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Environmental Risk Factors for Parkinson's Disease

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INTRODUCTION

The vast majority of Parkinson's disease (PD) is etiologically multifactorial, with important contributions from both genetic and environmental determinants. Very few cases of PD can be attributed to single gene disorders (1–5). For PD without single gene Mendelian inheritance, relative risks as high as 14 for first-degree relatives of PD cases have been reported (6), but most studies have found more modest risks, on the order of two- to fourfold (7–10). Tanner et al. (11), in a study of a World War II cohort of monozygotic (MZ) and dizygotic (DZ) twins, with at least one of each pair with PD, found no difference in concordance between MZ and DZ twins diagnosed after the age of 50, when most PD occurs (12–15). While these studies suggest that, on a population level, a major genetic contribution to

PD is unlikely, there is a potentially important role for genetic susceptibility to environmental exposures in both sporadic and familial cases (16–18). Therefore, to increase our understanding of the etiology of PD, future analytical PD epidemiological studies must focus on better defining environmental factors that confer risk or protection, identifying genetic factors that modify risk, and determining the roles played by these factors, alone and interactively. In this chapter, we will review research on environmental factors implicated in PD, initially with a focus on methodology, and thereafter with a concentration on selected analytical epidemiological studies.

ENVIRONMENTAL FACTORS ASSOCIATED WITH PD

Retrospective Assessment of Occupational Risks: The Paradigm of Metal Exposures

Determining the most suitable methods to assess past occupational exposures, which is essential in all retrospective case-control studies, is an important subject of ongoing research. It is inherently more difficult to evaluate exposures under these circumstances than in a prospective cohort, for which current occupational environments can be assessed and exposures determined directly. The use of expert review of job histories for retrospectively assessing occupationally related exposures has long been used in the field of cancer epidemiology (19,20). Taking a cue from that experience, our group was the first to apply such methodology to the field of neuroepidemiology (21–24).

In our study of occupational metal exposures and PD (21), a case-blind industrial hygienist assessed metal exposure in all jobs held for 6 months or longer for all subjects throughout adult life. The hygienist considered subjects' tasks involving specific metals, the tools used, the ambient environment, and measures taken for protection from exposure. In a parallel methodological study (22), we compared assessment by self-report, job titles linked to a job exposure matrix (JEM) (25), and assignment by an industrial hygienist. Data derived from self-report and a JEM separately, as well as information from both methods, were not comparable with industrial hygienist assessment. Taking industrial hygienist exposure assessment as the gold standard, we showed that the method of exposure assessment can have a large influence on the association between a disease outcome and exposure. This was further highlighted in a recent reanalysis (J. M. Gorell et al., in preparation) of our original published data (21). We found that, if we had relied on self-report alone instead of an industrial hygienist's case-blind rating of factors associated with exposure, no

significant results would have emerged. Moreover, had we only assessed ever-exposure to metals instead of also evaluating chronic exposure, no significant findings would have been seen. As opposed to self-report, our expert assessment methodology was very amenable to evaluating exposure duration, which, in hindsight, was critical in teasing apart the PD-occupational metal exposure association.

Despite what appears to be an advantage of expert assessment of metal exposures, similarly trained industrial hygienists can reach different conclusions in reviews of the same data set (19,23,26,27). This issue of subjectivity suggests that it is difficult to reliably transform an occupational history into an estimate of exposure, and implies that it may be desirable to combine such assessments with a more objective measure of chronic exposure to metals, if this is available. Wherever possible, it would seem desirable to compare such data with exposure measurements (e.g., blood and/or bone lead or other metal determinations, or assessments of ambient air, water or soil concentration of toxicants, as appropriate) taken at the time of presumed risk.

As an extension of our experience with retrospective metal exposure assessment, we suggest that employing industrial hygienists or occupational toxicologists with expertise in other fields (e.g., agricultural chemical, soil, water and farming lifestyle exposures; mixing, loading, applying or otherwise using pesticides, metals or organic solvents, etc.) will improve upon self-report or the use of a JEM. Resulting exposure assignments should be compared with specific records of relevant exposures at the time at risk, if available. Finally, it may be helpful to construct a cumulative lifetime exposure history to a toxicant of interest in order to best assess its dose effect on disease outcome.

Occupational Metal Exposure

Metals may be involved in the etiology and/or pathogenesis of PD. For example, manganese (28), copper (29), lead (28), and iron (30) have been shown to promote oxidative stress by free radical generation, an ongoing process in the PD substantia nigra (SN) (30). Iron (as Fe^{3+} and total levels) has been reported to be elevated in the PD SN (31), but copper has either been reported to be increased (32) or decreased (33,34). Manganese may have a role in catecholamine autoxidation (35), in the formation of neuromelanin (36), and, perhaps, in the production of Lewy bodies (37). Copper(II) can react with ascorbate (38) or levodopa (39) to produce genotoxic free radicals. Lead(II) may be directly genotoxic, as it inhibits DNA polymerase (40), possibly hampering DNA repair. This potential

action of lead (41) may be particularly important in a neurodegenerative disease associated with aging.

The relationship between occupational exposure to specific metals and PD has been examined infrequently in case-control studies with sizable populations (21,42–46). Results in these studies have varied, likely because of differences involving the means of exposure assessment, the duration of exposure, as well as the populations studied.

Occupational Exposure to Selected Metals and PD

Manganese. Semchuk et al. (42), in a population-based case-control study in Calgary, Alberta, reported no increase of PD risk for ever-exposure to manganese, assessed by self-report. Seidler et al. (43), in a case-control study of nine German clinics, reported no significant association of PD with any occupational exposure to manganese, assessed by a JEM. Gorell et al. (21) found a significant association of more than 20 years of occupational exposure to manganese [odds ratio (OR) = 10.61], though caution is needed in the interpretation of the relationship, as it was driven by just three cases and one control subject with chronic manganese exposure. Finally, when considering manganese exposure as a risk factor for PD, it is important not to reject a potential association because of confusion with the severe poisoning seen in manganism, in which there is preferential affection of the globus pallidus rather than the SN, with clinical dystonic parkinsonism produced most often (44,45).

Mercury. Ohlson and Hogstedt (46), in a hospital-based case-control study in Sweden, found no group difference in occupational exposure to mercury, assessed by self-report. Seidler et al. (43) found elevated, but nonsignificant, ORs with respect to neighborhood controls when assessing any occupational contact with mercury. Gorell et al. (21) found no significant association of PD with any occupational exposure to mercury. However, Ngim and Devathasan (47), in a hospital-based case-control study in Singapore, found a significant association between mercury exposure and PD, assessed by self-report. They also found a dose-response relationship when comparing blood mercury levels from the highest tertile (OR = 9.4; 95% CI 2.5–35.9) and middle tertile (OR = 8.5; 95% CI 2.2–33.2) with the lowest tertile of subjects. The lack of consistency in reports regarding an association between mercury exposure and PD weakens the likelihood of its biological significance. However, it is possible that differences in genetic susceptibility among ethnic or racial groups, or different routes of mercury exposure (e.g., ingestion of contaminated foods or medications), may account for the variability in the conclusions of studies thus far.

Iron, Copper, Lead, and Zinc. A potential relationship between occupational exposure to iron, copper, lead, or zinc with PD has been infrequently studied. Seidler et al. (43) did not assess a possible role of iron exposure, but found a slightly elevated, nonsignificant association with any occupational zinc exposure and no relation with copper exposure. However, these authors did find that ever-exposure to lead was associated with PD, though significantly only with reference to one of their two control groups. Gorell et al. (21) reported no association of more than 20 years of occupational zinc exposure with PD, a borderline association with lead alone ($p = 0.059$), and a significant association with more than 20 years of occupational exposure to copper (OR = 2.49; 95% CI 1.06–5.89).

Combinations of Metals. Zayed et al. (48), in a study in southern Quebec, reported that, among 42 cases and 84 controls, assessed by self-report, there was a significant association between PD and occupational exposure to a combination of manganese, iron, and aluminum, particularly for more than 30 years (OR = 13.64; 95% CI 1.52–76.28). However, the magnitude of contribution of individual metals to the risk of PD could not be determined. Semchuk et al. (42) did not find a significant association of aluminum exposure with PD, evaluated by self-report. In the only study thus far to assess occupational exposure to cadmium, nickel or arsenic, Seidler et al. (43) found no association with PD. Finally, Gorell et al. (21) found that greater than 20 years of occupational exposure to combinations of lead-copper (OR = 5.24; 95% CI 1.59–17.21), lead-iron (OR = 2.83; 95% CI 1.07–7.50), and iron-copper (OR = 3.69; 95% CI 1.40–9.71) were associated with PD. These combined metal exposure results showed a greater association with PD than did any metal alone.

To our knowledge, no investigators have assessed potential genetic risk factors as modifiers of occupational metal exposures, and further research is needed. However, we did evaluate risk modification by a history of PD in first- and second-degree relatives of subjects (10). Among participants in the study of Gorell et al. (21) with a PD family history, occupational exposure to copper, lead, or iron increased the risk, albeit nonsignificantly (OR = 3.0; 95% CI 0.7–13.3), but no such trend was found in those without a family history (OR = 1.1; 95% CI 0.7–1.6).

Pesticide Exposure

Certain human and animal models of PD have been produced only by exogenous toxicants, highlighting the potential importance of environmental factors in the etiology of the human disease. For example, parkinsonism has been produced by the intravenous injection of the meperidine analog, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

(49), which is chemically similar to the herbicide paraquat (50). MPTP exposure is associated with nigral neuronal death and mimicry of the clinical symptoms and signs and the neurochemical pathology of PD (49–55). MPTP is converted in the brain into 1-methyl-4-phenylpyridinium [MPP^+] by astrocytic monoamine oxidase B [MAO-B] (54). MPP^+ then enters nigral neurons through the dopamine transporter and is concentrated in mitochondria, where it inhibits Complex I, reduces adenosine triphosphate (ATP) levels, and produces cyto-destructive free radicals (55). Another animal model of PD has recently been produced by rotenone, an insecticide that binds to the same Complex I site as does MPP^+, causing nigral neuronal loss thereby (56) and, perhaps, by other biochemical mechanisms (57). Fleming et al. (58) found a significant association between PD, diagnosed postmortem, and the presence of the organochlorine insecticide dieldrin in these brains, and Corrigan et al. (59) confirmed these findings. Finally, exposure of animals to combinations of agents such as the herbicide paraquat and the fungicide maneb (60) also causes nigral neuronal loss. The latter observation suggests that multiple agents may be required to achieve, or to accelerate, the biochemical processes that produce PD.

We surveyed case-control investigations in which queries about pesticide use extended at least to the class level (i.e., insecticides, herbicides, fungicides, etc.), and were not listed simply as ''pesticides'' or ''pesticides/herbicides.'' All such studies were limited by one or more of the following factors: (1) poor recall of subjects of particular pesticides to which they might have been exposed; for example, both Semchuck et al. (61,42) and Gorell et al. (62) found no better than 40% recall of specific agents, despite the fact that subjects were given extensive lists of potential pesticides from which to choose; (2) assessment by self-report, rather than by case-blind determinations by agricultural industrial hygienists or agronomists; and (3) lack of validation of self-reported exposure histories.

Several investigations have shown an association between PD and pesticide classes such as insecticides or herbicides (42,61–63), though this has not always been found, and only rarely has the association held for specific agents (e.g., paraquat) (64). For example, Semchuk et al. (61), in Alberta, found in univariate analyses of self-reported exposures an association with insecticides (OR = 2.05; 95% CI 1.03–4.07) and a further increase after more than 46 years of contact (OR = 3.50; 95% CI 1.03–11.96). In the case of herbicide exposure, the overall crude OR was 3.06 (95% CI 1.34–7.00), and the association also increased with many years of contact (26–35 years: OR = 4.82; 95% CI 1.51–15.35). Moreover, Semchuk et al. (61) found that occupational herbicide exposure remained significant (OR = 3.06; 95% CI 1.34–7.00) after multiple logistical regression analyses that adjusted for other associated factors. Interestingly, this association held

against other, more general risk factors (i.e., head injury and a family history of PD) in a test of a multifactorial etiological hypothesis (42). In contrast, Hertzman et al. (65), in a population-based study in British Columbia in 1994, found no significant self-reported associations with insecticides, herbicides, or fungicides, as classes, nor did they find associations with more specific subclasses (i.e., chlorphenoxy herbicides, organochlorines, organophosphates, carbamates, borates, or copper salts). Seidler et al. (43), in a nine clinic–based study in Germany, with results assessed by self-report, found no consistent relationship of PD with exposure to insecticides or herbicides, as classes, and associations varied between PD and different control groups for specific agents (i.e., organochlorines, alkylated phosphates, and carbamates). Gorell et al. (62) found significant associations with occupational (not residential) exposure to insecticides (OR = 3.55; 95% CI 1.75–7.18) and herbicides (OR = 4.10; 95% CI 1.37–12.24), but no relationship with fungicide exposure. Finally, a recent investigation of signs of parkinsonism among career orchardists, professional pesticide applicators, and pesticide plant workers in Washington State (66) found an association with long-term pesticide and insecticide use, but no specific pesticides were identified as risk factors. Clearly, further studies that assess exposure to specific agents will be important, as will expert evaluations of such exposures over time.

One study (67) has assessed a potential association of pesticide exposure with polymorphisms of genes that metabolize such agents. These authors, in a study of just 95 PD patients and 95 controls from a variety of university clinic, hospital, and community settings in Australia, found no association between *GST P1* variants and PD. However, when they restricted their analysis to subjects with pesticide exposure (39 cases and 26 controls), a statistically significant ($p = 0.009$) relationship between *GST P1* variants and PD emerged. This work needs confirmation in a larger study.

Farming

The wide variation in the reported association of farming with PD has largely hinged on the definition of farming, whether the duration of farming was studied, and whether farming was examined independently of pesticide exposure. We surveyed case-control studies in which farming was defined by specific areas of work.

Tanner et al. (68), in a study of subjects in neurology clinics in Beijing or Guangzhou, China, found protective, self-reported associations with pig raising (OR = 0.17; $p < 0.001$), wheat growing (OR = 0.4; $p < 0.02$), and chicken raising (OR = 0.53; $p < 0.05$), but no association with corn growing (OR = 0.54; NS), soybean raising (OR = 0.67; NS), fruit growing

(OR = 1.00), rice growing (OR = 1.29; NS), or livestock raising (OR = 0.63; NS). In 1990, Hertzman et al. (69), in a population-based study of self-reported activities among subjects in a mountainous region of British Columbia, Canada, found an age- and sex-adjusted association of orchard work with PD (OR = 4.45; $p = 0.003$), as well as with planer mill work (OR = 3.89; $p < 0.05$). Semchuk et al. (61), in a population-based study in Alberta, Canada, found self-reported ever-farming in the areas of field crop farming, grain farming, market gardening, wood processing, or commercial greenhouse work to be unassociated with PD in overall univariate analyses. However, these authors also found a dose-response relationship with PD for the ages of exposure and duration of farming. That is, with exposure at ages 16–25 (10 years' exposure), ages 16–35 (20 years' exposure), and at ages 16–45 (30 years' exposure), for any form of agricultural work, the OR increased from 1.65 to 2.45 to 3.48. For field crop farming, the OR increased from 1.49 to 2.50 to 3.84; and for grain farming, the OR increased from 1.39 to 2.39 to 4.44. However, after multiple logistical regression, none of these areas of farming was statistically significant ($p < 0.05$), whereas only occupational exposure to herbicides survived these multiple adjustments (OR = 3.06; 95% CI 1.34–7.00). In contrast, Hertzman et al., in 1994 (65), did not find a significant association with PD in their study in a defined horticultural region of British Columbia, whether farming was evaluated overall, or whether animal farming, crop farming, mixed farming, or soft or hard fruit orchard farming were analyzed; this study, then, did not replicate their 1990 results (69) with orchardist activities. Gorell et al. (62) evaluated, as a single category, activities reported as either grain or vegetable farming, fruit or nut farming, field crop farming, diversified crop farming, domestic animal farming, domestic fowl farming and general farming, using codes in the *Dictionary of Occupational Titles* (70). Farming as an occupation after age 18, following adjustment for sex, race, age, and smoking status, was associated with PD (OR = 2.79; 95% CI 1.03–7.55). Moreover, in joint models with occupational exposure to herbicides and fungicides, farming remained significant after adjustment for occupational herbicide exposure, though it was of borderline significance ($p = 0.052$) after adjustment for occupational insecticide exposure. Our results suggest that pesticide exposure could not account for all the risk conferred by farming and that other lifestyle and environmental exposures related to farming need to be considered in future work.

Rural Living

This category of exposure is vague and has been variably defined. It has been difficult to find consistency in results. We reviewed studies in which some attempt at definition was made.

Rajput et al. (71) found a significant ($p = 0.015$) association between PD among 15 cases with onset under age 40 and living in communities in Saskatchewan of less than 140 persons. Tanner et al. (68), in a study in China, defined "rural" as a history of living in a village; so designated, the association with PD was protective (OR = 0.57; $p < 0.05$). In contrast, Koller et al. (72), in a study in Kansas, considered subjects who lived in a town with a population less than 2500 (U.S. Census Bureau criterion) and found a positive association with PD (OR = 1.9; $p = 0.01$). Butterfield et al. (63), working with several clinic and support group populations in Oregon and Washington, defined "rural" as living in a locale with less than 10,000 people at the time of diagnosis, and reported an OR of 2.72 ($p = 0.27$). Gorell et al. (62) defined "rural" as living in a "small town or less populated area" and found no association, nor was there a relationship with living or working on a farm (namely, independent of farming as an occupation).

Well Water Consumption

The study of Tanner et al. (68), in China, found no significant association of well water consumption and PD, and neither did Zayed et al. (48), in Quebec, Semchuck et al. (73) in Alberta, Butterfield et al. (63) in Oregon and Washington, Hertzman et al. (65) in British Columbia, Seidler et al. (43) in Germany, and Gorell et al. (62) in Michigan. In contrast, Koller et al. (72) in Kansas (OR 1.7; $p = 0.03$) and Jimenez-Jimenez et al. (74) in Madrid, Spain ($p < 0.02$), did find a relationship.

Smoking

Morens et al. (75) reviewed 35 separate case-control studies published by others through 1993, and found 34 reporting an inverse relationship with PD and smoking. Typically, the effect was robust, with odds ratios of about 0.5. Since then, Hellenbrand et al. (76), in a case-control study in Germany, found an inverse dose-response relationship relating never-smokers to ex-smokers and current smokers, stratified according to the pack-years smoked prior to diagnosis in cases versus neighborhood or regional controls. Gorell et al. (77) also found an inverse dose-response effect with PD, with those who were heavy, current smokers (>30 pack-years) being most protected (OR = 0.08 vs. never-smokers), and former smokers having an intermediate degree of protection. Nelson et al. (78) also showed an inverse dose-response effect, with a greater decrease with increased duration of smoking or pack-years. In contrast, Benedetti et al. (79), in Olmsted county, Minnesota, found no association of PD with smoking.

To our knowledge, the potential modification of smoking risk by specific genetic factors has not been studied. However, several investigations have used family history as a potential surrogate for genetic risk. For

example, Rybicki et al. (10) found that ever smoking cigarettes was inversely associated with PD in those without a PD family history (OR = 0.6; 95% CI 0.4–0.9), but was positively associated with PD in those with a PD family history (OR = 1.7; 95% CI 0.5–5.9). Elbaz et al. (80), in the Europarkinson Study Group's case-control investigation of the relationship between a family history of PD in first-degree relatives and smoking, found interesting results. That is, among individuals over the age of 75, exposure to both factors gave an OR of 17.6 (95% CI 1.9–160.5), whereas among younger subjects the OR for joint exposure was not significant. Results of these studies (10,80) suggest that one or more genetic or (unmeasured) environmental factors reverse the usual inverse relationship between smoking and PD, though the determination of the time during adult life when such factors act as modifiers will require further research.

Finally, findings concerning smoking among monozygotic (MZ) and dizygotic (DZ) twins in the World War II cohort have been published (81). There was a high within-pair correlation of smoking among MZ twins but not among DZ twins. Analysis of smoking among 33 MZ and 39 DZ twin pairs discordant for PD, in which at least one twin of each pair smoked, revealed that twins without PD had smoked more pack-years than those who had the disease. This effect was more marked among MZ pairs, implying that sharing a greater number of genes, of unspecified identity, magnifies the PD-smoking relationship.

The usual controversy in retrospective case-control studies involving smoking is whether the inverse association with PD that has been found most often is biologically meaningful or an artifact of study design. Potential artifactual explanations might include: (1) selective mortality of smokers who were destined to acquire PD, resulting in fewer smoking PD subjects available to recruit, (2) suppression of PD signs and symptoms by smoking, allowing PD cases to masquerade as controls, (3) a cause-effect bias, in which previous smokers who acquired PD would quit smoking after becoming symptomatic or being diagnosed with the condition, or (4) unmeasured confounding factors (e.g., premorbid personality factors; depletion of nonstriatal brain dopamine; an undiscovered genetic risk factor; consumption of alcohol or coffee; etc.) that may reduce the likelihood of smoking.

Despite such concerns, prospective cohort studies have supported conclusions reached in most case-control investigations regarding smoking and PD. For example, the Honolulu Asia-Aging Study, a prospective cohort investigation since 1965 of 8006 males of Japanese ancestry (82), reported an inverse dose-response relation with PD, depending on the history of pack-years smoked. Morens et al. (83), from the same group, found that age-specific mortality trends for smokers with and without PD was mostly

associated with the illness itself and not with smoking. Recently, Hernan et al. (84) reported analyses of data from the Nurses Health Study (1976–1996) and the Health Professionals Follow-Up Study (1986–1996). These authors found, in women, age-adjusted rate ratios for PD for past smokers versus never-smokers of 0.7 (95% CI 0.5–1.0) and 0.4 (0.2–0.7) for current smokers. In men, age adjusted rate ratios for PD in past smokers versus never-smokers were 0.5 (0.4–0.7) and 0.3 (0.1–0.8) for current smokers. Data from both cohorts revealed an inverse association with time since quitting among former smokers, which was strengthened considering the number of cigarettes smoked by current smokers and considering the number of pack-years smoked.

Possible biological explanations for a protective effect of smoking include: (1) the reduction of MAO B activity in smokers (85), which might slow dopamine catabolism (86) or diminish activation of MPTP-like neurotoxicants (87); (2) catecholamine stimulation by nicotine (88); (3) nicotine-induced production of neurotrophic factors that stimulate dopaminergic neuron survival (89); and (4) nicotine-induced attenuation of the expected dopaminergic cell loss from MPP^+ in mesencephalic neuron cultures (90) and nigral neuronal damage in animal models of parkinsonsim (91–94). Behavioral explanations, such as risk avoidance among persons who may be prone to PD (95), also deserve consideration, though definitive data are lacking. Finally, Ross et al. (96), in a postmortem study of Lewy body counts in SN from PD in the Honolulu Asia-Aging Study, were unable to find a relationship with lifetime smoking histories. However, there appears to be a PD-protective effect in the (indirect) action of a MAO-B G allele (97), which deserves further study.

Caffeine

There is evidence that caffeine is a significant protective factor in PD (79,98–100), inasmuch as its effects appear to be independent after adjustments for smoking are made. In the Honolulu Asia-Aging Study (99), among 102 incident PD cases in a cohort of 8006 Japanese-American men, the age-adjusted incidence of PD declined consistently with increased amounts of coffee intake, from 10.4 per 10,000 person-years in men who drank no coffee to 1.9 per 10,000 person-years in men who drank at least 28 oz./day. Similar trends were seen with total caffeine intake. Ascherio et al. (100) reported data from two prospective cohorts, the Health Professionals Follow-Up Study and the Nurses Health Study, with a total of 47,351 men and 88,565 women. Among men, after adjustment for age and smoking, there was a relative risk of PD of 0.42 for those in the top one fifth of caffeine intake compared with those in the bottom fifth. Similar trends were seen for coffee and tea, considered separately. Among women, the relationship between

caffeine or coffee intake and the risk of PD was U-shaped, with the lowest risk seen with moderate intake, equivalent to 1–3 cups of coffee/day, or the third quintile of caffeine consumption.

The mechanism underlying the action of caffeine in PD is not established, though recent work in animals (101) suggests that caffeine protects against MPTP-parkinsonism by antagonism of brain adenosine A2A receptors.

Alcohol

There is less consistency among reports of the relationship between alcohol intake and PD. Hellenbrand et al. (98) found an inverse association with beer and spirits, but not with wine. Nelson et al. (78) found a significant inverse association of alcohol intake just preceding the diagnosis of PD, as well as a significant inverse dose-response trend relating weekly alcohol consumption to PD risk. However, Gorell et al. (77) reported that both light to moderate and heavy drinkers had an inverse relationship with PD, though neither value was statistically significant, nor was there a dose-response trend between alcohol use and PD risk. In the latter study, alcohol attenuated, but did not abolish, the inverse association of PD with smoking. Clearly, further work will be needed to clarify these differing results.

Diet

Retrospective dietary assessments are notoriously difficult, but may give acceptable levels of misclassification for periods of food consumption up to 10 years before the time when questioning occurs (102). This may often be adequate since dietary habits rarely change significantly over the course of adult life, except during episodes of severe general medical illnesses or depression. However, we should remember that study participants are typically asked to mentally project themselves back in time to a period before the diagnosis was made. Such a procedure may be inaccurate. Moreover, there remains some concern that having the preclinical illness may change dietary habits. If that were to occur, there could be a bias because of systematic misclassification of cases relative to control subjects, whether the nutrient(s) in question was/were or was/were not related to the disease etiology. A final methodological point is that the more recent use of food frequency questionnaires that reduce food or nutritional supplement consumption to nutrients from all sources (103,104) appears to be an advance. However, unless all nutrients are included in assessment software programs, there is a possibility that data derived from food or supplement intake may not disclose relationships involving potentially important, unmeasured factors.

In the field of nutritional epidemiology in PD, there has been a continuing interest in a potential relationship between intake of antioxidant foods and/or supplements and the disease. However, there are inconsistent reports of a relationship between dietary intake of vitamin E–rich foods or vitamin E itself and PD, with most studies finding no association (105–111). Others have found an association of PD with the intake of carotenoids (106,109), as well as with lutein, individually (110). Two studies have had divergent results regarding whether iron intake differs between cases and controls, with Logroscino et al. (106) finding no such relationship and Johnson et al. (110) finding that iron intake was greater among PD patients in the highest quartile of consumption.

There is some suggestion of an elevated PD risk related to diets with high fat content (106,110,111), and with cholesterol, specifically (110). More studies will be needed to clarify this important area of PD epidemiology.

Head Trauma

There have been inconsistent associations of head trauma with PD (112,113). One important methodological issue is the frequent lack of specification of the neurological consequences of the injury. For example, there are reports of parkinsonism with other deficits (e.g., corticospinal, cognitive, and other functional disorders) in some case series. Moreover, much work involves the study of prevalent cases and the use of convenience controls (e.g., spouses, not sex-matched subjects), raising questions about the interpretation of results that have been found. Most authors recognize the potential of recall bias among cases, particularly if the injuries were dramatic, and especially in retrospective case-control series.

Semchuk et al. (42), in a population-based case-control study in Alberta, found head injury, without specification as to its neurological severity, to confer significant risk of PD (OR 3.67; 95% CI 1.86–7.26). Moreover, head injury was retained in a logistical regression model containing a number of unrelated risk factors found in univariate analyses. We also assessed head injury as a potential risk factor for PD (Gorell et al., in preparation), and required that it be associated with loss of consciousness, but found no significant relationship with the disease (OR = 1.07; 95% CI 0.64–1.76). We cannot account for the difference between our research and that of Semchuk et al. (42), but suggest that future work try to grade the severity of injury, particularly whether consciousness was lost and whether there were significant cognitive or motor complications.

Infectious Disease

This category of prior illness has been discussed as a potential risk factor since the occurrence of encephalitis lethargica in the early years of the

twentieth century (114). Because of the circumstantial association of postencephalitic parkinsonism with the influenza pandemic in 1918–1919 (115), attempts to isolate influenza A virus from PD brain (116), or to show a positive case-control difference in serum levels of antibody (117,118), were made, without success. Epidemiological studies by Kessler (119,120), in both hospital- and community-based settings, suggested that PD cases were less likely than matched controls to have had self-reported infections with measles, mumps, German measles and chickenpox, though no associations reached statistical significance. Sasco and Paffenbarger (121), in a case-control study that followed two cohorts of college undergraduates through adult life, found a significant inverse association of PD with measles prior to college entrance (OR = 0.53; 95% CI 0.31–0.93). However, this finding has remained unexplained.

More recently, a temporarily levodopa-responsive movement disorder in mice induced by *Nocardia asteroides* has been described in a group of infected animals with a head tremor (122). These mice had a loss of tyrosine hydroxylase-bearing neurons in the SN and ventral tegmental brain regions, with inclusions that resembled Lewy bodies in some respects. However, there were no specific remnants of nocardial infection, pathologically, at the time of the movement disorder. These intriguing results have not been matched with epidemiological support in the only study done so far (123).

Solvent Exposure

This potentially important area has not been explored very thoroughly. A few studies (43,46) found no overall association with solvent exposure. However, Smargiassi et al. (124) found a relationship with a broad category of ''industrial chemicals'' (OR = 2.13; 95% CI 1.16–3.91), and a more recent study (125), focusing on hydrocarbon exposure, reported a suggestive correlation with PD severity ($r = 0.311$) and an inverse relationship with disease latency ($r = -0.252$). More research involving specific exposures is warranted.

SUMMARY

Several risk and protective environmental factors for PD have been discovered. However, many areas of uncertainty remain, partly because of methodological issues:

1. Many studies have had small samples, often using tertiary medical referral or other convenience subjects and inappropriately chosen controls.
2. The diagnostic accuracy of PD cases has been variable.

3. Most studies have enrolled prevalent rather than incident or near-incident cases, raising the issue of not having identified etiologically relevant risk factors but, rather, factors related to survival with the disease.
4. Exposures have often been defined in broad categories, not at the level of specific agents, and objective, validated measures of exposures have rarely been found or tested.
5. Only a few cohort studies of PD that provide prospective risk factor data have been performed.

More sophistication can be expected in analytical PD epidemiology in the future. Thus far, it has been easier to measure genetic than environmental risk factors in PD. A sense of certainty seems to attach to identification of a potential genetic risk factor because a specific assay has been performed on some tissue sample (e.g., blood, postmortem brain tissue), whereas environmental risk factors have been assessed with variable methodology and sophistication. However, more complexity in both genetic and environmental research can be expected in the future. For example, it is likely that multiple genes helping to determine a phenotypic outcome, and the interactive, quantitative effects of gene activation or suppression, rather than only the presence or absence of polymorphisms of portions of genes, will be studied. In addition, increasingly sophisticated environmental measures of ever more specific risk and protective factors by experts such as industrial hygienists, agronomists, and occupational toxicologists will be done. Advances in molecular biology and further insights into toxicant exposure assessment may provide better biomarkers of chronic exposure. More analytical studies will become population-based (126) and will employ suitable samples of cases and controls. Reviewers of evidence for and against potential risk factors for PD will consider the adequacy of methods used by investigators in studies surveyed for such updates. More studies will investigate both environmental and genetic factors together, rather than simply evaluating one or the other influence on disease etiology. Finally, it will be appreciated that, to study gene-environment interactions properly, populations will need to be large enough to have sufficient statistical power to study environmental and genetic factors present at low frequency (127,128).

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