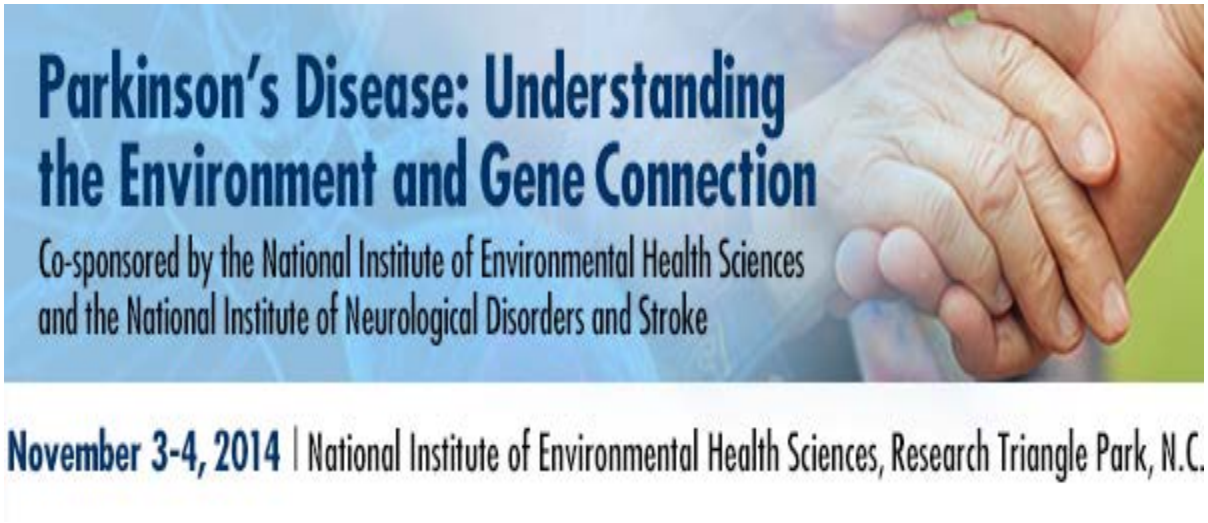

Meeting and Recommendations Report

National Institutes of Health • U.S. Department of Health and Human Services

Executive Summary

Background:
Parkinson's disease (PD) is a progressive neurodegenerative disease and the second most common disorder of this type after Alzheimer's disease. It was first described by James Parkinson in 1817, and today affects approximately 1 million people in the U.S. and 6.3 million people throughout the world, with diagnosis typically occurring after 55 years of age. The motor syndrome of PD progresses slowly as small clusters of dopaminergic neurons in the midbrain die. The gradual loss of these neurons in the substantia nigra pars compacta results in the reduction of dopamine, a chemical responsible for transmitting messages to parts of the brain that coordinate muscle movement. Extra-nigral neurodegenerative changes result in additional clinical features (cognitive, mood, autonomic). Further, the formation of Lewy bodies, or large deposits of proteins including alpha-synuclein, is classically observed in the brains of PD patients. While PD is more common in men, large epidemiological studies have been underway to determine the racial, ethnic and geographical profiles of those who are more susceptible to develop the disease. The exact cause of PD is unknown, though most researchers agree that the disease is caused by interactions between genetic susceptibility and environmental exposures.

If environment is defined broadly to include any factors that are non-genetic in nature, what are some of the environmental factors believed to be associated with PD? Accumulating evidence suggests that pesticide exposure (e.g., rotenone, paraquat, chlorpyrifos, dithiocarbamates and organophosphates), heavy metals (e.g., manganese and lead) and the major particulate pollutants of air pollution (e.g., ultrafine particles) may be associated with an increased risk for developing PD. Alternatively, researchers have identified dietary factors (e.g., low saturated fat intake), high levels of exercise and nicotine consumption may reduce PD risk. Despite these findings, we still do not have a full understanding of why and how PD develops.

Meeting Purpose
In January of 2014, the National Institute of Neurological Disorders and Stroke (NINDS) sponsored the conference "Parkinson's Disease 2014: Advancing Research Improving Lives" (PD2014), which resulted in prioritized recommendations for advancing basic, translational and clinical research in the field. (The final version of these recommendations can be found here: http://www.ninds.nih.gov/research/parkinsonsweb/PD2014/index.htm). Given the relatively low heritability of PD, it became clear that a follow-up meeting was necessary to address gene-environment interactions in the development and expression of PD, as well as translation from a public perspective. On November 3-4th, 2014 NIEHS and NINDS co-sponsored the conference "Parkinson's Disease: Understanding the Environment and Gene Connection" with the overall goal to develop prioritized recommendations for advancing basic, epidemiological and clinical research on the environmental contributors to PD. Two working groups were created with the task of generating these recommendations from a clinical/epidemiology and basic mechanism perspective.

High Priority Recommendation Themes

The recommendations for both working groups are presented in two sections: (1) The "Recommendation Summary" gives an overview of the top recommendations identified, and (2) The "Research Topic Areas with Detailed Discussion Points" is an extended narrative that describes the need for each recommendation as well as optimal approaches for addressing the data gaps and priorities in a given topic of PD research.

Thank you to all the planning staff, co-chairs, working group members, panelists and moderators who were instrumental in the coordinated effort for a successful conference as well as the development of the prioritized recommendations presented here. I respectfully submit this report on behalf of NIEHS/NINDS.

Sincerely,

Jonathan A. Hollander, Ph.D.
Program Director
Genes, Environment and Health Branch
Division of Extramural Research and Training
National Institute of Environmental Health Sciences

RECOMMENDATIONS

Recommendation Summary: Highest Priority Areas from Clinical/Epidemiology Group

1	Identify environmental factors that affect the development of prodromal PD, its clinical and pathological progression, and phenotypic conversion to clinically manifest PD.
2	Determine the influence of environmental exposures on progression of diagnosed PD, taking into account the complex interaction of exposure type, genetic makeup, treatment, behavior comorbidity and other factors.
3	The search for biomarkers and clinical correlates is of high priority. The two biomarkers of interest include those representing environmental exposure and those that are disease-specific.
4	Continue to focus work on environmental risk factors involved with various aspects of PD etiology, diagnosis, progression and prognosis.
5	Investigations need to include evaluation of combined environmental exposures that may have similar or different underlying mechanisms for development of PD
6	The challenges of exploring gene-environment interactions in large and rigorous longitudinal studies require “big data” approaches that go beyond traditional PD environmental studies, and must include pooling data and biological samples among multiple institutions that use common collection instruments.
7	Continued support for prevention studies, as this is the ultimate goal of all above topics. Emphasis of this recommendation is to develop methods and establish feasibility for implementing both primary and secondary prevention studies in a foreseeable future.

Recommendation Summary: Highest Priority Areas from Basic Mechanism Group

1	Systematically determine the effects of environmentally-relevant compounds on known genetic abnormalities (synuclein, LRRK2, parkin, PINK1, DJ-1) in PD.
2	Systematically determine the effects of environmentally-relevant compounds on known biological processes involved in PD pathogenesis (mitochondrial dynamics, protein processing, inflammatory processes, dopamine biochemistry).
3	Develop and provide access to a careful curated battery of compounds to be used for approaches identified in (1) and (2).
4	Identify assays or methods for analysis of environmental influences in large populations. These approaches could be used on banked samples or current epidemiological or clinical studies.

5	Establish animal models to evaluate the effects of environmental agents on preclinical progression of PD*

* Note: overlapping recommendation with Clinical/Epidemiology Group

Research Topic Areas with Detailed Discussion Points

CLINICAL/EPIDEMIOLOGY GROUP

Recommendation 1: Progression (Before Diagnosis): Identify environmental factors that affect the development of prodromal PD, its clinical and pathological progression, and phenotypic conversion to clinically manifest PD. The goals are to understand early PD etiology and natural history and to identify modifiable environmental exposures for future risk modification.

Need: The group concurs with the NINDS 2014 recommendation that it is important to define and understand the prodromal stage(s) of PD through research on prodromal symptoms and biomarkers. Defining prodromal PD will facilitate the search for environmental factors that contribute to the development of prodromal PD and later phenotypical conversion to clinical PD. This will eventually lead to a better understanding of the environmental origins of the disease and to the identification of modifiable risk factors for later research on disease prevention.

Approaches:

- Define prodromal features of PD in both clinical and population-based studies with concurrent characterization of environmental factors to characterize high risk populations and to investigate the natural history of prodromal PD. These markers include prodromal symptoms such as anosmia, REM sleep behavior disorder, mild-motor signs and biomarkers such as genetics, biochemistry, and neuroimaging.

- Identify environmental factors that may affect the development and/or progression of intermediate phenotypes that define prodromal PD (e.g. specific nonmotor symptoms, multiple nonmotor symptoms, or prodromal biomarkers)

- Longitudinal study of populations with multiple prodromal symptoms or otherwise at-risk for PD (individuals exposed to specific pesticides or traumatic brain injury, LRRK2 G2019S carriers or REM sleep behavior disorder patients) to search for environmental factors that modify phenotypic conversion of prodromal PD to clinical PD.

- Life-course approach to PD epidemiology with exposure assessments for various life periods (prenatal, early life, mid-life and late life) and examinations of their relationships to clinical PD and/or its intermediate phenotype(s).

- Examination of novel environmental hypotheses of PD etiopathogenesis, such as that initial PD pathology develops in the olfactory bulb and gut as results from environmental assaults and potential roles of virus, pesticides, and microbiome in this process.

- Establish animal models of prodromal PD to conduct experimental research on environmental neurotoxicants or protective chemicals in the prodromal stage(s) of PD.

Recommendation 2: Progression (After Diagnosis): Determine the influence of environmental exposures on progression of diagnosed PD, taking into account the complex interaction of exposure type, genetic makeup, treatment, behavior, comorbidity

and other factors. Because of this complexity, individual patient disease course can be remarkably variable.

Need: PD presents with a broad range of clinical phenotypes and highly variable rates of progression. The determinants of the clinical phenotype are unknown. Nevertheless, certain clinical patterns such as tremor- or gait-predominant disease, early dementia, and early motor fluctuations may be mediated by environmental exposures prior to, or during, disease. Standard clinical trial approaches to measuring disease progression may be inadequate to investigate the impact of environmental mediators of disease progression.

Approaches:

- To help explain the diverse clinical presentation of PD, conduct studies linking environmental exposures to disease phenotype. Ideally, these studies would use biomarkers of long-term exposures as well as well-validated questionnaire-based exposure reconstruction methods. Validated biomarkers of disease progression or neuropathology will be more quantitative than current clinical measures of disease progression.

- Conduct studies linking environmental exposures to disease progression using traditional measures of disease severity as well as critical disease related morbidities such as dementia, hip fracture, and death. These studies would need to incorporate novel objective methods to account for biases related to treatment decisions related to physician and patient preferences as well as changing treatment paradigms.

- Investigate the relationship between lifetime exposure windows and PD progression. Understanding critical time periods for neurotoxicity could inform exposure mitigation strategies that could influence disease outcome.

- Investigate the association between multiple toxicants on phenotype at presentation and on progression.

- Investigate the relationship between genetic susceptibility and environmental exposure(s) on phenotype at presentation and on progression.

<u>Recommendation 3:</u> Biomarkers: Two types of biomarkers are of interest, those representing environmental exposures and those that are disease-specific. The search for biomarkers and clinical correlates is of high priority. Identification of clinical biomarkers for early/premotor PD could also be useful to differentiate prodromal PD from other conditions that cause similar symptoms.

Need: Biomarkers are measures or indicators of the presence of the disease process or of environmental exposure. Studies on the use of alpha-synuclein as a biomarker of early disease in peripheral tissues have led to conflicting results. More definitive studies in peripheral tissues are needed to clarify its usefulness as an early biomarker of disease and if there is evidence of any environmental exposures tied to its presence. Further, there is little knowledge on when the initiation of the disease process begins in individuals. While PD is a disease of older age, the disease process likely begins long before diagnosis. Research is needed to explore if there are biomarkers of disease or environmental exposures that correlate with early disease processes.

Also, the recent insight into the GI-neuro axis raise the potential of environmental biomarkers that mark dietary exposure or changes in the microbiome that could be markers of an exposure increasing the susceptibility for PD.

Epigenetic marks, often driven by environmental factors, need to be explored in relevant tissues, as they could be important biomarkers both of exposure and the early disease process. Two existing environmental factors, smoking and exercise have both been shown to have strong effects on risk or progression of PD and may involve epigenetics. Understanding their mechanisms could yield important biomarkers useful in studies of disease progression as well as environmental exposures.

Most studies look at only one potential biomarker, but in complex disorders like PD, a need exists to explore the joint use of multiple biomarkers. Also, it is well understood that an environmental effect may have a stronger detrimental response on one subtype of PD than another. There is a need to develop diagnostic biomarkers that define different subtypes of PD.

For the purposes of exploring the association between environmental exposures and PD, biomarkers also have an important role to play in accurately assessing environmental exposures. Many such biomarkers exist (e.g. lead in blood or in bone), each with different characteristics that affect what the biomarker tells one about the environmental exposure (e.g. lead in blood reflects more recent exposures, lead in bone more cumulative long-term exposures). There is a need to develop biomarkers for more types of environmental exposures, and ones that capture both more recent and long-term exposures.

Approaches:

- Careful collection of multiple biologic samples over longitudinal studies, incorporating the measurement of known biomarkers, clinical, genetic, imaging and environmental exposures should be performed. These samples can be used to identify new biomarkers.

- The use of electronic health records (databases) should be explored as a mechanism to provide insight into new early biomarkers of disease or environmental exposures.

- Conduct definitive studies on the use of alpha-synuclein as a biomarker of disease in peripheral tissues. Develop standardized protocols that allow for samples to be easily obtained, using protocols. This should include the use of all modalities including proteomics.

- Develop protocols and datasets for microbiome studies, dietary intake and metabolomics to identify potential biomarkers.

- Evaluate the integration of multiple biomarkers together to maximize informational content.

- Develop methods for sharing data and tissues to allow combined analyses and to provide the large populations needed for these investigations.

- Develop biomarkers for estimating human exposure to environmental factors.

- Develop biomarkers that capture different exposure windows and time periods over the lifecourse.

<u>Recommendation 4</u>: Risk Factors: Continue to focus work on environmental factors involved with the various aspects of Parkinson disease etiology, diagnosis, progression and prognosis. The emphasis should be on novel approaches to better understand already established risk factors and the identification of new risk factors that influence the aforementioned aspects of disease.

Need: Despite extensive study and many large-scale prospective cohort studies, there remain few replicated risk and protective factors that modify the risk for PD. For risk and protective factors that have been reasonably well-established, there is a need to better understand the biological mechanisms by which these factors are acting. Other risk and protective factors have been examined in some studies, but there is a need to better establish their causal connection with PD. For these factors, issues like accurate exposure assessment and reverse causation need to be better dissected. Lastly, while considerable work remains to be done on the risk factors already identified, the search for novel environmental factors that modify PD risk should not be neglected. Across all of this, there is a need to better understand susceptible subgroups. Identification of specific "at risk" groups would better facilitate the implementation of population health measures which could impact on disease incidence or progression. Insofar as this involves big data, resources for data sharing, analysis and significant "informatics" support is needed.

Approaches:

- Study of exposures to established risk and protective factors across the lifecourse, including early life, and how these exposures correlate with other endophenotypes such as REM sleep behavioral disorder and affective disorder.

- Explore the use of Mendelian randomization to improve causal inference for potential risk and protective factors.

- Examine subgroups within the population who are most susceptible to the types of risk and protective factors considered of relevance to PD. For example, individuals of certain poor metabolizer genotype may be more "at risk" from pesticide exposures. Certain ethnic groups may be differentially impacted by lifestyle or occupational factors. A subset of athletes or military personnel may be at higher risk of factors such as head trauma.

- Utilize biomarkers of exposures, in particular ones using easily accessible biosamples, in assessing risk. The use of blood-derived methylation patterns is one possible example. This may enable these type of data to be used, in the absence of more formalized exposure assessment methods, in very large numbers of individuals. There is also a general need to develop "validated" proxies for modifiable disease-related factors that can be used in large population samples.

- Technological advances such as the increased availability of personal electronic devices (that can act as biosensors) may facilitate exposure assessment and identification of risk factors. Explore "big data" approaches to examining a wide range of factors (the "exposome") to generate new leads to examine in more focused studies.

- Conduct complementary and parallel investigations of risk and protective factors from the population and the laboratory-based perspectives. Investigate the biological mechanisms underlying associations with risk and protective factors.

<u>Recommendation 5</u>: Combined Exposures: Extend the study of specific risk factors to evaluate multiple risk factors acting in concert. This concept should encompass exposures that operate through both similar and different mechanisms, as well as interactions with genotype.

Need: When considering combined exposures, there is always an uncertainty regarding specific risk factors involved. Adding to this complexity is determining the relevant exposure period. For example, do exposures need to be simultaneous? There is also a lack of knowledge regarding potential mechanisms underlying combined exposures. Pooling data across multiple studies will be required; this in turn requires uniform approaches to collecting exposure data.

Approaches:

- To identify specific exposures, their relevant exposure periods, and their mechanisms using data from a number of sources including human studies, experimental studies and computational analysis. For example, data from experimental studies can be used to identify agents affecting animal and in vitro models. Further, data from experimental studies and computational analysis can be used to identify mechanisms underlying toxicity. Certainly, a focus on more well characterized exposures (e.g., smoking) would be most useful as a starting point. It is also important to note that agents with similar mechanisms may have additive effect on risk, while those with different mechanisms may be synergistic.

- Some large prospective studies may have data on more than one exposure (e.g., smoking, diet, exercise). Information on toxicant exposure is generally lacking in these studies except at the most basic level (e.g., occupation). Pooling of data across several studies is likely to be necessary to identify sufficient numbers of cases exposed to multiple agents; approaches to combining data collected with different instruments need to be developed. Further, agnostic computational analysis may identify groups of exposures with combined effects on risk.

- Case-control studies will have more detailed data on multiple specific exposures, particularly to toxicants. Studies nested in occupational cohorts (or others with specific exposures) will have larger numbers of exposed cases and thus be particularly useful. Genomic data may also be available and pooling data across several studies will be required.

<u>Recommendation 6</u>: Sample size/Data Pooling: While critical to our understanding of how environment impacts PD etiology, there are many challenges of exploring gene-environment interactions in large and rigorous longitudinal studies. The large sample sizes required for "big data" approaches go beyond traditional PD environmental studies. Pooling data and biological samples among multiple institutions that use common collection instruments will be essential.

Need:
The causes of PD are likely complex, involving both genetic and environmental factors and interactions among these factors. Recent large international consortia on PD genome-wide analyses led to the identification of nearly 30 susceptibility loci for late-onset PD. While it is appealing to adopt a similar approach to investigate how environment impacts PD etiology alone or in combination with genetic factors, there are many challenges. Examples include the massive sample sizes needed for genome-wide studies (e.g.,10,000 patients) that often go beyond traditional PD environmental studies, the need for quality environmental exposures from well-designed epidemiological studies, the challenge of data harmonization, and the need for statistical methods development.

Approaches:
- Identify quality studies with common data on environmental exposures. Large and high quality epidemiological studies are the cornerstones for any pooling projects
- Develop strategies for data harmonization and statistical methods including methods to conduct interaction analyses in pooling projects and approaches for analyzing populations with varying amounts and qualities of exposure information.
- Establish practical goals and strategies to conduct in-depth research on environmental risk factors of PD and interactions among environmental factors and/or with genetic risk factors.
- Search for environmental modifiers of Mendelian PD-associated genes (e.g., PARK1/PARK4, PARK2)

<u>Recommendation 7</u>: Prevention Studies: Supporting prevention studies is the ultimate goal of all above topics. The emphasis for this recommendation is to develop methods and establish feasibility for implementing both primary and secondary prevention studies in a foreseeable future.

Need: The group agrees that prevention studies depend on the progression and outcomes of all above topics, particularly related to a better understanding of the risk factors associated with the disease initiation and progression. There is also a need to resolve scientific, economic and political barriers in attempts to reduce environmental and biological exposure of the general population for primary prevention. Long preclinical periods may make secondary prevention studies challenging; efficient approaches to prevention taking this into account are needed.

Approaches:

- Identify/establish high risk populations based on their genetic, environmental (e.g., pesticides) and biological (e.g., uric acid) exposures and/or prodromal (e.g., non-motor features) phenotypes

- Determine the feasibility and potential impact of reducing environmental and biological "exposures" that are linked to the initiation and/or acceleration of prodromal progression

- Develop intermediate biomarkers of tissue damage or functional outcomes that could be used in proof-of-concept trials with shorter duration and lower cost.

- Determine the risk/benefit and health economics of prevention studies.

Research Topic Areas with Detailed Discussion Points

BASIC MECHANISM GROUP

Recommendation 1: Systematically determine the effects of environmentally-relevant compounds on known genetic abnormalities (synuclein, LRRK2, parkin, PINK1, DJ-1) in PD.

Need: NINDS 2014 recommendations indicate that certain genetic/cell biological targets, particularly a-synuclein and LRRK2, are important for understanding multiple aspects of PD, including disease vulnerability and preclinical progression (prodromal). Thus, it is essential that the effects of environmental compounds of interest on the genetic targets (synuclein, LRRK2, parkin) should be evaluated. In some cases, effects on one genetic target may secondarily impact another. For example, increase in LRRK2 activity may lead to increase vulnerability to a-synuclein toxicity. As indicated in NINDS 2014, there are daunting array of model systems that could be used for evaluation and the institutes (NIEHS and NINDS) should provide guidance for evaluation.

Approaches:

- Establish standard cell models for high/medium throughput screening of PD-relevant gene expression (at mRNA, protein, and enzyme activity levels). This could be accomplished by cell lines/resources identified through consensus developed from meeting of experts to develop and distribute these resources. They would include standard method for use and central depository for the data.

- Establish/advise availability of standardized human iPS cells for second level validation and possible phenotypic changes.

- Medium and long-term goal is to determine how environmental agents are affecting gene expression and whether these changes occur in vivo.

- Establish consensus on appropriate animal models for in vivo validation. This could be accomplished via focused workshop(s).

Recommendation 2: Systematically determine the effects of environmentally-relevant compounds on known biological processes involved in PD pathogenesis (mitochondrial dynamics, protein processing, inflammatory processes, dopamine biochemistry).

Need: It will be often the case that PD relevant environmental agents will impact neuronal vulnerability and PD-relevant genes as a secondary effects of impacting a "global" cell biological processes, including mitochondrial function, protein homeostasis (UPS, UPR, autophagy, chaperone), oxidative stress, inflammation. For example, defects in autophagy/lysosome could increase a-synuclein burden. Understanding proximal and distal cell biological targets of relevant environmental agents will facilitate mechanistic analysis and biomarker development.

Approaches:

- Define 4-6 cell biological categories that would most likely impact the biology of PD relevant proteins and/or vulnerability of PD relevant cell population.

- Define proximal cell biological effects of environmental agents. The agents could be categorized in to one or more of the relevant "cell biological" categories.

- Provide guidance on appropriate assays to categorize a given environmental agent.

- Establish consensus on appropriate animal models for in vivo validation. This could be accomplished via focused workshop(s).

- Establish genomic and proteomic signature and unbiased pathway analysis for exposure to "high-priority" agents, as defined by the epidemiological studies. This should be done for acute and chronic exposures as well as cell culture and in vivo. Hypothesis derived can be evaluated in the models relevant to PD.

Recommendation 3: Develop and provide access to a carefully curated battery of compounds to be used for approaches identified in 1 and 2. Ideally, findings from these efforts would be deposited into some existing or new database and shared. Similarly, development of dosing regimens for model toxicants would facilitate in vivo studies.

Need: Investigators often choose the chemicals to include in their assays based on recent papers without an understanding of how people are exposed to the chemicals. This has led to a literature that does not provide a comprehensive analysis of potential environmental culprits. If experts in toxicology work with NIEHS to create and distribute a battery of compounds (including positive and negative controls and known exogenous modifiers, caffeine, nicotine) to more systematically analyze potential environmental contributors it could greatly advance the field. This would be analogous to a scaled down version of the Tox21 approach. For example, generating data on alpha-synuclein aggregation, LRRK2 activity, receptor and transporter activation on key neurotransmitters, and mitochondrial function on the same controlled 50-100 compounds could provide a much-needed overview of the types of chemicals affecting the vulnerable targets and pathways.

Approaches:

- NIEHS investigators with experience in developing similar compound collections would work with members of this workshop to develop a list of representative compounds. The compounds could be distributed in stock solutions for dose-response studies. Positive hits could be followed up by expanding into that particular chemical class. Organophosphates (chlorpyrifos, parathion, dichlorvos), organochlorines (DDT, DDE, dieldrin), pyrethroids (deltamethrin, permethrin), neonicotinoids (also interesting from the nicotinic signaling side), fungicides (dithiocarbamates and their metal cores-maneb, ziram, mancozeb* cores under metals), herbicides (paraquat, diquat), rotenone, drugs of abuse, metals (mercury, manganese, lead, cadmium, zinc), and other PD-related chemicals, such as PCBs (perhaps Arochlor mixture 1254, 1260 and 2 or 3 congeners, 153, 180), trichloroethylene (and possible derivatives), bisphenol. Also agents that appear to be protective: caffeine (and a specific A2A antagonist), and nicotine and various agonists and antagonists. This approach should also use standardized nomenclature to facilitate data sharing.

- The list could likely be developed and vetted electronically with the research community. Compilation and distribution of the chemicals would require resources from NIEHS or NTP. This could potentially fall under initiatives like Tox21.

<u>Recommendation 4</u>: Identify assays or methods for analysis of environmental influences in large populations. These approaches could be used on banked samples or current epidemiological or clinical studies. Specific procedures for collection and archiving of such samples would be helpful. Discussion of benefits and limitations of various approaches should be discussed.

Need: Several large studies have accumulated biological samples. Many of these may be amenable to analysis of environmental chemicals. As these samples are precious, it is critical to identify the approaches that will provide the most useful data given the limitations of sample amount and collection and storage conditions. Such recommendations could also be used in studies of other neurological conditions, such as Alzheimer's disease or autism.

Approaches:

- Identify leading investigators in field to determine the current state of the art in chemical detection. Determine advantages, disadvantages, and costs for the various approaches. This could be accomplished via a one-day workshop that could be applied to a variety of disorders.

- Untargeted analysis. Mass spectrometry-based metabolomics.
  Targeted analysis. LC/MS, GC/MS, ICP-MS to measure known chemicals.
  Emerging approaches from exposome research-adduct chemistry, personal monitors, biosensors.

<u>Recommendation 5</u>: Establish models to evaluate effect of environmental agents on preclinical progression of PD*.
* Note: overlapping recommendation with Clinical/Epidemiology Group

Need: One of the priorities of NINDS 2014 was to provide more effective evaluation of prodromal or preclinical stage of PD. Given the environmental exposure profile being chronic/long term, effects of environmental agents during the prodromal phase, which may represent ~10-20 years prior to disease diagnosis, is a significant factor. Thus, model for evaluating effects of agents during prodromal phase is essential.

Approaches:

- Develop or define mechanism based model for prodromal PD. For example, brain stem alpha-synuclein pathology might represent a good starting point for prodromal model of PD.

- Define aspects of prodromal pathology that could be affected by agents characterized in Recommendations 1 and 2.

- Further examination of how environmental exposures during sensitive developmental time windows (e.g., prenatal) might increase the probability of later PD onset.

Appendix 1: Details on Meeting Format and Process of Generating Prioritized Recommendations

The format of the meeting agenda consisted of three inter-related parts: (1) Basic, epidemiological and clinical scientists presented emerging themes and discussed prioritized research recommendations involving environmental contributors to PD, (2) Panelists discussed challenges and opportunities for interdisciplinary research approaches in advancing research on PD and environment, and (3) PD patients, patient advocates, physician scientists and research funders shared their perspectives on communicating and acting on science linking environmental exposures and PD. Approximately 140 participants attended the meeting (~70 on site, 70 via webcast) and had an opportunity to share ideas and help further stimulate research on the interaction between environmental exposures and genetic susceptibility in the development of PD. A detailed listing of all key contributors to the meeting is shown in Appendix 2-5 at the end of this document.

The process of generating prioritized recommendations presented in this report began with the recruitment of co-Chairs, Drs. Caroline Tanner, Marc Weisskopf, Gary Miller and Michael Lee to lead the Clinical/Epidemiology and Basic Mechanism working groups. Additionally, a key part of the planning process was to engage patient advocacy groups early from the initial planning stages of the meeting, allow open communication via teleconference calls, ask for input as the plan was developed, provide consistent updates and solicit feedback on high priority areas. This information was distributed to the working groups, and these patient-advocacy groups were continually updated throughout the pre-meeting planning process. Subsequently, we solicited opinions from co-chairs, patient-advocate groups and Program Staff at NIEHS/NINDS for names of expert scientists to serve on the working groups. Over several months leading up to the meeting, both working groups independently had weekly teleconference calls to discuss top priority areas in their field and major themes emerged. Additionally, a request for information (RFI) was published to solicit feedback from the scientific and general community, as well as people with PD, their caregivers, family members and advocates on high priority areas when considering environmental contributors in PD. These responses were distributed to both groups, and this information informed content and priority in the generation of the recommendations.

In the last two weeks up to the meeting, both working groups were combined for group discussion to share recommendations and major themes that were generated independently and allowed for further modification/streamlining of the recommendation draft that was presented at the conference. Importantly, the strong synergy for how the prioritized recommendations were developed continued during and following the conference. For example, research priorities were modified following expert panelist discussion and feedback from the audience during the meeting, as well as during teleconference calls post-meeting. The recommendations presented in this report were constructed with the idea of not repeating priorities discussed in the earlier NINDS conference, but incorporating environmental factors when thinking about missing data gaps or the most promising scientific opportunities in PD research.

Appendix 2: Research Recommendation Panel Membership

Working Group Name	Panelist Name	Affiliation
Clinical/Epidemiology	Caroline Tanner, M.D., Ph.D. (co-chair)	University of California, San Francisco
	Marc Weisskopf, Ph.D. (co-chair)	Harvard T.H. Chan School of Public Health
	Alberto Ascherio, M.D., DrPH	Harvard T.H. Chan School of Public Health and Harvard Medical School
	Honglei Chen, M.D., Ph.D.	NIEHS (intramural)
	Xuemei Huang, M.D., Ph.D.	Penn State Milton S. Hershey Medical Center
	Freya Kamel, Ph.D.	NIEHS (intramural)
	George Mellick, Ph.D.	Griffith University
	Brad Racette, M.D.	Washington University School of Medicine
	Jeffery Vance, M.D., Ph.D.	University of Miami
Basic Mechanism	Michael Lee, Ph.D. (co-chair)	University of Minnesota
	Gary Miller, Ph.D. (co-chair)	Rollins School of Public Health, Emory University
	John Elsworth, Ph.D.	Yale School of Medicine
	Matthew Farrer, Ph.D.	University of British Columbia
	Jau-Shyong Hong, Ph.D.	NIEHS (intramural)
	Jeffrey Johnson, Ph.D.	University of Wisconsin
	Thomas Montine, M.D., Ph.D.	University of Washington
	Richard Myers, Ph.D.	Boston University School of Medicine
	David Standaert, M.D., Ph.D.	University of Alabama at Birmingham

Appendix 3: Meeting Session Panelists (excluding participants in Appendix 1)

Panelist Name	Affiliation
Jeff Bronstein, M.D., Ph.D.	Ronald Reagan UCLA Medical Center
Susan Gerbeth-Jones	Parkinson's Disease Foundation
Anumantha Kanthasamy, Ph.D.	Iowa State University
Beate Ritz, M.D., Ph.D.	University of California, Los Angeles, School of Public Health
Julie Sacks	American Parkinson Disease Association
Peter Schmidt, Ph.D.	National Parkinson Foundation
Jamie Tucker	Parkinson's Action Network
Allison Willis, M.D.	University of Pennsylvania

Appendix 4: Stakeholder Contributors

Name	Affiliation
James Beck	Parkinson's Disease Foundation
Hayley Carpenter	Parkinson's Action Network

Leslie Chambers	American Parkinson's Disease Association
Polly Dawkins	Davis Phinney Foundation
Michelle Duelley	Parkinson's Action Network
Brian Fiske	Michael J. Fox Foundation
Joyce Oberdorf	American Parkinson Foundation
Amy Comstock Rick, J.D.	Parkinson's Action Network
Todd Sherer	Michael J. Fox Foundation
Jennifer Sheridan	Parkinson's Action Network
Ronnie Todaro	Parkinson's Disease Foundation
Annesha White	Michael J. Fox Foundation

Appendix 5: NIH and DoD Planning Teams and Meeting Participants

Group	**Name**	**Affiliation**
NIEHS Leadership	Linda Birnbaum, Ph.D.	Director, NIEHS and NTP
	Gwen Collman, Ph.D.	Director, DERT
NINDS Leadership	Story Landis, Ph.D.	Director, NINDS
	Walter Koroshetz, M.D., Ph.D.	Acting Director, NINDS
Planning Team Leads	Jonathan Hollander, Ph.D.	Program Director, GEHB, NIEHS
	Cindy Lawler, Ph.D.	Branch Chief, GEHB, NIEHS
Planning Team Members	Deborah Babcock, M.D., Ph.D.	Program Director, NINDS
	Jennifer Collins, M.R.	Program Analyst, ERTB, NIEHS
	Kimberly Gray, Ph.D.	Program Director, PHB, NIEHS
	Michael Humble, Ph.D.	Program Director, GEHB, NIEHS
	Robert Kane, Ph.D.	Program Manager and Neuroscience Lead, DoD
	Robbie Majors, M.B.A	Extramural Support Assistant, GEHB, NIEHS
	Beth-Anne Sieber, Ph.D.	Program Director, NIEHS