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### **Do early environmental exposures contribute to neurodegenerative disease in later life?**

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Background: Evidence is increasing that toxic exposures - including exposures in fetal and in early postnatal life - may contribute significantly to the causation of Parkinson disease (PD) and Alzheimer disease (AD), the two most common neurodegenerative disorders of later life. The concept that early exposures are particularly harmful to the developing brain is consistent with the "Barker hypothesis".

Objectives: (1) To review the evidence linking toxic exposures to neurodegenerative disease; and (2) To develop a research agenda that will identify preventable environmental causes of PD and AD.

Findings: PD. The great majority (95%) of PD cases are of non-genetic and non-familial origin. Evidence for the environmental origins of PD is provided by the rising incidence of PD in the industrially developed nations, by twin studies, and by clinical and epidemiological studies of persons who developed PD following exposures to neurotoxic chemicals. Toxicologic data confirm and extend these human findings. AD. Lead is associated with increased risk of dementia in chronically exposed workers and also in older adults without occupational exposure. AD prevalence is highest in older adults with the greatest cumulative exposure, as shown by bone lead levels. The association between lead burden and dementia is strongest for individuals with at least one Epsilon 4 allele in their apolipoprotein E (ApoE) genotype as compared to those who lack an Epsilon 4 allele, suggesting a gene-environment interaction.

Unifying hypothesis: The proposed mechanism through which early – or later - environmental exposures to toxic chemicals may cause subsequent appearance of PD or AD is that these exposures cause destruction – immediate or delayed - of irreplaceable neurons in critical brain areas. Disease is not immediately evident, but becomes manifest years or decades later in the face of advancing age, as the number of remaining neurons falls below the threshold level needed to sustain function.