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Early insight into the potential contribution of aluminum to neurodegeneration - a tribute to the research work of Robert D. Terry, Igor Klatzo, Henryk M. Wisniewski and Donald R.C. Mclachlan

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Abstract

The first successful attempt to obtain purified aluminum metal was accomplished by the Danish physicist and chemist Hans Christian Orsted in 1824, however it was not until about ~140 years later that aluminum's capacity for neurological disruption and neurotoxicity was convincingly established. The earliest evidence of the possible involvement of this biosphere-rich metallotoxin in Alzheimer's disease (AD) originated in the early-to-mid-1960's from animal and human research investigations that arose almost simultaneously from independent laboratories in the United States and Canada. This short communication pays tribute to the pioneering research work on aluminum in susceptible species, in AD animal models and in AD patients by the early investigators Drs. Robert D. Terry, Igor Klatzo and Henryk M. Wisniewski with special acknowledgement to the late Dr. Donald RC McLachlan, and their contemporary physician-scientist colleagues and collaborators. Together these researchers established the groundwork and foundation towards our understanding of the potential contribution of aluminum to progressive, age-related and lethal neurodegenerative diseases of the human central nervous system.

Graphical Abstract

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Author Contributions

JHM, MEP and WJL searched and reviewed the current aluminum-in-AD relevant literature; WJL assembled, collated and integrated the data and wrote the article.

Research in the early 1960's suggested that aluminum salts induced neurological dysfunction in higher mammals, including the human disorder Alzheimer's disease. The pioneering research work of the independent investigators R.D. Terry, I. Klatzo, H.M. Wisniewski and their laboratories are here reviewed, paying special tribute to the late D.R.C. McLachlan.

Origins of the idea of aluminum involvement in the Alzheimer's disease (AD) process

The combined research efforts of at least four independent research groups pioneered aluminum neurotoxicology studies in susceptible AD animal models, with direct implications to age-related neural pathology in the human central nervous system (CNS) with particular reference to Alzheimer's disease (AD). It was the early investigative work of these researchers from about ~1960–1965 who: (i) established a link between the ability of the environmentally abundant trivalent neurotoxin aluminum to induce neurofibrillary tangles (NFT), neurofibrillary degeneration and the aggregation of amyloid peptides into senile plaques (SP), two early hallmarks of AD neuropathology; and (ii) these studies were followed by evidence both *in vitro* and *in vivo* of the remarkable ability of aluminum to compact normally 'open' or euchromatic brain chromatin and thereby restrict the flow of genetic information in the CNS:

Robert D. Terry (1924–2017)

Robert Davis Terry BS, MD (affiliations: Albert Einstein College of Medicine, New York, USA and the University of California San Diego CA USA; 1924–2017; age 93) was an eminent neurologist, neuropathologist and dedicated Alzheimer researcher whose life-long research career yielded ground-breaking discoveries in the structure, function and biophysical character of the blood-brain barrier, cellular transplantation and was the first proponent of the concept that synaptic atrophy and loss were the best single predictor of cognitive decline and memory failure in humans afflicted with AD [1,2; <https://www.alzforum.org/news/community-news/robert-d-terry-93-co-founder-us-alzheimers-research>; <https://www.neuropath.org/assets/InMemoriamArticles/2017-terry.pdf>]. In the early 1960's scientific research in the US into AD was negligible when Terry activated the AD research field with neuropathological and neurochemical studies on the formation of both amyloid-containing senile plaques (SP) and neurofibrillary tangles (NFT). Terry was successful in assembling an interdisciplinary group in New York that was to become an international powerhouse of AD research including the recruitment of Henryk M. Wisniewski from Poland and Peter Davies from the UK, Khalid Iqbal and others (<https://www.alzforum.org/news/community-news/robert-d-terry-93-co-founder-us-alzheimers-research>). Much of Terry's research work involved the then newly upgraded and refined science of electron microscopy (EM) and the EM-based dissection of AD-relevant intracellular lesions such as SP and NFT, and with EM was able to monitor their progressive development in AD brain. Using Igor Klatzo's aluminum-phosphate technique in rabbits [4–6] RD Terry pioneered the experimental production of neurofibrillary degeneration that mimicked NFT neuropathology as first described in the brain of a 51-year old AD patient by Alois Alzheimer in 1906 [7]. The first peer-reviewed research papers suggesting an

aluminum involvement in AD came from Terry's extensive publications during the years 1963–1965 that first described the experimental production of NFT and neurofibrillary degeneration using Klatzo's aluminum-phosphate fixation techniques and the injection of experimental animals, chiefly rabbits (*Oryctolagus cuniculus*), an extremely aluminum-sensitive species, with Al compounds which reproducibly induced the formation of NFT-like structures, highly similar to those lesions observed in AD brains [1–6].

Igor Klatzo (1916–2007)

Igor Klatzo BS, MD, [affiliations: University of Vilnius; Albert-Ludwig University of Freiburg Germany; Montreal Neurological Institute; and the retired Chief of the Laboratory of Neuropathology and Neuroanatomical Sciences at the National Institute of Neurological Diseases and Stroke (NINDS) at the National Institutes of Health (NIH), Bethesda, MD, USA; 1916–2007; age 91] was a remarkable neuroscientist and extraordinary character who made many original discoveries on the blood-brain barrier and blood-cerebrospinal spinal fluid (CSF) barrier permeability, the characterization of their roles in cerebral edema and in mechanisms of ischemic brain injury, proposing novel concepts of barrier formation and the selective permeability of these biophysiological barriers to environmental neurotoxins such as lead (Pb) and aluminum (Al) salts. Klatzo was strongly influenced in his early career by the German physician and neurologist Oskar Vogt, BS, MD at the Brain Research Institute in Neustadt, Southern Germany, and Vogt's original ideas that certain of the brain's anatomical regions were the selective focus of specific metal neurotoxins, such as the observation of lead salts targeting the mossy fibers, one of the major afferent inputs to the cerebellum (<https://academic.oup.com/jnen/article/67/2/170/2916931>). From 1961–1965 Igor Klatzo with Henryk Wisniewski pioneered in rabbits the experimental production of neurofibrillary degeneration, by then widely recognized as the single most important pathological hallmark of AD, via the intracerebral instillation of aluminum phosphate, the basic ingredient of Holts fixative solution and adjuvant [8,9]. This was followed by progressive degenerative alterations throughout the entire CNS '*with widespread nerve cell changes of the type known as toxic degeneration*'; as described in a paper by Klatzo et al., 1963 and by Wisniewski et al., in 1965 [4,5]. These exciting breakthrough outcomes, however, were subsequently tempered by the findings that aluminum-induced neurofibrillary degeneration in rabbits differed, antigenically, for example, from neurofibrillary tangles in AD and their ability to stain with SMI-31 immunoreactivity against the phosphorylated neuron-specific neurofilament heavy NF-H chain protein (<https://www.antibodypedia.com/gene/3579/NEFH/antibody/1457869/SMI-31R>). It was at this point in time scientific ideas began to diverge on the nature of the involvement of aluminum with AD and these introduced both disagreement and conflict within the aluminum-in-AD research communities in laboratories throughout the Americas, while new research provided clues to aluminum involvement in AD not pertaining to neurofibrillary pathology and the pathological generation of aluminum-induced AD-type lesions [9–11].

Henryk M Wisniewski BS, MD, PhD (1931–1999)

Henryk Miroslaw Wisniewski BS, MD, PhD (affiliations: Medical School of Gdansk, Poland; Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw,

Poland; National Institutes of Health National Institute of Neurology and Communicative Diseases and Stroke (NIH-NINCDS); Albert Einstein College of Medicine, Bronx NY, USA; Director of the New York State Institute for Basic Research in Mental Retardation, Staten Island NY, USA and currently the New York State Institute for Basic Research in Developmental Disabilities; 1931–1999; age 68) was a highly dynamic, truly inspirational and energetic Polish-American neuropathologist, psychiatrist and clinician-scientist whose major achievements included ‘*what the lesions for Alzheimer’s disease looked like, what they were made of, and how they worked*’ in an remarkable series of over 700 original peer-reviewed publications [12]. Between 1965–1977 Henryk Wisniewski’s laboratory produced a flood of scientific investigative reports linking aluminum with the age-related lesions of AD, mainly neurofibrillary tangle (NFT) pathology, the intricacies of NFT formation and the mechanism of neurofibrillary degeneration in AD brain [see for example 5,8,12–15]. However, as time progressed Wisniewski’s research emphasized some very fundamental differences in the topography, the 3-dimensional structure and dynamics of neurofibrillary degeneration and NFT formation in aluminum-induced encephalopathy compared to the neuropathology of AD, culminating with an equally large number of peer-reviewed papers such as appeared in the Lancet in 1977 stating that ‘*There was no significant difference in aluminum concentration between normal brains and brains from patients with dementia, in the material as a whole or in the regions rich in neurofibrillary degeneration (hippocampus and frontal and temporal cortex)*’; and that ‘*high levels of aluminum are not specific for Alzheimer’s disease and may be age-associated*’ [14]. Some aluminum researchers claim that there was undue influence from the aluminum industry in this reversal of the concept of a role for aluminum in the pathogenesis of AD. A review from the same laboratory ~15 years later stated that ‘*the hypothesis that aluminum is a cause of (or a risk factor in) the development of beta-amyloid SP, NFT and dementia in AD is based on studies by Wisniewski et al, Klatzo et al and Terry & Peña in 1965 that showed that injection of experimental animals with Al compounds induces the formation of NFT*’, and further that ‘*..... extensive studies of the pathology of AD and Al-induced encephalopathy by our group and others indicate that Al does not cause Alzheimer’s disease neuropathology*’ [15]. This was an exceptionally strong signal and weighty statement from a highly recognized and respected leader in the field of basic AD research, and it was left up to subsequent aluminum-in-AD researchers to maintain and strengthen the connection between aluminum and the initiation, development and/or maintenance of the AD process in other areas, excluding the aluminum-mediated induction of neurofibrillary tangle pathology in the pathological state.

Donald RC McLachlan BS, MD (1931–2017)

Donald RC McLachlan BS, MD, OC, FRCPC (affiliations; University of Waterloo, Canada; University of Toronto, Canada; early in his career was known as DR Crapper; 1931–2017; age 86; see footnote below) was widely considered a superstar in Canadian medicine, and especially in the field of human neurological diseases, neurology, neuropathology and

Footnote: The communicating author of this Short Communication had the opportunity and privilege of working over several ‘sabbatical’ and ‘summer break’ periods from 1966 to 1991 in the laboratories of Drs R.D. Terry and H.M. Wisniewski during the earliest days of the idea of the possible involvement of aluminum as a contributory factor to the etiopathogenesis of AD. With the research work done in H.M. Wisniewski’s laboratory on Staten Island NY, USA in 1986 we produced a paper concerning a significantly compacted chromatin structure in both scrapie [a transmissible, species-specific, prion disease of the domesticated goat

neuroscience, and during his 65+ year career was the principal advocate of promoting the idea that environmental factors such as aluminum might play a role in the development and/or propagation of sporadic forms of AD. More specifically, from 1973–1975 DRC McLachlan and his research group provided much of the original experimental evidence, and provided the novel hypothesis of an involvement of aluminum with AD, including the seminal paper entitled '*Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration*' published in the journal *Science* in 1973 [16] and other high impact journals [17–20], and the extremely high affinity of aluminum for the genetic material of brain cells in a study entitled '*Intracellular aluminum binding; a histochemical study*' in the journal *Histochemistry* in 1974 [20]. McLachlan's more refined experimental approach of aluminum administration to experimental animals, including the use of more soluble aluminum salts (these included aluminum lactate, maltolate and sulfate), and more diverse and extensive neurochemical and neurogenetic analysis compared to previous investigators strengthened the idea of the potential contribution of this neurotoxin and genotoxin to the AD process [9,16–23]. In this research area McLachlan published over 200 papers in high profile, peer-reviewed clinical-medical and scientific journals involving experimental animal models of neurofibrillary degeneration and chromatin changes induced by aluminum, backed up by extensive studies in human brains, including the aluminum content of brain tissues obtained from multiple human neurodegenerative diseases at autopsy. A very recent paper is available that summarizes these later findings over the last 36 years with extensive data on the aluminum content in the temporal lobe (an anatomical area targeted by the AD process) of 18 neurological diseases including Alzheimer's disease, ataxia Friedreich's type, amyotrophic lateral sclerosis, autism spectrum disorder, dialysis dementia syndrome, Down's syndrome (trisomy, 21), Huntington's chorea, multiple infarct dementia, multiple sclerosis, Parkinson's disease, prion diseases including bovine spongiform encephalopathy ("mad cow disease"), Creutzfeldt-Jakob disease and Gerstmann-Straussler-Sheinker syndrome, progressive multifocal leukoencephalopathy, progressive supranuclear palsy, schizophrenia as well as multiple controls of the same age and gender and from the same anatomical regions [21]. Subsequent to the amassing of experimental

(*Capra aegagrus hircus*) and Alzheimer's disease (a unique, progressive, age-related and ultimately lethal neurological disorder of *Homo sapiens* for which there is currently no cure or adequate treatment) [28], but we did not know at that time that aluminum may have been playing a significant role in the compaction of human brain chromatin [21–27]. H.M. Wisniewski was one of my external advisors on my PhD thesis entitled '*Chromatin structure, gene expression and nuclear aluminum in Alzheimer's disease*' published in 1991 which he endorsed; most of this thesis work was performed at the Medical Sciences Building at the University of Toronto, CANADA, in the laboratory of D.R.C. McLachlan and in H.M. Wisniewski's laboratories in Staten Island New York, USA. In the later years of his life a semi-retired I. Klatzo in his mobile home would visit established Neuroscience, Alzheimer and neuropathology laboratories all across the USA and he stayed briefly at the LSU Neuroscience Center of the Louisiana State University School of Medicine in New Orleans, LA USA; he was an avid outdoorsman and we spent time fishing together in the '*primordial and murky*' waters of the Louisiana bayous where we discussed at length the potential of environmental contributions to the onset and development of neurodegeneration. These discussions included Professor Oscar Vogt's ideas of selective neurotoxic metal targeting to specific anatomical regions of the human brain, and how different aluminum salts (including those of aluminum chloride, sulfate, maltolate, and nitrate) exhibited slight variations in their degree of neurotoxicity [16,18,27,29,30]. D.R.C. McLachlan [who in 1989 changed his name from 'DR Crapper' to 'DRC McLachlan' (his mother's maiden name)] lived just down the street from our family home in East York ON, CANADA and it was through my initial meeting(s) with Donald McLachlan in 1966–1974 that first struck my interest in the contribution of environmental factors to sporadic AD, and the potential contribution of aluminum neurotoxicity to this devastating, uniquely human and ultimately lethal neurological disorder. Working with D.R.C. McLachlan and his extended laboratory research group that included the late Drs. Arthur S. Dalton, Theodore P.A. Kruck and Catherine Bergeron, and Drs. Umberto de Boni, Steven J. Karlik, Susan Quittkat, Peter St. George Hyslop, Peter N. Lewis, P. Roy Walker, S.S. Krishnan, Bhuma Krishnan, Lee Wong and others, and their combined guidance, instruction and expertise in the neurotoxicology of aluminum and the neuropathology and neurogenetics of AD was truly inspirational, stimulating and motivating in the early stages of my own scientific career.

evidence that aluminum played some as yet undefined neurogenetic role in AD, in 1981 McLachlan's group published a key paper entitled '*Changes in chromatin structure associated with Alzheimer's disease*' [22,23], which later was shown to be the consequence of aluminum's remarkable affinity for the polyphosphates of DNA [probably as the result of aluminum's unchanging 3+ valence and extremely high charge density, with a Z^2/r of 18; with ' Z ' being the charge of the ' Al^{3+} ' ion and ' r ' being its ionic radius (0.5 nm)], and aluminum's extraordinary capacity to compact brain nuclear chromatin when compared to other divalent and trivalent biosphere-accessible neurotoxic metals on the periodic table [24]. In 1991 McLachlan et al., published the results of the first study using the trivalent aluminum chelator *desferrioxamine* (DFO) in the chelation of aluminum from the brains of AD patients [25]; these early clinical trials showed promise, however additional studies were discontinued largely due to the refusal of the DFO supplier to continue to cover the cost of DFO, McLachlan's declining state of health, and problems associated with the co-chelation of iron (Fe^{3+}) by trivalent chelators such as desferrioxamine in elderly AD patients with already compromised kidney and liver function [25,26].

In 1990 McLachlan was awarded the prestigious '*Member of the Order of Canada*' (the Canadian equivalent of the United States Congressional Medal of Honor, the highest federal government-endorsed award to scientists for research excellence in the system of orders, decorations and medals of Canada) for his pioneering and lifelong scientific work on the potential contribution of aluminum to AD and dialysis dementia, including the development and advancement of animal models to study the potential neurobiological, pathological and molecular-genetic roles of aluminum in the human CNS. This research work also included state-of-the-art methodologies to quantify aluminum in brain samples using electrothermal atomic absorption spectroscopy (ETAAS), a type of spectrometry that uses an electromagnetic graphite-coated furnace to vaporize brain tissue samples from different anatomical regions which was a significant improvement over prior 'flame spectroscopy' techniques. McLachlan et al., also pioneered other innovative spectroscopic and neurogenetic analytical methods for the determination and role of aluminum in complex biological samples that were proposed, advanced and developed [21,27–30].

In the very same year McLachlan managed the oversight, planning, creation and development of the University of Toronto's Tanz Neuroscience Centre for Research in Neurodegenerative Diseases (CRND; now located at the Krembil Discovery Tower, Toronto Western Hospital), the largest dedicated research facility of its kind in Canada, which since 1990 has been devoted to the multi-disciplinary study of human neurological disease with research focus on neurotoxicology, Alzheimer's disease, Parkinson's disease and prion disease, and other classes of progressive and lethal inflammatory degenerations of the human CNS.

In summary, since investigated and originally researched by Drs. R.D. Terry, I. Klatzo, H.M. Wisniewski and D.R.C. McLachlan and others, and beginning almost 60 years ago, our ideas, beliefs and perceptions on the potential involvement of aluminum in AD have waxed and waned, and this is reflected in the content of the enormous body of scientific evidence for or against this concept. As one index, if you cross the words '*aluminum*' and '*Alzheimer's disease*' on MedLine (a database of the National Center for Biological

Information, National Library of Medicine, National Institute of Health, compiled and updated daily by the US government, Bethesda MD, USA), and providing the most up-to-date biomedical information; freely available at www.ncbi.nlm.nih.gov/pubmed; last accessed 5 September 2019) to date there are over ~1200 papers on this subject, from Terry and Pena's original peer-reviewed paper in 1965.

The continuing controversy of the involvement of aluminum in AD can be fairly summed up in communications from two of the earliest aluminum-in-Alzheimer's disease researchers:

'Finally, a simple, linear, causal formula for the pathogenesis of AD is not necessary. Several genes might be involved in different familial AD patients, both those with early and those with late onset. Each gene abnormality may have its own set of cofactors, some of which may be environmental and others physiological, such as early life malnutrition, aluminum, head trauma, education and aging, and so on. Each of these phenomenon might well lie along several separate pathogenetic streams flowing in parallel from the underlying, still uncertain primary source'

– R.D. Terry, *Annals of Neurology*, 1991

and

'If the tragic Camelford Cornwall water pollution incident* of 1988 tells us anything, it indicates that aluminum poisoning or neurotoxicity is not the whole story in Alzheimer's disease (AD), although it may be a significant contributor in some cases to the AD process

– D.R.C. McLachlan, Abstract, personal communication 2011'.

*The Camelford water pollution incident of July 1988 involved the accidental contamination of the municipal water supply to the village of Camelford, Cornwall UK, and is generally regarded as Britain's worst mass poisoning event. In this incident 20 tons of aluminum sulfate [as alum; $KAl(SO_4)_2 \cdot 12H_2O$] was inadvertently dumped into the Camelford drinking water supply, raising the aluminum concentration to 3,000 times the normal admissible aluminum levels of the government water authorities. As the aluminum sulfate dissolved and decomposed it produced several tons of sulfuric acid which *"stripped a cocktail of chemicals from the pipe networks as well as lead and copper piping in people's homes"* (see <https://www.irwinmitchell.com/client-stories/2009/july/camelford-water-pollution-case>; last accessed 5 September 2019). Citizens of Camelford who were exposed to the contaminated water experienced a wide range of short-term health effects and many victims appeared to have suffered long-term effects (whose implications continue to remain unclear). Post-mortem analyses of people who died many years after the Camelford water pollution incident found elevated levels of aluminum in their CNS [see <http://www.bbc.co.uk>; "BBC News – The Camelford water poisoning incident of 1988 (2012); last accessed 5 September 2019].

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Conflict of Interest/disclosure/ethics statement

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Abbreviations

AD	Alzheimer's disease
Al	aluminum
BBB	blood brain barrier
CNS	central nervous system
NFT	neurofibrillary tangles
SP	senile plaques
Z^2/r	the charge density of an ion; where Z = ionic charge; r = ionic radius; for Al the Z^2/r is 18

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HIGHLIGHTS

- early toxicology research suggested a contribution of aluminum to neurodegenerative disease;
- this stemmed from aluminum's ability to induce neurofibrillary pathology in susceptible animals;
- these observations came largely from four independent research groups in the USA and Canada;
- this included the research of R.D. Terry, Igor Klatzo, H.M. Wisniewski and D.R.C. McLachlan;
- research continues to strengthen the view that aluminum is toxic to brain genetic systems.

Figure 1.

The Alzheimer's disease (AD) researchers pictured above originally proposed a role for aluminum in the production of neurofibrillary tangles (NFT) and neurofibrillary degeneration in AD, with evidence largely derived from studies in experimental animal models of NFT production and a progressive aluminum-induced neurofibrillary degeneration in these animal models; their affiliations, major research interests and lifespans are given in the caption below their photo; interestingly domesticated cats (*Felis catus*) and rabbits (*Oryctolagus cuniculus*) were found to be far more sensitive to aluminum neurotoxicity and proved far superior models for experimental NFT production and genetic alterations than the common rat (*Rattus rattus*) or the brown rat (*Rattus norvegicus*) [1–8]; their initial observations not only provided a series of suitable and experimentally-defined animal models for analyzing the effects of aluminum neurotoxicity *in vivo*, but also provided initial evidence for a species susceptibility to aluminum neuro-intoxication [16–19]. Further, R.D. Terry, H.M. Wisniewski and I. Klatzo provided the very first evidence of the accumulation of NFT and neurofibrillary degeneration in cats and rabbits subjected to experimental aluminum encephalopathy, however, the geometry of the aluminum-induced and experimentally produced NFT in these aluminum-sensitive mammals were not identical to those found in human AD; after 8 additional years of intensive research and a more thorough and refined analysis of the pathogenic roles for aluminum in inducing AD-type change, including aluminum-induced genetic, epigenetic and chromatin structural changes, D.R.C. McLachlan's laboratory was first to propose a causative, or strong contributory role, for aluminum in AD both in senile plaque (SP) and NFT formation and later, in driving changes in gene expression similar to those observed in AD. That laboratory further suggested in 1973 that '*Neurofibrillary degeneration is an important pathological finding in senile and presenile dementia of the AD-type; experimentally, aluminum induces neurofibrillary*

degeneration in neurons of higher mammals; and aluminum concentrations approaching those used experimentally have been found in some regions of the brains of patients with AD [16–22].

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