National Institute of Environmental Health Sciences
Division of Extramural Research and Training
Cellular, Organs, and Systems Pathobiology Branch

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL
February 20-21, 2013

Concept Clearance

Role of the Environment in Neurodegenerative Disease

Introduction

This concept clearance represents a new effort to stimulate neurodegenerative disease (ND) research in several promising areas that are not well represented in our current portfolio. The goal is to facilitate continued advancement of neurodegenerative research at all levels from basic mechanistic discovery to human-based research, to better establish the importance of environmental exposure in disease causation, and to adhere to the goals of the new strategic plan. This new effort will foster work to further our understanding of the combined roles of exposure and genetic susceptibility in ND, with emphasis in the areas of Alzheimer's (AD) and Amyotrophic Lateral Sclerosis (ALS).

NIEHS's interest in neurodegenerative disease (ND) stems from twin studies of Parkinson's disease (PD) showing that concordance between aging monozygotic twins was no greater than that for dizygotic twins, indicating that PD does not arise strictly through genetic mechanisms. Over the last decades good epidemiological and animal evidence implicating the interaction of environmental and genetic factors in the etiology of PD. has accumulated. In fact, no neurodegenerative disease results purely from genetics or exposure, though in familial forms of AD, PD or ALS, heritable traits may play a greater role. But the ability to translate any data into meaningful prevention and/or therapeutic strategies is made difficult by several factors. These include: 1) a long preclinical period prior to the onset of neurodegeneration; 2) multifactorial inputs (both environmental and genetic) from a large number of potential agents, genes, and cellular regulatory mechanisms that may play a role; 3) lack of reliable human biochemical, molecular, or imaging biomarkers; and 4) a lack of animal models that have translational validity.

Starting in the late 1990s, a series of initiatives were developed to encourage Parkinson's research culminating first in an RFA for program projects in Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER), and then with an RFA for Centers for Neurodegeneration Science (CNS). These human and animal studies, which were highly interdisciplinary, identified both genetic and environmental factors associated with disease risk. Center researchers were able to identify genes affected by specific exposures and then study them in a variety of systems from human, non-human mammalian to non-mammalian, and *in vitro* systems. At the May 2012

council meeting, our Program Analysis Branch reported on their analysis of the neurodegeneration portfolio (1994 - 2009). They indicated that we had achieved a robust program in neurodegeneration, heavily focused on PD, which could now be sustained through investigator-initiated applications because of the number of researchers we have attracted to the field.

Research on ALS also suggests a link between genetic variability and environmental exposure in disease risk, though this area of research is far less developed than that for PD. Several human and animal studies have identified certain paraoxonase (PON) mutants that are linked to ALS. The PON gene cluster is one of the most robust genetic risk factors for familial and sporadic ALS. PON proteins play a role in preventing lipid peroxidation and detoxifying organophosphates. Therefore the altered function of the PON mutants may increase susceptibility to OP and other environmental exposures, reinforcing the risk for GXEI in ALS. Where we have less evidence in determining a link between genetics, exposure and disease is in AD. However, some animal studies have recently shown that chronic exposure to lead, beginning in early development, may be a risk factor for AD through its effects on the metabolism of β amyloid. This finding also has some support from cognition studies in young adults. Cognition studies in older adults exposed to air pollution also support the role of environmental exposures as a risk factor for AD since cognitive impairment may be an early stage of AD. In addition, cyanobacterial neurotoxin β-N-methylamino-L-alanine (BMAA) has been detected and quantified in autopsy brains of AD, ALS, and Huntington's (HD) patients. The finding that toxic exposure to heavy metals, air pollution, BMAA interferes with cognition supports the argument that gene/environment interaction in susceptible individuals is a risk factor for AD or ALS.

To determine the most productive research to pursue, we benefitted from a series of workshops and meetings in neurodegenerative diseases, as well as a request for information (RFI) http://grants.nih.gov/grants/guide/notice-files/NOT-ES-12-001.html. Several major themes emerged: 1) the role of exposure susceptibility including across the life span. 2) the role of inflammation and 3) the role of genetic, and especially epigenetic variability in response to exposure and disease risk. This is by no means an exhaustive list of current research gaps which also includes proteinopathies, protein degradation and preclinical symptoms, but it pointed to a need to stimulate new approaches. This concept clearance is designed to help us focus on a set of priorities to address over the next 5 years. We plan to primarily focus on stimulating AD research, mainly because of a greater paucity of information about the role of exposure in the etiology of the disease, but also because of the intense interest on both the international and national level in AD research and therapeutics. We also would like to increase our research presence in the area of ALS to better understand the role of the environment in disease pathogenesis and to maintain our presence in PD.

Research Goals and Scope

The objective of this concept clearance is to develop funding opportunities for research in neurodegenerative diseases, with emphasis on the mechanisms by which environmental exposures may contribute to disease. These opportunities will facilitate collaboration between researchers to enhance progress. The program will focus on elucidating the role of environmental exposure in disease risk, with specific emphasis on two likely underlying mechanisms: neuroinflammation/immunology and epigenetics, both of which have been linked to responses to environmental insults.

- Environmental Exposures

Studies that enable assessment of the timing of exposures across the life span (primarily in animals) are needed to determine whether there are susceptible periods. Such studies could establish linkages between early exposures and risk of later life AD or ALS disease progression. In addition, research on the effect of exposure on the function of non-neuronal cells in the brain such as: (1) Glial cells which make up close to 90% of the cells in the brain and are involved in neuroinflammation/immunity; (2) Macroglia (astrocytes which regulate the chemical environment of neurons, and recycle neurotransmitters, in particular glutamate which has been implicated in ALS); and (3) Oligodendricytes and Schwann cells, which provide myelin sheath for the axons of the CNS and PNS, would add to establishing a definitive understanding of the role of environmental exposure in the etiology of AD and ALS.

- Neuroinflammation

It has been proposed that environmental exposures from heavy metals and air pollution can exacerbate neuroinflammation effects. A role for inflammation in AD pathogenesis has recently gained strong support from genome-wide association studies that have identified genes involved in inflammation associated with increased disease risk but whether this represents a cause or a response to pathology is unclear. Research is needed for all phases of the immune response to understand both the toxicity of the pro-inflammatory response, and immune suppression in AD. (Recent GWAS studies in AD clearly show that genes involved in immune suppression, not immune expression, are prominent. Immune activation from heavy metals and pesticide exposure have also been detected in ALS. The overall effect of immune activation may be attributable to individual genetic variability and susceptibility since individual ALS patients have different immune responses. What is needed now are studies that use robust measurements of disease progression to see if patients with evidence of greater immune activation have a different prognosis from those who do not, and to explore whether disease modifying genes include genes with immune function. It is important to know whether inflammation and immune responses are helpful or harmful, so that possible immunomodulatory therapies can be pursued.

- Epigenetics

In the last decade, the field of epigenomics has emerged, revealing that DNA modifications, including DNA-bound histones, DNA methylation, and chromatin remodeling also provide levels of gene regulation and alter gene expression. There is evidence that AD is associated with epigenetic dysregulation at various levels, and that epigenetic mechanisms may mediate the effects of exposures on AD risk. More research is needed to clarify the exact role of epigenetic regulation in the pathophysiology of environmental exposure in AD. This work may also contribute to the establishment of early diagnostic markers, as well as the development of more effective preventative or therapeutic strategies. There is also indirect evidence demonstrating epigenetic alterations associated with various risk factors for AD, such as nutritional factors, stress, depression, and brain trauma, implying that epigenetic processes may be the key mechanism mediating GXE interactions.

Epigenetic factors may be more suited than genetic factors to explain disease onset and progression in other neurodegenerative diseases, since aberrant epigenetic patterns may be acquired throughout one's life. One hypothesis is that environmental life exposures result in a failure to maintain epigenetic homeostasis in the nervous system which in turn leads to aberrant gene expression, contributing to nervous system dysfunction and in some cases the development of ALS. Metals are one of the most likely culprits to be a key exposure risk factor in the development of ALS given their well-documented potential for neurotoxicity and involvement in oxidative mechanisms of injury. However, to date the epidemiologic literature supporting the role for metals in ALS pathogenesis has been inconsistent. One potential reason for this discrepancy is the failure to understand the importance of the epigenomic background of patients and its interaction with exposures. Future studies are needed to investigate this relationship in any of the ND.

The goals of the new NIEHS Strategic Plan support what we envision as the best way to approach the complexity of AD and ALS studies. For example, goal 1-- to "Identify and understand fundamental shared mechanisms or common biological pathways, e.g., inflammation, epigenetic changes, oxidative stress, mutagenesis, etc., underlying a broad range of complex diseases,…" supports the research strategy to understand the mechanisms by which exposure becomes a risk factor for ND. Also, goal 2-- to "understand individual susceptibility across the life span to chronic, complex diseases resulting from environmental factors, in basic and population-based studies,…" supports needing (1) more research studying the timing of exposures, and (2) the collaboration of researchers doing human and animal research.

Mechanism and Justification

From our experience with the achievements of our CCPDER and CNS programs we shall encourage multidisciplinary research, where feasible, in order to stimulate collaborations. It is within the context of supporting such research that we can try to

duplicate the advances that were made in our PD centers in a more affordable manner. Two RFAs are proposed initially. One will use the R01 mechanism for applications from Multiple Principle Investigators (MPI) to foster research in which several investigators from several disciplines (geneticists, exposure experts, animal neurotoxicologists, epidemiologist with pre-existing cohort, clinicians etc.) can contribute to the overall problem. Individual investigators will also be able to apply. The first R01 initiative will primarily focus on AD. The other RFA using the R21 mechanism will be to develop feasibility data for new concepts or to adapt new technologies, tools and methods in ND. These could be followed in a phased manner by other initiatives in ALS and PD.

	Due Dates			
Initiative	NIH Guide	Application	Review	Council
RFA R01 Focus on Alzheimer's	5/2013	9/2013	2/2014	5/2014
RFA R21 Focus on Neuro/tools	5/2013	9/2013	2/2014	5/2014
PA R01 Focus on AD, ALS, PD	5/2014	9/2014	2/2015	5/2015
PA R21 Focus on AD, ALS, PD	5/2014	9/2014	2/2015	5/2015
PA R01/R21 AD, ALS, PD	5/2015, 16, 17	9/2015, 16, 17	2016, 17, 18	5/2016, 17, 18

In addition, investigators will be encouraged to apply for ongoing programs as appropriate, such as the ViCTER program which can allow for the development of a translational/transdisciplinary collaborative grant, and our ONES research program for new investigators.