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Consensus Statement
Parkinson's Disease and the Environment
Collaborative on Health and the Environment and Parkinson's Action Network (CHE PAN)
Conference June 26–28, 2007

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Parkinson's Action Network (CHE PAN) ConferenceJune 26–28, 2007

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Abbreviations:

IOM	Institute of Medicine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PD	Parkinson's disease

Outline:

Abstract

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- **Sufficient Evidence of a Causal Relationship**
- **Sufficient Evidence of an Association**
- **Inadequate/Insufficient Evidence to Determine Whether an Association Exists**
- **Limited/Suggestive Evidence of No Association**
- **Consensus Not Reached on Category of Association**

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Research questions

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Abstract:

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder. People with PD, their families, scientists, healthcare providers and the general public are increasingly interested in identifying environmental contributors to PD risk.

Methods: In June 2007, a multidisciplinary group of experts gathered in Sunnyvale, CA, to assess what is known about the contribution of environmental factors to PD.

Results: This paper describes the conclusions around which they came to consensus with respect to environmental contributors to PD risk. It concludes with a brief summary of research needs.

Conclusions: Parkinson's disease is a complex disorder, and multiple different pathogenic pathways and mechanisms can ultimately lead to PD. Within the individual there are many determinants of PD risk and, within populations, the causes of PD are heterogeneous. Although rare recognized genetic mutations are sufficient to cause PD, these account for less than 10% of PD in the U.S. population, and incomplete penetrance suggests environmental factors may be involved. Indeed, interplay among environmental factors and genetic make-up likely influences the risk of developing PD. There is a need for further understanding of how risk factors interact, and studying PD is likely to increase understanding of other neurodegenerative disorders.

Background:

Parkinson's disease is the second most common neurodegenerative disorder. The likelihood of developing PD increases with age. PD is rare before age 50. The average age of onset is in the mid to late 60s (Bower et al. 1999; de Rijk et al. 1995; Marras and Tanner 2002; Van den Eeden et al. 2003). As the US population ages, prevalence of this disabling disorder is expected to rise dramatically (Dorsey et al. 2007). Unfortunately, few valid data that address changes in PD incidence or prevalence over time are available. In fact, active case-finding efforts in communities detect as many as 10-40% of cases of PD for the first time, suggesting that under-estimation of PD prevalence is common (de Pedro-Cuesta 1991; de Rijk et al. 1997).

The symptoms of PD are slowly progressive. Well-recognized clinical features of PD are slowed movements, tremor, rigidity, and gait and balance difficulties. However, other features commonly occur, including changes in olfaction, autonomic function, cognitive function, affect, sleep and energy level (Alves et al. 2005; Burn et al. 2006; Pfeiffer 1998; Stern et al. 1994).

In PD, specific neuronal populations degenerate. Neurodegeneration occurs in concert with the deposition of aggregates of the protein, alpha synuclein, in neuronal cell bodies and processes (Spillantini et al. 1998). The classical focus has been on dopamine-releasing cells in the substantia nigra, because dopamine replacement can partially correct some of the motor features of PD. It has long been known, however, that many other neuronal populations are also affected in PD. Recently, converging epidemiological and

pathological data suggest that years or even decades prior to the onset of these classical features of PD, neurons outside of the central nervous system may be injured (Abbott et al. 2005, 2007; Braak et al. 2004; Langston 2006; Ross et al. 2008). If this is correct, current concepts of PD will need revision. Clarification may provide exciting new opportunities for treatment and intervention.

In the 1980s, the observation that intravenous exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) caused parkinsonism in humans offered important insights into environmental triggers (Langston et al. 1983). Even though relatively uncommon genetic mutations are sufficient to cause some cases of PD, twin studies conclude that the contribution of genetic makeup to the risk of most cases of PD is limited (Tanner et al. 1999; Wirdefeldt et al. 2004). Moreover, studies of uncommon genetic forms of PD have shown that changes in the structure of proteins that can lead to neural dysfunction and death can also be caused independently by some environmental toxicants (Lee 2003; Purisai et al. 2005; Uversky et al. 2001; Vila et al. 2000). As a result, a general view has evolved that the vast majority of cases of PD are caused by environmental factors interacting with genetic makeup.

People with PD, their families, scientists, healthcare providers and the general public are increasingly interested in identifying environmental contributors to PD with an eye toward not only more effective treatments but also prevention. What percentage of cases involves preventable causes? What precautionary interventions would be warranted and

effective, and when must they be implemented? Can individuals destined to develop neurologic dysfunction due to PD be identified before typical motor symptoms manifest? The current scientific literature does not provide conclusive answers to most of these and other relevant questions. But indications from epidemiology, basic neurobiology, and toxicology increasingly support the conclusion that a large portion of the risk of developing PD may be attributable to environmental exposures. Therefore, the risk of PD is theoretically reducible to the extent that some cases may be preventable.

Purpose of conference:

Responding to these questions and concerns, a multidisciplinary group of experts gathered in Sunnyvale, CA, from June 26-28, 2007 to assess what is known about the contribution of environmental factors to Parkinson's disease. Participants included toxicologists, epidemiologists, geneticists, neuroscientists, and medical practitioners. They were joined by representatives of Parkinson's disease advocacy groups and people with Parkinson's disease to review the state of environmental health science as it pertains to PD.

The purposes of the meeting were:

- To review findings from diverse research disciplines concerning environmental factors that alone or in combination with genetic variables provide a biologic basis of Parkinson's disease
- To identify conclusions that could be drawn with confidence from existing data
- To identify plausible but uncertain conclusions

- To identify research gaps and needs and to describe features of a coherent research agenda

Participants recognized the existence of various syndromes that may share some clinical and neurobiological features with classic PD. Sometimes the term "parkinsonism" is used to refer to these syndromes. They often involve more extensive (or less specific) brain injury than is typically seen in classic PD and can be degenerative or non-degenerative (e.g., CO-induced parkinsonism, CCl_4-induced parkinsonism, vascular parkinsonism). However, boundaries between PD and parkinsonism are evolving concepts. For this reason, participants were not asked to discuss and come to a consensus definition of PD.

Participants did not attempt to rank specific pathogenic mechanisms with respect to their relative importance in PD causation. Nonetheless, various combinations of alpha-synuclein deposition, mitochondrial dysfunction, proteosome dysfunction, oxidative stress, and inflammation arose in discussions of potential contributors in causal pathways.

Participants were also not asked to address and did not consider:

- An exhaustive list of toxicants that have been associated with PD (examples of toxicants not considered include organic solvents, electromagnetic fields)
- Factors that may influence the progression of PD (as differentiated from causes of onset of PD)

Over the course of the meeting, the following core points of consensus were identified, which we offer in this summary to acquaint scientists, medical professionals, public health advocates, and policy makers with the current state of understanding in the field, as seen by conference participants, and to help in identifying fruitful research strategies.

Findings:

Based on existing evidence, we are confident of the following:

Parkinson's disease is a complex disorder, and multiple different pathogenic pathways and mechanisms can ultimately lead to PD. Within the individual there are multiple determinants of PD risk, and within populations the causes of PD are heterogeneous. The interplay among environmental factors and genetic make-up likely influences the risk of developing PD (Chade et al. 2006; Warner and Schapira 2003).

PD risk increases with age (Bower et al. 1999; de Rijk et al. 1995; Van den Eeden et al. 2003; Zhang et al. 2003).

Studying PD is likely to increase understanding of other neurodegenerative disorders.

Rare recognized genetic mutations are sufficient to cause PD (Singleton et al. 2003; Warner and Schapira 2003). However, collectively, these genetic mutations account for less than 10% of PD in the U.S. population. Moreover, even in these rare instances, incomplete penetrance suggests that environmental factors may be involved (Elbaz 2008)

In addition to rare genetic mutations, PD or parkinsonism can also rarely be induced primarily by exposure to toxicants that directly target the area of the brain involved in PD. MPTP is an example of such a toxicant (Langston et al. 1983).

In the following, PD risk factors are categorized according to the Institute of Medicine's terminology for strength of evidence. Institute of Medicine committees sometimes classify the evidence of association between exposure to a specific agent and a specific health outcome into five previously established categories, as set forth below. The group of experts gathered in Sunnyvale decided to use these categories as a means of describing their evaluation of the state of the evidence with respect to the influence of various factors on Parkinson's disease risk. Criteria for inclusion in each category are described at the outset.

Participants felt that these categories for describing the strength of evidence pertaining to individual risk factors were useful even though not based here on a systematic evidence-based literature review. Risk factors were assigned to the various categories based on consensus opinion of those attending the conference. Moreover, within each category there is no attempt to list the entries in any particular order.

Sufficient evidence of an association

In this IOM category, evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which

chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Men are at greater risk of PD than women (Bower et al. 1999; de Rijk et al. 1995; Van den Eeden et al. 2003). However, increased risk to a disease can occur because of inherently increased susceptibility, increased exposures to causal agent(s), or combinations of the two (Wooten et al. 2004). Current evidence is not sufficient to explain the increased risk in males with confidence.

Evidence is sufficient to conclude with confidence that cigarette smokers have a lower risk of PD than non-smokers (Hernan et al. 2002; Ritz et al. 2007). PD risk may also be lower for people who use other tobacco products though the evidence is not as extensive or persuasive as for cigarette smokers, and conference participants were less confident in drawing conclusions.

Evidence is also sufficient to conclude that male coffee drinkers have a lower risk of PD (Ascherio et al. 2004; Ross et al. 2000). For women coffee drinkers and people consuming other caffeinated beverages, evidence is limited, but a similar pattern seems to emerge (Ascherio et al. 2001).

Conference participants are confident of the associations but uncertain about the causal relationship or pathways by which smoking and coffee consumption might have a

neuroprotective effect. Various biologic mechanisms have been proposed. For example, nicotine in cigarettes and caffeine in coffee are hypothesized to be agents that may confer a lower PD risk. However, non-causal explanations for these associations are also plausible (Hernan et al. 2002), uncertainties remain, and no consensus has been achieved. Nonetheless, further investigation into the biological mechanisms by which female gender, cigarette smoking, and coffee consumption lower PD risk is warranted and may result in important insights into the etiology and progression of PD.

Limited suggestive evidence of an association

In this IOM category, evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent positive associations, and the results are probably not due to bias, including confounding.

Available scientific studies suggest an association between a number of different factors and PD risk. Here, the data are limited but tend to point toward a valid association with PD risk. Causal mechanisms explaining the associations, if they exist, are not well understood.

People with higher levels of physical activity have a reduced risk of PD (Thacker et al. 2008).

Men, and possibly women, with higher blood urate levels have a reduced risk of PD (Davis et al. 1996; Weisskopf et al. 2007).

People taking nonsteroidal anti-inflammatory drugs have a lower risk of PD (Powers et al. 2008; Wahner et al. 2007).

Men with high dietary intake of dairy products have an increased risk of PD (Chen et al. 2002; Park et al. 2005).

Farmers and agricultural workers have an increased risk of PD (Hertzman et al. 1994; Gorell et al. 1998; Tuchsen and Jensen 2000). Epidemiologic studies often classify study participants according to their occupation and examine for associations between occupations and outcomes of interest. In these cases, inferences about potential exposures that characterize those occupations may be drawn, but they remain as inferences and should not be confused with estimates of exposure to specific environmental agents.

People exposed to pesticides have an increased risk of PD (Dick et al. 2007; Gorell et al. 1998; Hancock et al. 2008; Kamel et al. 2007). It is important to note, however, that

epidemiologic study designs may classify study participants according to reported exposures to classes of chemicals or other agents. In these cases, associations between the class of environmental agents and outcome of interest may be identified, but in most cases specific agents that account for the association cannot be further identified from those data. Meeting participants note the evidence suggesting a direct association between pesticide exposure and PD risk but are unable to draw any conclusions about specific agents that may be responsible.

People with traumatic brain injury have an increased risk of PD (Bower et al. 2003, Dick et al. 2007; Goldman et al. 2006).

Certain variants of genes can modify the risk of PD. The risk may be higher or lower depending on the variant (Warner and Schapira 2003).

Inadequate/insufficient evidence to determine whether an association exists

In this IOM category, evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

People with higher dietary intake of polyunsaturated fatty acids have lower risk of PD (de Lau et al. 2005).

People with higher blood cholesterol have lower risk of PD (Hu et al. 2008; Simon et al. 2007).

Dietary sources of urate lower the risk of PD (Annanmaki et al. 2007; Gao et al. 2008).

People taking statins are at lower risk of PD (Becker et al. 2008; Wahner et al. 2008).

Post-menopausal women taking exogenous estrogen are at reduced risk of PD (Currie et al. 2004; Popat et al. 2005).

People with increased body-mass index or body fat are at increased risk of PD (Hu et al. 2006; Logroscino et al. 2007).

Women occupationally exposed to polychlorinated biphenyls (electrical capacitance workers) are at increased risk of PD (Prince et al. 2006; Steenland et al 2006).

People with higher educational level are at higher risk of PD (Frigerio et al. 2005). People exposed to some specific pesticides have an increased risk of PD (paraquat, maneb, dieldrin) (Dick 2006; Drechsel and Patel 2008; Kamel et al. 2007). In vitro and in vivo laboratory animal studies of some specific pesticides (e.g., rotenone, paraquat, maneb) demonstrate toxicity to nigral dopaminergic neurons and reveal biological mechanisms by which exposure to those pesticides is plausibly linked to PD risk (Thiruchelvam et al. 2000; Uversky 2004).

People exposed to some heavy metals have an increased risk of PD (Gorell et al. 1998; Mergler et al. 1994).

Limited suggestive evidence of no association

In this IOM category, evidence from available studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

Welding is not associated with risk of PD (Marsh and Gula 2006; Santamaria et al. 2007).

Consensus not reached on category of association

In this IOM category, if the entire committee did not agree on a conclusion, then the association was not assigned a category.

People living in rural areas have/do not have (Kuopio et al. 1999; Priyardarshi et al. 2001) an increased risk of PD.

Vitamin E, C and carotenoids are/are not associated with PD risk (Etminan et al. 2005; Zhang et al. 2002).

Dietary saturated fats are/are not associated with risk of PD (de Lau et al. 2005; Gao et al. 2007; Powers et al. 2008).

Well water drinking is/is not associated with PD risk (Kuopio et al. 1999; Priyardarshi et al. 2001).

Race/ethnicity is/is not associated with PD risk (Mayeux et al 1995; Van den Eeden et al. 2003; Zhang and Roman 1993).

Research needs:

Well designed case-control studies with sufficient power—perhaps through consortia or multi-center. Strict attention to bias, as well as confounding.

Consider the question of appropriate control groups. Consider alternatives to traditional sources of controls used in the past such as random digit dialing and Centers for Medicare and Medicaid Services, as these sources are now often impractical due to privacy and other considerations.

PD registries, particularly inclusive, legally-mandated population-based registries, are essential to description of demographic, geographic and temporal patterns and trends. Diagnostic criteria for cases need to be well defined in studies. Criteria and disease definition may vary depending on the specific hypothesis being tested. Similarly,

characterization of clinical features is critical. Some risk factors may be specific for classic PD, while others may be common for all types of parkinsonism.

Need for biomarkers of disease, beginning with early stages.

More consistent attempts to look at both susceptibility genes and environmental agents in combination.

Better measures of the exposures of interest.

Research questions:

In addition to known risk factors for PD, conference participants identified a number of others in need of further investigation. Even for those that are well established, however, there is a need for additional information about mechanisms by which they influence PD risk. Moreover, in addition to individual risk factors, conference participants recognized a need for further understanding of how risk factors interact as they contribute to the multiple pathogenic pathways that may ultimately result in PD.

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