified experts were available on Curaçao, highly specialized knowledge had to be attained in The Netherlands and Belgium. Such experts may lack the necessary perspective of community clinical reality and introduce the risk that opinions are not based on the common local practice and technical possibilities. As an example, dialysis centers in Europe have a higher need for a WTS, because the drinking water quality in Europe is far worse³⁴ than that of Curaçao.²⁶

The process of criminal investigations in The Netherlands and United States compared

The Dutch criminal procedure differs much from the common law systems employed in Anglo-American law, and cases like this would follow a different path in each system of law. The Netherlands has professional judges and no jury or other form of lay participation in the decision-making exists in contrast with American trial judges that possess little power over the course of the litigation.^{8,31-33,35,36} The Dutch code on criminal proceedings regulates the criminal procedure as a whole: starting with preliminary inquiries and investigation and concluding with rules about the execution of court decisions. In the Dutch criminal justice system, experts are to be appointed by the (investigative) judge. If this is not contrary to the interest of the investigation, the investigating judge will select the experts from the persons recommended by the defendant. This is meant to ensure that the expert remains an impartial actor, with no interests in advance but the general interest of the pursuit of justice. In the Dutch criminal justice system records of police officers (including expert statements obtained by them) constitute admissible evidence, and may even constitute the sole means in proving guilt.^{8,32,36}

The United States has the most complex and restrictive set of exclusionary rules of evidence in the world: American courts can routinely bar evidence which would be admitted as a matter of course by tribunals in other countries.^{8,31,32,35-37} Experts' reports are generally not admissible in criminal proceedings. To be admissible, they must comport with certain conditions outlined in Federal Rule of Evidence 803 or state equivalents to that rule.^{38,39} These rules provide an expert evidentiary barrier to conviction. If American prosecutors want to introduce expert evidence, they have to call the expert to

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give testimony at trial, thus allowing the opposing party to cross-examine the expert with regards to his knowledge and reasoning process. This difference is due to the fact that in the United States the parties often retain experts and therefore more assurances of trustworthiness may be considered necessary.⁴⁰ Under Dutch and United States law, the prosecutor is entitled to decide whether to prosecute or to drop a case. In contrast to with the United States, however, the Dutch law allows involving parties to appeal the prosecutor's decision not to file criminal charges,⁸ as happened in this case.

The right of the defendant to participate in the discourse of the expert witnesses testimony is similar in Continental and American systems of law. According to the European Convention on Human Rights and Fundamental Freedom, the Treaty of Rome 1950, the defendant has the right "to examine or have examined the witness against him and to obtain the attendance and examination of witnesses on his behalf under the same conditions as witnesses against him".^{29,41} Under circumstances this provision of the European Convention can also be applied to expert witnesses testimony. In the United States the Sixth Amendment to the American Constitution states that criminal defendants have the right "to be confronted with the witnesses against him; [and] to have compulsory process for obtaining witnesses in his favor".⁴¹ According to the European Court all evidence must be produced in the presence of the accused at a public hearing and the prosecution must, therefore ensure the presence of these witnesses.^{8,42} Nevertheless, in contrast with the United States, in The Netherlands, experts are still infrequently called to testify in open court and more often than not, courts limit themselves to documented expert evidence contained in the case file.⁸

The use of expert evidence in the Dutch criminal justice system has not escaped criticism. In the last 10 years there have been calls for reform of the law affecting expert evidence. Proposals include the adoption of standard questionnaires for experts; of criteria whether the person testifying can be considered as an "expert"; of standards for deciding whether the expert's oral or written statements are sufficiently reliable to be used by the trial courts; and broader proposals for revision of the procedural and evidentiary rules affecting this type of evidence.^{8,32,36}

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Doctors charged for manslaughter may face years of uncertainty, the threat of imprisonment or revoking of license and negative publicity. The only thing an accused can do is to try and understand the litigation process in order to reduce the anxiety that comes from the sometimes seemingly random course of the prosecution and ruling by the judges. Moreover, the accused should become an active participant in the preparation of the case, critical to ensuring that his interests are properly protected. At trial he should have more knowledge and valid opinions about the case than the experts. It has an added benefit of reducing the psychological burden of standing helplessly by, while the verdict unfolds.

To conclude, in the United States the erroneous expert witness evidence in this case would probably not have been admissible due to the better protection by the federal rules of evidence.

As expert witness testimony is both unavoidable and decisive in medical cases, it obligates experts to be very aware of the legal and ethical impact of their testimony as their evidence may form the central core of a case that may lead to life imprisonment. It is important to audit expert medical evidence but courts are not the appropriate place for this.⁴³ Courts and legislators should realize that expert testimony can be erroneous even if the expert is unpaid, neutral and court-appointed and therefore medicolegal work should be similarly peer-reviewed and subject to quality assurance even if the expert appears to be neutral.^{43,44}

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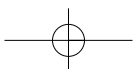
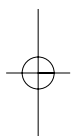
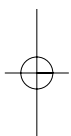
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Prosecution after an outbreak of subacute aluminum intoxication in a hemodialysis center



CHAPTER VII

Summary and closing remarks

CHAPTER VII

In **chapter I**, an introduction was given with general information on aluminum toxicity and an outbreak of subacute aluminum intoxication in a hemodialysis clinic, with related aspects such as drinking water management and forensic and legal consequences.

Water quality and cement linings

In **chapter II**, the impact of the use of water distribution pipes with an inner cement lining on aluminum levels in tap water, is described. In Curaçao, drinking water is prepared by distillation of seawater, after which calcium carbonate (CaCO_3) is added at the water plant for corrosion prevention of iron water mains. In the beginning of the nineties, this calcium carbonate level was low (25-40 mg/L¹; preferred value > 50 mg/L²) and one of the main reasons of corrosion of the water mains.^{1,3-11} The water distribution avoided this problem by using other pipes with an interior cement lining and these pipes (with a total length of 2.2 km) were installed at Diatel in May, 1996, in order to assist Diatel with low water pressure problems. Cement layers, however, are not inert and will always react with water, especially as a protective calcium layer will not be formed on the cement lining with low calcium carbonate ("soft") water.^{1,3-11} In this case, calcium and aluminum leached for a long period of time from the cement layer into the tap water of Diatel. The aluminum concentration increased from less than 5 µg/L at the water plant to the highest level on the island (550 µg/L to 690 µg/L) at the dialysis center, 2 months after the pipe was put in use. Factors which might have contributed to these excessively high levels, were a) the newly installed pipe, b) the aggressiveness of the water, c) the low pH and d) high temperature of the water, e) the cement composition with a four times higher aluminum content than usual,⁵ f) a long residence time and g) the use of the corrosion inhibitor polyphosphate.^{1,6}

In 1996, after the tragedy in Diatel Curaçao, KIWA investigated the leaching of aluminum from cement-mortar water pipelines in The Netherlands. Samples were taken on twenty locations with cemented pipes and asbestos cement-pipes. Locations with 'worst case scenarios' favoring the leaching of aluminum were chosen, defined as low flow, soft water, new pipes and small diameter. The aluminum levels in the tap water never reached levels above

11 µg/L at any location.⁵ As the cement types in the study in The Netherlands were probably different from the ones used in the present situation, manufacturers have to prove the appropriateness of the cement linings when other cement types than those recommended, are applied.¹²

Aluminum

In **chapter III**, the outbreak of subacute aluminumencephalopathy in a dialysis center is described. In 1996, 27 hemodialysis patients of Diatel Curaçao were exposed to contaminated dialysate with calcium and aluminum. Initially 7 patients showed symptoms of a 'hard water syndrome' with nausea, vomiting, and postdialysis hypercalcemia. The hypercalcemia disappeared with low-calcium dialysate and the withdrawal of calcium and vitamin D supplements, but microcytic anemia and neurological symptoms developed. Of the 27 patients who had a similar exposure (approximately 60 hours) to the contaminated dialysate, 10 died from subacute aluminum encephalopathy, whereas 17 patients had minor symptoms and survived. Serum aluminum concentrations, available in seven non-survivors were significantly higher than in the survivors (808 +/- 127 vs. 255 +/- 25 microg/L, $P < 0.01$). We found that comparable aluminum loads appear to induce a more severe intoxication in malnourished, older patients with a low lean body mass and low residual diuresis. The hypercalcaemia was probably partly due to the aluminum intoxication.^{13,14} As there will always be a latent phase of days to weeks before encephalopathy can develop, we found that "acute" encephalopathy -implicating neurotoxic symptoms to occur within hours- as such does not exist.¹⁴

In **chapter IV**, the post-mortem toxicological findings in subacute aluminumencephalopathy are presented. In an outbreak of aluminum intoxication in 27 hemodialysis patients, 10 patients died of subacute aluminum encephalopathy with convulsions, sepsis, and coma. The court requested post-mortem toxicological analysis of four patients. Aluminum concentrations in liver, bone, and cerebral cortex were significantly increased as compared with background levels. Aluminum intoxication was therefore considered to be the most likely cause of death in these patients. The high levels of aluminum that were found in liver and bone may implicate that these organs serve as a storage pool for aluminum

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in order to protect the brain. Nevertheless, a significant amount of aluminum was observed in the brain, in the hippocampus and the occipito-parietal cortex, implicating that liver and bone storage was relatively oversaturated.^{14,15}

In **chapter V**, the literature on symptomatology, the sources of aluminum exposure and pathogenic mechanisms of aluminum intoxications is reviewed. Also a treatment schedule to treat hemodialysis patients with aluminum intoxication was developed.¹⁴

There are wide variations in the clinical manifestations and degrees of expression of aluminum toxicity. The most obvious clinical problems are toxic effects on the brain, bone and hemopoietic tissue.¹³⁻¹⁷ Despite a rapidly growing amount of literature on aluminum toxicity, few data are available on (sub)acute aluminum encephalopathy. For practical purposes aluminum encephalopathy can be divided in two types: "chronic" aluminum encephalopathy and "acute" (or subacute) aluminum encephalopathy indicating the time span between the onset of the intoxication and the development of symptoms. When the exposure level is relatively low, aluminum toxicity symptoms develop after months to years ("chronic"), whereas with extremely high exposure, symptoms develop within weeks ("acute" or "subacute"). In both subacute and chronic aluminum intoxications microcytic anemia¹³⁻¹⁷ and EEG changes^{13,14} are noted and sometimes precede clinical symptoms.^{17,18} The most severe symptoms in both forms of aluminum encephalopathy are convulsions, coma and myoclonic jerks of the extremities. Some of the clinical manifestations of chronic aluminum encephalopathy, however, seem to be "bypassed" in subacute aluminum encephalopathy, probably due to the overpowering of the storage capacity of liver, spleen and bones. While absent in subacute aluminum encephalopathy, speech disorders are an important clinical sign of chronic aluminum intoxication, besides bone fractures.^{14,20,21} The severe neurotoxic symptoms in subacute aluminum encephalopathy can even develop days to weeks after the exposure is terminated. It seems as if brain pathology ultimately reaches a point of no return where frequent epileptic insults will inevitably lead to coma and death.¹³⁻¹⁵

Treatment of aluminum intoxication. As aluminum intoxications are preventable, every effort should be undertaken to limit exposure to this

neurotoxicant. To date, desferrioxamine (DFO) is the single most used drug for the treatment of aluminum intoxication. It has been clinically used since 1963 as an iron-chelating agent in patients with iron overload²² and since 1980 it has also been used in the diagnosis and treatment of aluminum overload in dialysis patients.²³ Especially in the latter case a number of serious side effects such as the exacerbation of encephalopathy have been reported²² and the optimal dose of DFO for long-term chelation in dialysis patients is uncertain. We developed a practical treatment schedule for severely intoxicated hemodialysis patients to avoid unnecessary treatments in the weekends or dangerously high aluminum levels induced by DFO, for a prolonged time. We found that in severe intoxications with serum aluminum levels of 300-500 µg/L, DFO can be safely administered two times a week, five hours before high flux dialysis, in a dose of 5 mg/kg and a dialysis schedule of four times a week. If serum aluminum levels are below 300 µg/L, DFO can be administered in the same dose during the last hour of dialysis session with a dialysis schedule of three times a week. The treatment duration was significantly related to the residual diuresis as all patients with a residual diuresis of a liter/day or more required treatment of less than two months while other patients with anuria had to be treated for up to 91 weeks.¹⁴

Forensic aspects

In **chapter VI**, the judicial implications of the outbreak of subacute aluminum intoxication are set out. When Diatel was opened in 1992, it was common to use tap water for hemodialysis on Curaçao. In the nineties most dialysis centers in other countries made use of a water treatment system (WTS) with reverse osmosis membranes. Usually such a device is capable of rejecting 99% of the aluminum in the water supply, but in some cases, especially when the water contains large amounts of aluminum over a prolonged time, these devices may be insufficiently able to reject aluminum.^{24,25} After the interruption of the water supply in Diatel –to establish the connection to a newly installed water pipe-, the dialysis machines functioned normally the same day. The next two days extra alarms were noted intermittently for seconds to minutes on several machines. In retrospect this was probably due to technical problems, which may have been the result of air bubbles in the water supply.²⁶

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A criminal investigation, started in September 1996, evaluated the possibility of a criminal liability of the water authorities or the board and medical staff of the dialysis center. After an extensive investigation with the aid of The Netherlands Health Inspectorate, Water Authorities from The Netherlands and the Pan American Health Organization, the prosecutor decided to dismiss the case. The relatives of the deceased however, appealed the decision not to prosecute and the Court of Appeal then ordered the prosecutor to reopen the investigation of the case. Some patients also requested the prosecution of board members of the water utilities but neither the water utilities, nor the board members of Diatel could be prosecuted, because the local law -which was amended the following year-,²⁷ did not permit the prosecution of board members of legal entities like foundations.²⁸ After a preliminary judicial inquiry, the prosecutor did not consider it criminally negligent performing dialysis treatments without a WTS, but charged both physicians guilty with the death of at least eight patients for not testing the water after the water interruption, or after the extra alarms on the dialysis machines. A prison sentence on probation of 6 months was demanded. The District Court however, disagreed with the prosecutor on all issues but still found the medical director guilty of performing dialysis without a WTS, even though the absence of a WTS was not an element of the charge. The medical director was sentenced to the maximum penalty of 10,000 Antillean guilders (approximately 6,500 US dollars). The other physician was acquitted because he was not involved in the purchase of the WTS. The Court of Appeal held that since the indictment of the prosecutor did not include the omission to install a WTS, it was not allowed to address this element. As the Court of Appeal sustained the other issues of the first ruling, both defendants were acquitted.²⁶

Expert witnesses played an important role both in the initial conviction and the reopening of the prosecution due to errors in their testimony. The preliminary judicial inquiry process particularly introduced a series of risks for errors in testimony. Firstly, the expert witness testimony was obtained behind closed doors in the absence of the defendants or an expert on behalf of the defendants. During such cross-examinations it is difficult to avoid subjective interpretations, mainly since opinions were not required to be supported by peer-reviewed publications. Secondly, experts who are not trained in giving evidence can

easily underperform on account of the unusual and stressful circumstances. Thirdly, because highly specialized knowledge had to be obtained from other countries, these foreign experts lacked the necessary perspective of local facts. Accordingly, some of their opinions were not based on common local practice and technical possibilities. And finally, the expertise that was required, served the exclusive purpose of the criminal proceedings and were not particularly directed towards data that scientists are normally interested in or necessarily knowledgeable of.²⁶ Therefore, guidelines should be enacted not only to ensure the independence of expert witnesses, but also to assure the scientific quality of their testimony.

Closing remarks

The intoxication

After a seemingly unimportant interruption of the water supply, the aluminum level in the water supply of the dialysis center Diatel unexpectedly increased more than 40 times. This resulted in the death of ten dialysis patients, a flood of media coverage in Curaçao and The Netherlands, the resignation of the Minister of Health and the criminal prosecution of two physicians. Calamities generally only occur when more parts of a safety chain are disrupted simultaneously as was the case in this incident. People in charge of dialysis facilities and water utilities in Curaçao encounter several specific problems related to limitations confronted on a small island pertaining to lack of legislation, standards or regulations that would have prevented these incidents. Although hemodialysis had been performed using tap water in many countries in the past, this is the first event of intoxication during dialysis caused by a water distribution pipe.⁶ Many countries make use of cement coatings in water distribution pipes to protect the pipe from corrosion, but it is very unusual that these cement coatings release aluminum, one of the main constituents. The release of aluminum and the subsequent intoxication of the patients in this case can be attributed to several coinciding unfortunate factors:

1. A water distribution industry, which at that time manufactured water distribution pipes with a cement lining that can leach aluminum to very

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high levels under certain conditions.⁶ A cement composition that appeared to be different from those recommended in the United States^{8-11,29} or in The Netherlands, where the applicator has to prove the appropriateness of the pipe, when other types than those recommended, are applied.¹² A local water distribution company that used this pipe in an area with a low water flow enhancing the built-up of aluminum.⁶

2. A local water company producing water with an unusually low calcium carbonate content (25-40 mg/L), favoring the deterioration of cement-lined water pipes.¹ In comparison, in a number of European countries (for example The Netherlands,³⁰ Germany, Denmark, and some parts of France) the authorities require that drinking water should be high in calcium carbonate (above 60-80 mg/L)³ to reduce corrosion or deterioration of cement linings especially with regard to metal release.³⁰
3. Absence of legislation requiring standardized drinking water quality. The WHO has no health-based guideline value for aluminum but recommends a level below 200 µg/L,³¹ which is much lower than the highest value of 690 mg/L reported in this case.⁶ The European Union applies a resolution that defines a maximum aluminum level of 30 µg/L for water, used for hemodialysis and emphasizes that the drinking water companies should warn the health authorities if the aluminum level in drinking water exceeds this level. In addition, the resolution states that "The authorities responsible for water distribution and hemodialysis shall inform all dialysis units, if possible in advance, of any important change in the treatment of water which might increase the aluminum level in the water distributed, and also of any accidental pollution of the water distributed".³² These regulations, however, are intended for cases where aluminum salts are used to prepare drinking water and are not intended as a risk warning of the use of cement linings in drinking water distribution.
4. Diatel did not make use of a water purification system, which would probably have reduced the mortality rate.
5. The physicians in charge of Diatel nor the water utility companies realized that the water quality could change dramatically after a change in water distribution. As a consequence the physicians did not see the need for a sophisticated water treatment device. In addition to this, routine water quality tests had been performed infrequently. However, because Diatel

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was closed soon after the patients became symptomatic and because it takes 6-8 weeks before these test results are available. And finally, because the water distribution pipe was flushed after installation, the aluminum concentration would have been low at that time. It remains therefore unlikely that more frequent water tests would have prevented serious intoxication of the patients.

From these events it is clear that although the quality of the water delivered by a factory may be constant, it can inadvertently change and in the case of a hemodialysis unit, the physician in charge will be held responsible for the consequences.

The patients

New observations on aluminum intoxication and new therapeutic insights were obtained in relation to this tragic incident. The early stages of the aluminum intoxication passed by unnoticed for weeks since the patients had minimal (or no) symptoms, because it takes time and a certain cumulative amount of toxicant to produce symptoms. In spite of the fact that patients were transferred to the dialysis facility of the hospital, some patients that had been symptom-free developed severe neurological symptoms such as convulsions and coma. Medical textbooks lacked specific information for use in elucidating the source of the complaints. In addition, no information could be obtained from the water utilities, as they were also unaware of the toxicological properties of the water distribution system. The lack of laboratories on Curaçao that could determine aluminum levels further delayed adequate diagnosis and therapy.

Due to logistic limitations, detoxification treatment could not be initiated in Curaçao and the survivors had to be transferred to The Netherlands. A new treatment protocol had to be developed because data on these severe intoxications were very limited. Fortunately, the seventeen patients could be treated successfully and all these patients returned to Diatel for dialysis treatment.

The judicial system

The court system in general is particularly dependent on specific expertise

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in science and medicine.³³⁻³⁵ The preliminary judicial inquiry as part of the prosecution was also influenced by the limitations confronted on a small island. Court appointed expert witnesses had to be attained from other countries whereas these experts lacked the necessary perspective of community clinical reality. It is unjustified however, that courts assume that medical professionals always disclose reliable knowledge when the expert is court-appointed and not at the request of the defense. Some expert witnesses make statements that would not hold firm in a scientific forum, especially when they lack the necessary knowledge of certain facts, the practical applications of which solely confined to the purposes of jurisprudence, and are therefore entirely overlooked in the usual routine of medical study.³⁵ Therefore, the increasing presence of scientific and technical matters in civil and criminal litigation implicates that the legal system should find ways to assure the best science available in order to make rational decisions. Guidelines should be enacted to ensure the quality of expert witness testimony, which should include analysis of common local practice and technical possibilities.

The defendant

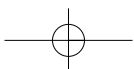
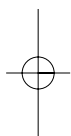
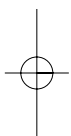
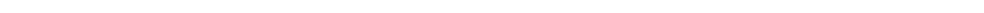
For the medical practitioner, prosecution for the death of patients is one of the most distressing experiences in his medical career, not only because the judicial process may last several years, but primarily because it touches upon the foundation of medical ethics.

Most physicians are unacquainted with the intricacies of judicial inquiry and few physicians involve themselves in the preparation of their cases.³⁵ Even in areas where the law is difficult to comprehend, a proper understanding of the litigation process can make the stressful experience more bearable. Health care practitioners should therefore understand how trials are conducted and be acquainted with the basic standards for the admission of evidence. The only thing an accused can do is to try and understand this process, in order to reduce the anxiety that comes from the sometimes seemingly random course of the prosecution and ruling by the judges. Moreover, the defendant should become an active participant in the preparation of the case, ensuring that his interests are properly protected. At a trial he should have more knowledge about the case

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than the experts. It has the added benefit of reducing the psychological burden of standing by helplessly, while the verdict unfolds.

In conclusion, it should be evident that although sophisticated medical treatment like hemodialysis is technically feasible and qualified physicians available, introduction of innovative medical techniques in small communities should only take place after a thorough analysis and implementation of necessary legislation and protocols for all parties involved. People in charge of medical facilities on small islands or similar communities should also be aware that for quality assurance they have to be knowledgeable of many more factors than is the case in many large developed countries where one can rely on regulations and laws that protect patients. The water distribution industry should be aware that cemented water distribution pipes may have toxic properties. Guidelines should be enacted to ensure the quality of expert witness testimony, which should include analysis of common local practice and technical possibilities.



CHAPTER VIII

Samenvatting en slotwoord

CHAPTER VIII

Hoofdstuk 1 biedt een introductie met algemene informatie over aluminiumtoxiciteit en over een epidemie van subacute aluminiumintoxicatie in een dialysekliniek met daaraan gerelateerde waterleidingkundige aspecten alsmede forensische en juridische consequenties.

Waterkwaliteit en de cementlaag in de drinkwaterleiding

Hoofdstuk II beschrijft de gevolgen van het gebruik van drinkwaterbuizen met een binnenlaag van cement, op de aluminiumconcentratie in het kraanwater. Op Curaçao wordt drinkwater bereid door distillatie van zeewater, waarna in de waterfabriek o.a. calciumcarbonaat (CaCO_3) wordt toegevoegd, om metalen drinkwaterbuizen tegen interne corrosie te beschermen. Aan het begin van de jaren 90 was de calciumcarbonaat concentratie laag (25-40 mg/L¹; streefwaarde > 50 mg/L²), hetgeen een van de belangrijkste oorzaken van corrosie van metalen drinkwaterbuizen was.^{1,3-11} Het drinkwaterdistributiebedrijf omzeilde dit probleem door andere buizen met een binnenlaag van cement aan te schaffen en deze buizen (met een totale lengte van 2,2 km) zijn bij Diatel geïnstalleerd om Diatel te helpen met problemen van lage waterdruk.¹ Cement is echter niet inert en bestanddelen (waaronder calcium en aluminium) kunnen in contact met water in oplossing gaan en vooral als het calciumcarbonaat gehalte van het water laag is ("zacht water"), omdat er dan geen beschermend kalklaagje op de cementbekleding gevormd kan worden.^{1,3-11} Aluminium is langdurig uit deze laag blijven uitlogen en heeft het water wat in het dialysecentrum Diatel voor dialyse werd gebruikt vervuild.^{1,5-9} De aluminiumconcentratie steeg daarbij van minder dan 5 µg/L (ter plaatse van de waterfabriek) tot tenminste 550 µg/L à 690 µg/L (bij Diatel, ten tijde dat de drinkwaterbuis ruim twee maanden in gebruik was). Deze waarden waren de hoogste aluminiumconcentratie die op het eiland gemeten zijn.¹ Factoren die vermoedelijk hebben bijgedragen tot deze uitzonderlijk hoge waarden zijn a) het in gebruik nemen van een nieuwe drinkwaterbuis, b) de agressiviteit van het drinkwater, c) de lage zuurgraad en d) de hoge temperatuur van het water, e) de cementsamenstelling met een viermaal hoger aluminiumgehalte dan gebruikelijk,^{1,5} f) de trage doorstroomsnelheid van het water en g) mogelijk ook het gebruik van de corrosieremmer polyfosfaat die cementlagen kan aantasten.^{1,6}

In 1996 heeft het Keuringsinstituut voor Waterleiding Artikelen (KIWA) na de tragedie in Diatel onderzocht of het uitlogen van aluminium uit cementlagen van drinkwaterbuizen ook in Nederland een probleem was. Monsters werden genomen op 20 locaties waar buizen met een binnenbekleding van cement of asbestcement werden gebruikt. De locaties die werden onderzocht waren die, welke risicovol zijn voor het uitlogen van aluminium, t.w. die met "zacht" water, een lage doorstromingsnelheid van het water en het gebruik van drinkwaterbuizen met een kleine diameter die slechts kort in gebruik waren. De aluminiumwaarden in het kraanwater stegen in deze situaties tot maximaal 11 µg/L.⁵ In Nederland worden vermoedelijk andere cementbuizen toegepast dan in het onderhavige geval. Geconcludeerd kan worden dat niet alle cement-samenstellingen geschikt zijn voor gebruik in de drinkwaterindustrie. Fabrikanten moeten daarom de toepasbaarheid in verschillende situaties aantonen indien afgeweken wordt van de gebruikelijke cementsoorten.¹²

Aluminium

In **hoofdstuk III** wordt een epidemie van subacute aluminiumencephalopathie beschreven bij patiënten van het dialysecentrum Diatel Curaçao. In 1996 werden 27 hemodialyse patiënten blootgesteld aan een contaminatie van het dialysaat met calcium en aluminium. In eerste instantie vertoonden 7 patiënten na enkele weken symptomen van het 'hard water syndroom' met misselijkheid, braken en hypercalcaemie na dialyse. De hypercalcaemie verdween na behandeling met calciumarm dialysaat en het onthouden van de onderhoudsmedicatie van calcium en vitamine D supplementen. Desondanks ontwikkelden een aantal patiënten microcytaire anemie, sepsis, epileptische insulpen en coma. Van de 27 patiënten die evenredig waren blootgesteld (ongeveer 60 uur) aan het gecontamineerde dialysaat, overleden er 10 aan subacute aluminiumencephalopathie, terwijl 17 patiënten geringe symptomen hadden en het hebben overleefd. Serumconcentraties van aluminium werden bepaald bij zeven overleden patiënten. Deze waren significant hoger dan bij de overlevenden (808 + 127 vs. 255 + 25 µg/L, $P < 0.01$). We constateerden dat vergelijkbare parenterale blootstelling aan aluminium vooral een ernstiger intoxicatie veroorzaakt bij oudere patiënten met een slechte voedingstoestand, een relatief laag lichaamsgewicht en/of een geringe restdiurese.

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De vastgestelde hypercalcaemie werd in geringe mate medeveroorzaakt door de aluminiumintoxicatie.^{13,14} Aangezien er altijd een latente fase van dagen tot weken zal zijn voordat de encephalopathie kan optreden, kunnen we stellen dat "acute" aluminium encephalopathie –te weten het optreden van neurotoxische symptomen binnen enkele uren- als zodanig niet bestaat.¹⁴

In **hoofdstuk IV** worden post-mortem toxicologische bevindingen van subacute aluminiumencefalopathie beschreven bij vier patiënten in het kader van een strafrechtelijk onderzoek. Aluminiumgehalte in lever, bot en hersenschors waren significant verhoogd in vergelijking tot normale waarden. De hoge concentraties van aluminium die in deze studie werden gevonden in lever en botten impliceert dat deze organen als opslagplaats kunnen fungeren om de hersenen te beschermen. De significant hoge concentratie van aluminium die werd gevonden in hippocampus en occipito-parietale cortex van de hersenen, maakt duidelijk dat de opslagcapaciteit van lever en botten werd overschreden.^{14,15} Aluminiumintoxicatie was derhalve de meest waarschijnlijke doodsoorzaak bij deze patiënten.

Hoofdstuk V geeft een overzicht van de literatuur aangaande symptomen, bronnen van aluminiumintoxicatie en pathogenetische mechanismen van aluminiumintoxicatie. Tevens wordt een therapieschema voor de behandeling van hemodialysepatiënten met aluminiumintoxicatie beschreven.¹⁴

Er is een grote variatie in klinische manifestatie en mate van expressie bij aluminiumintoxicatie. De meest markante verschijnselen zijn de effecten op hersenen, botten en rode bloedcellen.¹³⁻¹⁷ Er zijn tal van publicaties betreffende aluminiumintoxicaties in het algemeen, maar er is weinig bekend over de (sub)acute aluminiumencefalopathie. Uit praktische overwegingen wordt meestal onderscheid gemaakt tussen twee vormen, t.w. "*chronische*" aluminiumencefalopathie en "*acute*" (of subacute) aluminiumencefalopathie. Dit onderscheid heeft betrekking op de duur van de incubatietijd alvorens symptomen optreden. Indien de (parenterale) blootstelling relatief laag is, treden symptomen van aluminiumencefalopathie op zijn vroegst op na maanden tot jaren ("*chronisch*"), terwijl bij extreem hoge blootstelling

deze symptomen na weken ("subacuut") kunnen optreden. Aangezien er altijd een latente fase van dagen tot weken is voordat de symptomen van encephalopathie manifest worden, kunnen we stellen dat "acute" encephalopathie –oftewel het optreden van neurotoxische symptomen binnen enkele uren-, als zodanig niet bestaat. Bij zowel subacute als chronische aluminiumintoxicatie worden microcytaire anemie¹³⁻¹⁷ en EEG veranderingen^{13,14} gezien, die soms voorafgaan aan de klachten.^{17,18} De meest ernstige symptomen bij beide vormen van aluminiumencefalopathie zijn epileptische insulden, coma en myocloniën van de extremiteiten. Het lijkt aannemelijk dat sommige manifestaties van chronische aluminiumencefalopathie "gebypassed" worden bij acute aluminiumencefalopathie, mogelijk doordat de opslagcapaciteit van lever, milt en botten wordt overschreden. Daardoor worden spraakstoornissen niet gezien bij subacute aluminiumencefalopathie, terwijl deze (samen met botbreuken) juist een belangrijke symptoom zijn bij de chronische vorm.^{14,20,21} Het blijkt dat bij subacute aluminiumencefalopathie de neurologische symptomen zelfs dagen tot weken na beëindiging van de blootstelling kunnen optreden. Vermoedelijk bereikt de hersenpathologie op een gegeven moment een punt waarbij er geen weg terug is en o.a. frequente epileptische insulden zullen leiden tot coma en het overlijden van de patiënt.¹³⁻¹⁵

Therapie van aluminiumintoxicatie. Aangezien aluminiumintoxicaties te voorkomen zijn, moet er alles aan gedaan worden om de iatrogene blootstelling te minimaliseren. Tot op heden is desferrioxamine (DFO) het enige middel voor de behandeling van aluminiumintoxicaties. Sinds 1963 wordt DFO toegepast bij de ijzer chelatie therapie bij patiënten met hemosiderose²² en vanaf 1980 wordt het tevens toegepast bij de diagnose en therapie van aluminiumintoxicaties.²³ Dit middel heeft echter vooral in dit laatste geval een aantal ernstige bijwerkingen, zoals bijvoorbeeld een exacerbatie van encephalopathie.²² De optimale dosis voor de veelal langdurige behandeling met DFO bij dialyse patiënten met ernstige aluminiumintoxicatie is onbekend, zodat wij een behandelingsschema hebben moeten ontwikkelen. Bij dit schema worden risico's zoveel mogelijk vermeden en het blijkt dat DFO veilig tweemaal per week te weten vijf uur voor aanvang van de zgn. "high flux" dialysebehandelingen kan worden toegediend in een dosis van 5 mg/kg bij ernstige aluminiumintoxicaties (aluminiumwaarden van 300-500 µg/L). Als de serumaluminiumwaarden onder de 300 µg/L zijn

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kan DFO in dezelfde dosis worden toegediend maar dan in het laatste uur van de dialysesessie, bij voorkeur aan het begin van de week. De behandelingsduur is vooral gerelateerd aan de urine-uitscheiding aangezien patiënten met een urineproductie van een liter of meer per dag in circa twee maanden uitbehandeld zijn, terwijl sommige patiënten met anurie bijna 2 jaar behandeling nodig hebben.¹⁴

Forensische aspecten

In hoofdstuk VI, worden de juridische implicaties van de subacute aluminiumintoxicatie beschreven. Bij de opening van Diatel in 1992, was het gebruikelijk op Curaçao om kraanwater, zonder verdere waterzuivering, te gebruiken voor hemodialyse. Sinds de jaren negentig maken de meeste dialysecentra elders gebruik van een waterzuiveringsinstallatie met reverse osmosis membranen. In normale omstandigheden kunnen deze installaties tot 99% van de hoeveelheid aluminium uit het kraanwater verwijderen, maar in specifieke omstandigheden kan dit veel minder zijn waardoor patiënten onvoldoende beschermd worden.^{24,25} Voor de aansluiting van een nieuwe drinkwaterbuis op het drinkwaternetwerk bij Diatel was er een korte onderbreking van de drinkwatervoorziening. Aanvankelijk werden er geen bijzonderheden opgemerkt, terwijl de volgende twee dagen, intermitterend, gedurende enkele seconden tot minuten, extra alarmsignalen bij de dialysemachines afgingen. Retrospectief waren deze alarmen vermoedelijk het gevolg van technische problemen, zoals bijvoorbeeld de aanwezigheid van luchtballen in de drinkwatervoorziening.²⁶

In september 1996 werd een strafrechtelijk onderzoek gestart, om na te gaan of er strafbare feiten waren gepleegd door het drinkwaterproductie- of distributiebedrijf, of door de medische staf of het bestuur van het dialysecentrum. Na een uitgebreid onderzoek met de hulp van het openbaar ministerie in Nederland, drinkwaterexperts van Nederland en de Pan American Health Organization besloot de officier van justitie de zaak te seponeren. De nabestaanden gingen echter in beroep tegen deze beslissing en in hoger beroep werd besloten het strafrechtelijk onderzoek te heropenen. De drinkwaterbedrijven en de bestuursleden van Diatel werden evenwel niet strafrechtelijk vervolgd omdat

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de wet, die het jaar daarop werd gewijzigd,²⁷ geen mogelijkheid bood om bestuursleden van stichtingen strafrechtelijk te vervolgen.²⁸ Na een gerechtelijk vooronderzoek heeft de officier van justitie vastgesteld, dat het niet strafrechtelijk verwijtbaar was om dialysebehandelingen zonder een waterzuiveringsinstallatie uit te voeren. In de tenlastelegging werden de twee artsen van Diatel schuldig geacht aan de dood van ten minste acht van de tien patiënten wegens het niet analyseren van het kraanwater na de onderbreking van de drinkwatervoorziening of gedurende de twee dagen dat er extra alarmeringen waren bij de dialysemachines. Er werd een voorwaardelijke gevangenisstraf van zes maanden geëist. Alhoewel het geen onderdeel van de dagvaarding was, oordeelde de rechter in eerste aanleg dat het dialyseren zonder een waterzuiveringsinstallatie strafrechtelijk verwijtbaar was en werd de medische directeur veroordeeld tot de maximale boete van 10,000 Antilliaanse gulden (ca. 6500 US dollars). De andere arts werd vrijgesproken omdat hij niet betrokken was bij de aanschaf van de waterzuiveringsinstallatie. In hoger beroep werden de artsen vrijgesproken aangezien de waterzuiveringsinstallatie geen element was van de dagvaarding en de rechters het eens waren met de overige beslissingen van de rechter in eerste aanleg.²⁶

De getuige-deskundigen speelden een belangrijke rol in het juridische proces. De wijze waarop het gerechtelijk vooronderzoek plaatsvond verhoogde het risico van fouten in verklaringen. Ten eerste werden deze verklaringen afgenomen achter gesloten deuren, zonder dat de verdachten (of een deskundige in hun naam) waren uitgenodigd. Het is dan moeilijk om bij een verhoor onder dergelijke omstandigheden subjectieve interpretaties te vermijden; vooral ook omdat het geen vereiste was om verklaringen te ondersteunen met "peer-reviewed" publicaties. Ten tweede hadden deze getuige-deskundigen geen ervaring in het geven van verklaringen in juridische zaken, zodat ze onder stressvolle omstandigheden eerder geneigd zouden kunnen zijn om minder goed onderbouwde verklaringen af te leggen. Ten derde bleek het nodig om deskundigen uit andere landen te horen omdat de vereiste "know-how" lokaal niet aanwezig was. Deze "superspecialisten" uit andere landen missen echter kennis over lokale omstandigheden en technische mogelijkheden. Tenslotte zijn deskundigenverklaringen in dit soort situaties enkel en alleen bedoeld om strafrechtelijk bewijs te vergaren; dit is een andere insteek dan de gebruike-

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lijke toepassing van hun vakkennis.²⁶ Daarom moeten niet alleen richtlijnen worden opgesteld die de onafhankelijkheid van de deskundigen zoveel mogelijk garanderen, maar tevens richtlijnen voor de wetenschappelijke kwaliteit van hun verklaringen.

Slotwoord

De intoxicatie

Na een ogenschijnlijk onbelangrijke onderbreking van de watertoevoer steeg de aluminiumconcentratie in de watertoevoer naar het dialysecentrum Diatel onverwachts meer dan veertigmaal. Hierdoor overleden tien nierpatiënten, trad de minister van Volksgezondheid af en volgde een strafrechtelijk onderzoek tegen de twee artsen van Diatel. Calamiteiten ontstaan in het algemeen alleen als meerdere onderdelen van een veiligheidsketen tegelijk deficiënt zijn; dat was ook hier het geval. Personen die verantwoordelijk zijn voor dialysefaciliteiten en ook degenen die dat zijn voor drinkwaterbedrijven op Curaçao, worden geconfronteerd met diverse beperkingen en problemen die gerelateerd zijn aan een klein eiland; specifieke wetten en regelgeving kunnen dit soort incidenten voorkomen. Alhoewel hemodialyse met kraanwater in het verleden in veel landen werd toegepast, is dit het eerste geval waarbij een intoxicatie het gevolg was van het afgeven van stoffen uit een drinkwaterbuis.⁶ In veel landen wordt gebruik gemaakt van cementlagen als binnenbekleding van ijzeren drinkwaterbuizen om deze te beschermen tegen corrosie, maar het is zeer ongebruikelijk dat deze cementlagen aluminium tot zeer hoge concentraties kunnen afgeven. Deze aluminiumintoxicatie was een tragische samenloop van omstandigheden:

1. De drinkwaterdistributie-industrie, die een drinkwaterbuis produceerde met een binnenlaag van cement die in staat was de aluminiumconcentratie in het water tot zeer hoge concentraties te laten stijgen onder bepaalde omstandigheden.⁶ Een cementsamenstelling die afweek van de richtlijnen in bijvoorbeeld de Verenigde Staten^{8-11,29} en in Nederland. In Nederland moet de applicator de geschiktheid aantonen als afgeweken wordt van de standaard cementtypen.¹² Een drinkwaterdistributiemaatschappij die zulk een drinkwaterbuis toepast in een gebied met een lage doorstroomsnelheid

- van het drinkwater, waardoor er ongebruikelijk hoge concentraties van uitgeloopte stoffen kunnen ontstaan.⁶
2. Een lokale waterfabriek die water produceerde met een ongebruikelijk lage concentratie van calciumcarbonaat (25-40 mg/L) waardoor de cementlaag van de buis langdurig kon worden aangetast.¹ In een aantal Europese landen (bijvoorbeeld Nederland,³⁰ Duitsland, Denemarken en sommige delen van Frankrijk) eist de overheid dat drinkwater een hogere concentratie van calciumcarbonaat (boven de 60-80 mg/L)³ moet hebben om corrosie van drinkwaterbuizen met de kans op het uitloggen van metalen tegen te gaan.³⁰
 3. Het ontbreken van wetgeving aangaande de drinkwaterkwaliteit, zoals dat in veel landen wel via de wet geregeld is. De WHO (World Health Organization) geeft geen richtlijn voor aluminium aan in drinkwater ten aanzien van de volksgezondheid, maar adviseert wel om de concentratie beneden de 200 µg/L³¹ te houden, hetgeen veel lager is dan de hoogst gemeten waarde van 690 µg/L in het onderhavige geval.⁶ De Europese Gemeenschap heeft een resolutie aangenomen die aangeeft dat indien de maximale aluminiumconcentratie in het drinkwater de grens van 30 µg/L overschrijdt, de drinkwaterautoriteiten medische instellingen dienen te waarschuwen. Ook stelt de resolutie dat de autoriteiten die verantwoordelijk zijn voor de drinkwaterdistributie alle dialyseafdelingen, bij voorkeur van tevoren, moeten waarschuwen bij elke belangrijke verandering in de drinkwaterproductie die in staat is het aluminium gehalte in het drinkwater te verhogen en tevens bij elke accidentele vervuiling van het gedistribueerde water met aluminium.³² Deze bepalingen zijn overigens bedoeld voor die gevallen waar aluminiumzouten gebruikt worden bij de drinkwaterbereiding en niet zozeer om te waarschuwen voor risico's die inherent zijn aan het uitloggen van aluminium uit cementbekledingen van drinkwaterbuizen.
 4. Diatel maakte geen gebruik van een waterzuiveringsinstallatie, die op zijn minst de mortaliteit zou hebben verminderd.
 5. Noch de artsen, noch de drinkwaterbedrijven hebben zich gerealiseerd dat de waterkwaliteit in die mate kon verslechteren na de korte wateronderbreking voor de installatie van de nieuwe drinkwaterbuis. Dientengevolge hebben de artsen geen noodzaak gezien om een waterbehandelingsinstallatie te plaatsen. Bij Diatel werden er sporadisch routine-waterkwaliteitstesten gedaan. Het lijkt echter niet waarschijnlijk dat deze

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testen een ernstige intoxicatie bij de patiënten zou hebben voorkomen, aangezien Diatel kort nadat de patiënten symptomatisch werden, werd gesloten en het bovendien minstens 6-8 weken zou duren voordat deze bepalingen beschikbaar zouden zijn. Tenslotte is de buis na installatie doorgespoeld zodat de aluminiumconcentratie bij het testen laag zou zijn.

Dit incident maakt duidelijk dat een constante kwaliteit van het water als dit de drinkwaterfabriek verlaat, geen garanties geeft voor het distributienetwerk: de drinkwaterkwaliteit kan in korte tijd veranderen, waarbij in het geval van dialyseafdelingen, de behandelende artsen verantwoordelijk kunnen worden gehouden voor de gevolgen.

De patiënten

Aangaande aluminiumintoxicaties zijn er nieuwe bevindingen gedaan en werden met deze studie nieuwe therapeutische inzichten verkregen. De vroege stadia van een subacute aluminiumintoxicatie kunnen enkele weken ongemerkt blijven aangezien patiënten dan minimale symptomen vertonen; er is tijd nodig voordat neurotoxische effecten kunnen manifesteren. Ondanks het feit dat de patiënten overgeplaatst waren naar de dialysefaciliteit van het ziekenhuis en zij niet meer blootgesteld werden aan parenteraal aluminium kregen sommige patiënten die tot op dat moment nagenoeg klachtenvrij waren, ernstige neurologische symptomen. Uit medische handboeken kon onvoldoende informatie verkregen worden om de bron van de klachten te achterhalen. Bovendien kon er geen informatie verkregen worden van de lokale drinkwaterautoriteiten, aangezien deze zich evenmin bewust waren van de toxicologische aspecten van hun drinkwaterdistributie. Het niet aanwezig zijn van laboratoria op Curaçao die in staat waren om op adequate wijze aluminiumbepalingen te verrichten, veroorzaakte een verdere vertraging van de diagnose en de therapie.

Om logistieke redenen kon de behandeling van de aluminiumintoxicatie in eerste instantie niet op Curaçao plaatsvinden en moesten de patiënten naar Nederland worden overgeplaatst. Een nieuw therapieprotocol moest worden ontwikkeld aangezien de literatuur onvoldoende praktische behandelingsmogelijkheden bood. De zeventien patiënten die de intoxicatie hebben overleefd

konden succesvol behandeld worden en al deze patiënten keerden terug voor dialysebehandeling in Diatel.

Het juridische proces

Rechtbanken zijn in hoge mate afhankelijk van specifieke expertise indien medische aspecten moeten worden geëvalueerd.³³⁻³⁵ Zoals dat voor bovengenoemde aspecten van de intoxicatie gold, werd was het gerechtelijk vooronderzoek als onderdeel van het strafrechtelijk proces beïnvloed door de beperkingen van een klein eiland. Voor een grondige evaluatie waren getuige-deskundigen uit het buitenland nodig. Deze laatste ontbrak de kennis met betrekking tot lokale omstandigheden. Uit deze zaak blijkt dat rechtbanken er niet zondermeer vanuit kunnen gaan dat hoog gekwalificeerde deskundigen, die als onafhankelijke deskundigen zijn aangetrokken door de rechtbank, altijd betrouwbare getuigenverklaringen zullen afgeven. Aangezien technische aspecten aan de orde kunnen komen die enkel en alleen van belang zijn voor de jurisprudentie en derhalve niet altijd onderbouwd hoeven te zijn met gegevens uit de specifieke medische vakliteratuur, kunnen deskundigen verklaringen afleggen die geen stand zouden houden in een wetenschappelijk forum.³⁵ Door een toenemende vertechnering van de geneeskunde zullen rechtbanken in toenemende mate afhankelijk worden van specifieke wetenschappelijke kennis in civiele en strafrechtelijke zaken. Om een rationeel oordeel te kunnen vormen moet het juridische systeem oplossingen vinden om betrouwbaar gebruik te kunnen maken van wetenschappers. Er dienen richtlijnen opgesteld te worden die in wetenschappelijke zin de kwaliteit van getuige-deskundigen garanderen en in kleine gemeenschappen moeten deze tevens een analyse omvatten aangaande de lokale technische mogelijkheden.

De verdachte

Voor een medicus is de strafrechtelijke vervolging voor de dood van patiënten een van de meest ingrijpende ervaringen in zijn medische carrière. Dit niet alleen omdat het proces vele jaren duurt, maar vooral ook omdat het ingrijpt in de fundamenteën van de medische ethiek.

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De meeste artsen en gezondheidswerkers zijn onervaren in juridische aangelegenheden en bij aanklachten tegen hun persoon blijken zij zich vaak onvoldoende bezig te houden met de voorbereiding van hun zaak.³⁵ Ook al is het moeilijk om vanuit een medisch standpunt het juridische proces goed te begrijpen, het blijft wenselijk dat artsen zich actief opstellen, zich in de materie verdiepen en op de hoogte te raken van de wijze waarop men in een gerechtelijk onderzoek met bewijsmateriaal omgaat. Dit kan als bijkomend voordeel hebben dat de stress die een dergelijke zaak oplevert beter gehanteerd kan worden.

Concluderend kunnen wij stellen, dat zelfs indien hoogtechnologische medische behandelingen zoals hemodialyse technisch mogelijk zijn en er gekwalificeerde medici ter beschikking staan, de introductie van deze technieken in kleine gemeenschappen pas dient plaats te vinden na een grondige analyse en implementatie van de relevante wetgeving en protocollen. Het creëren van kwaliteitsgaranties stelt speciale eisen aan degenen die verantwoordelijkheid dragen voor de medische zorg in kleinschalige gemeenschappen. Het feit dat op een eiland met beperkte mogelijkheden protocollen uit landen met hoog ontwikkelde technologie niet zomaar kunnen worden overgenomen, impliceert dat het scheppen van nieuwe kaders voor medisch handelen gepaard moet gaan met een uitvoerige, lokaal relevante studie. Dit heeft hier een hogere prioriteit dan in de zogenaamde eerste wereldlanden waar de patiënten veelal beschermd worden door een reeds bestaand veiligheidsnet van wetten en voorschriften. De drinkwaterindustrie moet rekening houden met het feit dat drinkwaterbuizen met een bekleedende binnenlaag van cement toxische eigenschappen kunnen hebben. Richtlijnen moeten worden opgesteld die de kwaliteit van de getuigenverklaringen van deskundigen zoveel mogelijk garanderen.

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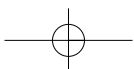
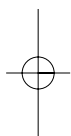
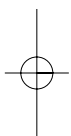
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CHAPTER IX

Korte samenvatting in het Nederlands en Resúmen kortiku in Papiamentu

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In dit proefschrift wordt achtereenvolgens beschreven:

- een incident van subacute aluminiumintoxicatie bij nierpatiënten, alsmede nieuwe medische inzichten in aluminium-toxiciteit,
- de oorzaken van het incident, in relatie met waterleidingkundige aspecten en
- de juridische gevolgen hiervan.

Na de inleiding in deze problematiek (**hoofdstuk I**) wordt in **hoofdstuk II** de aspecten van de drinkwaterdistributie beschreven die de basis vormt van deze intoxicatie.

Het aantal nierpatiënten op Curaçao is de laatste jaren sterk toegenomen omdat de incidentie van de belangrijkste oorzaken van nierproblemen, te weten suikerziekte en hoge bloeddruk sterk is toegenomen. Als de nieren niet meer functioneren kan met behulp van "hemodialyse" het zuiveren van het bloed gedeeltelijk door machines worden overgenomen. Met behulp van de Nierstichting Nederland en Diatel Amsterdam is in 1992 het dialysecentrum Diatel Curaçao geopend. Bij hemodialysebehandelingen wordt veel water gebruikt. Aangezien er problemen waren met lage waterdruk heeft het drinkwaterdistributiebedrijf in mei 1996 een nieuwe drinkwaterbuis geïnstalleerd. Enkele weken later ontwikkelden 7 van de 27 patiënten klachten van misselijkheid en braken, waarbij een verhoogd calcium in hun bloed werd vastgesteld. Aanvankelijk werd verondersteld dat het enige dat de klachten van de dialysepatiënten had veroorzaakt een hoger calcium van het leidingwater was, waarna Diatel werd gesloten en de patiënten overgeplaatst. Desondanks werden na een kortdurend herstel tien patiënten binnen enkele weken ernstig ziek en overleden zij na epileptische insulten en coma. Uit onderzoek bleek dat er zowel calcium als aluminium uit de cementen binnenbekleding van de drinkwaterbuis was vrijgekomen. Deze buizen werden toegepast omdat de oorspronkelijke, metalen, drinkwaterbuizen snel corrodeerden door het relatief kalkarme gedestilleerde drinkwater; de cementlaag aan de binnenkant van de buizen zou deze corrosie moeten voorkómen. De cementlaag bleek evenwel een viermaal hoger aluminiumgehalte dan gebruikelijk te hebben en was bovendien niet bestand tegen bovengenoemde eigenschappen van het drinkwater. Achteraf gezien blijkt aluminium jarenlang uit de cementlaag uit te kunnen logen waarbij de concentratie in het drinkwater maandenlang boven de streefwaarde van de World Health Organization kan komen; derhalve dient deze cementsoort niet

toegepast te worden bij drinkwaterbuizen.

In **hoofdstuk III** worden de klinische bevindingen beschreven van subacute aluminiumintoxicatie bij de onderhavige patiëntengroep. De overleden patiënten waren gemiddeld ouder, minder goed doorvoed en hadden een lagere urineproductie dan de zeventien patiënten die het overleefd hebben.

Het postmortem onderzoek van vier patiënten wordt weergegeven in **hoofdstuk IV**. Aluminiumgehalte in lever, bot en hersenschors was significant verhoogd in vergelijking tot normale waarden, wat duidelijk maakt dat de normale opslagcapaciteit van lever en botten werd overschreden.

Hoofdstuk V geeft een overzicht van de literatuur aangaande symptomen, bronnen van aluminiumintoxicatie en pathogenetische mechanismen van aluminiumintoxicaties. Tevens wordt een therapieschema voor de behandeling van hemodialysepatiënten met aluminiumintoxicatie met het medicament desferrioxamine beschreven, waarmee zeventien patiënten succesvol werden behandeld.

In **hoofdstuk VI** worden de juridische implicaties van het incident beschreven. Het openbaar ministerie voerde een strafrechtelijk onderzoek uit en concludeerde aanvankelijk dat er geen strafbare feiten waren gepleegd en dat de patiënten waren overleden als gevolg van een uitzonderlijke samenloop van omstandigheden. De nabestaanden gingen in beroep tegen deze beslissing en na een gerechtelijk vooronderzoek in Curaçao, Nederland en België werden de twee artsen van Diatel door het openbaar ministerie gedagvaard. Enkele patiënten eisten tevens vervolging van de drinkwaterinstanties, maar hun eis werd niet ontvankelijk verklaard omdat het volgens de toen geldende wet niet mogelijk was rechtspersonen strafrechtelijk te vervolgen. In de dagvaarding werden de artsen verantwoordelijk geacht voor het overlijden van de patiënten, omdat er na het plaatsen van de drinkwaterbuis onvoldoende op alarmeringen van dialysemachines zou zijn gereageerd en het water niet was getest in die periode. Het openbaar ministerie was namelijk van mening dat de toegenomen frequentie van alarmeringen het gevolg zou zijn van een hoge concentratie aluminium in het dialysewater. De rechter oordeelde evenwel dat dit niet mogelijk kon zijn, noch dat het testen van het water het overlijden van de patiënten met zekerheid had kunnen voorkomen. Alhoewel het geen element van de dagvaarding was, veroordeelde de rechter de medisch directeur voor het niet-installeren van een waterzuiveringsinstallatie bij Diatel en legde een

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geldelijke boete en een voorwaardelijke gevangenisstraf op. In hoger beroep werd de arts vrijgesproken.

Concluderend kunnen wij stellen dat zelfs indien op kleine eilanden hoogtechnologische medische behandelingen zoals hemodialyse technisch mogelijk zijn, de introductie en implementatie van deze technieken alleen plaats dient te vinden na een grondige analyse en implementatie van de relevante wetgeving en protocollen.

Den e disertashon akí ta deskribí supsiguientemente:

- un kaso di intoksikashon sup-agudo di aluminio serka algun pashènt di nir, ademas ideanan médiko nobo riba toksisidat di aluminio,
- loke a kousa e intoksikashon, en relashon ku aspektonan di awa di pipa, i
- konsekuenshanan hurídiko di un ke otro.

Despues di un introdukshon den e problemátika akí (**kapítulo 1**) ta deskribí na **kapítulo 2** e aspektonan di distribushon di awa di bebe ku a forma base di e intoksikashon en kuestion.

Último añanan e kantidat di pashènt di nir a oumentá konsiderablemente na Kòrsou, komo e prinsipal kousanan di problema di nir, esta malu di suku i preshon haltu di sanger, a oumentá supstansialmente. Ora e nirnan no ta funshoná mas, tin aparato ku, hasiendo uso di "hemodiálisis", parsialmente por purifiká e sanger. Na 1992 a inougurá e sentro di diálisis Diatel Curaçao, ku sosten di Nierstichting Nederland i Diatel Amsterdam. Na tratamentu ku hemodiálisis ta usa mashá awa. Ya ku tabata eksistí problema ku preshon di awa ku tabata muchu abou, e kompania di distribushon di awa a instalá na mei 1996 tuberia nobo. Algun siman despues a presentá serka 5 di e 27 pashèntnan keho, den sentido ku nan tabatin walmentu di stoma i gana di arohá. Ademas a konstatá oumento di kalsio den nan sanger. Na prinsipio a suponé ku oumento di kalki den e awa di pipa tabata úniko kousa di e kehonan serka e pashèntnan ku tabata dialisá. E or'ei a sera Diatel i a trasladá e pashèntnan. No opstante, despues di un rekuperashon ku a dura poko tempu, dies pashènt a bira grave i a fayesé despues di a presentá síntoma di atake di epilepsia i a bai den koma. Di investigashon a bin resultá ku tantu kalki komo aluminio di e furu di paden di e pipanan a bruha den e awa. A introdusí e pipanan ku un furu di semènt parti paden, komo esunnan original di metal tabata frusa lihé debí na e defisiensia di

kalki den e awa destilá di bebe; e furu di semènt parti paden di e pipanan mester a prevení ku e pipanan lo a frusa parti paden. A resultá, sin embargo, ku e nivel di aluminio di e furu di semènt tabata kuater biaha mas haltu ku normal i ademas e no tabata resistente kontra e karakterístikanan ariba menshoná di e awa di bebe. Di e investigashon a resultá tambe ku pa añanan largu aluminio di e furu di semènt por a lòs dreña e awa di bebe, pa motibu di lokual pa lunanan largu e konsentrashon di aluminio den e awa di bebe tabata mas haltu ku e nivel ku Organisashon Mundial di Salú (WHO) ta konsiderá rekomendabel; konsekuentemente no mester usa e tipo di semènt akí den pipa di awa di bebe.

Na **kapítulo 3** ta deskribí e resultadonan klíniko di intoksikashon sup-agudo di aluminio serka e grupo di pashènt en kuestion. E pashèntnan ku a fayesé tabatin un promedio di edat avansá, nan tabata ménos bon nutrí i nan tabatin produkshon di orina mas abou ku e diesshete pashèntnan ku a sobreviví.

E eksamen despues di morto di kuater pashènt ta deskribí na **kapítulo 4**. Nivel di aluminio den higra, wesu i "herschors" tabata signifkantemente haltu kompará ku e nivelnan normal, loke ta mustra klaramente ku a surpasá e kapasidat normal di higra i wesu pa akumulá aluminio.

Kapítulo 5 ta duna un bista di loke tin den literatura tokante sítomanan, fuentenan di intoksikashon di aluminio i mekanismonan ku a kousa e intoksikashon di aluminio. Ta deskribí ademas un skema di terapia pa tratamentu di pashèntnan di hemodiálisis ku intoksikashon di aluminio ku e remedi desferrioxamine, ku kua a trata diesshete pashènt ku éksito.

Kapítulo 6 ta deskribí e implikashonnan hurídiko di e kaso. Ministerio Públiko a efektuá un investigashon penal i a konkluí na promé instansia ku no a kometé aktonan kastigabel i ku e pashèntnan a fayesé debí na un koincidensia i sirkunstansha ekstraordinario. Famianan di e difuntunan a apelá e desishon di Ministerio Públiko i, despues di un investigashon hudisial preliminar na Kòrsou, Hulanda i Bélgika, Ministerio Públiko a dagfar e dos dòkternan di Diatel. Algun pashènt a eksigí ademas pa pèrsiguí e instanshanan di awa di bebe, pero Korte a disidí ku no por a atmití nan demanda, pasobra segun lei vigente e tempu ei no tabata posibel pèrsiguí penalmente un persona hurídiko. Den e dagvaarding a konsiderá ku e dòkternan ta responsabel pa morto di e pashèntnan, komo, despues ku a instalá e pipanan di awa di bebe, e dòkternan en kuestion a reakshoná insufisientemente riba señalnan di alarma di e aparatonan di diálisis i komo no a tèst e awa den e periodo ei. Ministerio Públiko tabata di opinion ku

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oumento di frekuensha di e señalnan di alarma tabata komo konsekuensha di e konsentrashon haltu di aluminio den e awa di diálisis. Pero hues a opiná ku esei no por tabata posibel, ni ku tèstmentu di e awa lo por a prevení ku siguridat morto di e pashèntnan. Ounke no tabata parti di e dagvaarding, hues a kondená e direktor médiko pa e echo ku no a manda instalá un instalashon di purifikashon di awa na Diatel i a dun'é un but i kondén'é na un kastigu di prizòn kondishonal. Den un siguiente huisio di apelashon e dòkter a sali liber.

Konkluyendo por bisa ku hasta ora na islanan chikí tratamentu di teknologia haltu riba tereno médiko, manera hemodiálisis, ta téknikamente posibel, introdukshon i aplikashon di e téknikanan en kuestion únikamente mester tuma lugá despues di un análisis profundo i implementashon di leinan i protokòlnan relevante.

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Nawoord

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Mijn medeleven gaat uit naar de nabestaanden. Moge de patiënten die zijn overleden in vrede rusten in de hoop dat hun overlijden ertoe kan bijdragen andere patiënten te helpen.

Dit proefschrift is tot stand gekomen met de hulp en medewerking van velen. Hiervoor mijn oprechte dank. Enkele personen wil ik met name noemen. Op de eerste plaats wil ik de geïntoxiceerde patiënten bedanken voor hun blijk van vertrouwen; zonder hun steun was ik nimmer aan dit proefschrift begonnen. De medewerkers van het Laboratorium voor Toxicologie in het Leids Universitair Medisch Centrum ben ik dankbaar voor het vele extra werk dat zij hebben verzet en het feit dat zij altijd behulpzaam wilden zijn bij het verschaffen van literatuur. Collega Hilton Hewitt was mijn kompaan in donkere tijden en wist me altijd te motiveren om door te gaan. Achter de schermen waren Ashley Duits en Rob Rojer onmisbaar als coeditors en klankbord voor ideeën, vooral wanneer ik diverse aspecten te eenzijdig had belicht. Speciale dank gaat ook uit naar de directe collega's waaronder Rauf Engels, Nouaf Ajubi en Cay Winkel die altijd klaar stonden om voor me waar te nemen als ik weer voor onderzoek het land uit moest of me moest terugtrekken om stukken te schrijven. Cay, bedank ik ook voor het beschikbaar stellen van de prent van Curaçao. Yvonne en Peter Baauw bedankt voor het anders leren denken en het leren reduceren van te veel informatie tot precies genoeg. Leo Spigt was een rots in de branding en ik kijk met genoegen terug naar de discussies en de wijze lessen. Mijn hartelijke dank gaat ook uit naar Ella Rijnschot, mijn secretaresse, die altijd klaar stond voor het verzetten van bergen typwerk, het maken van tabellen, of het doen van extra klusjes. Elisabeth Statius Muller, Els dank ik hartelijk voor de hand- en spandiensten. Christa Weijer ben ik dankbaar voor het bijstellen van Nederlandse en Engelse teksten en ook Ingrid Schuringa heeft geholpen om het Engels leesbaarder te maken. Michael en Julie, jullie waren mijn inspiratiebron om me op te laden als ik weer ergens voor moest gaan zitten. Jullie hebben je vader vele uren moeten afstaan aan de voorbereiding voor dit proefschrift. Gerardine, het schrijven van een proefschrift is voor de wederhelft een minstens zo inspannende aangelegenheid. Jou wil ik bedanken voor je steun, het geduld en de support die je me de afgelopen jaren hebt gegeven en het feit dat je je hebt kunnen bedwingen de PC het raam uit te gooien.

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De schrijver van dit proefschrift is geboren op 21 maart 1955 te Willemstad, Curaçao. Hij heeft zijn middelbare school gevolgd in Amersfoort, Paramaribo, Maastricht en Heerlen en behaalde in 1976 het VWO diploma (Atheneum B) aan het Grotius College te Heerlen. In datzelfde jaar werd begonnen met de studie Geneeskunde aan de Universiteit van Utrecht, waarna in september 1983 het artsexamen werd behaald.

Het eerste deel van de opleiding Inwendige Geneeskunde werd gedaan van oktober 1983 tot maart 1986 in het St. Elisabeth Hospitaal te Curaçao (opleider: Prof. Dr. A.E.C. Saleh). Aansluitend werd de specialisatie voltooid in het Academisch Ziekenhuis Utrecht (opleider: Prof. Dr. A. Struyvenberg). Na zijn registratie in maart 1989 als internist werkt hij sindsdien in het St. Elisabeth Hospitaal te Curaçao. Van 1992 tot aan de fusie met het St. Elisabeth Hospitaal in 1999 was hij tevens medisch directeur van Diatel Curaçao.