Emerging Links between Chronic Disease and Environmental Exposure

Parkinson's Disease

PHYSICIANS FOR SOCIAL RESPONSIBILITY

Emerging Links between Chronic Disease and Environmental Exposure

Parkinson's Disease

PHYSICIANS FOR SOCIAL RESPONSIBILITY

Introduction

AS OUR KNOWLEDGE about the etiology of disease progresses, the evidence for environmental contributions to disease grows. There is a need to evaluate the findings from this research to assess possible emerging trends in chronic diseases. Physicians for Social Responsibility (PSR) has partnered with environmental health researchers to assess the emerging links between chronic diseases and environmental exposures and to generate a set of policy and research recommendations. PSR's goals are to elucidate and raise awareness of health care providers, researchers, and policy makers about increased evidence suggesting linkages between environmental factors and chronic diseases. PSR has chosen Parkinson's disease, non-Hodgkin's lymphoma, and diabetes as the three focus areas.

The next few pages review the diseases that were considered when conceptualizing this project. The comprehensive report that follows delves much more deeply into the three specific chronic conditions and their connections to the environment.

In evaluating the candidate diseases, PSR used three sets of criteria:

1. Public health importance: disease incidence and prevalence, years of productive life lost, and associated costs;
2. Scientific evidence supporting a link between the disease and environmental exposures;
3. Public concern and interest: the likelihood that the disease is of significant concern to the public and to health care providers treating the public.

In developing the initial process to examine emerging environmental links to chronic conditions, PSR identified several possible candidate conditions for evaluation: attention deficit hyperactivity disorder (ADHD); amyotrophic lateral sclerosis (ALS); Alzheimer's disease; autism, i.e., the spectrum of pervasive developmental disorders; diabetes; non-Hodgkin's lymphoma (NHL); and Parkinson's disease (PD). Though PSR could only select three chronic illnesses on which to focus, PSR wanted to consider many different illnesses before making a selection. These three reports review the existing research and provide a framework and a context for the future work. PSR

encourages this research because it will clearly assist in building a foundation for understanding the total impact of the environment on our nation's health.

This report is intended to further discussion among health care providers about the emerging links between chronic disease and environmental exposure. PSR understands that these connections are not always automatically drawn by clinicians, and this report does not intend to produce diagnostic expertise on the diseases, but instead offers an assessment of the scientific evidence about possible associated and causative factors related to chronic disease. Diseases such as asthma, cancer, diabetes, and Parkinson's disease all have delineable associations with environmental problems such as air pollution, drinking water contamination, and exposure to toxic chemicals. It is important to emphasize this connection and encourage the health care community to begin to recognize that these relationships do exist.

During the last two decades, chronic disease has replaced infectious disease as the major focus of public health concern, even with the appearance of AIDS. Seventy percent of all deaths annually are attributable to chronic illness. The top four and seven out of the top ten leading causes of death in the U.S. are chronic diseases (*1*). These illnesses account for more than $750 billion of the $1 trillion spent annually on health care. If anything, the economic impact of chronic diseases will increase in this century as this pattern becomes predominant worldwide. According to the World Health Organization, chronic diseases will become the top cause of death in most countries in the next few decades.

Among chronic diseases, cancer has received much attention. The "War on Cancer," initiated in the 1970s, resulted in the creation of national tracking efforts like cancer registries and large expenditures of research dollars. Much of the research, however, has focused on treatment and the search for cures, while very little is known about the etiologies of many cancers. Other chronic diseases, such as chronic degenerative diseases of the central nervous system, have received even less attention. Such diseases, most notably Alzheimer's disease and Parkinson's disease (PD), place very heavy burdens on society. Most people have a family member or friend who has been affected by one of these diseases . However, we do not have the kinds of tracking systems in place to monitor these conditions that we have for cancer. The discovery of causes and cures is even more elusive. As society ages, these diseases are expected to exact a greater burden on families and the medical care system and human suffering overall.

Whether it is cancer or autism that is affecting our families and showing up in our examination rooms, the growing rates of chronic disease compel us to search for clues and answers to determine the true causes of these increasingly prevalent illnesses. Evidence from disease cluster investigations has shown that exposure to certain chemicals increases the risk for certain cancers. However, a comprehensive analysis of existing research and better tracking mechanisms are key to truly differentiating real science from coincidence.

These three brief overviews introduce the three diseases PSR has chosen for in-depth analyses. Though a significant review of the existing research was done on all seven of the possible conditions prior to selection, these conditions met the three-project criteria most directly. This in no way minimizes the potential links of the environment to the other conditions, and certainly PSR would encourage additional research to assess links on the four remaining conditions as well as other critical chronic illnesses.

PARKINSON'S DISEASE

More than 60,000 people each year are diagnosed with PD in the U.S., and more than a million Americans are living with the disease at any one time (*2*). PD is a progressive brain disorder that affects patients for many years. The disease usually strikes people over age 60, but in some cases can develop much earlier. Idiopathic PD, the most common form, is defined by the absence of an identified, specific cause, as opposed to forms of

parkinsonism that are due to a specific environmental exposure, like manganese poisoning (3) or other defined nosologic entities. PD affects both men and women and is the second most common neurodegenerative disorder of the elderly, after Alzheimer's disease. The disease is associated with progressive and irreversible damage to the dopaminergic projections from the substantia nigra to the dorsal striatum, and with the formation of Lewy bodies, the pathological hallmark of idiopathic PD.

Parkinson's disease involves the death of brain cells that produce dopamine, a necessary chemical messenger that serves to control movements mediated by the extrapyramidal system. Loss of dopamine and the secondary effects on other neural systems lead to the cardinal symptoms of PD, tremor, rigidity, bradykinesia (slow movements) and a loss of postural reflexes. As the disease progresses, other problems may emerge, including personality changes, bradyphrenia (slowing of thought processes), sleep disturbances, sexual dysfunction, Alzheimer's-like dementia, paranoia, psychosis, and even hallucinations and severe depression.

Although some patients have an inherited form of PD (particularly those with an onset prior to age 50) a large twin study showed that hereditary factors are of little importance among patients who contract the disease in later life (4). Among identical twins with one affected member of the pair, the probability of the second twin contracting the disorder was no higher than in the general population. An editorial that accompanied this landmark article urged a return to the focus on environmental chemicals, especially pesticides, as a cause (5).

The causes of PD have been a subject of debate for decades. In the 1980s, the medical community began thinking of Parkinson's disease as a neurological disorder that might be caused by chemical exposures because a group of young people developed Parkinson's-like symptoms after taking an illegal designer drug contaminated with a chemical byproduct called MPTP. Subsequently, similar symptoms were induced in monkeys by administering MPTP. This type of parkinsonism is very similar to idiopathic PD. This led to the realization that a single adverse exposure could start a complex chain of events leading to regionally specific neurodegeneration (3). Oxidative stress, induced by a variety of factors, including pesticides, might contribute to the development of parkinsonism. The structure of MPTP is similar to that of paraquat, a widely used herbicide. This finding led to investigations of PD and pesticide exposure. Pesticide exposure has been identified as a risk factor for the development of PD in numerous epidemiological and case control studies (6,7).

NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphomas form a group of related cancers. A lymphoma is a cancer of the white cells that is localized in lymph nodes or location other than the bone marrow. NHL is the fifth most common cancer and the sixth most common cause of cancer death, accounting for about 16 new cases per 100,000 people each year (8). Rates of NHL have risen sharply in the U.S. over the last 20 years, especially among older people and those who have AIDS.

A recent twin study on cancer and heredity indicates that a genetic contribution to NHL, if present, is small, although the authors could not provide a quantitative estimate because of a small sampling size (9).

Non-Hodgkin's lymphoma seems to be caused by factors that are involved with genetic damage to cells and/or factors that are associated with immunosuppression. People with inherited immunodeficiency syndromes (which are very rare) have elevated rates of NHL, as do people who receive immunosuppressive drugs for transplants or have immunosuppression for some other

reason. NHL tumors have a high rate of genetic alterations; these are thought to be due to various environmental and infectious exposures. People with inherited defects in DNA repair (for example, ataxia telengectasia syndrome) have high rates of NHL.

For many years it has been recognized that Epstein-Barr virus plays an important role in NHL incidence. However, in the U.S., Epstein-Barr virus seems to play a relatively minor role compared to in African cases.

More recently, infection with HIV/AIDS has been recognized as a risk factor for NHL and may be responsible for about 60% of the rise in incidence over the last 20 years (*10*). A rare type of rapidly progressive NHL is related to infection caused by HTLV-I (human T-cell lymphotropic virus type I), a retrovirus similar to HIV.

Numerous agricultural and industrial chemicals have been associated with NHL. Farmers have higher rates of NHL than non-farmers, and exposure to herbicides (including Agent Orange) and to certain insecticides (including organophosphates) seem to be important risk factors (*11–14*). There is also good evidence for involvement of PCBs and dioxins (*15–16*).

NHL is an example of where we still have much to do in the "war on cancer." While cancers related to smoking are falling, NHL rates have risen and now seem to have reached a plateau.

DIABETES MELLITUS TYPE II

Diabetes is a disease in which the body does not produce or use insulin properly. The cause of diabetes is unknown, although both genetic and environmental factors, such as obesity and lack of exercise appear to play roles. There are two major types of diabetes: Type I is a disease in which the body does not produce enough insulin, most often occurring in children and young adults. People with Type I diabetes must take daily insulin injections to stay alive. Type I diabetes accounts for 5 to 10% of all diabetes cases. Type II is a metabolic disorder resulting from the body's inability to make enough or properly use insulin. Type II diabetes is nearing epidemic proportions, due to an increased number of older Americans and a greater prevalence of obesity and sedentary lifestyles.

Diabetes mellitus is one of the most serious threats to American health. Recent studies indicate that the prevalence of diabetes is increasing among the general population in the U.S. and worldwide. More than 135 million people are affected by diabetes worldwide including more than 8.5 million Americans. In many developed countries, 10 to 20% of people over 45 are affected by non-insulin dependent diabetes mellitus. About 15% of people over age 70 have type II diabetes. The World Health Organization has concluded that diabetes is becoming a global epidemic and predicts that the disease will be one of the world's major contributors to morbidity by 2025 (*17*). Blacks and Hispanics have a twofold to threefold increased risk of developing type II diabetes; poverty is also an important risk factor. Diabetes increases the risk of blindness, loss of limbs, heart disease, stroke, kidney failure, and depression (*18*) and generally reduces life expectancy. The costs of diabetes arise from the treatment of the disease, its complications, lost workdays, and disability. Of the three diseases under consideration, diabetes clearly has the greatest public health impact.

There is strong evidence for both inherited and environmental risk factors for diabetes. Type II diabetes has been associated with certain genetic sequences in the NIDDM1 region of chromosome 2. Recently, Horikawa and colleagues (*19*) have proposed that the gene in this region might be CAPN10, a gene that encodes calpain. The authors estimate that the removal of the risk factor resulting from the combination of two genetic variants would reduce the prevalence of diabetes by 14% in Mexican-Americans and 4% in Europeans.

Environmental risk factors, including lifestyle factors like diet and exercise habits, are even more important than environmental exposures. Obesity is a risk factor for type II diabetes; 80 to 90% of the people with this disease are obese. The incidence of non-insulin dependent diabetes mellitus has also been found to increase, up to a point, with the number of cigarettes smoked per day. Rates of diabetes have risen with those of obesity and poor physical fitness.

However, a component of diabetes seems to be related to environmental exposures, most notably arsenic and dioxins. Specifically, diabetes has been linked to exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Low-level dioxin exposure has been shown to affect glucose metabolism and thyroid function in some (but not all) occupationally exposed populations (*20*–23) The most compelling evidence is from a study of Vietnam veterans who were involved in handling Agent Orange, an herbicide that contained dioxin as a contaminant (*24*). A total of 989 of these so-called "Ranch Handers" were compared with 1,276 veterans who served elsewhere in Southeast Asia during the same period. The study found higher rates of diabetes among the Ranch Hand group, with a dose-response relationship between blood dioxin level and severity of diabetes.

Arsenic is also of interest, in the U.S. and worldwide, because of continual high exposures in communities due to natural and industrial sources of arsenic pollution of water. The strongest evidence for a linkage between arsenic and diabetes comes from several epidemiological studies in Taiwan that identify higher prevalence levels of diabetes in arseniasis-endemic areas relative to non-endemic areas (25–27).

Diabetes is an important and growing health problem that brings with it a number of interesting environmental dimensions. Certainly the problems of obesity and lack of physical exercise could be related to the environment in which individuals live as well as the natural environment; communities today are not designed to facilitate walking and other forms of physical exercise.

EDUCATION, RESEARCH AND POLICY RECOMMENDATIONS

As a nation, we can begin to address an emerging link between chronic disease and the environment in a number of ways. It is time to bring together the mounting information from health and scientific researchers, clinicians, and public health officials and call for additional research, public education, and as appropriate, policy changes to reduce exposures. There are a number of policy steps that should be taken to address this critical issue.

First, we need a public health infrastructure to track chronic diseases in the U.S., including the three addressed in these papers, and to monitor the environmental exposures that may be related to these diseases. Such a system will allow us to determine whether linkages exist and the strength of those linkages. Public health policies and programs that effectively link exposure monitoring, biomonitoring of chemicals in the human body, and chronic disease will greatly enhance our ability to understand and reduce these emerging links in the future.

A Nationwide Health Tracking Network, the beginnings of which have been established through the Centers for Disease Control and Prevention (CDC), should contain three primary components and should be organized to facilitate a search for interactions (28):

HAZARDS TRACKING: measuring the amount, concentration, and geographic distribution of known and potential toxic chemicals in the environment (such as the Toxics Release Inventory).

EXPOSURE TRACKING: assessing and measuring human exposure to environmental chemicals, including levels of exposure among population subgroups (such as CDC biomonitoring capacity).

HEALTH OUTCOME TRACKING: monitoring disease events and trends in health risk behaviors within populations over time through tracking systems such as vital statistics, health surveys, and disease registries.

As of January 2003, representatives from 17 states, three large cities, and three schools of public health began to develop the infrastructure and pilot projects to launch the first phase of this network. The national tracking system will collect data that will help further illustrate the link between chronic conditions and environmental exposures, thereby supporting the calls by public health and environmental advocates for health-protective policies.

Second, we need to educate physicians, nurses, and other health care providers about the possible connections between the environment and disease. Health care providers are on the front lines of protecting the nation's health and can identify and prevent environmental exposures in their patients that may lead to disease later in life. Health care providers are one of the most trusted sources of information for their communities and their patients.

Third, we need to invest in further research of these and other emerging links between chronic disease and the environment. Adequate funding of centers of excellence, academic researchers, and community-based prevention intervention research is required to ask the next set of questions. As an example, the proposed National Children's Study will track exposures to children over a 30-year period to determine when and how exposures at different developmental stages impact growth, development, and morbidity.

Finally, environmental policy solutions exist that can begin to reduce human exposures to a number of the toxicants—such as agricultural pesticides, dioxin, arsenic, and PCBs—implicated in the evaluation of the three chronic conditions we have targeted. These policies include

- Ratification of the **Stockholm Convention on Persistent Organic Pollutants (POPs)** by the U.S. and ratification by 49 other countries for entry into force by the end of 2003;
- Full implementation of the **Stockholm Convention in the U.S.**, including
  - An expedited phase-out of PCBs still in use;
  - Additional funding for international development, particularly focused on alternatives to DDT in malaria control; and
  - Provisions for domestic action on future POPs, such as the brominated flame-retardants known as PBDEs that might be added to the treaty in the future.
- Release of EPA's **Dioxin Reassessment** and development of an EPA regulatory scheme focusing on pollution prevention measures aimed to achieve significant reductions in dioxin releases and human exposures.
- Additional regulatory action on **pesticides**, including further restrictions and phase-outs of organophosphate insecticides, federal legislation restricting pesticide use in schools, a permanent ban on the use of human subjects in tests of pesticide toxicity, and full implementation of the Food Quality Protection Act.
- Protection of hard-earned **"right-to-know"** provisions such as the Toxics Release Inventory and passage of further protections and the expansion of public information guarantees for people with chemical hazards in their communities.

These reports are not meant to provide health care providers with all of the answers, but to start clarifying the links between environmental exposures and causes of chronic illness so that preventive measures can be taken, more comprehensive diagnoses made, and more effective treatments explored. Certainly more research needs to be done to understand these links and to develop evidence that will effectively impact important policy action.

REFERENCES

1. Centers for Disease Control. National Center for Health Statistics. Health, United States 2002 Edition. http://www.cdc.gov/nchs/hus.htm [cited April 22, 2003]
2. Scheife RT, Schumock GT, Burstein A, Gottwald MD, Luer MS, Impact of Parkinson's disease and its pharmacologic treatment on quality of life and economic outcomes. American Journal of Health System Pharmacy 57:953–62 (2000).
3. Foley P, Riederer P. Influence of neurotoxins and oxidative stress on the onset and progression of Parkinson's disease. Journal of Neurology 247:W82–W94 (2000).
4. Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. Parkinson disease in twins: an etiologic study. Journal of the American Medical Association 281:341–6 (1999).
5. Cummings JL. Understanding Parkinson disease. Journal of the American Medical Association 281:376–8 (1999).
6. Lockwood, A.H. Pesticides and parkinsonism, is there an etiological link? Current Opinion in Neurology, 13: 687–690 (2000).
7. Hertzman C, Wiens M, Bowering D, Snow B, Calne D. Parkinson's disease: a case-control study of occupational and environmental risk factors. American Journal of Industrial Medicine 17:349–355 (1990).
8. Ries L, Eisner M, Kosary C, Hankey B, Miller B, Clegg L, Edwards B, (eds). SEER Cancer Statistics Review, 1973–1998. Bethesda, MD:National Cancer Institute, 2001.
9. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer analyses of cohorts of twins from Sweden, Denmark, and Finland [see comments]. New England Journal of Medicine 343:78–85 (2000).
10. Cote TR, Biggar RJ, Rosenberg PS, Devesa SS, Percy C, Yellin FJ, Lemp G, Hardy C, Geodert JJ, Blattner WA. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. International Journal of Cancer 73:645–50 (1997).
11. Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Research 52:5485s–5488s (1992).
12. Dalager NA, Kang HK, Burt VL, Weatherbee L. Non-Hodgkin's lymphoma among Vietnam veterans. Journal of Occupational Medicine 33:774–9 (1991).
13. O'Brien TR, Decoufle P, Boyle CA. Non-Hodgkin's lymphoma in a cohort of Vietnam veterans. American Journal of Public Health 81:758–60 (1991).
14. Pearce N, Bethwaite P. Increasing incidence of non-Hodgkin's lymphoma: occupational and environmental factors. Cancer Research 52:5496s–5500s (1992).
15. IARC. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. Lyon, France: International Agency for Research on Cancer, 1997.
16. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer. Cancer Causes and Control 8:420–43 (1997).
17. World Health Organization. Diabetes Mellitus Fact Sheet. http://www.who.int/inf-fs/en/fact138.html [cited April 22, 2003]
18. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults. Diabetes Care 23:1556–1562 (2000).
19. Horikawa Y, Oda N, Cox NH, Li X, Orho-Melander M, Hara M, et. al. Genetic variation in the gene encoding calpain-10 is associated with Type II diabetes mellitus. Nature Genetics 26:163–175 (2000).
20. Institute of Medicine. Veterans and Agent Orange: Health Effects of Herbicides used in Vietnam. Washington, DC:National Academy Press, 1993.
21. MH Sweeney, RW Horning, DK Wall, MA Fingerhut, and WE Halperin. Prevalence of diabetes and increased fasting serum glucose in workers with long-term exposure to 2,3,7,8-tetrachlorodibenz-p-dioxin. Organohalogen Compounds 10:225–226 (1992).
22. Zober A, Ott MP, Messerer G. Morbidity follow up study of BASF employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident, Occupational and Environmental Medicine 51:479–486 (1994).
23. Ott MP, Zober A, Germann C. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Chemosphere 29:9–11(1994).
24. Henriksen GL, Ketchum NS, Michalek JE, Swaby JA. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 8:252–258 (1997).
25. Lai M, Hsueh Y, Chen C, Shyu M, Chen S, Kuo T, Wu M, Tai T. Ingested inorganic arsenic and prevalence of diabetes mellitus. American Journal of Epidemiology 139:484–492 (1994).
26. Tseng C, Tai T, Chong C, Tseng C, Lai M, Lin BJ, Chiou H, Hsueh Y, Hsu K, Chen C. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: A cohort study in arseniasis-hyperendemic villages in Taiwan. Environmental Health Perspectives 108:847–851 (2000).

27. Tsai I, Wang J, Ko N. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Archives of Environmental Health 54:186–193 (1999).

28. Centers for Disease Control. Environmental Public Health Tracking Program. http://www.cdc.gov/nceh/tracking/default.htm [cited April 22, 2003]

Parkinson's Disease

WHAT IS PARKINSON'S DISEASE?

PARKINSON'S DISEASE (PD) is one of the major neurodegenerative disorders first described by Dr. James Parkinson in 1817 as "Shaking Palsy" (*1*). Among neurodegenerative disorders, it is second only to senile dementia of the Alzheimer type in prevalence. It is the most common of the akinetic-rigid syndromes, collectively referred to as parkinsonism. PD is characterized by tremor at rest, rigidity, and akinesia or bradykinesia (absence or paucity of movement), and loss of postural reflexes (*1*).

PD has a distinct clinical picture with respect to symptoms, signs, and changes in brain function. Clinical symptoms of PD are usually expressed after age 50, often with a slow and insidious onset. Tremor and slowness or unilateral stiffness are frequent initial complaints. As the disease progresses, other problems may emerge, including personality changes, slowness of thought, sleep disturbance, autonomic dysfunction, Alzheimer's-like dementia, paranoia, psychosis and even hallucinations, and severe depression. The disease is associated with progressive and irreversible damage to the dopaminergic neurons that project from the substantia nigra to the striatum. Lewy bodies are frequently seen in surviving neurons and are the hallmark neuropathological features of the disease.

Other forms of parkinsonism resemble PD in many respects. In some cases, they are due to specific factors, such as drugs and environmental exposures like acute manganese poisoning (2). Drug-induced parkinsonism is defined as follows: 1) symptom onset occurs while on a neuroleptic drug or dopamine-depleting drug treatment; 2) no symptoms occurred before drug treatment; and 3) symptoms significantly resolve or diminish after withdrawal of drug treatment. However, other forms of parkinsonism may be difficult to distinguish from idiopathic PD, particularly early in the course of the disease. These include progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy with autonomic insufficiency and others. The difficulties associated with making an accurate diagnosis are a major problem and source of inaccuracies in retrospective studies and investigations conducted by individuals without specific neurological expertise.

Diagnosis

Clinical definition:

- An adult-onset, slowly progressive, motor disorder combining two or more of the following: rest tremor, slow movements (bradykinesia), limb rigidity, and gait instability.
- Response to levodopa or dopaminergic agonists such as bromocriptine.
- Accepted associated phenomena: depression (early or late), cognitive decline (late), limited autonomic involvement (e.g. constipation) (3).

Pathological criteria:

- Depigmentation of the cells of the substantia nigra due to the loss of dopaminergic neurons.
- Formation of intracytoplasmic eosinophilic inclusions (Lewy bodies), predominantly in the substantia nigra and other pigmented brain-stem nuclei (3).

The clinical diagnosis of PD is complicated by numerous diseases with akinetic-rigid features as mentioned above. The differential diagnosis is very large (4).

Classification

PD is the most common of a set of motor disorders collectively referred to as the akinetic-rigid syndromes, or parkinsonism. These disorders differ from each other by symptoms and pathology.

DESCRIPTIVE EPIDEMIOLOGY

Current status

In the U.S., there is no tracking system for incidence or prevalence of PD on state or national levels. The only information we have is from a few geographic areas where special studies have been conducted. Moreover, these studies have used various case definitions. Some have attempted to

SYMPTOMS OF PARKINSON'S DISEASE

RIGIDITY is an increased tone or stiffness in the muscles. Unless it is temporarily eased by antiparkinsonian medications, rigidity is always present. However, it increases during movement. Rigidity and bradykinesia are responsible for a mask-like expression of the face.

TREMOR is the symptom the public most often identifies with PD, but in fact, up to 25% of patients experience very slight tremor or none at all. When it is present, the tremor may be worse on one side of the body, particularly in early stages of the disease. Besides affecting the limbs, tremor sometimes involves the head, neck, face, and jaw.

BRADYKINESIA means slowness of movement. Bradykinesia is a cardinal feature of PD and the source of the greatest disability.

POOR BALANCE tends to affect people with PD. This is particularly true when they move abruptly, causing a sudden change in the position of their bodies. Some patients experience repeated falls due to poor balance.

WALKING PROBLEMS commonly include a decreased or nonexistent arm swing; short, shuffling steps; difficulty in negotiating turns; and sudden freezing spells (inability to take the next step).

People with PD may also suffer from any of a long list of secondary symptoms. These include **depression, sleep disturbances, dizziness, stooped posture, constipation, dementia**, and **problems with speech, breathing, swallowing, and sexual function**. Again, it is important to note that different patients experience different symptoms.

SOURCE: http://www.parkinsons-foundation.org/aboutdisease/overview/symptoms.html

strictly limit analysis to PD; others have used a more inclusive definition that would encompass all diseases with parkinsonism. It is estimated that PD affects between 1.5 and 2.5% of Americans by the end of the seventh decade (5). Estimates of incidence and prevalence vary by location and by mode of assessment. Bennett looked at rates of parkinsonism in a Massachusetts community and found that the overall prevalence for parkinsonism was 14.9% for people 65 to 74 years of age, 29.5% for those 75 to 84, and 52.4% for those 85 and older (6). In a community in Minnesota, the average annual incidence rate of parkinsonism (per 100,000 person-years) in the age group 50 to 99 years was 114.7; incidence increased from 0.8 in those age 0 to 29 years to 304.8 in those 80 to 99 years of age. The cumulative incidence of parkinsonism was 7.5% up to age 90 years (7). A collaborative study in Europe reported a lower prevalence: 1.8% in persons 65 years of age and older (8). There are no reliable data on the prevalence of PD in the U.S. or worldwide. Based on current research, it is estimated that there are more than 1.5 million people in the U.S. with PD, and approximately 60,000 new cases diagnosed annually (9). While PD can have an early onset, it is most common in the elderly. The average patient is over 50 years old at the onset of the disease; approximately 10% of cases are early onset and affect those under age 40. Approximately 40% are between the ages of 50 to 60, effectively removing them from the work force. Treatment of patients with levodopa improves symptoms and functionality of people with PD, but does not mitigate all symptoms.

Secular trends and geographic variations in the U.S. and worldwide

We know little about trends in incidence and prevalence of PD or parkinsonism over time. Nor do we have information about geographic variation in rates. There have been no international collaborative efforts to describe rates and trends over time. Given its distinctive diagnostic features, it is likely that it was much more rare prior to its first description in 1817 by James Parkinson. Mortality from PD has been studied in the U.S. because PD can be coded as among the causes of death (primary or contributing) on the death certificate. Over the period between 1962 and 1984, there was a marked rise in age-adjusted deaths attributed to PD. This rise occurred mostly among the elderly, and there was a decline in deaths attributed to PD among middle-aged people. This trend was attributed by the authors to "improved treatment, better case ascertainment, and a true rise in the incidence of PD, particularly among the elderly" (*10*). Comparable data are not available for PD incidence and prevalence, on either a national or an international basis. It has been suggested that estimates of incidence most likely reflect a real pattern of PD in a population, because prevalence studies may be biased by disease-associated mortality that is not reflected on death certificates (*11*). As is discussed below, generally (but not always) rural living is a risk factor for PD in the U.S. and elsewhere. Data are hard to come by, but it is thought that prevalence of PD is lower in China, Japan, and Africa (on the basis of lower prevalence ratios) (*12*); it is unknown whether this difference is due to genetic or environmental differences or is an artifact of medical care and reporting systems.

Demographic factors

PD is a disease of the elderly, with prevalence increasing rapidly from age 50 on. Some studies have found that men are at greater risk; for example, a population-based study in Italy found that men were 1.6 times more likely to have parkinsonism and two times more likely to have PD than women (*13*). Men were also somewhat more likely than women to have both PD and parkinsonism in a community in Minnesota (*14*). A mortality study of

the U.S. population found that men generally had double the risk of death due to PD than did women (*15*). A European collaborative study did not find an increased risk of PD incidence for men (*8*). The U.S. mortality study found that whites had three times the risk of death from PD than nonwhites (*15*), however, it is unclear whether this is due to a genetic difference, differences in exposures, or artifacts due to differences in diagnosis and recording of causes of death on the death certificate.

BURDEN OF DISEASE

Morbidity and mortality

People with PD and parkinsonism have two to five times the mortality rate of nonaffected Americans of the same age (*16*). The risk of mortality may be underestimated since it was found (in the U.K.) that the diagnosis of PD is under reported on death certificates (*17*). Bennett reported that gait disturbance was the symptom most strongly associated with an increased risk of death (*6*). Morgante (2000) reports that the principal causes of death in patients with PD are heart disease, infections of the lungs, and cerebrovascular disease (*18*). Pneumonia was the cause of death most significantly associated with PD compared with controls (*18*). This was also found by Gorell et al. and was attributed by the authors to immobility that occurs at later stages of the disease (*19*). Mortality rates among people with PD seem to have increased over time (*10*). By 2040, Parkinson's may surpass cancer as the second most common cause of death among the elderly (*20*).

Treatment costs

Since we have no reliable data on the prevalence of PD, we also have few data on the associated costs. We could identify no peer-reviewed publications that provide an estimate of costs associated with PD. Estimates have been developed by the Parkinson's Foundation, and according to testimony before the Senate Committee on Aging, PD is estimated to cost the U.S. an estimated $25 billion per year (*9*). Costs are spread among afflicted families, health and disability benefit providers, Medicare, and Medicaid. The cost of L-dopa and related drugs runs $1,000 to $6,000 per year, per patient. Ongoing care includes visits to neurologists, various physical therapies, and often, treatment for depression. Typical early-stage annual medical cost per patient is $2,000 to $7,000, however, the cost of advanced treatment is much higher. Treatment and hospitalization for falls associated with PD progression can run $40,000 or more per patient. An estimated 38% of PD sufferers do fall; 13% fall more than once a week (*21*). As the disease progresses, substantial disability due to inability to maintain balance, walk, speak, and/or move can require assisted living and nursing home care, which can exceed $100,000 per patient annually (*9*).

Burden on society

There are more than 1.5 million people in the U.S. with PD and approximately 60,000 new cases diagnosed annually (*9*). The annual cost to society in the U.S. has been estimated to be up to $25 billion (*9*). Costs include not only medical care, but also the cost of unemployment; it is estimated that 31% of individuals diagnosed with PD lose employment within a year. On average, the societal and family burden per person with PD, taking into consideration direct and indirect costs, has been estimated at $25,000 (*9*). Since PD victims remain alive but incapacitated for many years, these costs escalate as the disease progresses. Many of the costs are incurred because family members are diverted from the work force by their role as caregivers.

ETIOLOGY

Areas of determinants of health

In assessing potential causal factors for PD, we organized the discussion according to the three areas of determinants of health: biological, environmental, and social (*22*).

The causes of PD have been a subject of debate for decades. The pathogenesis of idiopathic PD is not known, but it is believed to be multifactorial, deriving from environmental factors acting on genetically predisposed individuals as they age. In the 1980s, the medical community began thinking of PD as a neurological disorder that might be caused by chemical exposures, when a group of young people developed Parkinson's-like symptoms after taking an illegal drug (meperidine) contaminated with a chemical byproduct called MPTP (1-methyl-4-phenyl-1,2,3,6-tetradropyridine). MPTP inadvertently was created as a contaminant in an illegally manufactured synthetic opioid that was distributed to recreational IV drug users. Subsequently, similar symptoms were induced in monkeys by dosing them with MPTP. The discovery of MPTP-related parkinsonism led to the realization that a single adverse exposure could start a complex chain of events that leads to regionally specific neurodegeneration (*2*). It is hypothesized that oxidative stress, induced by a variety of factors, including pesticides, may be part of the causal pathway for Idiopathic PD. Post-mortem studies have indicated that there is evidence for oxidative damage and mitochondrial impairment in the pathogenesis of PD (*23*). Mitochondrial dysfunction causes "generation of reactive oxygen species, disregulation of calcium homeostasis and induction of apoptosis, each of which may be important in Parkinson's disease. Thus the mitochondrial dysfunction observed in PD may be responsible for further oxidative damage to cells" (*24*). MPTP is similar in chemical structure to several pesticides and herbicides; this observation has led to investigations of PD and pesticide exposure. Certain pesticides (paraquat, rotenone, and others) have been linked to PD in epidemiological studies (*25,26*). As described below, this association has not been confirmed as causal.

Biological determinants

Biological determinants of health are factors that cannot be manipulated, such as inherited genes, age, and sex. It is important to consider them since biological and environmental determinants can interact in complex ways in PD. A small proportion (10%) of PD is inherited (*3*). Case- control studies have shown a positive association between family history and PD (*27,28*). There are numerous literature reports of families with large numbers of individuals who are affected with PD at an early age. At least three autosomal dominant traits and one autosomal recessive trait have been identified (*29*). The genes involved in the hereditary forms of the disease are not found in most people with PD (*30*). However, it is felt that given the similarity of both pathologic changes and symptoms of hereditary and sporadic PD, similar mechanisms may be involved in both types. In the hereditary form of the disease, the mutation may activate or speed up the cascade of events; in sporadic disease, environmental triggers may be responsible (*5*). "Identifying genes that can cause Parkinson's disease is crucial for understanding the disease process, revealing drug targets," and "improving early diagnosis" (*24*).

Idiopathic PD is sporadic and may involve environmental as well as genetic factors. Numerous twin studies have shown a small role for inherited factors in the general population (*31-34*). Recently a large (20,000) twin study showed a low rate of hereditary factors in the general population (*35*). The study identified 193 twin pairs for which at least one twin had PD. No genetic component was evident for disease beginning after age 50 years. In an accompanying editorial, it was urged that researchers return to the focus on environmental chemicals, especially pesticides, as a cause (*5*).

Age is the most important biological determinant of PD. While the inherited form of the disease often occurs in the third or fourth decade of life, most cases of idiopathic PD begin after age of 50, and PD incidence increases as a function of age (*3*). As is discussed above, gender may be an important factor, with males being at greater risk before the age of 60; however, these findings have been inconsistent and have not controlled for exposure differences.

Environmental determinants

Numerous environmental etiologies of PD have been suggested by research, including rural living; well water consumption; and pesticide, heavy metals, and hydrocarbon exposures. Several lifestyle factors have been evaluated. Evidence from epidemiological, twin, animal, and individual case studies strongly suggest environmental factors. No single exposure has been consistently implicated (*30,36*). It seems likely that a number of agents that increase oxidative stress on cells—certain pesticides, heavy metals, hydrocarbons, dietary fat, and plant toxins—increase the risk for PD. The epidemiological studies selected for review are shown in Table 1.

Rural living and well water

In the last 20 years, numerous lines of evidence have accumulated that suggest that factors associated with farming and rural living play a role in the processes that lead to PD (*27,37,38*). Some of these studies implicate drinking well water (*39,40*), but others have not (*25,38*). Other studies have found little or no association with rural living and PD (*41–43*).

Farming and pesticides

Farming has been associated with PD in a number of studies (*25,37,38*), but not in others (*43,44*). Generally, studies that have assessed past pesticide usage have found significant associations with PD. Data from PD mortality and pesticide exposure in California show an increased PD mortality in California counties using agricultural pesticides on at least 37% of the land area (*45*). In cases where both pesticides and rural living were assessed, pesticides generally are significantly associated, suggesting that this factor may be at least partly responsible for the association with rural living (*25,27,37,38*). Hertzman found an association between PD and overall occupational exposure to pesticides, but not exposures to specific types of pesticides (*26*). There were, however, relatively few pesticide-exposed subjects, and there is a possibility that subjects did not have accurate recall of pesticide use. Moreover, use of pesticides may not serve as a good proxy of exposure.

Herbicides and insecticides show strong relationships with PD in a number of studies. A recent study produced similar results in terms of overall pesticide risk; much but not all of the excess risk was associated with exposures to herbicides and insecticides, but not fungicides (*25*). This study was particularly strong from the standpoint of verifying the diagnosis for PD, but there were relatively few subjects with histories of exposures to pesticides. Exposure history was based solely on recall of subjects, and it was not possible to pinpoint specific pesticides within broad classes. A number of other studies seem to support an association between use of herbicides and PD as well (*26,46–48*). Liou found a strong relationship between PD and pesticide usage, particularly the herbicide paraquat, in Taiwan. There was evidence of a dose- response relationship with time of use of all pesticides and paraquat and increased risk of PD. However, the exposure information came from an open-ended, structured interview and thus might be more subject to recall bias (*38*).

Not only Gorell (*25*) but also Seidler (*46*) found evidence for an association between PD and insecticide exposure history. Seidler found significantly elevated odds ratios (OR) for two classes of insecticides as well, organochlorines and alkylated phosphates/carbamates (*46*). Fleming et al. assayed levels of organochlorine pesticides in the brains of PD autopsy patients and controls (*49*). They found higher levels of the organochlorine insecticide dieldrin in the PD patients' brains. This study was limited by its small size and the fact that a number of pesticides were assayed; one could have been elevated in cases by chance

alone. Overall, there appears to be strong evidence for an association between pesticide exposures and PD. Epidemiology studies point to herbicides and insecticides as a class, and specifically to paraquat and organochlorine pesticides that may be associated with PD.

It should be cautioned that data from retrospective epidemiology studies are prone to misclassification problems, particularly in the case of diseases like Parkinson's, where it may be necessary to obtain history from family members because of dementia in patients (28). Moreover, most studies have not been able to pinpoint the specific pesticide exposures. Broad classes of pesticides, like insecticides and herbicides, have members that exhibit a wide array of toxicities. It is thus necessary to consider biologic mechanisms, toxicology data, and other information in assessing whether a link between pesticides and PD is plausible. Although the precise biologic mechanisms contributing to the risk of PD associated with exposure to herbicides and insecticides are unknown, many pesticides are known to induce oxidative stress by inhibiting mitochondrial oxidative phosphorylation, potentially generating hydroxyl radicals, and depleting levels of reduced glutathione in cells, thereby diminishing the ability to scavenge toxic free radicals (25). Specific pesticides have been identified as risk factors in human or animal studies, most notably rotenone (50), paraquat (37,38,46), organochlorine pesticides (48,49), diethyldithiocarbamates (48), and organophosphate pesticides (27).

Rotenone is a pesticide that is used for insect control in home gardens and agriculture, for louse and tick control on pets, and for invasive fish eradications as part of water body management. It is a natural pesticide derived from plants. A potent inhibitor of the electron transport chain, it easily crosses biological membranes (50). In chronically exposed laboratory rats, it appears to reproduce the neurochemical, pathological, and behavioral features of PD (50).

Paraquat and diquat herbicides are known to deplete dopamine and to produce PD-like symptoms in frogs (51) and cause long-lasting reduction of catecholamines in the midbrain of mice (52). Paraquat is similar in structure to MPTP. Although rarely found to be associated with PD in humans, a recent case control study in Taiwan found a significant relationship between PD and paraquat exposure (38).

A role for organophosphate insecticides has been suggested by case reports in which PD followed organophosphate poisoning (53). It is not clear whether these cases are relevant to lower level exposures to organophosphate insecticides in the environment.

Diethyldithiocarbamate herbicides (a class of carbamate pesticides that do not inhibit acetyl cholinesterase) have been found to enhance the neurotoxicity of MPTP and methamphetamine (54–56). A recent rodent study suggests that a diethyldithiocarbamate pesticide (maneb) in combination with paraquat may cause PD (57).

Metals

Studies that have assessed metals exposure in general have supported the hypothesis that metals exposure is associated with PD. Occupational exposure to a number of metals has been associated with PD (43,58). A community study in Michigan indicated that counties with chemical, iron, copper and pulp/paper industries had higher prevalence of PD (58). Zinc has not been associated with PD (46). This study had a weak ecological design; many later studies provide stronger evidence as described below.

One study (59) showed a strong association between blood and urinary mercury levels and PD, with large and significant adjusted odds ratios of 21.0 and 18.6 for the two highest tertiles of mercury levels compared with the lowest tertile of blood mercury. Blood mercury levels in the population generally reflect body burdens of methylmercury (60). Other studies did not find associations with mercury work exposure history (44,46,61). However, studies that rely on exposure histories rather than blood and urine mercury levels

may have two problems. First, actual exposures may have been different because of inaccuracy of exposure assessment by recall. Second, the form of mercury that would be present in work environments (elemental mercury and inorganic mercury compounds) has different toxicity than methylmercury. Methylmercury is more toxic to the brains of developing infants (*60*) and in adults as well. However, blood mercury levels measure exposures that are more recent, and occupational histories are the only way to quantify exposures in the past that may have changed over time.

A recent population-based case-control study of PD and occupational exposure to iron, copper, manganese, mercury, zinc, and lead came to the following conclusions. More than 20 years exposure to copper and manganese was associated with elevated odds of PD: for copper, OR=2.5 and for manganese OR=10.6. Combinations of lead-copper (OR=5.2), lead-iron (OR=2.8), and iron-copper (OR=3.7) had greater association with PD than any of these metals alone. Gorell concluded that "chronic exposure to these metals is associated with PD, and that they may act alone or together over time to help produce the disease" (*61*). Other studies have not found an association with copper (*46,62*).

For several metals, there is a strong theoretical basis for a causal role in PD. Iron, copper, manganese, and lead are transported across the blood brain barrier. All have shown the potential to cause oxidative stress via generation of free radicals (*63-65*). One of these, manganese, is of particular concern because of the approval of MMT (methylcyclopentadienyl manganese tricarbonyl) as a fuel additive. Methylmercury also crosses the blood brain barrier and is a potent neurotoxicant.

Workers exposed to high levels of manganese develop a neuromotor disorder called manganism, which has symptoms similar to PD (*51,66*). Studies of highly manganese-exposed humans show damage in the striatum and in areas that are post synaptic to substantia nigra efferents (*67–72*). The effects of manganese exposure from MMT in the general population have not been assessed, and use of MMT in the U.S. reportedly is low at this time. Animal studies have produced conflicting results about manganese and central nervous system effects relevant to PD, largely due to differences in species, dosing, and other study design issues. However, studies in primates indicate that manganese can produce a decrease in dopamine content and/or neuronal loss in the globus pallidus (*73–76*). The U.S. Environmental Protection Agency (EPA) in 1994 attempted to delay the introduction of MMT into the U.S. fuel supply pending further toxicology studies. A federal court overturned the EPA decision, and thus, MMT is allowed for use in the U.S. Subsequently, an effort by the government of Canada to ban MMT was overturned using a provision of the North American Free Trade Agreement. Environmental groups have urged the U.S. petroleum industry to refrain from using MMT, pending further tests, but there is no legal bar from its use in the U.S. or elsewhere in the world. PSR took a strong position in opposition to the use of MMT as a fuel additive pending proof of safety (*77*).

Industrial chemicals

For the purpose of this paper, industrial chemicals are defined as chemicals (other than metals) that are used for purposes other than pesticidal and pharmaceutical. In 1989, Tanner reported an association between exposure to industrial chemicals and PD in China (*43*). Case reports and population studies have pointed to hydrocarbon exposure as causative of parkinsonism. (See Table 1) Solvents that have been implicated include: carbon tetrachloride (*78*), fluoralkane solvent mixture with nitromethane (*79*), n-hexane (*80*), petroleum wastes (*81*), and solvent abuse (*82*). A survey of elderly Canadians assessed the odds for subjects reporting PD from a cohort study of reported exposure to 30 different environmental and occupational factors (*83*). For five of these factors, there were significantly ($p<0.05$) elevated ORs for PD: exposure to plastic resins (OR=8.79), epoxy resins (OR=6.94), glues (OR=4.26), paints (OR=3.84), and petroleum products (OR=2.30). Although this

is one of few studies with measures of exposures, it was not designed as a study of PD, and the diagnoses of PD were obtained by history from the subject and/or caretakers, without medical validation. Seidler also found significant associations for history of exposure to solvents at work or home and exposure to glues, paints, or lacquers at work (*46*). Hertzman reported a significant association between solvent exposure history and solvents among males and not females (*26*). Ohlson did not find a relationship with solvent exposure (*44*). Exposure to hydrocarbon solvents has been shown to be a risk factor for earlier onset and greater severity of disease in people with PD (*84*). N-hexane and its principal toxic metabolite (2,5-hexanedione or 2,5-HD) are well known neurotoxins. In rodents, n-hexane and 2,5-HD induce neurochemical deficits similar to those in PD (*85,86*). It is unknown whether a chronic lower level exposure to solvents increases the risks of PD, however, the evidence would support the notion that a number of industrial chemicals contribute to the development of PD.

MPTP

MPTP was a contaminant of an illegally manufactured synthetic opioid (meperidine) that was sold as a recreational IV drug. At least 400 people are known to have self-administered MPTP; several of them went on to develop parkinsonism (*87-89*). The fact that not all users developed parkinsonism could be related to variations in dose, susceptibility, and other factors (such as differential exposures to other PD risk factors). Subsequent to the episode, a metabolite of MPTP, MPP+(1-methyl-4-pyridinium), was found to be a mitochondrial poison that inhibits mitochondrial respiration (*90,91*).

Lifestyle factors

Consumption of coffee and other caffeine-containing foods is generally associated with a modest but significantly decreased risk of PD that does not seem to be related to nutrients in coffee (*92*). Whether this is a causal association or vice versa (perhaps aversion to caffeine being among the first symptoms of PD) is unknown. Caffeine does not improve symptoms of parkinsonism in clinical studies, so it is unlikely that this is a matter of self-medication and obscuring of PD in coffee drinkers (*92*).

A number of studies have supported a small but significant inverse relationship between smoking and PD (*38,93–96*). Some case-control studies have not supported these findings (*27,37,97,98*). Morens, Grandinetti, et al. (1996) looked for evidence that the association was due to earlier mortality by smokers and found that this was not the case (*96*). Different authors have interpreted this inverse association in a number of ways. Some believe that smoking is a confounder for some other protective factor; others believe that nicotine may confer some benefit. Still others have hypothesized that those who are at risk for development of PD have either less effective detoxification enzymes or lower dopamine levels, which makes them less likely to smoke (*99*). In either case, the effect is not strong and would not support arguments in favor of smoking.

Studies that have examined alcohol consumption have generally been negative or have shown an inverse association with PD (*27,37,38,100–105*).

In conclusion, caffeine, smoking, and alcohol consumption are not risk factors for PD. In some studies, they seem to have a protective effect, and it has been suggested that this may be the case on a biochemical basis (*100*). It may be that these are markers for other factors that confer a lower risk of PD (*100*). Others have speculated that early stages of PD may involve changes in olfaction that would decrease enjoyment of consuming these substances.

Diet

Associations between diet and the development of PD have been inconsistent. There is a theoretical concern that diets high in saturated fat might increase oxidative injury to neurons (*106*). In one study, high intake of animal fat was associated with a threefold risk of PD (*107*).

Another dietary concern has to do with the presence of toxins that naturally occur in certain foods. In the French West Indies, consumption of herbal teas or fruit from the *Annonaceae* family was associated with an increased risk of atypical parkinsonism (*108*). On Guam, the Chamorro population has suffered from a neurodegenerative disorder known as the Guam amyotrophic lateral sclerosis-parkinsonism-dementia syndrome, which has been linked to consumption of seeds from the plant *Cyas circinali (109)*.

Injury

There is some limited evidence that head trauma is another risk factor for PD (*28*). This would be consistent with the hypothesis that PD may result from the cumulative impacts of a number of insults to the brain.

Social determinants

Little information is available about social factors in association with PD.

RECOMMENDATIONS FOR FUTURE RESEARCH

Epidemiological investigations would be useful to determine the environmental risk factors for PD. A recent report by the Department of Health and Human Services concluded that a prospective study, which follows people who do not yet have the disease, would help identify the causes of PD (*24*). We agree with this conclusion.

The National Institute for Environmental Health Sciences is encouraging research in the following areas:

- Development of biomarkers of preclinical disease to identify people at risk for selected environmental toxicants and to identify people who would benefit from neuroprotective drugs.
- Epidemiological studies to identify specific agents and/or combinations of chemicals associated with an increased risk of neurodegenerative disorders.
- Development of models of chronic exposure to environmental agents and potentiating chemical interactions leading to neuronal injury.
- Studies using genetically modified animals to identify increased susceptibility to environmentally induced neurodegeneration.
- Studies on the effects of aging and of inflammation on toxicant-induced neurodegeneration.

Overall, these recommendations are sound, although PSR would not support the use of neuroprotective drugs as a means of allowing preventable exposures to known toxicants. There is also the need to specifically recommend that the National Institute for Environmental Health Sciences fund research with a focus on exposures to pesticides and metals and PD. Such studies should consider that exposures very early in life could be relevant, given the pathogenesis of the disease. In addition, to elucidate environmental exposures

that may cause PD, more study of women with PD is warranted. Much of the research has been of occupationally exposed males, and their exposure patterns may be very different than that of females.

In addition, there is a need to create new research capabilities. The National Institute for Environmental Health Sciences has concluded that resources and tools that could promote research on PD include genetic screening technologies, models of PD, biomarkers, neuroimaging, and brain banks and other repositories (*24*). In addition, establishment of a patient registry would be useful for identification of risk factor genes and important for understanding epidemiology, prevalence, and trends.

TRACKING THE DISEASE AND POSTULATED TOXIC EXPOSURES

The data on incidence and prevalence of PD are inconsistent among studies and do not give the ability to examine trends. What is needed is an effort to track cases of PD and parkinsonism. The Centers for Disease Control and Prevention should develop case definitions that are appropriate from the standpoint of surveillance, in being capable of consistently monitoring the general levels and trends of PD in the population, as well as to better understand its distribution in society. Whereas the more reliable etiologic studies have used strict clinical criteria and examinations by neurologists, tracking efforts will rely upon more readily available data like medical records and/or health interviews. It may be necessary to conduct research for the purpose of establishing and validating methods for surveillance of PD and other chronic neurodegenerative disorders. Given the complexity of the diagnosis, most likely, a registry approach for surveillance (similar to the approaches that have been taken for birth defects and cancer) would be more appropriate than a health interview approach (which has been used for asthma and diabetes). In any case, development of surveillance tools for PD should be in the context of surveillance for other major neurologic disorders (most notably Alzheimer's Disease as well as parkinsonism) and chronic diseases in general. Any surveillance program for PD needs to collect information on exposures as well. Important information would include the place of residence (because of the importance of rural living and especially proximity to pesticide applications) and occupation (because of the strong relationship with numerous occupational risk factors.)

Among the exposures that might be related to PD, very few are monitored in the human population by the federal government. These include organophosphate pesticides and certain metals. Exposures that might be related to PD need to be tracked so that the needed research and public health investigations can be carried out. Tracking of exposure to these agents should occur for both the general population and in the occupational setting. Ideally, one would seek information on exposures to a number of herbicides, including chlorphenoxy herbicides and paraquat/diquat; major classes of insecticides, including organochlorines, organophosphates, and carbamates; heavy metals, especially manganese and mercury; and solvents and other components of plastics, plastic resins, paints, and glues. Reporting of pesticide usage, as is currently carried out several states, would also be warranted.

RISK REDUCTION

Given that the causes of PD are largely unknown, it makes sense to take steps to reduce exposures to toxic compounds that may be associated with PD. Such exposures can occur in a number of ways: through occupational activities, in food and water, in air, and via use of products. PSR already supports the phase out of the "dirty dozen" persistent organic pollutants, which include organochlorine pesticides that have been suspected to be associated with PD. In the future, it is expected that the United Nations Environment Program will begin to address the problem of mercury on a global basis. Although the evidence for association with PD is not strong (being

based on only one study), it nonetheless adds weight to the strong argument for global phase out of many uses and emissions of mercury to the environment (*110*).

Generally, there is much room for reduction of pesticide exposures to people in rural areas. First, there is a need to support ongoing efforts to generally reduce the use of pesticides and to move toward integrated pest management approaches that emphasize minimum pesticide usage and using less toxic pesticides. Second, an increased level of attention and support needs to be provided for farm workers, who have much less protection than industrial workers, who handle the very same pesticide chemicals. Strong EPA implementation of the Food Quality Protection Act, including assurance that the full health impacts are assessed, would also result in reduction of risks from pesticides. This would be a sensible precautionary step to take even while continuing research to determine whether the associations between pesticides and PD are causal in nature.

Manganese poses a special challenge for PSR and other environmental groups. As mentioned previously, the fuel additive MMT was allowed to enter the market in the U.S. without adequate toxicity testing. When EPA later attempted to remove it pending tests, the courts supported the industry contention that EPA was not allowed to do so under the Clean Air Act. EPA could take action with respect to MMT under another act, the Toxic Substances Control Act, but has not done so. Several key organizations have already has taken a strong position against the use of MMT in gasoline (77). Potentially, the EPA should be petitioned to take this action, but would need to be prepared to follow up with a court hearing. Alternatively, there could be an attempt to educate Congress to amend either the Toxic Substances Control Act or the Clean Air Act to ban MMT pending proof of its safety (which is unlikely, especially considering the worker exposures to gasoline from refinery to pump to automobile.) At this time, given the decision under the North American Free Trade Agreement (and the likelihood of similar decisions under the General Agreement on Tariffs and Trade) MMT truly poses a global concern, especially given that it is marketed as a substitute for lead fuel additives in countries that are still phasing out lead in gasoline.

CONCLUSION

In total, there is strong evidence supporting the notion that PD is caused by environmental exposures. Since PD results from the interaction between normal aging and environmental or genetic risk factors, the incidence of PD is bound to increase with advancing age. Census Bureau population estimates predict that between 1990 and 2040, the elderly population in the U.S. will more than double, from 31.6 to 68.1 million (*20*). With the increasing age of the population and growth of the number of elderly individuals, a substantial increase in PD is inevitable. This changing demographic trend creates a scientific imperative to understand better the causes and means of preventing PD. Many of the critical needs for research, tracking, and risk reduction, if solved for PD, would have widespread benefits for the health of populations.

REFERENCES

1. Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely, and Jones, 1817.
2. Foley P, Riederer P. Influence of neurotoxins and oxidative stress on the onset and progression of Parkinson's disease. Journal of Neurology 247 Suppl 2: II82–94 (2000).
3. Korczyn AD. Parkinson's disease: one disease entity or many? Journal of Neural Transmission Suppl 56:107–11 (1999).
4. Riess O, Kruger R. Parkinson's disease—a multifactorial neurodegenerative disorder. Journal of Neural Transmission Suppl 56:113–25 (1999).
5. Cummings JL. Understanding Parkinson disease. Journal of the American Medical Association 281:376–8 (1999).
6. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA. Prevalence of parkinsonian signs and associated mortality in a community population of older people. New England Journal of Medicine 334:71–6 (1996).
7. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. Neurology 52: 1214–20 (1999).
8. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, et al. Prevalence of Parkinson's disease in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54:S21–3 (2000).
9. Scheife RT, Schumock GT, Burstein A, Gottwald MD, Luer MS. Impact of Parkinson's disease and its pharmacologic treatment on quality of life and economic outcomes. American Journal of Health-System Pharmacy 57:953–62 (2000).
10. Lilienfeld DE, Chan E, Ehland J, Godbold J, Landrigan PJ, Marsh G, Perl DP. Two decades of increasing mortality from Parkinson's disease among the US elderly. Archives of Neurology 47:731–4 (1990).
11. Tanner CM, Aston DA. Epidemiology of Parkinson's disease and akinetic syndromes. Current Opinion in Neurology 13:427–30 (2000).
12. Zhang ZX, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. Neuroepidemiology 12:195–208 (1993).
13. Baldereschi M, Di Carlo A, Rocca WA, Vanni P, Maggi S, Perissinotto E, et al. Parkinson's disease and parkinsonism in a longitudinal study: two-fold higher incidence in men. ILSA Working Group. Italian Longitudinal Study on Aging. Neurology 55:1358–63 (2000).
14. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Influence of strict, intermediate, and broad diagnostic criteria on the age- and sex-specific incidence of Parkinson's disease. Movement Disorders 15:819–25 (2000).
15. Lilienfeld DE, Sekkor D, Simpson S, Perl DP, Ehland J, Marsh G, et al. Parkinsonism death rates by race, sex and geography: a 1980s update. Neuroepidemiology 9: 243–7 (1990).
16. Louis ED, Marder K, Cote L, Tang M, Mayeux R. Mortality from Parkinson disease. Archives of Neurology 54:260–4 (1997).
17. Phillips NJ, Reay J, Martyn CN. Validity of mortality data for Parkinson's disease. Journal of Epidemiology and Community Health 53:587–8 (1999).
18. Morgante L, Salemi G, Meneghini F, Di Rosa AE, Epifanio A, Grigoletto F, et al. Parkinson disease survival: a population-based study. Archives of Neurology 57:507–12 (2000).
19. Gorell JM, Johnson CC, Rybicki BA. Parkinson's disease and its comorbid disorders: an analysis of Michigan mortality data, 1970 to 1990. Neurology 44:1865–8 (1994).
20. Lilienfeld DE, Perl DP. Projected neurodegenerative disease mortality in the United States, 1990–2040. Neuroepidemiology 12:219-28 (1993).
21. Koller W, O'Hara R, Weiner W, Lang A, Nutt J, Agid Y, et al. Relationship of aging to Parkinson's disease. Advances in Neurology 45:317–21 (1987).
22. Blum HL. From a concept of health to a national health policy. American Journal of Health Planning 1:3–22 (1976).
23. Dexter DT, Carter CJ, Wells FR, Javoy-Agid F, Agid Y, Lees A, et al. Basal lipid peroxidation in substantia nigra is increased in Parkinson's disease. Journal of Neurochemistry 52:381–9 (1989).
24. Kirschstein R. Parkinson's disease research agenda. Bethesda: Department of Health and Human Services. National Institutes of Health, 2000.
25. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 50:1346–50 (1998).
26. Hertzman C, Wiens M, Snow B, Kelly S, Calne D. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Movement Disorders 9:69–75 (1994).
27. Menegon A, Board PG, Blackburn AC, Mellick GD, Le Couteur DG. Parkinson's disease, pesticides, and glutathione transferase polymorphisms. Lancet 352: 1344–6 (1998).

28. Semchuk KM, Love EJ. Effects of agricultural work and other proxy-derived case-control data on Parkinson's disease risk estimates. American Journal of Epidemiology 141:747-54 (1995).
29. Riess O, Kuhn W, Kruger R. Genetic influence on the development of Parkinson's disease. Journal of Neurology 247 Suppl 2:II69–74 (2000).
30. Checkoway H, Nelson LM. Epidemiologic approaches to the study of Parkinson's disease etiology. Epidemiology 10:327–36 (1999).
31. Vieregge P, Schiffke KA, Friedrich HJ, Muller B, Ludin HP. Parkinson's disease in twins. Neurology 42:1453–61 (1992).
32. Ward CD, Duvoisin RC, Ince SE, Nutt JD, Eldridge R, Calne DB. Parkinson's disease in 65 pairs of twins and in a set of quadruplets. Neurology 33:815–24 (1983).
33. Piccini P, Burn DJ, Ceravolo R, Maraganore D, Brooks DJ. The role of inheritance in sporadic Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. Annals of Neurology 45:577–82 (1999).
34. Marttila RJ, Kaprio J, Koskenvuo M, Rinne UK. Parkinson's disease in a nationwide twin cohort. Neurology 38:1217–9 (1988).
35. Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. Parkinson disease in twins: an etiologic study. Journal of the American Medical Association 281:341–6 (1999).
36. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. Neurology Clinic 14:317–35 (1996).
37. Ho SC, Woo J, Lee CM. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology 39:1314–8 (1989).
38. Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, et al. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology 48:1583–8 (1997).
39. Rajput AH, Uitti RJ, Stern W, Laverty W. Early onset Parkinson's disease in Saskatchewan— environmental considerations for etiology. Canadian Journal of Neurological Science 13:312-6 (1986).
40. Wong GF, Gray CS, Hassanein RS, Koller WC. Environmental risk factors in siblings with Parkinson's disease. Archives of Neurology 48:287–9 (1991).
41. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to rural environmental factors: a population based case-control study. Canadian Journal of Neurological Science 18:279–86 (1991).
42. Stern M, Dulaney E, Gruber SB, Golbe L, Bergen M, Hurtig H, et al. The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. Archives of Neurology 48:903–7 (1991).
43. Tanner CM, Chen B, Wang W, Peng M, Liu Z, Liang X, et al. Environmental factors and Parkinson's disease: a case-control study in China. Neurology 39:660–4 (1989).
44. Ohlson CG, Hogstedt C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury—a case-referent study. Scandanavian Journal of Work, Environment and Health 7:252-6 (1981).
45. Ritz B, Yu F. Parkinson's disease mortality and pesticide exposure in California 1984–1994. International Journal of Epidemiology 29:323–9 (2000).
46. Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, et al. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology 46: 1275–84 (1996).
47. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 42:1328–35 (1992).
48. Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. Neurology 43:1173–80 (1993).
49. Fleming L, Mann JB, Bean J, Briggle T, Sanchez-Ramos JR. Parkinson's disease and brain levels of organochlorine pesticides. Annals of Neurology 36: 100–3 (1994).
50. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nature Neuroscience 3:1301–6 (2000).
51. Barbeau A, Dallaire L, Buu NT, Poirier J, Rucinska E. Comparative behavioral, biochemical and pigmentary effects of MPTP, MPP+ and paraquat in Rana pipiens. Life Sciences 37:1529–38 (1985).
52. Endo A, Hara S, Kano S, Kuriiwa F. Effects of a paraquat-containing herbicide, Gramoxon, on the central monamines and acetylcholine in mice. Research Communications in Psychology and Psychiatry Behavior 13:261–70 (1988).
53. Bhatt MH, Elias MA, Mankodi AK. Acute and reversible parkinsonism due to organophosphate pesticide intoxication: five cases. Neurology 52:1467–71 (1999).
54. Bocchetta A, Corsini GU. Parkinson's disease and pesticides. Lancet 2:1163 (1986).
55. Corsini GU, Pintus S, Chiueh CC, Weiss JF, Kopin IJ. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in mice is enhanced by pretreatment with diethyldithiocarbamate. European Journal of Pharmacology 119:127–8 (1985).

56. Irwin I, Di Monte D, Thiruchelvam M, Verma M, Karich A, Putagnari G, et al. Diethydithiocarbamate (DDC): A promoter of dopominergic toxicity. Fundamental and Applied Toxicology 30:263–4 (1996).
57. Thiruchelvam M, Richfield EK, Baggs RB, Tank AW, Cory-Slechta DA. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. Journal of Neuroscience 20:9207–14 (2000).
58. Rybicki BA, Johnson CC, Uman J, Gorell JM. Parkinson's disease mortality and the industrial use of heavy metals in Michigan. Movement Disorders 8: 87–92 (1993).
59. Ngim CH, Devathasan G. Epidemiologic study on the association between body burden mercury level and idiopathic Parkinson's disease. Neuroepidemiology 8: 128–41 (1989).
60. Clarkson TW. Mercury: major issues in environmental health. Environmental Health Perspectives 100:31–8 (1993).
61. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology 48:650–8 (1997).
62. Wechsler LS, Checkoway H, Franklin GM, Costa LG. A pilot study of occupational and environmental risk factors for Parkinson's disease. Neurotoxicology 12: 387–92 (1991).
63. Goldstein S, Czapski G. The role and mechanism of metal ions and their complexes in enhancing damage in biological systems or in protecting these systems from the toxicity of O_2. Journal of Free Radicals in Biology and Medicine 2:3–11 (1986).
64. Gerlach M, Ben-Shachar D, Riederer P, Youdim MB. Altered brain metabolism of iron as a cause of neurodegenerative diseases? Journal of Neurochemistry 63:793–807 (1994).
65. Kawanishi S. Role of active oxygen species in metal-induced DNA damage. In: Handbook of Experimental Pharmacology, vol 115 (Goyer RC, MG, ed) [au: is there a name missing here?]. Berlin:Springer-Verlag, 1995;349–371.
66. McMillan DE. A brief history of the neurobehavioral toxicity of manganese: some unanswered questions. Neurotoxicology 20:499–507 (1999).
67. Butterworth RF, Spahr L, Fontaine S, Layrargues GP. Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metabolic Brain Disorders 10: 259–67 (1995).
68. Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganism and idiopathic parkinsonism: similarities and differences. Neurology 44:1583–6 (1994).
69. Lang AE, Lozano AM. Parkinson's disease. First of two parts. New England Journal of Medicine 339:1044–53 (1998).
70. Shinotoh H, Snow BJ, Chu NS, Huang CC, Lu CS, Lee C, et al. Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: a positron emission tomography study. Neurology 48:1053–6 (1997).
71. Wolters EC, Huang CC, Clark C, Peppard RF, Okada J, Chu NS, et al. Positron emission tomography in manganese intoxication. Annals of Neurology 26:647–51 (1989).
72. Yamada M, Ohno S, Okayasu I, Okeda R, Hatakeyama S, Watanabe H, Ushio K, Tsukagoshi H. Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain. Acta Neuropathology 70:273–8 (1986).
73. Bird ED, Anton AH, Bullock B. The effect of manganese inhalation on basal ganglia dopamine concentrations in rhesus monkey. Neurotoxicology 5: 59–65 (1984).
74. Enan E, Liu PC, Matsumura F. 2,3,7,8-Tetrachlorodibenzo-p-dioxin causes reduction of glucose transporting activities in the plasma membranes of adipose tissue and pancreas from the guinea pig. The Journal of Biological Chemistry 267:19785–91 (1992).
75. Eriksson H, Magiste K, Plantin LO, Fonnum F, Hedstrom KG, Theodorsson-Norheim E, et al. Effects of manganese oxide on monkeys as revealed by a combined neurochemical, histological and neurophysiological evaluation. Archives of Toxicology 61:46–52 (1987).
76. Olanow CW, Good PF, Shinotoh H, Hewitt KA, Vingerhoets F, Snow BJ, et al. Manganese intoxication in the rhesus monkey: a clinical, imaging, pathologic, and biochemical study. Neurology 46:492–8 (1996).
77. Frumkin H, Solomon G. Manganese in the U.S. gasoline supply. American Journal of Industrial Medicine 31:107–15 (1997).
78. Melamed E, Lavy S. Parkinsonism associated with chronic inhalation of carbon tetrachloride. Lancet 1: 1015 (1977).
79. Sandyk R, Gillman MA. Motor dysfunction following chronic exposure to a fluoroalkane solvent mixture containing nitromethane. European Neurology 23: 479–81 (1984).
80. Pezzoli G, Barbieri S, Ferrante C, Zecchinelli A, Foa V. Parkinsonism due to n-hexane exposure. Lancet 2:874 (1989).
81. Tetrud JW, Langston JW, Irwin I, Snow B. Parkinsonism caused by petroleum waste ingestion. Neurology 44: 1051–4 (1994).

82. Uitti RJ, Snow BJ, Shinotoh H, Vingerhoets FJ, Hayward M, Hashimoto S, et al. Parkinsonism induced by solvent abuse. Annals of Neurology 35:616–9 (1994).
83. Chaturvedi S, Ostbye T, Stoessl AJ, Merskey H, Hachinski V. Environmental exposures in elderly Canadians with Parkinson's disease. Canadian Journal of Neurological Science 22:232–4 (1995).
84. Pezzoli G, Canesi M, Antonini A, Righini A, Perbellini L, Barichella M, et al. Hydrocarbon exposure and Parkinson's disease. Neurology 55:667–73 (2000).
85. Pezzoli G, Ricciardi S, Masotto C, Mariani CB, Carenzi A. n-hexane induces parkinsonism in rodents. Brain Research 531:355–7 (1990).
86. Tuckwell DS, Laszlo L, Mayer RJ. 2,5-Hexanedione-induced intermediate filament aggregates contain ubiquitin-protein conjugate immunoreactivity and resemble Rosenthal fibres. Neuropathology and Applied Neurobiology 18:593–609 (1992).
87. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science 219:979–80 (1983).
88. Ballard PA, Tetrud JW, Langston JW. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): seven cases. Neurology 35: 949–56 (1985).
89. Burns RS, LeWitt PA, Ebert MH, Pakkenberg H, Kopin IJ. The clinical syndrome of striatal dopamine deficiency. Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). New England Journal of Medicine 312:1418–21 (1985).
90. Nicklas WJ, Vyas I, Heikkila RE. Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4- phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl- 1,2,5,6-tetrahydropyridine. Life Sciences 36:2503–8 (1985).
91. Tipton KF, Singer TP. Advances in our understanding of the mechanisms of the neurotoxicity of MPTP and related compounds. Journal of Neurochemistry 61: 1191–206 (1993).
92. Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, et al. Association of coffee and caffeine intake with the risk of Parkinson disease. Journal of the American Medical Association 283:2674–9 (2000).
93. De Michele G, Filla A, Volpe G, De Marco V, Gogliettino A, Ambrosio G, et al. Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Movement Disorders 11: 17–23 (1996).
94. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. British Medical Journal 309: 901–11 (1994).
95. Morens DM, Grandinetti A, Reed D, White LR, Ross GW. Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? Neurology 45:1041–51 (1995).
96. Morens DM, Grandinetti A, Davis JW, Ross GW, White LR, Reed D. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic Parkinson disease. American Journal of Epidemiology 144:400–4 (1996).
97. Mayeux R, Tang MX, Marder K, Cote LJ, Stern Y. Smoking and Parkinson's disease. Movement Disorders 9:207–12 (1994).
98. Wang WZ, Fang XH, Cheng XM, Jiang DH, Lin ZJ. A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China. Neuroepidemiology 12:209–18 (1993).
99. Hellenbrand W, Seidler A, Robra BP, Vieregge P, Oertel WH, Joerg J, et al. Smoking and Parkinson's disease: a case-control study in Germany. International Journal of Epidemiology 26:328–39 (1997).
100. Benedetti MD, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. Neurology 55:1350–8 (2000).
101. Fall PA, Fredrikson M, Axelson O, Granerus AK. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Movement Disorders 14:28–37 (1999).
102. Godwin-Austen RB, Lee PN, Marmot MG, Stern GM. Smoking and Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry 45:577–81 (1982).
103. Grandinetti A, Morens DM, Reed D, MacEachern D. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. American Journal of Epidemiology 139:1129–38 (1994).
104. Haack DG, Baumann RJ, McKean HE, Jameson HD, Turbek JA. Nicotine exposure and Parkinson disease. American Journal of Epidemiology 114:191–200 (1981).
105. Nelson L, Van Den Eeden S, Tanner C. Association of alcohol and tobacco consumption with Parkinson's disease: a population-based study. Neurology 53:A538–A539 (1995).
106. Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. Annals of Neurology 39:89–94 (1996).

107. Anderson C, Checkoway H, Franklin GM, Beresford S, Smith-Weller T, Swanson PD. Dietary factors in Parkinson's disease: the role of food groups and specific foods. Movement Disorders 14:21–7 (1999).

108. Caparros-Lefebvre D, Elbaz A. Possible relation of atypical parkinsonism in the French West Indies with consumption of tropical plants: a case-control study. Caribbean Parkinsonism Study Group. Lancet 354: 281–6 (1999).

109. Spencer PS, Nunn PB, Hugon J, Ludolph AC, Ross SM, Roy DN, et al. Guam amyotrophic lateral sclerosis-parkinsonism-dementia linked to a plant excitant neurotoxin. Science 237:51–22 (1987).

110. Goldman LR, Shannon MW. Technical report: mercury in the environment: implications for pediatricians. Pediatrics 108:197–205 (2001).

This is a publication of Physicians for Social Responsibility. For reprint information or for additional copies, please contact: Physicians for Social Responsibility, 1875 Connecticut Ave., NW, Suite 1012, Washington, DC 20009; Phone: 202-667-4260; Fax: 202-667-4201; Homepage: http://www.psr.org, www.envirohealthaction.org

PHYSICIANS FOR SOCIAL RESPONSIBILITY
Robert K. Musil, Ph.D., M.P.H., Executive Director and CEO
Susan West Marmagas, M.P.H., Director, Environment and Health Program
Karen L. Perry, M.P.A, Deputy Director, Environment and Health Program
Michelle Chuk, M.P.H., Public Health Program Director, Environment and Health Program

PRIMARY AUTHORS
Lynn Goldman, M.D., M.P.H., Professor, Environmental Health Science, Johns Hopkins University Bloomberg School of Public Health
Shayna Cunningham, M.H.S. Ph.D.(c), Johns Hopkins University School of Public Health
Luca Bucchini, Ph.D., Johns Hopkins University School of Public Health (Author of Introduction)

CONTRIBUTING AUTHORS
Michelle Chuk, M.P.H., Public Health Program Director, Environment and Health Program
Robin Clarke, Intern, Environment and Health Program
Lisa Jacobson, Intern, Environment and Health Program

MEDICAL AND SCIENTIFIC ADVISORS
Robert G. Feldman, M.D., Professor Emeritus, Department of Neurology and Professor of Pharmacology, Boston University School of Medicine; Professor of Environmental Health, Boston University School of Public Health
Howard Frumkin, M.D., Dr. P.H., Professor and Chair, Environmental and Occupational Health, Rollins School of Public Health, Emory University
Thomas Guilarte, Ph.D., Professor, Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health
Alan Lockwood, M.D., Professor of Neurology and Nuclear Medicine, University at Buffalo

May 2003

PHYSICIANS FOR SOCIAL RESPONSIBILITY
1875 Connecticut Avenue, NW, Suite 1012
Washington, DC 20009

1985 NOBEL PEACE PRIZE

US Affiliate of International Physicians for the Prevention of Nuclear War