Parkinson disease (PD) and Alzheimer disease (AD), the two most common neurodegenerative disorders in American adults, are of purely genetic origin in a minority of cases and appear in most instances to arise through interactions among genetic and environmental factors. In this article we hypothesize that environmental exposures in early life may be of particular etiologic importance and review evidence for the early environmental origins of neurodegeneration. For PD the first recognized environmental cause, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), was identified in epidemiologic studies of drug abusers. Chemicals experimentally linked to PD include the insecticide rotenone and the herbicides paraquat and maneb; interaction has been observed between paraquat and maneb. In epidemiologic studies, manganese has been linked to parkinsonism. In dementia, lead is associated with increased risk in chronically exposed workers. Exposures of children in early life to lead, polychlorinated biphenyls, and methylmercury have been followed by persistent decrements in intelligence that may predate dementia. To discover new environmental causes of AD and PD, and to characterize relevant gene–environment interactions, we recommend that a large, prospective genetic and epidemiologic study be undertaken that will follow thousands of children from conception (or before) to old age. Additional approaches to etiologic discovery include establishing incidence registries for AD and PD, conducting targeted investigations in high-risk populations, and improving testing of the potential neurologic toxicity of chemicals. Key words: Alzheimer disease, maneb, manganese, National Children’s Study, neurodegenerative disease, paraquat, Parkinson disease, pesticides. Environ Health Perspect 113:1230–1233 (2005). doi:10.1289/ehp.7571 available via http://dx.doi.org/ [Online 26 May 2005]

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Address correspondence to P.J. Landrigan, Center for Children’s Health and the Environment, Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, New York.

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data are available—from the Centers for Disease Control and Prevention (CDC) list AD as the eighth leading cause of death in the United States, responsible for 62,000 deaths annually (CDC 2003a).

PD and AD may co-occur and may share some etiologic or predisposing factors. Elderly patients who develop rapidly progressive PD may be at up to 8 times increased risk of developing AD (Wilson et al. 2003). Although the risk of developing AD and PD increases with age, neither of these diseases nor the symptoms of dementia are part of normal aging. In the absence of disease, the human brain can function well into the tenth decade (National Institute on Aging (NIA) 2000).

The Barker Hypothesis

Through detailed reconstructions of neonatal and medical histories of birth cohorts in the United Kingdom, David Barker of the University of Southampton proposed what is now termed “the Barker hypothesis” (Osmond and Barker 2000), the concept that parameters of fetal, infant, and childhood growth may be predictors of disease in later life. Barker found that infants with low birth weight, small head circumference, and low ponderal index at birth are at increased risk of developing coronary heart disease, hypertension, stroke, insulin resistance, and diabetes as adults. He found also that reduced fetal growth and impaired development during infancy were associated with increased mortality from cardiovascular disease (CVD) in both men and women, independent of social class and other confounders such as smoking, alcohol consumption, and obesity (Barker et al. 1993; Osmond et al. 1993). This association is strong and graded, is observed in various populations, and is specific to CVD. In Barker’s studies, low birth weight followed by obesity in later life led to a particularly high risk of CVD and insulin resistance. Further analysis indicated that hypertension may begin in utero and become magnified with age (Law et al. 1993).

Barker hypothesized that fetal undernutrition during critical periods of vulnerability in early development leads to persistent changes in hormone levels and in altered tissue sensitivity to these hormones, permanently altering the metabolism and body structure (Hinchliffe et al. 1992; Lumbers et al. 2001).

The Expanded Barker Hypothesis

At the 2003 Mount Sinai Conference on Early Environmental Origins of Neurological Degeneration, we explored the plausibility of extending the Barker hypothesis to encompass brain development and to explore the impacts of toxic chemicals on brain development.

Conferences generally supported the hypothesis that early exposures to environmental toxicants could later affect the brain and that such associations are biologically plausible (De la Fuente-Fernandez and Calne 2002). This consensus was based on experimental studies of associations between early-life exposures to pesticides and PD (Thiruchelvam et al. 2000a, 2000b), as well as on epidemiologic studies of the toxic and apparently irreversible effects on the developing brain of in utero exposures to lead, methylmercury, and polychlorinated biphenyls (Grandjean et al. 1997; Jacobson et al. 1990; Needleman et al. 1990). A mechanistic hypothesis proposed (Langston et al. 1999) that early exposures to neurotoxic chemicals reduce the number of neurons in critical areas of the brain such as the SN to levels below those needed to sustain function in the face of the neuronal attrition associated with advancing age (Figure 1).

Evidence for the Environmental Origins of Parkinson Disease

Twin studies. A large-scale study of twins designed to assess genetic versus environmental factors in the etiology of PD found a high degree of concordance within twin pairs for early-onset PD (onset before age 50) but much less concordance for disease of late onset (Tanner et al. 1999). This finding suggests that early onset PD may be of genetic origin in most cases (although the etiologic role of a shared environment can never be completely excluded), whereas beyond 50 years of age environmental factors become increasingly important (Tanner et al. 1999).

MPTP and PD. Several clinical and epidemiologic studies have demonstrated that exposures to certain synthetic chemicals are associated with increased incidence of PD. The first of these studies was the description in 1982 of severe Parkinson-like symptoms among a group of drug users in northern California who had taken synthetic heroin contaminated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Langston et al. 1999). This episode strongly supported the concept that exogenous chemicals can cause or contribute to causation of PD (Priyadarshi et al. 2001). MPTP was subsequently shown to act selectively—specifically injuring dopaminergic neurons in the nigrostriatal system in manganism, a condition characterized by tremors, rigidity and psychosis (Mergler and Thiruchelvam et al. 2000a, 2000b).

Rotenone and PD. The insecticide rotenone induces clinical and pathologic features in rats similar to those induced by PD, including selective degeneration of the nigrostriatal dopaminergic system and abnormalities in motor response that were more severe than those produced by either agent alone. These effects were amplified by aging (McCormack et al. 2002; Thiruchelvam et al. 2000a, 2000b).

Manganese and PD. Although manganese is an essential trace element, chronic occupational exposure to high levels of this metal causes accumulation in the basal ganglia, resulting in manganism, a condition characterized by tremors, rigidity and psychosis (Mergler and Thiruchelvam 2000).

Figure 1. Long-term consequences of early loss of critical neurons after developmental damage. DA, dopaminergic. The impact of early developmental damage is not immediately evident but produces disease years or decades later as the number of neurons decreases with advancing age.
This condition has been reported in manganese miners. Concern exists that widespread introduction of the manganese-containing fuel additive MMT (methylcyclopentadienyl manganese tricarbonyl) to the U.S. gasoline supply may increase population exposure to manganese and thus increase risk of parkinsonism in sensitive populations (Needleman and Landrigan 1996).

**Other chemicals and PD.** Exposures to pesticides and other organic compounds are widespread in the American population (CDC 2003b). Levels of organochlorines have been found to be elevated in the brains of persons with PD (Fleming et al. 1994). A study of French elderly individuals found an association between past occupational exposure to pesticides, low cognitive performance, and increased risk of developing AD or PD (Baldi et al. 2003). Other reported links between environmental factors and PD include increased risks from drinking well water, rural living, farming, and exposure to agricultural chemicals (Liou et al. 1997; Priyadarshi et al. 2001).

Epidemiologic studies have shown inverse, apparently protective relationships between cigarette smoking, coffee consumption, and PD (Herman et al. 2002).

**Inflammation and PD.** Inflammation of the brain in early life caused by exposure to infectious agents, toxicants, or environmental factors has been suggested as a possible cause or contributor to the later development of PD (Liu et al. 2003). The inflammatory process in such cases may involve activation of brain immune cells (microglia and astrocytes), which release inflammatory and neurotoxic factors that in turn produce neurodegeneration (Liu and Hong 2003). This concept first arose in the suggestion that infection with influenza virus in the pandemic of 1918 produced an increased risk of PD. More recently, infection with certain microorganisms such as the soil bacterium *Nocardioides asteroxides* has been proposed as a risk factor for PD (Kohbata and Beaman 1991). In animal experiments, exposure to bacterial endotoxin lipopolysaccharide in utero induced dopaminergic neurodegeneration (Gao et al. 2002; Liu et al. 2000, 2003).

**Isolated populations of high risk for PD.** PD incidence and mortality rates differ among ethnic groups and exhibit strong regional variation, thus providing additional evidence that environmental factors may be involved in causation (Ben-Shlomo 1997; Foster 2002).

For example, the Chamorros population of Guam and Rota in the western Pacific have an unusually high prevalence of motor neuron disease, a syndrome that includes amyotrophic lateral sclerosis (ALS), parkinsonism, and progressive dementia. It has been proposed that this syndrome of parkinsonian dementia is related to the consumption of flour made from cycad seeds (Spencer 2003) or to inhalation of pollen from cycad plants (Seawright et al. 1995). Consumption of cycad flour may have been especially common on Guam in the famine years before and during World War II. The declining incidence and increasing age at onset of ALS and parkinsonism–dementia complex among the Chamorros over the past 50 years together with the decreasing prevalence of ALS over the same time in high-incidence areas of Japan and Indonesia suggests the disappearance of an environmental factor unique to these population groups (Kurland and Mulder 1954; Plato et al. 2003).

**Evidence for the Environmental Origins of Dementia**

**Lead and cognitive function.** Childhood exposure to lead, even at relatively low levels (Canfield et al. 2003), results in a decline of cognitive function that persists into adulthood and that manifests as a persistent lowering of IQ score plus alteration in behavior (Needleman et al. 1990). Each increase of 10 μg/dl in the lifetime average blood lead concentration was found to be associated with a 4.6-point decrease in IQ (Schwartz et al. 2000). There appears to be no minimum threshold level below which lead does not cause brain injury (Canfield et al. 2003). In addition, elevated lead levels in childhood have been associated with lower class standing in high school, lower vocabulary and grammatical-reasoning scores, poorer hand–eye coordination, and self-reports of minor delinquent activity (Needleman et al. 1990).

Occupational exposure to lead among adults is associated with poorer neurobehavioral test scores and with deficits in manual dexterity, executive ability, verbal intelligence, and verbal memory (Schwartz et al. 2000).

Recent data suggest that cognitive function can decline progressively in older lead workers in relation to cumulative past occupational exposure to lead (Stewart et al. 1999). Susceptibility to the persistent effect of lead on the central nervous system may be enhanced in persons who have at least one apolipoprotein E-4 allele (Stewart et al. 2002).

**Recommendations**

The conferees agreed on recommendations for future research into the environmental etiology of chronic neurodegenerative disease.

**Conduct long-term prospective epidemiologic and genetic studies of the impact of environmental factors on the development of neurodegeneration.** Most previous research on the causation of the neurodegenerative disorders has been either cross-sectional or retrospective in design and thus has been extremely limited in its ability to discern environmental etiologic factors that may have been encountered in early life. Most previous studies have had to reconstruct past exposures from imperfect memory, from incomplete records, or from biologic markers of uncertain half-life. The conferees offered the suggestion that a large prospective cohort study would provide a most powerful tool to explore possible early environmental causes of neurodegenerative disease. If such a study were to include genetic analyses, it would provide a unique means for exploring the gene–environment interactions that likely are involved in the genesis of PD and AD. Ideally such a study should enroll subjects at or even before conception and follow them through old age and should incorporate numerous biologic makers of exposure as well as detailed evaluations of behavioral and lifestyle factors, including information on occupational exposures and pesticide use. Such a prospective design would permit the real-time assessment of exposures as they occur and avoid the need for retrospective re-creation of past exposures. These features are now incorporated into the proposed National Children’s Study.

Four factors that make this a propitious time to launch a massive prospective epidemiologic study of the impact of the environment on health and development, such as the National Children’s Study, are 1) the development of better skills in conducting and analyzing data from large prospective studies; 2) the refinement of highly sensitive, extremely accurate chemical analyses that permit detection and quantification of xenobiotics in body fluids even at very low levels; 3) advances in information technology; and 4) capacity for rapid, relatively inexpensive genetic analysis (Berkowitz et al. 2001).

Establish registries for Parkinson and Alzheimer patients. Current data sources that rely principally on mortality statistics likely undercount the number of persons with neurodegenerative diseases. It is important to foster collaborations among agencies and to create new links across databases in different regions of the country to better track incidence rates of these disorders.

**Pursue suspected links between environmental exposures and neurobehavioral disorders in unique, high-risk populations.** Targeted studies of persons with unique patterns of disease such as the residents of Guam (Kurland and Mulder 1954) or persons with unusual environmental exposures such as those exposed to MPTP (Langston et al. 1999) demonstrate the value of undertaking clinical and epidemiologic pursuit of disease clusters.

**Improve toxicity test methods to better assess chronic neurodegeneration** (Slutkin 2004). Too few chemicals are tested for chronic neurotoxicity, and those that are examined are typically studied under test protocols in which the chemicals are administered during adolescence and the animals sacrificed and studied 12–24 months later. Functional
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assessment of neurologic function is often not included. This approach misses the opportunity to study possible late effects of early exposures. To overcome these limitations in design, conferences recommended that the duration of toxicity testing protocols should be extended to incorporate administration of chemicals in early life ideally in utero or even before conception, coupled with lifelong follow-up. Such expanded protocols may also incorporate functional neurobehavioral test batteries as well as neuropathologic examinations of relevant areas of the brain (Landrigan et al. 2003).

REFERENCES


