Neurodegenerative Memory Disorders: A Potential Role of Environmental Toxins

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Age-associated neurodegenerative disorders are widely recognized by clinicians, researchers, and epidemiologists as sharing common features, including the accumulation of altered proteins within the brain and an average age of onset after the sixth decade. These disorders appear to encompass both inherited and sporadic forms. A recently published review\textsuperscript{1} highlights the clinical features, genetics, risk factors, and potential treatment approaches of these disorders across the spectrum of Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS). As Mayeux\textsuperscript{1} notes in his summary, epidemiologic studies of neurodegenerative disorders are shifting their focus away from descriptive studies (disease incidence and prevalence) to the analyses of genetic and environmental factors that may expand our understanding of causality. As causes and risks factors for neurodegenerative disorders are identified, more effective treatment approaches may develop as well. Environmental factors such as neurotoxins have been evaluated as risks for the dementias and...
motor neuron disease, but most studies to date have remained more descriptive in nature.

The present review provides a summary of the research literature that evaluates putative environmental exposure to toxins and its potential association with these neurodegenerative disorders. It should be remembered, however, that much of what we know about toxins and neurodegeneration is derived from laboratory models and epidemiologic research. Therefore, causality is often difficult to infer when these data are generalized to populations or applied to individual patients.

**Demographics of dementia**

Alzheimer’s disease is by far the most common form of adult onset dementia, affecting over 4 million individuals in the United States. With the aging of our society, it has been estimated that approximately 14 million individuals in the US alone will have AD by the year 2050 [2] unless preventive measures are found. The economic burden of AD is estimated to be over 100 billion dollars per year [3]. AD is not the only adult onset dementia but its prevalence reflects approximately 60% to 75% of all cases, given that AD often coexists with other dementia disorders. Prevalence estimates for dementia with Lewy bodies (DLB) and vascular dementia (VaD) suggest that these are the second most common dementias (20% and 16%, respectively) followed by AD with PD and AD with stroke (8% each). Other dementing conditions such as Pick’s disease, corticobasal degeneration, and primary progressive aphasia, for example, account for an additional 5% of cases, with PD plus dementia reflecting another 3% of prevalent cases [4].

Epidemiologic studies have consistently shown that the prevalence and incidence of AD increase dramatically after age 65. Population-based epidemiologic studies published before 1998 have been reviewed in two meta-analyses [5,6] and will not be discussed in detail here. Furthermore, important epidemiologic concepts and study design issues related to determining factors for elevated AD risk, along with potential protective factors, are elegantly summarized in reviews by Kukull and Ganguli [7] and Garabrant [8]. However, several important points raised by Kukull and Ganguli [7] and Garabrant [8] are relevant to this review of neurotoxins as risk factors for dementing disorders. First, without a biological measure for diagnosing AD or other dementias, the methods that are used to determine the presence of dementia generally involve the use of operational clinical criteria that encompass tests of mental functioning and clinical examinations of patient symptoms and functional skills. As a result, the identification of a case is less than perfectly accurate even though AD diagnosis is no longer a diagnosis of exclusion [9,10]. Second, additional sources of error and bias arise in studies depending on the sampling strategies (in addition to case ascertainment methods), how well the selected sample reflects the total population of interest, and how the population sample was obtained. Third,
disease severity may result in underestimates in a given population. For example, early or mild AD may not be detected, or if it is specifically studied, it may result in estimates that differ from epidemiologic studies in which moderate or severe cases are identified. Finally, the design of the epidemiologic study that intends to evaluate risk factors for dementia can result in important sources of potential bias. Prospective longitudinal studies suffer from biases, including the loss of subjects to follow-up because of dropout, death (especially before the dementia evolves or is detected), and how exposure is defined. These factors could therefore underestimate the incidence (development of the dementia) in a given study, as could the variability in actual and measured exposure to a potential risk factor. Case-control studies have similar sources of bias, including the definition of a case, how exposure is determined, and because these studies compare groups of individuals with a given disease versus similar persons without the disease, the study may suffer from selection bias (the groups differ from the general population), misestimation of age, duration, and degree of exposure, or recall bias (which could reduce or inflate the exposure to an assumed risk factor).

Added sources of bias in studies that prospectively attempt to define risk factors linked to dementia and other neurodegenerative disorders are highlighted by reports that AD often is unrecognized, particularly in the mild stages, by physicians and family members of the patient [11,12]. As a result of methodological components, studies of environmental toxins and dementia risk can be expensive, time consuming, and difficult to replicate, and the interpretation of results may reflect unrecognized sources of bias [13]. In the case of dementia, an age-associated condition, a potentially complex spectrum of risks, subject factors, and genetic predispositions clearly require careful attention to study design if associations between environmental toxins and neurodegeneration are to be uncovered [14].

**Dementia diagnosis and screening**

The evaluation of the demented patient has received a great deal of attention in the past two decades and will not be summarized in this review. Readers are referred to excellent reviews of AD diagnosis and management by Morris’ [15] handbook reference, Grossberg and Desai [16], and Cummings [17]. These reviews contain standard approaches for the evaluation of suspected neurodegenerative disorders, clinical criteria, and treatment. Dementia is defined as “an acquired and sustained deterioration of memory and other intellectual functions in an alert patient. Dementia results from brain dysfunction and is a symptom of many diseases” [15]. Relevant to the evaluation of the literature on environmental toxins and dementia, the American Academy of Neurology practice parameter [9] summarizes the usefulness of current diagnostic criteria for degenerative disorders. The reliability of AD diagnostic criteria ranges from 0.51 to 0.73, and inter-rater reliability is as high as 95% between the initial diagnosis and the diagnosis
after 1 year, with a sensitivity of approximately 80% and a specificity of approximately 70%. For non-AD dementias, diagnostic criteria fare less well with generally low sensitivity but high specificity [9]. Clearly, studies attempting to ascertain risk factors for neurodegenerative or dementing disorders could be greatly influenced by the relatively low prevalence of various neurodegenerative disorders, how screening procedures are implemented [18], and the selection, application, screening procedures, and limitations of diagnostic criteria in a given study.

Environmental exposure and Alzheimer’s disease

As noted previously, AD is the most common disease process of pathologic aging. AD is a multifactorial disease, and numerous hypotheses have been proposed to explain its causes, including genetic defects, oxidative stress, β-amyloid toxicity, and environmental factors [19–22]. Over the past several years, an abundance of research has focused on the exploration of environmental factors such as solvents, metals, pesticides, and magnetic field exposure in the neurodegenerative process. Therefore, this review provides an overview of the literature as it pertains to environmental toxins and neurodegeneration, with reference to solvents, metals, pesticides, magnetic field exposure, and smoking.

Solvents and Alzheimer’s disease

It is recognized that exposure to solvents can be neurotoxic [23]. However, an association between solvent exposure and neurodegeneration, particularly AD, has yet to be established. Three epidemiologic studies [24–26] did not find a relationship between lifetime occupational exposure to solvents and AD. Graves et al [24] used a case-control design to compare 89 subjects with probable AD with 89 controls and obtained their lifetime job histories with an industrial hygienist rating exposure for each job. An increased risk for developing AD was noted with the increasing number of years of solvent exposure; however, an inverse relationship between exposure intensity and AD was reported. Palmer et al [25] compared individuals diagnosed with dementia based on computed tomography records with controls with brain cancer or another non-disabling disorder on lifetime occupational exposure to organic solvents. Their findings did not yield a positive association between occupational exposure to solvents and dementia. Shalat et al [26], using a case-control design, evaluated the effect of occupational history and subsequent diagnosis of AD on a total of 98 case and 162 control subjects. The 98 cases were all men from the Geriatric Research, Education, and Clinical Center at the Edith N. Rogers Memorial Veterans Hospital in Bedford, MA. These men had been diagnosed with Alzheimer’s type dementia between July 1975 and July 1985, based on criteria of the Diagnostic and Statistical Manual III-R (DSM-III-R) [27]
and the National Institute of Neurologic, Communicative Disorders, and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [28]. Control subjects were selected from Massachusetts voter registration lists and matched by gender, year of birth, and town of residence. No increased risk for the development of AD was evident with a history of occupational exposure to organic solvents or lead.

In contrast to the above findings, Freed and Kandel [29] and Kukull et al [30] provide data suggesting a possible relationship between occupational exposure and dementia diagnosis. The authors [29] provide evidence from a single-case study, a case series study, and a preliminary case-control study of the relationship between chronic exposure in the workplace and later development of dementia. Specifically, in the single-case study, serum levels of perchlorethylene (745 parts per billion [ppb]) elevated to approximately 15 times that seen in a normal population were found in a man who worked as a dry cleaner for over 30 years and was subsequently diagnosed with probable AD. Their case series used 80 AD patients screened post hoc for occupational exposure based on their performance on a delayed match-to-sample recognition memory test. Analyses of the memory performances in these individuals showed a pattern of greater decline in delayed (72 hr) recognition in those AD cases with a history of occupational exposure (based on family member interviews). A medical records review found that four of five individuals had been exposed to metal vapors (primarily copper), and the fifth case had been exposed to solvent. All of the subjects had histories of memory impairment, coronary artery disease, left temporal slow wave activity on electroencephalography, cortical atrophy on CT scans, and impaired short-term memory and word-finding problems on neuropsychologic testing. Neurologic findings also showed extrapyramidal signs, including impaired gait, coordination, and posture. Therefore, the authors pointed out the need to further study metals as potential contributors to the AD process. The final data set reported by Freed and Kandel [29] considered data of long-term occupational exposure to a variety of compounds (eg, metals and solvents) from 150 patients diagnosed with AD. Occupational exposure was defined as a minimum of 2000 hours in the workplace, based on questionnaires completed by the patients’ family members. The authors found that 55 of the 150 patients with AD (37%) met the operational definition for long-term occupational exposure, whereas only 7 of the 57 (12%) healthy controls met the same operational definition.

Kukull et al [30] conducted a community-based case-control study with 139 individuals diagnosed with AD based on the NINCDS-ADRDA criteria and 243 controls randomly drawn from the Group Health Cooperative population (case-control design). Results of the study were interpreted as demonstrating a moderate-to-strong association between solvent exposure and AD, with a greater effect in men and more years of exposure. Specifically, a history of exposure to one or more solvent groups (benzene and toluene, phenols and alcohols, and ketones plus other solvents) resulted in an adjusted
AD odds ratio (OR) of 2.3 (95% confidence interval [CI], 1.1–4.7); however, among men the odds ratio increased to 6.0 (95% CI, 2.1–17.2).

**Heavy metals**

Many metals such as iron, copper, and manganese are essential for normal brain function. However, many of these same elements have also been implicated in neurotoxicity and subsequent neurodegeneration, specifically AD. Iron, in particular appears to be important, given theories concerning AD pathophysiology that link oxidative stress to neurodegeneration [20,21].

**Aluminum**

Klatzo et al [31] were the first to present a hypothesis linking aluminum to the cause of AD. They found that injecting aluminum salts into the brains of rabbits resulted in neurofibrillary changes. Subsequent work by Crapper et al [32] replicated this finding in cats and demonstrated that aluminum concentration was increased in AD patients. Furthermore, Beal et al [33] found a reduction of up to 40% in choline acetyltransferase activity in the entorhinal cortex and hippocampus, as well as a reduction in serotonin and norepinephrine as a result of aluminum-induced neurofibrillary degeneration in their rabbit model of AD.

Crapper et al [32,34] provided the first reports of neurotoxic concentrations of aluminum in the brains of AD patients. Based on these early findings, it was been suggested that aluminum exposure represented a risk factor for the development of AD. Additional data showed that aluminum could be detected in the characteristic neuropathologic hallmarks of AD (senile plaques and neurofibrillary tangles [35–37]) lending further support to a link between AD and aluminum. Evidence was also reported [38] suggesting that aluminum potentiates oxidative and inflammatory events in the brain, leading to tissue damage. Although no direct relationship has been established between aluminum and AD, numerous studies suggest that aluminum may exacerbate events associated with AD. In contrast, many authors have presented results that do not support the aluminum hypothesis [39,40], having found no increase in AD risk with aluminum exposure. The most solid epidemiologic evidence comes from the case-control study by Graves et al [24] in Seattle, Washington. In 178 matched cases of AD and controls, ORs adjusted for age and education ranged from 0.89 (low) to 2.04 (high) for aluminum exposure duration (neither value was statistically significant). Furthermore, the intensity of exposure showed an inverse and nonsignificant relationship with an OR of 4.52 for low exposure and 0.76 for high levels of aluminum exposure.

Neuropathologic investigations such as the one by Candy et al [41] demonstrated the presence of minuscule insoluble aluminum silicate granules
in the brain of patients with AD. These granules were described as being surrounded by amyloid protein plaques, suggesting to the authors that these granules represented an early or initiating factor in plaque formation. In addition, Ward and Mason [42] found higher concentrations of aluminum in certain brain regions of autopsy samples from patients with AD. In contrast, the extensive work (and review) on aluminum in the brains of AD patients by Markesbery and Ehmann [20] as well as other investigators has tried to answer the question of aluminum as a primary factor in AD, in contrast to aluminum as a secondary mechanism. As covered in their reviews [20,21], aluminum is not directly toxic to hippocampal neurons in vitro, but aluminum tends to accumulate in degenerating neurons (and therefore represents a marker of neurodegeneration).

Other clinical data come from the role of aluminum in the development of Alzheimer-like symptoms in patients with renal failure, although these findings have also been inconsistent [43–45]. Generally, aluminum toxicity has been documented in patients with impaired renal functions secondary to aluminum accumulation through hemodialysis fluids and aluminum-containing pharmaceutical agents administered for the treatment of hypophosphatemia [46]. The primary symptoms of this well-known complication of dialysis, dialysis encephalopathy, consist of disordered speech, dementia, convulsions, myoclonus, and accompanying anemia and osteomalacia. Although some of these symptoms are evident in patients with AD, dialysis encephalopathy does not result in pathologic neurofibrillary tangles [46], which are a hallmark of AD.

Many epidemiologic studies have examined the possible link between exposure to aluminum in drinking water and the incidence of AD [47–49]. In drinking water, aluminum sulfate is used in water treatment to remove suspended particles and to reduce the dose of chlorine. The ingestion of aluminum in drinking water has been suggested to have a positive relationship to the occurrence of AD [50–55]. Martyn et al [56] found the risk of AD to be 1.5 times higher in districts where the mean aluminum levels in tap water exceeded 0.11 mg/l than in districts where the concentration was less than 0.01 mg/l. In contrast, Wettstein et al [57] found no relationship to an increased risk of AD in their study of 800 male octogenarians consuming drinking water with aluminum concentration up to 98 mg/L. Interestingly, the regular ingestion of aluminum through daily antacid consumption supplies thousands of times the amount of aluminum ingested through drinking water. Yet the findings of epidemiologic studies of AD and antacid exposure have been largely negative. For example, a Canadian population-based case-control study [58] found no association between the use of aluminum-containing antacids and AD in 285 cases clinically diagnosed with probable AD compared with 535 controls. Flaten et al [59] obtained similar findings, with no association between antacid use and AD mortality.

The neurotoxic effects of aluminum through occupational exposure have also been studied in different groups of workers [60,61]. Although numerous
studies [62–68] have attempted to demonstrate a possible link between the inhalation of aluminum dust and neurologic disorders, no study has yet to develop a causal link between aluminum inhalation and AD. Polizzi et al [50] compared retired foundry workers with nonexposed workers, and found that retired foundry workers had cognitive test scores suggestive of mild cognitive impairment [69,70]. They subsequently speculated that aluminum affects primarily the entorhinal cortex through the absorption of the metal through the olfactory bulb, resulting in symptoms compatible with mild cognitive impairment, a potential prodrome for AD [50]. Graves et al [24] and Salib and Hiller [71] published two epidemiologic studies that attempted to evaluate the relationship between AD and occupational exposure to aluminum. These studies taken together suggest that lifetime occupational exposure to aluminum does not appear to be a strong risk factor for AD, with ORs of approximately 1.0.

In summary, earlier evidence implicated aluminum in the development of AD; however, the aluminum hypothesis appears to have fallen out of favor as a major component of AD pathophysiology. Early studies [72] demonstrated evidence of elevated levels of aluminum in the brains of AD patients, and one small single-blind clinical trial [73] with an aluminum chelating agent (desferrioxamine) showed a reduced rate of decline in the activities of daily living in treated AD cases. Subsequent studies [74] continued to demonstrate small but significant elevations of aluminum in the AD hippocampus, inferior parietal lobule, and superior and middle temporal gyri compared with corresponding control tissues. In contrast, other studies [75,76] have failed to find differences between aluminum levels in AD brain compared with age-matched controls. Therefore, aluminum has an unclear causative role in AD neurodegeneration but may contribute to neurodegeneration through mechanisms such as its promotion of oxidative stress and, therefore, may play a secondary role in this disease [21].

Copper, iron, lead, manganese, and zinc

The oxidative stress hypothesis is believed to be a major mechanism accounting for cumulative neurodegeneration in AD [77–79]. Metals such as iron and copper act as catalysts in oxygen free-radical generation and may therefore increase the risk for AD [77,80]. Deibel et al [77] compared 10 AD brain specimens and 11 age-matched control subjects and found a significant decrease in copper along with significant increases in zinc and iron in the hippocampus and amygdala, areas with evidence of considerable histopathologic alterations in AD. Lovell et al [81] reported similar results in their study of metal concentration in the rims and cores of senile plaques and neuropil of the amygdala of nine AD and five control subjects. They found statistically significant increases in iron and zinc in the rims and cores of senile plaques in the AD amygdala compared with AD neuropil and elevated copper in the rim of senile plaques. Zinc was noticeably elevated in
the neuropil of AD subjects when compared with the controls. In contrast, mouse models of AD pathology have suggested that increasing amounts of copper appear to reduce β-amyloid concentrations, resulting in fewer pathogenic β-amyloid plaques [82,83], whereas the cholesterol-fed rabbit model of AD shows that copper-fed (0.12 parts per million [ppm]) animals developed structures in the brain resembling β-amyloid plaques and showed reduced classical conditioning performance [84].

Molina et al [85] ascertained serum and cerebrospinal fluid (CSF) levels of numerous metals in 26 patients with AD and 28 matched controls. Serum levels of zinc and CSF and serum levels of iron, copper, and manganese did not differ significantly between the two groups, whereas CSF zinc levels were decreased in AD patients compared with controls. It was hypothesized that the main finding of decreased CSF zinc levels suggested that low CSF zinc levels were related to the presence of oxidative stress processes or possibly the interaction of β-amyloid or amyloid precursor protein with zinc, resulting in a depletion of zinc levels [86]. Therefore, Cuajungco and Lees [86] argue that zinc is associated with AD pathology through its ability to precipitate β-amyloid and influence various exogenous and endogenous risk factors for AD pathology. In contrast, Price et al [87] found that zinc supplementation at normal concentrations appeared to slow down the progression of AD. However, a number of studies [77,88,89] have resulted in contradictory findings, with evidence of increased zinc in the brain or CSF of individuals with Alzheimer’s disease. The importance of zinc as a risk factor for neurodegeneration rests on data suggesting that zinc may play a role in brain-based oxidative stress as well as its observed effects of direct neuronal toxicity [21].

Mercury has been suggested as a factor in the formation of neurofibrillary tangles [90]. Thompson et al [91] and Pendergrass et al [92] demonstrated elevations of mercury in the nucleus basalis of Meynert in greater than 80% of AD brains studied. Webb [93] suggests that mercury inactivates enzymes by slowing down the repair and metabolism of vital functions, which in turn may result in neurofibrillary tangles and memory loss of AD. In sum, there may be an association between mercury and AD, but the strongest data to date suggest that it is not related to the pathogenesis of AD based on a careful study of dental amalgams. Saxe et al [94] derived direct estimates of mercury vapor exposure from dental amalgams in 33 autopsied normal elderly and 68 autopsied AD cases. Using intraoral video recordings of dental restorations, they measured (1) amalgam location, (2) surface area, (3) time in the mouth, (4) type of filling, (5) the degree of opposing dentition (as an index of abrasion leading to release of mercury), and (6) other environmental sources of mercury exposure (eg, occupation and diet). They then evaluated brain tissues (eight regions in each hemisphere) using instrumental and radiochemical neutron analysis to determine the mercury load in the tissue. Even though the control cases were, on average, 4 years older than the AD cases, no differences in dental exposure, and more importantly, mercury levels were found between
the two groups. In fact, when the data were analyzed for olfactory tissue, controls (30.9 ng/g) had higher mean values of mercury than did AD cases (14.0 ng/g). As a result, the data were interpreted as providing no support for the hypothesis that dental amalgams, and therefore mercury, were involved in AD pathogenesis.

Inorganic (eg, lead paint) and organic (ie, tetraethyl lead) lead have been investigated as possible risk factors for AD. Two cases [95] of workers with long-term occupational exposure to lead demonstrated neuropathologic features of AD at autopsy, with one individual reporting a history of dementia for many years before his death. In contrast, no consistent evidence is available to support a relationship between increased levels of manganese and the development of AD [95].

**Pesticides**

Rural areas appear to account for a higher incidence of AD cases than urban settings [96,97]. Growth and productivity in these rural communities have resulted in the increased use of pesticides [98]. Many families of pesticides are known to contain neurotoxic properties [98] that cause serious central nervous system damage (eg, carbamates, organophosphates, organochlorines, and bipyridyles [99]). Organophosphates are known inhibitors of acetylcholine, bipyridyles are able to generate free radicals that cross the blood-brain barrier, and organochlorines are capable of impairing mitochondrial function and producing free radicals [100–105]. As such, it has been hypothesized that pesticides may contribute to the cholinergic system dysfunction and production of free radicals present in AD [98].

Epidemiologic data suggest an OR of 2.17 for AD as derived from the Canadian Study of Health and Aging [58] with respect to occupational exposure to pesticides. More recently, Gauthier et al [98] conducted an epidemiologic study by randomly selecting subjects from the Saguenay-Lac Saint-Jean, Quebec, region to evaluate their long-term exposure to pesticides and a possible association between pesticide exposure and AD. In their study, AD was not significantly related to long-term exposure to herbicides and insecticides. In contrast, a cohort study of French elderly found an association between past occupational exposure to pesticides and low cognitive performance, with an increased risk of developing AD or PD [106]. This elevated risk was exclusively found in men who worked predominantly in vineyards. Based on these studies, more work clearly is needed to ascertain the impact of exposure, dose, and duration of specific pesticides.

**Magnetic fields**

Although no documented causal relationship between occupational electromagnetic field (EMF) exposure and AD has been found, a link between occupations involving exposure to electric and magnetic fields and
the subsequent development of AD has been hypothesized. Some research findings [107] suggest that EMF exposure may contribute to an increased production of β-amyloid in the brain, which might eventually result in AD. In southern California and Finland, Sobel et al [107] used a case-control method to analyze a sample of 387 AD patients and 475 hospital patients, vascular dementia cases, and community controls. After evaluating exposure through surrogate interviews, they found an association between AD and employment in occupations (seamstress, tailor, and dressmaker) associated with elevated EMF exposure, with an OR of 3.0 when the Finnish and Southern California cases were combined, and with a higher OR (3.8) for women, however, the OR varied greatly. Based on the first Finnish group (AD and vascular cases) medium to high EMF exposure was associated with an OR of 2.9 with a 95% CI, of 0.7 to 12.2, with women having greater risk with exposure (women OR 7.3, men OR 0.7). In the second series (AD and hospital controls), the EMF exposure OR for all cases was 3.1 (95% CI, 0.7–8.9), with women at a higher risk (OR 3.3) than men (OR 2.5). In the Southern California series of subjects, the OR was 3.0 (95% CI, 0.8–11.1), with women again showing an elevated risk (OR 4.2) than men (OR 2.7). Part of the difficulty with these analyses rests on the fact that there were only 36 AD cases with medium to high EMF exposure and 16 controls in the combined sample.

However, a larger study by Savitz et al [108] found only modest associations between EMF occupational exposure and AD, with an adjusted OR of 1.2 (95% CI, 1.0–1.4) in a sample of electrical workers who died during the period between 1985 and 1991. This study ascertained 256 cases of AD and randomly matched 768 controls of a larger sample of men who had occupations associated with electrical field exposure. Furthermore, the odds of AD did not change because of age, year of death, or social class. In a related study, Savitz et al [109] examined mortality in men employed at five large electric utility companies in the United States who had worked for more than 5 months at these facilities during the years 1950 to 1986. Death certificates were obtained on over 20,000 men and estimated their exposure to magnetic fields in microtesla years. Causes of death were further reviewed by evaluating any mention of neurodegenerative disorders on the death certificate (mentioned cause, 56 cases of AD) as well as any neurodegenerative disorder listed as the cause of death (underlying cause, 24 AD cases). Analyses were adjusted for several factors including solvent and polychlorinated biphenyl exposure. Overall, AD was not strongly associated with EMF exposure based on years of employment (risk ratios of 1.0–1.4 for mentioned cause and 0.9–2.1 for underlying cause). The highest risk ratio (RR) for AD was found for 9 cases (RR, 2.0, 95% CI, 0.6–7.0) who had more than 19.9 years of exposure (microtesla years) during their careers.

A positive relationship between EMF occupational exposure and AD has also been reported by Feychting et al [110] and Hakansson et al [111]. Feychting et al conducted a cohort study by evaluating all “economically active individuals” in the Swedish 1980 census and following them for
neurodegenerative disease mortality from 1981 through 1995. EMF exposure was determined by development of a job exposure matrix based on magnetic field measurements. Findings indicated an increased risk of AD (based on mortality records) observed among exposed men both in 1970 and 1980, with a relative risk of 2.3. The associations were most pronounced for early onset AD mortality or with follow-up limited to 10 years after the last known exposure. Hakansson et al [111] completed a cohort study with a large population of resistance welders who were exposed to high levels of extremely low-frequency magnetic fields. These welders completed spot, flash, butt, projection, and seam welding with high electrical currents. They found an increased risk of AD (and ALS but not PD) in workers exposed to extremely low-frequency magnetic fields. One potential factor that confounds the findings of this study is that welders were also exposed to heavy metal vapors and solvents.

**Smoking**

Studies evaluating smoking as a risk for AD have demonstrated a “protective effect,” an unrelated effect, or a modestly increased risk for AD. Lee [112] conducted a meta-analysis of 13 case-control studies from 1984 through 1993 and found a significant 40% reduction in the risk of AD among smokers. Ott et al [113] used a cohort study design involving 6870 persons over the age of 55 with approximately 2 years of follow-up to compare former smokers with “never” smokers and observed an increased relative risk of 1.4 for AD. Their results also showed that current smokers had an increased relative risk for AD of 2.2 relative to never smokers. Ott et al therefore demonstrated a doubling of risk for AD among smokers, with men at a greater risk than women. These investigators [113] subsequently assessed the simultaneous effects of smoking and apolipoprotein E genotype. For those individuals with an E4 allele, in either current smokers or former smokers, smoking had no effect. However, among persons without an E4 allele, the risk of AD caused by smoking appeared to be elevated. Merchant et al [114] and Launer et al [115] found results similar to the study by Ott et al [113], with no association found between former smokers and never smokers and AD and a modestly increased risk seen with current smokers to never smokers. Merchant et al [114] also demonstrated an increased risk with non-E4-containing genotypes and a null association between smoking and AD among those carrying the E4 allele.

A more recent report from the Honolulu-Asia Aging Study by Tyas et al [116] studied the association between dementia and mid-life smoking of 3232 men. Pack years were derived for each participant and then grouped into light (less than 26.8 pack years), medium (26.8 to 40.5 pack years), heavy (40.6 to 55.5 pack years), and very heavy (55.6 to 156 pack years) smokers. Dementia diagnosis was based on DSM-III-R [27] and NINCDS-ADRDA [28] criteria and the accuracy of the clinical diagnosis was validated in some cases (218) with autopsy examination in which approximately 67% of the clinical AD...
cases met neuropathologic criteria for AD. After adjustments for age, education, and apolipoprotein E genotype, AD risk increased at the medium (OR 2.18) and heavy (OR 2.40) levels of smoking. These derived risks agree well with the data from the Rotterdam study [113] demonstrating a doubling of AD risk with smoking. However, very heavy smoking did not increase the risk of AD (OR 1.08), and the authors suggested that this lack of elevated dementia risk might have been because of a “hardy survivor effect.” More importantly, however, the data from Tyas et al [116] also included estimates of smoking and the presence of neuritic plaques, a hallmark of AD neuropathology, in the brain. Medium and heavy smokers had more neocortical neuritic plaques at autopsy than those men who had never smoked. In contrast, data from the Multi-Institutional Research in AD Genetic Epidemiology Study by Bachman et al [117] did not find an elevated risk for AD in white and African American smokers in a sample of 2779 individuals. In this study, current and past smokers were compared with nonsmokers for risk of AD. In whites the risk for AD in smokers after adjusting for age and education was 0.88 (OR), whereas it was 1.0 for African Americans.

Clearly, the data on smoking as a risk for AD are conflicting and reflect study design and population differences. Additionally, as neurodegeneration in AD is believed to involve oxidative stress, no information is available from these studies about diet and antioxidant supplements that may moderate the risk of AD with smoking, especially given the findings that antioxidant levels are affected by smoking [118–120] and may also moderate oxidative damage in smokers [121,122]. As a result, smoking as an environmental toxin and AD risk will require more careful study to more clearly define their association.

**Parkinson’s disease and environmental toxins**

In PD, the main pathologic change is the loss of pigmented neurons in the substantia nigra [123]. These neurons project their axons to the striatum and use dopamine as their neurotransmitter. A reduction of the striatal dopamine represents the primary neurochemical alteration in PD. Another primary feature is the presence of cytoplasmic inclusions called Lewy bodies within the nigral dopaminergic neurons as well as in other areas of the brain such as the locus ceruleus, the dorsal motor nucleus of the vagus, the sympathetic ganglia, and the cerebral cortex. The loss of nigrostriatal dopaminergic projection neurons is largely responsible for the extrapyramidal movement disorder and may also be responsible for cognitive changes such as impaired dual task performances [124]. Because the function of Lewy bodies in the processes resulting in PD is unknown and Lewy bodies are often seen in postmortem AD cases, it is believed may suggest an overlap in these clinical entities [123,125].

The typical symptoms of PD are resting tremor, slowness in movements, rigidity, postural instability, loss of facial expression, gait disturbance, micrographia, constipation, and excessive sweating. Over time, the disease can cause depression, personality changes, dementia, sleep disturbance,
speech impairment, and sexual dysfunction [1]. PD is typically idiopathic [123], however, age appears to be the most apparent risk factor for developing PD. PD is rare before the age of 50 and increases with age thereafter.

The rate of dementia incidence in idiopathic PD ranges between 10% and 15%. Mayeaux et al [126] reviewed the clinical records of a cohort of patients with PD in a major medical center and estimated the overall incidence rate of dementia in this cohort to be 69 per 1000 person years of observation. Furthermore, these authors found that by age 85 more than 65% of the surviving cohort was demented. The age-specific rates of dementia in the cohort group were significantly greater than for a similarly aged sample of healthy elderly individuals. As with AD, multiple studies have evaluated potential risk factors including environmental toxin exposure as a contributing factor for PD.

Parkinson’s disease dementia

In terms of dementia in PD, autopsy data show that cortical Lewy bodies are present but that they differ in their distribution from those seen in AD [124,127,128]. The major clinical difference reported by Mayeaux et al [129] between PD patients with and without dementia was a later age at the onset of motor manifestations. In multiple logistic regression analyses, significant predictors of dementia in PD were lack of education, severity of motor deficit, and PD onset at an age greater than 60 [130,131]. These findings are similar to those of Levy et al [132] who showed that an increased risk of incident dementia in PD is associated with the age and severity of extrapyramidal signs, but this association is primarily related to their combined effect rather than separate effects. Interestingly, Marder et al [133] found that a family history of dementia was present in 30% of their demented PD patients but only 5.6% of their nondemented group. Thus PD patients with a family history of dementia may be predisposed to developing dementia during the course of PD. Overall, the age at onset of PD, motor symptoms, lower education level, and family history of dementia may increase the chances of PD patients becoming demented. McKeith and Burn [124] suggest that the precise diagnosis of a dementia syndrome in PD is problematic, particularly in the early stages. They state, “Minor performance deficits in set-shifting, retrieval of learned material, and reduced verbal fluency are very frequent and usually do not warrant a diagnosis of dementia...because they fail to impact substantially on the person’s day-to-day functioning...Cognitive screening tools that have been developed for the detection of AD...are poorly sensitive to the subtle subcortical deficits.”

Parkinson’s disease versus dementia with Lewy bodies

A variant of PD and AD, termed dementia with Lewy bodies (DLB), is defined by the presence of Lewy bodies throughout the neocortex and
brainstem. In this disorder, cortical Lewy bodies are frequently accompanied by neuritic plaques and neurofibrillary tangles as seen in AD [134]. McKeith and Burn [124] point out that a few cortical Lewy bodies can be found in most PD cases, even those without dementia, suggesting that the distribution and density of cortical Lewy bodies are important in determining their effects on clinical symptoms, rather than simply their presence. The researchers define DLB as a dementing disorder with prominent neuropsychiatric features, which are associated with the degeneration of cortical neurons, particularly in frontal, anterior cingulate, insular, and temporal regions. DLB presents mainly in late life, with a mean age of onset between 75 and 80 years [127].

Searches of the current literature yielded little data exploring connections between DLB and neurotoxins. Perhaps the pathological and clinical similarities inherent in PD and DLB may be obscuring the conclusions of toxicologic studies of these diseases, thus making it particularly difficult to differentiate the unique effects of environmental toxins on each of these diseases. Consequently, our knowledge of DLB and its potential connection to toxins is awaiting additional epidemiologic and toxicologic investigations. Thus, the present review focuses on the significantly larger literature on PD with dementia and environmental toxins, rather than on DLB and toxins.

Environmental toxins and Parkinson’s disease

In terms of environmental toxins, those related to agricultural work have been closely studied in relation to neurodegenerative diseases. Of particular interest to researchers have been herbicides, pesticides, fungicides, and to a lesser extent rural living in general and well water consumption. Unfortunately, the literature in these areas is fraught with contradictory findings, probably because of the methodological differences that exist between studies.

Parkinson’s disease and herbicides

Herbicidal compounds have generally been explored as a potential risk factor for PD. Gorell et al [135], in a case-control study, found a significant association between PD and occupational exposure to herbicides (OR 4.10, 95% CI). One herbicide in particular that has been closely examined is paraquat. Used extensively during the mid 20th Century, this herbicide has been found to be associated with PD incidence [136]. A study by Li and Sun [137] theorized that paraquat leads to oxidative stress, which results in the death of dopaminergic neurons. Paraquat has been shown to induce parkinsonian symptoms such as increased rigidity, bradykinesia, and tremor [138]. Further implicating the potential danger of this specific herbicide are the findings of a study by Liou et al [139] that show PD risk was highest in those who had used paraquat (OR 4.74) compared with other herbicides.
(OR 2.17) and control subjects who had no exposure to pesticides (OR 1.00). However, Kuopio et al [140] did not find an association between exposure to herbicides and PD.

**Parkinson’s disease and fungicides**

The neurotoxic effect of Maneb, a manganese-containing dithiocarbamate fungicide, is the inhibition of the activity of the mitochondrial respiratory chain. It has been shown in animal studies to enhance the toxicity of the herbicide paraquat toward the nigrostriatal neurons [141]. Thus, the combination of fungicides and herbicides may pose an even higher risk for PD than exposure to either one individually.

**Parkinson’s disease and pesticides**

Baldereschi et al [142] showed that occupational pesticide exposure is significantly associated with PD (OR 3.33). Furthermore, their results suggest that by virtue of obtaining a pesticide use license, regardless of the actual amount of time spent in contact with pesticides, pesticide is related to an increased risk of PD. Additional evidence comes from a cohort study of French elderly that describes a significant association, in men only, between PD and occupational exposure to pesticides (adjusted RR 5.63 [106]).

The neurotoxic effect of rotenone, a plant-derived pesticide, is to increase the formation of cytoplasmic inclusions in the substantia nigra neurons and α-synuclein aggregation. Data from rat studies [143] demonstrate that rotenone promotes degeneration of the dopaminergic neurons and induces parkinsonian symptoms.

Organochlorine pesticides, such as Dieldrin, are believed to increase α-synuclein formation, reactive oxygen species formation, and lipid peroxidation [144]. Other investigators have found contrary results. Corrigan et al [145] analyzed frozen samples of human substantia nigra using gas chromatography with electron capture detection. These investigators found that organochlorines did not produce a direct toxic action on the dopaminergic system but may contribute to PD through cytochrome P-450 polymorphism. They compared the concentrations of organochlorine compounds in the tissues of the substantia nigra of patients diagnosed with PD, AD, cortical Lewy body dementia, and nondemented nonparkinsonian controls. It was found that the levels of organochlorine compounds were significantly higher in the brains of PD patients but not in those of the other groups. These results suggest that organochlorine insecticides do not produce a direct toxic effect on the dopaminergic tracts of the substantia nigra and may contribute to the development of PD in those rendered susceptible by virtue of a cytochrome P-450 polymorphism, excessive exposure, or other factors. Taylor et al [146] found no association between exposure to pesticides or herbicides and PD.
Parkinson's disease and farm work and rural living

Employment in agriculture and living in a rural environment have both been examined in regard to environmental toxins and neurodegeneration. Similar to the risks for lung diseases that appear to be associated with agriculture [147], it has been speculated that working on a farm may be related to neurodegeneration because of the potential for increased exposure to pesticides, herbicides, and fungicides, which are used in the large scale growth and harvesting of vegetation. Research from the Honolulu Heart Program/Honolulu-Asia Aging Study [148] found that working on a farm increased the relative risk of PD from 1.0 to 1.9 (in individuals who worked 20 years on plantations in Honolulu). Conversely, Kuopio et al [140] did not find an association between farm and rural work as an occupation and PD. Rural residence has also been examined as a potential risk factor for toxin exposure because people live closer to areas where pesticides, herbicides, and fungicides may be spread, and the higher likelihood of using well water for drinking. A study by Gorell et al [135] concluded that farming is a risk factor for PD (OR 2.79, 95% CI); however rural or farm residence was not found to increase the risk of the disease. Other research has found no difference in the history of rural residence, farm residence, previous farming activity, or employment in agricultural work between PD patients and control subjects in Germany [149]; yet, it has been shown that the risk for PD appears to be elevated for those living in a rural area (OR 3.62 [149]). The results of research on well water are in direct opposition. DePalma et al [149] found that well water increases the risk of PD to 2.09 (OR). However, this finding of increased risk of PD was associated with well water in African Americans only, whereas other investigators [135,149] have not found such an association between well water and increased PD risk. As a result, the data in this area remain unclear and contradictory. Additional investigation is needed in this area to elucidate the connections between these factors.

Parkinson's disease and methyl-4-phenyl-1,2,3,6-tetrahydropyridine

In 1983, Langston et al [150] reported on a series of narcotic addicts in northern California who developed parkinsonism after exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP was formed as a byproduct during the synthesis of a meperidine derivative. With the exception of its relatively rapid onset, the syndrome experienced by these individuals has been indistinguishable from idiopathic PD. In subsequent studies, MPTP was found to exert its toxic effect in the central nervous system after being oxidized by monoamine oxidase-B to 1-methyl-4-phenylpyridinium (MPP+) [151]. MPP+ is concentrated in mitochondria and blocks oxidative phosphorylation and ATP production [152], leading to cell death. Hence, these chance occurrences have significantly informed our knowledge of the mechanisms related to the development of PD.
Parkinson’s disease and metals

Heavy metals have been implicated in the development of PD because high concentrations of iron, zinc, and aluminum have been found in the substantia nigra tissue of PD patients compared with controls [153]. Gorell et al [154] found an increased risk of PD with exposure to combinations of metals (e.g., lead-copper, lead-iron, and iron-copper) compared with any metal alone. This study determined that short-term exposure to metals (20 years or less) was not statistically related to the development of PD.

Parkinson’s disease and manganese

Manganese is well-known for its neurotoxic effects in humans, such as extrapyramidal symptoms and neuropsychiatric difficulties [155]. Symptoms of manganese exposure syndrome reportedly include extrapyramidal and neuropsychiatric symptoms. As summarized by Zatta et al [155], the clinical features of manganese neurotoxicity involve (1) an early phase consisting of fatigue, headache, muscle cramps, loss of appetite, apathy, insomnia, diminished libido, and psychotic reactions (aggression and emotional lability); (2) extrapyramidal signs, including monotone speech, expressionless face, impaired writing dexterity, and antero- and retropulsion; and (3) an established phase in which individuals present with dystonia and a “cock-walk” gait.

Manganese is present in the pesticide Maneb and in the engine anti-knock compound MMT (methylcyclopentadienyl manganese tricarbonyl), which is used in gasoline. Gorell et al [154] found that 20 years’ of exposure to manganese increases PD risk by 10.61 (OR). This finding was replicated more recently by Gorell et al [156], who reported that persons with more than 20 years’ of exposure had a significantly increased risk of developing PD (OR 10.63, 95% CI, 1.07–105.99).

Parkinson’s disease and copper sulfate

Twenty years’ exposure to copper increases the risk of PD by 2.49 (95% CI, 1.06–5.89) as reported by Gorell et al in two separate studies [154,156]. This finding was confirmed by DePalma et al [150] in which copper exposure increased the odds of PD by 2.69.

Parkinson’s disease and mercury, iron, and zinc

Gorell et al [154] found no association between PD and exposure to mercury or iron. There is also little available evidence implying a direct link between an abundance of zinc and PD [155]. In fact, Jiménez-Jiménez et al [157] found low zinc levels in the cerebrospinal fluid of PD patients but not in controls.
Parkinson’s disease and aluminum

One of the proposed mechanisms in PD by which metals may produce an effect is through oxidative stress, a mechanism that, as discussed above, is also implicated in AD. Investigators have studied the effects of the presence of aluminum and zinc on the oxidative stress induced by the neurotoxin 6-hydroxydopamine (6-OHDA) in the mitochondria from the brains of rats [158]. It has been found that the consumption of O₂ during 6-OHDA auto-oxidation was significantly decreased in the presence of aluminum and zinc. Uversky et al [153] propose that oxidative stress may result from increased levels of redox-active metal ions within the substantia nigra as metal accumulation occurs. The authors conducted a systematic analysis of the effect of various metal ions on the structural and aggregation properties of human recombinant Α-synuclein in vitro. Α-Synuclein is a presynaptic protein that has been shown to be a component of the Lewy body and may trigger Lewy body formation in PD and DLB [159]. They concluded that aluminum was the most effective of the metals examined in accelerating the rate of Α-synuclein fibril formation. Taken together, these results suggest that aluminum, through its promotion of Α-synuclein and fibril formation may play a substantial role in the development of PD and DLB.

One pathway by which PD patients may encounter aluminum may be through aluminum-containing antacids. Altschuler [160] re-examined the work of Strang [161], who studied 200 PD patients and 200 controls and found that there was a significantly higher incidence of ulcers in the PD patients compared with the controls. Altschuler [160] states that the use of aluminum-containing antacids may intensify the absorption of aluminum, but few other data are available to support this hypothesis.

Parkinson’s disease and carbon monoxide poisoning

Shuichi et al [162], using an animal model, found that increases in extracellular dopamine accompanied with the enhancement of its oxidative metabolism in rat striatum exposed to CO had a deleterious effect on the striatal dopamine system. This finding would suggest that CO could be related to the development or progression of PD, although Kuopio et al [140] did not find an association between CO poisoning and PD.

Parkinson’s disease and solvents

DePalma et al [149] found that exposure to solvents alone was not associated with PD. Research by Pezzoli et al [163] concluded that exposure to hydrocarbon solvents is a risk factor for the earlier onset of symptoms of PD and more severe disease throughout its course. However, Jacques et al [164] dispute the findings of Pezzoli et al’s study, stating that the study design and conclusions were misconstrued.
Parkinson’s disease and magnetic fields

Savitz et al [108] looked at the occurrence of neurodegenerative disease in male electrical workers in the United States. The researchers examined the death certificates of men over the age of 20, who were employed primarily in an electrical occupation and who died between 1985 and 1991. No evidence was found that suggests any demographic variable considered (eg, age, race, year of death, social class) had any affect on the development of PD. However, looking at specific occupations yielded an interesting finding. Men who were employed as power plant operators were at a higher risk of developing PD (adjusted OR 2.1, 95% CI, 0.9–4.7). In another study by Savitz et al [109] that looked at disease mortality by duration of employment in electrical occupations, the findings for PD risk were inconsistent, with no clear association between the length of employment and PD being demonstrated. The only significant finding was shown in eight men who were exposed for a period of 10–20 years or longer to 0.490–0.888 microtesla years of electromagnetic field (EMF), whose underlying cause of death was PD. The adjusted rate ratio for this group was found to be 2.4 (95% CI, 1.0–5.8). However, no strong findings were shown for men who had undergone similar EMF exposure whose cause of death from PD was mentioned on their death certificate or for men whose EMF exposure was at a higher level or for a greater length of time. Thus, there is little evidence that EMF has a substantial affect on PD risk.

Parkinson’s disease and smoking

Research on cigarette smoking and PD is one area that has been widely researched and yields consistent findings across studies. Overall, cigarette smoking appears to be a protective factor against developing PD. Gorell et al [156] showed that smoking more than 30 packs per year was associated with a decreased chance of developing PD (OR 0.42, 95% CI, 0.25–0.71). In monozygotic and dizygotic twin pairs in which at least one twin had PD, the risk of developing PD was inversely related to the amount of cigarette smoking [165]. In an animal model of PD initiated by MPTP intoxication, exposure to cigarette smoke led to a decrease in the loss of dopaminergic neurons in substantia nigra. Taken together, such results suggest that frequent nicotine exposure may have a neuroprotective effect on the dopaminergic nigrostriatal system [166]. Although the mechanism by which nicotine produces its effect is not known, several have been hypothesized. One mechanism that has been proposed is through the ability of nicotine to block the effects of two endogenous or exogenous dopaminergic proneurotoxicants, 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro-β-carboline [1,167]. Alternatively, nicotine may also act by stimulating a neurotrophic factor, fibroblast growth factor-2, which is believed to protect the dopamine-containing cells in the substantia nigra [1,168]. DiMonte et al [123] reviews the
mechanisms behind the association between smoking and neuroprotection with regard to PD. Two possible mechanisms they propose are that nicotine may be neuroprotective in itself or nicotine may inhibit monoamine oxidase activity and dopamine turnover, thereby preventing nigrostriatal damage.

**Frontotemporal dementia and Pick’s disease**

Frontotemporal dementia (FTD) involves the progressive dysfunction of the anterior temporal and frontal lobes. The usual presenting features in FTD relate to cognitive function, but personality and behavioral symptoms are prominent. Behavioral features include the loss of personal and social awareness, disinhibition, dampening of affect, and loss of insight. The neuropsychologic profile of FTD is characterized by impairment in executive and attentional abilities disproportionate to the degree of memory impairment. This clinical pattern is opposite to that found in AD, in which memory functions are more impaired than executive abilities [169].

Three patterns of behavior and cognitive dysfunction were outlined in sets of formal criteria for the diagnosis of FTD. The first pattern, labeled FTD, is characterized by the classic behavioral symptoms associated with FTD and Pick’s disease. The other two syndromes, called semantic dementia and progressive nonfluent aphasia, are characterized primarily by disorders of language and semantic knowledge [169].

Progressive nonfluent aphasia is a second clinical syndrome identified in FTD. Progressive nonfluent aphasia involves primarily unilateral left frontal, left frontoparietal, or left frontotemporal degeneration and is characterized by dysfunction in expressive language [169]. Semantic dementia is a third clinical syndrome identified in FTD. In semantic dementia there is a progressive loss of semantic knowledge. Because content becomes progressively devoid, this syndrome is characterized by frequent vague references to people, objects, and places. Semantic dementia is characterized as a fluent aphasia. The loss of word meaning is apparent in anomia and impaired comprehension [169]. Given the rarity of these disorders, no epidemiologic data are yet available from the standpoint of environmental exposure and FTD, with the exception of zinc.

**Pick’s disease and zinc**

Wallwork [170] proposes that zinc concentration and metabolism may lead to neurodegeneration. Evidence from Constantinidis and Tissot [171] found that hippocampi from patients with Pick’s disease contained 25% more zinc than normal controls. The researchers suggest that the excess hippocampal zinc may interfere in glutamate metabolism, causing some of the symptoms of the disease. However, Ehmann et al [172] found that hippocampal zinc concentrations in patients with Pick’s disease were similar
to controls. The authors suggest that this conflict may be caused by the difficulty of diagnosing this disease.

**Amyotrophic lateral sclerosis**

ALS is a well-known motor neuron disease caused by the gradual degeneration of nerve cells in the brain and spinal cord [173]. Investigations of environmental risks for ALS have been ongoing and have recently received greater public attention because of speculation about exposure during the Desert Storm campaign.

**Amyotrophic lateral sclerosis and metals**

Using a case-control study design, Gresham et al [174] examined the association between occupational heavy metal exposure and the risk of developing ALS in 66 ALS patients and 66 age- and gender-matched controls. The participants responded to questionnaires that probed for occupational heavy metal exposure (i.e., aluminum, lead, lead alkyl, magnesium, mercury, mercury alkyl, nickel, and selenium), medical events (e.g., polio, thyroid, and other conditions), and travel history (including travel to the southern and western Pacific). Women were excluded from the analyses because of the low numbers of women who had been potentially exposed to heavy metals during their occupational service. The analyses determined that, in men only, there was no association between heavy metal exposure and ALS. Furthermore, no increased risk was found with increased exposure to lead or mercury. The authors deduced that given the disparity between men and women in terms of occupational exposure to metals, it is not likely that occupational exposure to metals would be a primary causative factor in the development of ALS.

**Amyotrophic lateral sclerosis and magnetic fields**

Work by Savitz et al [108] has provided some evidence for the hypothesis that EMF exposure increases the risk of ALS. The investigators studied a population of men whose occupations exposed them to EMF. It was determined that working in electrical occupations increased the risk of ALS. Specifically, telephone installers and repairers (adjusted OR 2.2), electrical equipment repairers (adjusted OR 3.9), supervisors, power installers, and repairers (adjusted OR 2.9), and power plant operators (adjusted OR 4.8) were all found to be at a greater risk of developing ALS. A related study by Savitz et al [109] compared mortality rates of men exposed to EMF through their occupations with the risk of ALS. Again, several significant findings were shown. In cases in which ALS was listed as the cause of death, the risk of ALS increased with the number of years of exposure to EMF (0 to ≤5 years RR 1.0, 5–20 years RR 1.8, and ≥20 years RR 2.4). Furthermore, in the group with the greatest number of years of working in electrical occupations (≥20 years), those with the highest levels of exposure were
shown to have the highest risk of developing ALS (0.000–0.386 microtesla years, RR 1.0; 0.386–1.060 microtesla years, RR 1.9; 1.060–2.033 microtesla years, RR 2.3; and 2.033–14.547 microtesla-years, RR 2.4). Similar patterns of risk were shown for men in whom the underlying cause of death was ALS. In terms of the number of years of exposure, those with longer employment in exposed occupations were more likely to develop ALS (0 to \(\leq 5\) years RR 1.0, 5–20 years RR 2.0, and \(\geq 20\) years RR 3.1). In this group as well, among the men who underwent the longest length of exposure, those with the highest levels of exposure were at greater risk of ALS (0.000–0.386 microtesla years, RR 1.0; 0.386–1.060 microtesla years, RR 2.3; and 1.060–2.033 microtesla years, RR 3.0). The data from these two studies suggest that men who are exposed to EMF at higher levels and for longer periods of time are at the greatest risk of developing ALS. If this is the case, additional research into the mechanisms by which these neurodegenerative changes are affected by EMF is needed.

Amyotrophic lateral sclerosis and the Persian Gulf War

After the Persian Gulf War ended in 1991, veterans began reporting a number of inexplicable symptoms including memory loss, headaches, joint pains, chronic fatigue, nervous system disorders, limb weakness, paresthesias, and sexual dysfunction [173,175,176]. Reports of troops coming into contact with potentially neurotoxic chemicals during their deployment (eg, insect repellants, flea collars, medications containing pyridostigmine bromide, and other substances) [177,178] have spurred several investigations. Investigations by the military and by research scientists have looked into these phenomena to determine whether these symptoms are indicative of a diagnosable syndrome or have a determinant cause. Gray et al [179] studied the health of the US Naval Mobile Construction Battalion (NMCB) after the Persian Gulf War using questionnaire methods. Compared with those who did not go to the Persian Gulf, NMCB personnel who spent time in the Gulf reported a higher prevalence of four physician-diagnosed multisymptom conditions: chronic fatigue syndrome, posttraumatic stress disorder, multiple chemical sensitivity, and irritable bowel syndrome.

A nationwide epidemiologic study conducted by Horner et al [176] identified all of the new occurrences of ALS among Gulf War veterans in the mobilized Reserves and National Guard since their initial deployment in 1990. Deployed military personnel were defined as those who served in the Gulf region during Operation Desert Shield and Desert Storm or in the period after Desert Storm. The study included 2,482,333 veterans, of whom 696,118 were deployed to the Gulf region. It was shown that the risk ratio for the development of ALS for deployed military was almost twice that of the nondeployed (1.92), with an age-adjusted relative risk of 2.41. In another study [180] of 690,000 Gulf War veterans who were followed for 8 years, findings show that by 1998, the observed incidence of ALS was 3.19 times
higher than what was expected given the age distribution of the Gulf War veteran population and the age-specific death rates of the US population.

There have been several critiques of the aforementioned studies. Rose [181] explains that the degree of excess risk is not significant given the small number of ALS cases in the young, healthy military personnel being studied. In a correspondence note, Armon [182] critiqued the research of Horner et al [176], stating that the “lower-than-usual number of cases identified in the non-deployed veterans would make even a ‘usual’ number of cases in the deployed veterans appear excessive.” The critique goes on to explain that the study design did not take the confounding effect of smoking frequency into consideration in their analyses.

Furthermore, other researchers suggest their own data do not corroborate the findings of elevated risk resulting from Gulf War deployment. Smith et al [173] studied deployed (n = 551,841) and nondeployed (n = 1,478,704) Gulf War veterans. The authors found a risk ratio of 1.66 (CI, 0.62–4.44) for deployed veterans developing ALS. They imply that their statistical power to detect risk factor associations with ALS hospitalizations was low, as demonstrated by the broad CI around the risk ratio. Overall, the authors reported that the ALS outcomes were “sparse,” despite having a large subject pool.

Another case-control study of general neuromuscular symptoms of European Gulf War veterans did not demonstrate significant findings. Sharief et al [178] looked at reports of symptoms of neuromuscular dysfunction in Gulf War veterans with more than four symptoms (Gulf-ill, n = 49) consisting of 26 healthy (Gulf-well) veterans, 13 symptomatic Bosnian veterans (Bosnian-ill), and 22 symptomatic troops who had not been deployed to the Gulf (Era-ill) in a random sample selected from a larger cohort. Numerous procedures were administered to the study population including a clinical assessment, nerve conduction studies, quantitative sensory and autonomic function tests, and needle and single-fiber electromyogram. Although some troops reported symptoms that might be related to conditions such as carpal tunnel syndrome or ulnar neuropathy, common neurologic syndromes not specifically related to active service in the Gulf region, overall results showed no objective evidence of peripheral neurologic disorders in Gulf War veterans who described neuromuscular symptoms. Taken as a whole, the current literature in this area appears to give conflicting accounts as to whether deployment in the Gulf region is associated with neuromuscular dysfunction, including ALS. However, the preponderance of the research thus far does not support Gulf War deployment as a contributing factor in the development of ALS.

Parkinsonism-dementia complex and amyotrophic lateral sclerosis on the island of Guam

Over the past 60 years or more, a puzzling neurologic phenomena has been observed in the Western Pacific Ocean region. Specifically, the Chamorro
people of Guam and other Marianas Islands have experienced a highly elevated rate of neurodegenerative diseases, with a complex that neuropathologically demonstrates a combination of ALS, parkinsonism, and dementia complex (termed ALS/PDC) being the most prevalent of the diseases recorded [183]. Significant investigation has been conducted in an attempt to understand the reasons for the large number of neurologic disease occurrences in this region.

Neuropathology of the amyotrophic lateral sclerosis/parkinsonism, dementia complex

Descriptions of the ALS/PDC of Guam have evolved. An early investigation by Kurland et al [184] describes two distinct diseases, ALS and PDC, occurring in epidemic proportions in the Guamanian population. On microscopic examination, the brains of persons diagnosed with PDC showed intraganglionic fibrillary changes and scattered intracytoplasmic granulovascular bodies but no plaques, Pick, or Lewy bodies. The authors also describe diffuse loss of ganglion cells and reactive gliosis, particularly in the substantia nigra and globus pallidus. The presence of the neurofibrillary tangles distinguishes PDC from idiopathic PD, Creutzfeldt-Jakob disease, Shy-Drager syndrome, and supranuclear palsy [186]. However, in a number of their autopsied PDC cases, there were clinical features of ALS in addition to the PDC. Specifically, in terms of pathology findings for these subjects, the authors stated, “in addition to Parkinsonism-dementia complex, there was also degeneration of motor neurons and demyelination of the pyramidal tracts throughout the brain and spinal cord.” Kurland et al [184] conducted histologic examinations of Chamorro cases of ALS and reported classical changes expected in ALS as well as Alzheimer’s fibrillary changes and Simchowicz’s granulovascular bodies but in a distribution less than that observed in PDC. Overall, there were a number of Chamorro cases, which, on pathological examination, did not clearly fit into a diagnostic category for ALS or PDC but were a combination of ALS, PDC, and AD. The diagnosis for these persons has been termed ALS/PDC to incorporate the totality of their brain pathology.

Recent research by Morris et al [186] has brought the exploration of the Guamanian neurodegenerative phenomena full circle by suggesting, as in earlier research, that the Guamanian ALS and PDC may be separate diseases, in which the ALS of Guam is classical ALS rather than a form unique to the Chamorro people. In their study, the authors reviewed 45 cases of motor neuron disease seen on Guam between 1983 and 1998 and categorized them according to their clinical and pathological similarity to classical motor neuron disease in other areas of the world. Clinically, they found that the majority of the Guamanian patients studied met the criteria for ALS, with progressive bulbar and limb upper and lower motor neuron involvement without sensory signs or evidence of compressive pathology. Their data also supported findings that tau neurofibrillary degeneration in the ALS patients
on Guam occurred at a higher level than in asymptomatic whites of similar age; yet, in the Chamorro cases, the neurofibrillary degeneration was not associated with significant nerve cell loss, clinical dementia, or extrapyramidal syndromes, a finding that contrasts with the features of typical PDC. The authors conclude that tau disorders may produce both diseases with the neurofibrillary tangle symptomology, varying from classical ALS in this population, resulting from some unknown factor specific to Guam or the Chamorro people. Pérez-Tur et al [187] undertook a genetic study of the TAU gene in five Chamorro participants (two with PDC, one with ALS, and two normal controls). The results showed no abnormalities in the sequence of the TAU gene in any of the study groups. The findings suggest that TAU gene abnormalities may not be the primary cause of PDC or ALS in the Chamorro people, but rather that some environmental factor is a more likely cause of the high incidence of neurodegenerative diseases in Guam. Taken together, the evidence in this area is not conclusive about whether ALS and PDC of Guam are separate or combined diseases or what role the TAU gene plays in the development of these neurologic disorders.

Amyotrophic lateral sclerosis/parkinsonism, dementia complex of Guam, and metals

There has been significant speculation about the cause of the high rate of ALS/PDC on Guam. Gellein et al [188] analyzed brain tissues of Guamanian patients with ALS (n = 8), PDC (n = 4), and normal controls (n = 5) to determine whether concentrations of various metals are related to the disease incidence. The authors speculated that some metals in the Guamanian environment may be deficient (eg, magnesium and calcium), whereas other metals may be highly “bioavailable” (eg, aluminum). The significant findings of the Gellein et al [188] study were that in the Guamanian study population, ALS patients had significantly higher concentrations of cadmium in their gray and white matter than patients with PDC and controls. The other significant finding was that PDC patients were shown to have more zinc in their gray matter than ALS patients or controls. Interestingly, no differences were found in this study between the three groups for levels of cobalt, copper, iron, manganese, rubidium, or vanadium. The authors suggest that the limited number of subjects, formalin tissue preparation methods, diagnostic difficulties, and low power of the statistical tests used may have contributed to the lack of findings for other significant metal concentration differences between the groups. Thus, metals may play a role in the development of PDC; however, more evidence for this hypothesis needs to be gathered.

Amyotrophic lateral sclerosis/parkinsonism, dementia complex of Guam, and cyad

Another potential environmental culprit for the high occurrence of ALS/PDC on the island of Guam is cyad, the seed of the false sago palm, which is
unique to the Western Pacific. The cyad seed has been used by the Chamorro people as a food source as well as a topical medicine for skin lesions [185]. The cyad seed contains several toxins, two of which have been closely studied: cycasin, a potent cytotoxin and carcinogen, and β-methylamino-L-alanine (BMAA) [185]. Large doses of isomers of BMAA have been shown to be related to muscle weakness in rhesus monkeys [189]. However, other animal studies have not shown such results. Perry et al [183] administered large doses of BMAA (15.5 g/kg of the L-isomer) to mice over a period of 11 weeks. They found that during the course of the experimental protocol all mice that were given BMAA maintained their weight and did not exhibit any behavioral abnormalities. On microscopic examination of the brain and spinal cord, no pathological changes were seen in any of the mice. Specifically, there was no evidence of neuropathologic changes suggesting ALS or PD. Research by Wilson et al [190] suggests that BMAA may not be the cyad toxin responsible for the ALS/PDC seen on Guam. These investigators fed mice pellets made of washed cyad flour. High-performance liquid chromatography-mass spectrometry failed to show significant amounts of BMAA, cycasin, methylazoxymethanol, or β-N-oxalylamino-L-alanine (the compound responsible for lathyrism [191]), all potentially neurotoxic compounds. However, they did identify another compound in the cyad flour that they propose may be the responsible agent for the cyad-induced neurodegeneration, β-sitosterol-β-D-glucoside. Khabazian et al [192] found that mice fed with cyad seed flour containing isolated sterol glucosides showed behavioral and neuropathologic outcomes. Thus, some investigators disagree that BMAA in cyad is the cause of the neurodegenerative diseases on Guam. Evidence seems to be gathering that implicates sterol glucosides as the responsible toxin found in cyad seeds.

Overall, evidence continues to suggest that the consumption of the cyad in some form is responsible for ALS/PDC. Patients with PDC have been shown to have a preference for local food and lead a more traditional lifestyle, which includes the consumption of cyad flour and fruit-eating bats [185,193]. It is believed that the Chamorro people may be particularly exposed to toxic amounts of the cyad toxins through the consumption of fruit bats (called flying foxes), which are part of the traditional celebratory diet. Flying foxes eat the cyad seed, the toxins of which accumulate in high doses in the fat molecules of the fruit bats [194,195].

Additional evidence for the relationship of ALS/PDC to bat consumption comes from studies that have charted the changes in the flying fox population and the rates of ALS/PDC on Guam. Cox and Sachs [195] compared the recorded rates of ALS to the flying fox population size. They found that when the native flying fox population on Guam declined and the importation of flying foxes from Western Samoa (where there are no indigenous cyad seeds) occurred during the 1970s, the rates of ALS on Guam also began to decline. Furthermore, the rapid modernization and westernization of Guam in the late 1960s had a profound effect on the eating
habits of the local population [196]. Present day Chamorro now eat a diet that is much more western in style and are not exposed to cyad through flour or fruit-bats to the same extent as they had been in earlier times. Thus, in the Guamanian population, the rates of exposure to cyad toxins through diet appear to coincide with “socioeconomic, ethnographic, and ecologic changes brought about by the rapid westernization of Guam” [195], lending more support to the cyad seed as a factor contributing to the high incidence of ALS/PDC on the island of Guam. Additional dietary and exposure data may shed further light on this potential environmental risk.

Summary

The hypothesis that neurotoxins may play a role in neurodegenerative disorders remains an elusive one, given that epidemiologic studies often provide conflicting results. Although these conflicting results may result from methodological differences within and between studies, the complexity of chemical disruption of the central nervous system cannot be ignored in attempts to evaluate this hypothesis in different neurodegenerative disorders. Spencer [197] provides a detailed review of the complex processes involved in defining the neurotoxic potential of naturally occurring and synthetic agents. Even concepts such as exposure and dose, as often reported in studies attempting to evaluate the risk imparted by a potential compound, can be deceptive. For example, although dose reflects “that amount of chemical transferred to the exposed subject” [197], factors such as time and concentration in the organism, the ability to access the central nervous system, and how a compound reaches the central nervous system (routes of administration) or secondarily affects other organ systems leading to central nervous system disruption are clearly important to the concept of neurotoxic risk in neurodegenerative disorders.

These factors would appear to explain the observed disagreements between studies using animal or neuronal models of neurotoxicity and population-based studies in humans. The importance of these factors and how a potential neurotoxin is investigated are clearly seen in the data on AD and aluminum. In contrast, the impact of MTPT on the central nervous system is more direct and compelling. Added complexity in the study of neurotoxins in human neurodegeneration is derived from data showing that agents may have additive, potentiating, synergistic, or antagonistic effects [196]. Therefore, data from studies evaluating EMF risks could be readily confounded by the presence or absence of heavy metals (eg, arc welding).

Other factors that may conceal neurotoxic causes for a given disorder focus on additional features such as genetic predispositions, physiologic changes that occur with aging, and even nutritional status that can support or hinder the affect of a given agent on the central nervous system. Finally, many studies that investigate exposure risk do not readily incorporate the five criteria proposed by Schaumburg [198] for establishing causation. For example, if we
apply Schaumburg’s first criterion, epidemiologic studies often determine the presence of an agent through history, yet they cannot readily confirm exposure based on environmental or clinical chemical analyses to fulfill this criterion for causation [198,199]. Additional limitations in research design along with the populations and methods that are used to study neurotoxins in human neurodegenerative disorders often fail to meet other criteria such as linking the severity and onset with duration and exposure level. Therefore, although studies of agents such as MTPT provide compelling models of neurotoxins and neurodegeneration in humans, disorders such as ALS, PD, and particularly AD will require additional effort if research is to determine the contribution (presence or absence) of neurotoxins to these neurologic disorders.

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