Parkinson's disease:
A test of the multifactorial etiologic hypothesis

Karen M. Semchuk, PhD; Edgar J. Love, MD, PhD; and Robert G. Lee, MD, FRCP(C)

Article abstract—We studied the relative etiologic importance upon the development of Parkinson's disease (PD) of occupational exposure to herbicides and other compounds, ionizing radiation exposure, family history of PD and essential tremor, smoking, and history of various viral and other medical conditions. We identified patients (n = 130) with neurologist-confirmed idiopathic PD through contacts with Calgary general hospitals, long-term care facilities, neurologists, the Movement Disorder Clinic, and the Parkinson's Society of Southern Alberta, and selected two matched (by sex and age ± 2.5 years) community controls for each case by random digit dialing. We obtained lifetime work, chemical, radiation, medical, and smoking exposure histories and family histories of PD and essential tremor by personal interviews, and analyzed the data using conditional logistic regression for matched sets. After controlling for potential confounding and interaction between the exposure variables, using multivariate statistical methods, having a family history of PD was the strongest predictor of PD risk, followed by head trauma and then occupational herbicide use. Cases and controls did not differ in their previous exposures to smoking or ionizing radiation; family history of essential tremor; work-related contact with aluminum, carbon monoxide, cyanide, manganese, mercury, or mineral oils; or history of arteriosclerosis, chicken pox, encephalitis, hypertension, hypotension, measles, mumps, rubella, or Spanish flu. These results support the hypothesis of a multifactorial etiology for PD, probably involving genetic, environmental, trauma, and possibly other factors.

NEUROLOGY 1993;43:1173-1180

Calne and Langston,[1] in their review on the etiology of idiopathic Parkinson's disease (PD), suggested that the disease is caused by the combined effects of genetic and environmental factors, and age, and that an environmental toxin might be involved. However, there have been few empirical tests of the multifactorial etiology hypothesis, that is, studies that used multivariate statistical methods to examine any potential confounding or interaction between putative genetic, environmental, and other risk factors. Kondo[2] used a multivariate logistic model to evaluate the possible combined effects of risk factors and found a dramatically increased relative risk for PD in those with more than one risk factor. Stern et al[3] used a matched case-control design and multiple logistic regression analysis to estimate the adjusted relative risk for PD associated with rural environmental and pesticide exposures, head injury, and smoking.

Recent case reports,[4-11] exploratory research,[12,13] and five case-control studies[14-18] suggest that farmers and other agricultural workers might have an increased risk of developing PD because of their regular occupational contact with pesticide chemicals. In contrast, four[3,19-21] case-control studies found no significant increase in PD risk associated with agricultural or pesticide exposures. All of the previous case-control studies were hospital based. A number had small sample sizes and, hence, low statistical power. The majority used only univariate (single variable) statistical methods to estimate the crude PD risk associated with each potential risk factor, considered separately; thus, there was no control for confounding or interaction between factors.

We conducted a population-based, case-control study of PD in the city of Calgary, Alberta, Canada, to determine the relative etiologic importance of agricultural occupational exposure to pesticides and various other putative nonagricultural risk factors suggested by the literature.

The results of the preliminary analysis, which considered only agricultural occupational exposures and the rural environmental factors, have been reported in detail elsewhere.[22,23] Briefly, in the preliminary analysis we found no significant

From the Departments of Community Health Sciences (Drs. Semchuk and Love) and Clinical Neurosciences (Dr. Lee), Faculty of Medicine, the University of Calgary, Calgary, AB; and the Centre for Agricultural Medicine, Department of Medicine (Dr. Semchuk), College of Medicine, and the College of Nursing (Dr. Semchuk), University of Saskatchewan, Saskatoon, SK, Canada.

Supported in part by the National Health Research and Development Program, Health and Welfare Canada, through grant no. 6609-1473-53 and through a National Health PhD Fellowship to Dr. Semchuk.

Received June 30, 1992. Accepted for publication in final form October 29, 1992.

Address correspondence and reprint requests to Dr. Karen M. Semchuk, Centre for Agricultural Medicine, University of Saskatchewan, Royal University Hospital, Saskatoon, SK S7N 0X0, Canada.

increase in risk for PD associated with a history of rural living, farm living, or the drinking of well water at any time during the first 45 years of life.[22] The study had a statistical power of 92.9% or greater to detect a twofold increase (or decrease) in PD risk associated with exposure to Alberta rural environmental factors. However, we found a consistent statistically significant increase in risk for PD associated with the occupational use of herbicide (weed-killing) chemicals.[23] The estimated threefold increase in PD risk associated with occupational herbicide use remained statistically significant even after controlling for the type of agricultural work (crop farming, grain farming, market gardening, or wood-processing) and the use of other pesticides (insecticides or fungicides). When we controlled for the occupational use of herbicides and for agricultural work, insecticide use and fungicide use were not significant risk factors for PD. However, the occupational use of herbicides explained only 10% of the cases in the study.

This present paper reports the results of our attempt to test the multifactorial etiology hypothesis for PD using occupational and chemical exposure data, medical and smoking history data, and family history data from the Alberta population-based case-control study of PD.

Methods. The cases were selected from a population-based case register of Calgary residents with neurologist-confirmed idiopathic PD. The detailed methodology for the development of the case register and the eligibility criteria for the cases have been described previously.[22] Only living and nondemented patients with idiopathic PD were recruited into the study by the attending physician. For every case, the diagnosis of idiopathic PD was made by a qualified neurologist. The decision regarding the presence or absence of dementia was a clinical decision of the attendant physician. For each case, two individually matched (by sex and age ± 2.5 years) community controls were selected by random-digit dialing.[22,24] To permit analysis of any bias due to institutionalization, for each of 23 cases who resided in long-term care facilities, one additional matched control was selected from the resident censuses of six long-term care facilities in which the institutionalized cases resided. The details on the response rates for the cases and the two groups of controls have been presented elsewhere.[22] All of the data were obtained by personal interviews by trained experienced interviewers. The interviewer was not blind as to the respondent's case-versus-control status. To minimize interviewer and respondent bias, the underlying hypotheses of the study were not revealed to either the interviewers or the respondents. For both the cases and the controls we obtained detailed lifetime occupational histories, including exposure dates and descriptive information on all work-related contacts with pesticide (herbicide, insecticide, and fungicide) chemicals, and work-related exposures to aluminum, carbon monoxide, cyanide, manganese, mercury, mineral oils, and ionizing radiation. We also recorded detailed information on the medical history (arteriosclerosis, chicken pox, encephalitis, head trauma, hypertension, hypotension, measles, mumps, rubella, and Spanish flu) and family history of PD and essential tremor. A positive family history was recorded if the respondent identified one or more affected first-degree (mother, father, sister, brother), and/or second-degree (grandmother, grandfather, aunt, uncle), and/or third-degree (cousin) blood relatives. Step-relatives were not considered. We also collected basic demographic (date of birth, sex, marital status, educational level, annual family income, ethnic background, and household size) and case profile (age at symptom onset and age at diagnosis) data.

Each completed exposure history was reviewed by one of the authors (K.M.S.) who coded the respondent's past exposures (ie, exposed versus not exposed) to the various exposure factors. With the exception of the family history data, the exposure period of interest was the time prior to disease onset, estimated by the date of diagnosis, in the index case. The various occupational and chemical exposures were coded for the period between the respondent's 16th and 55th birthdays, and for each 10-year age interval between the respondent's 16th and 55th birthdays. We used both univariate (single variable) and multivariate (multiple variable) conditional logistic regression analysis methods[25] to estimate the relative risk (odds ratio) for PD associated with each exposure variable. In the univariate analysis, we estimated the crude, or unadjusted, relative risk for PD separately for each exposure variable. In the multivariate analysis, we estimated the adjusted relative risk for PD, after controlling for potential confounding or interaction effects due to the other exposure variables of interest. All analyses used all of the available data, taking account of the full complement of controls selected for each case. While a missing value for the case or for both controls led to exclusion of the entire matched set, a missing value for one control meant that the number of controls in that set was reduced by one.[25] We examined potential gender differences using stratified analysis techniques and by testing for interaction between each exposure variable and the variable sex. For all statistical tests, we made parallel comparisons between the cases and their matched community controls and between the cases and a mixed control group, comprised of the 23 institutional controls, each of whom was substituted for one of the two original community controls who were individually matched to 23 institutionalized cases, plus the remaining 237 individually matched community controls. Statistical significance was indicated by an alpha level of 0.05 or less. Since none of the results differed depending on which control group was used, and because there was no evidence of a gender effect, only the results for the cases versus the community controls are presented here, for men and women combined.

Results. One hundred thirty cases (75 men and 55 women) and 260 community controls (150 men and 110 women) were studied. The overall response rate was 88.4% for the cases and 75.8% for the controls. The mean age (±1 SD) of the cases was 68.5 ± 11.5 years (range, 36.5 to 90.7) compared with 68.3 ± 11.3 years (range, 34.9 to 92.7) for the controls. The cases and the controls were comparable with respect to educational level, annual family income, and ethnic background. However, a larger proportion of the cases were married and fewer cases lived alone. For the cases, the mean age at symptom onset was 58.0 ± 12.2 years, and the mean age at diagnosis by a neurologist, obtained by medical

Table 1. Crude and adjusted odds ratios for Parkinson's disease (PD) by exposure variable and logistic regression model: Calgary, Canada, 1989

Model	Case/control sets*	Family history of PD	Head trauma	Herbicide use	Family history of essential tremor	Smoking
1	128	5.76# (2.60-12.77)†	—	—	—	—
2	130	—	3.10# (1.67-5.75)	—	—	—
3	127	—	—	3.06§ (1.34-7.00)	—	—
4	125	—	—	—	2.37‡ (1.20-4.69)	—
5	130	—	—	—	—	0.48§ (0.29-0.80)
6	122	5.07# (2.15-11.92)	4.01# (1.93-8.31)	2.83‡ (1.13-7.06)	2.16‡ (1.03-4.57)	0.58 (0.33-1.02)
7	122	5.36# (2.29-12.56)	4.23# (2.04-8.74)	2.93‡ (1.17-7.28)	2.06 (0.98-4.33)	—
8	125	5.49# (2.39-12.60)	3.91# (1.93-7.89)	3.09‡ (1.27-7.56)	—	—

* Each set represents one index case and one or two matched controls.
† Odds ratio (95% confidence limits); results of conditional logistic regression for matched sets (cases and controls were individually matched by sex and age ± 2.5 years).
‡ $p < 0.05$; § $p < 0.01$; # $p < 0.001$.

chart review, was 61.1 ± 12.4 years. The mean duration of disease, based on the age at diagnosis, was 7.8 ± 6.8 years. Eleven (9.1%) cases were diagnosed before age 40. The male and the female cases did not differ significantly in age or in the estimated age at diagnosis. The estimated duration of disease, however, was somewhat longer for the women (9.4 ± 7.9 years) compared with the men (6.7 ± 5.7 years).

Table 1 shows the crude and adjusted PD risk estimates (odds ratios) associated with the five variables found in the univariate conditional logistic regression analysis to be significantly related to PD. In the univariate analysis, we found significantly increased crude PD risk estimates associated with four exposure factors: family history of PD, history of head trauma, history of occupational herbicide use, and family history of essential tremor. A history of smoking resulted in a significantly reduced crude PD risk estimate of 0.48. Although not shown, the cases and controls did not differ in their previous work-related contacts with aluminum, carbon monoxide, cyanide, manganese, mercury, or mineral oils; previous exposure to ionizing radiation; or history of arteriosclerosis, chicken pox, encephalitis, hypertension, hypotension, measles, mumps, rubella, or Spanish flu. In addition, there were no significant interactions between the variable sex and any of the exposure variables examined.

We submitted all five exposure factors that were statistically significant in the univariate analysis to multiple conditional logistic regression analysis, to control for any potential confounding or interaction between the exposure variables. Table 1 summarizes the results of this multivariate analysis, which was conducted in three steps. In the first step, the analysis considered the effects of all five exposure factors simultaneously (see model 6, table 1). When all five exposure variables were included in the conditional logistic regression model, the variable family history of PD was the strongest predictor of PD risk followed by history of head trauma, occupational herbicide use, and familial tremor, which was of borderline statistical significance. After controlling for the effects of the other four exposure factors, a history of smoking, initially a negative predictor, was no longer related to PD risk.

In step 2, we dropped (the statistically nonsignificant variable) smoking history from the logistic model. In the resultant four-variable model, the variables family history of PD, head trauma, and previous occupational herbicide use were each associated with statistically significant PD risk estimates, while the variable familial tremor did not achieve statistical significance (see model 7, table 1).

In step 3, we dropped (the nonsignificant variable) familial tremor from the logistic model. This resulted in a three-variable model comprised of the variables family history of PD, history of head trauma, and previous work-related herbicide use, each of which was associated with a statistically significant PD risk estimate (see model 8, table 1). There were no significant interactions between any of the exposure variables examined in the multivariate analysis or between any of the exposure variables and the variable sex. We estimated the population attributable risk (proportion of cases explained by the potential risk factor) for each of the three significant exposure variables included in the final logistic model. Two exposure factors, family history of PD and history of serious head trauma, each

Table 2. Crude odds ratios for Parkinson's disease (PD) by definition of exposure-variable family history of PD: Calgary, Canada, 1989

Definition of family history of PD	Case/control sets*	Crude odds ratio	95% Confidence limits
First-, second-, or third-degree blood relative with PD	128	5.76‡	2.60, 12.77
First- or second-degree blood relative with PD	128	3.73‡	1.75, 7.95
First-degree blood relative with PD	128	2.36†	1.03, 5.40

* Each set represents one index case and one or two matched controls.
† $p < 0.05$; ‡ $p < 0.001$.

explained 22% of the cases in this study, while having a history of occupational herbicide use explained 10% of the cases.

In all of the conditional logistic models examined in this analysis, family history of PD was consistently the strongest predictor of PD risk, followed by history of serious head trauma, and then previous occupational herbicide use. To further understand the relationships between these significant exposure factors and PD risk, we conducted an exploratory descriptive analysis of each variable and further PD risk estimation using more conservative definitions of the variables family history of PD and head trauma to examine the stability of the results.

Twenty-nine cases (22.7%) and 16 controls (6.3%) gave a positive family history of PD; that is, they reported having one or more first-degree (mother, father, sister, brother), second-degree (grandmother, grandfather, aunt, uncle), or third-degree (cousin) blood relatives who were affected with PD. Twenty-three cases (18.0%) and 16 controls (6.3%) reported having one or more first-degree, second-degree, or both first- and second-degree relatives with PD. Fourteen cases (10.9%) and 13 controls (5.1%) reported having at least one first-degree relative with PD. Table 2 shows that the significant increase in the crude estimate of the PD risk associated with having a family history of PD held, regardless of whether the variable family history of PD included first-, second-, and third-degree relatives; only first- and second-degree relatives; or only first-degree relatives. Controlling for previous head trauma (adjusted odds ratio, 3.67; 95% confidence limits, 1.86, 7.26; $p < 0.001$) and occupational herbicide use (adjusted odds ratio, 3.29; 95% confidence limits, 1.36, 7.95; $p = 0.008$), the adjusted odds ratio for PD associated with having a family history of one or more first-degree or second-degree relatives with PD was 3.61 (95% confidence limits, 1.64, 7.95; $p = 0.001$). The adjusted odds ratio associated with a family history of one or more first-degree relatives with PD was 2.23 (95% confidence limits, 0.94, 5.29; $p = 0.070$), after controlling for previous head trauma (adjusted odds ratio, 3.69; 95% confidence limits, 1.89, 7.19; $p < 0.001$) and occupational herbicide use (adjusted odds ratio, 3.20; 95% confidence limits, 1.34, 7.64; $p = 0.009$).

Twenty-three cases (18.0%) and 15 controls (5.5%) reported having only one PD-affected relative (table 3). Five cases (3.9%) reported having two affected relatives. One case (0.8%) and one control (0.4%) reported having three relatives with PD (table 4). Of the 29 cases who gave a positive family history of PD, 16 cases reported having one or more

Table 3. Cases and controls with a family history of only *one* blood relative with Parkinson's disease (PD): Calgary, Canada, 1989

PD-affected relative	Cases (n = 128)	Controls (n = 255)	Total
First-degree relative	11	12	23
Father*	2	6	8
Mother*	3	4	7
Brother†	3	1	4
Sister†	3	1	4
Second-degree relative	7	3	10
Father's brother*	2	1	3
Father's sister*	1	0	1
Mother's father	0	1	1
Mother's brother*	0	1	1
Mother's sister*	4	0	4
Third-degree relative	5	0	5
Cousin, father's side	1	0	1
Cousin, mother's side	4	0	4
Total	23	15	38

* Based on the family history data, the families of the cases included PD-affected first- and/or second-degree blood relatives in two successive generations.
† Based on the family history data, each case's family included a sibship in which one of the case's siblings was reported to have PD.

Table 4. Respondents with a family history of *more than one* blood relative with Parkinson's disease (PD): Calgary, Canada, 1989

Respondent	Sex	Age at disease onset	Relative 1	Relative 2	Relative 3
Case 1*†	F	37	Father	Father's sister	None
Case 2*†	M	65	Mother	Brother	None
Case 3†	M	68	Brother	Sister	None
Case 4*	M	39	Mother's brother	Father's sister	None
Case 5	M	67	Cousin (male)‡	Cousin (female)‡	None
Case 6*†	F	66	Cousin‡	Mother's sister	Mother's sister
Control 1*†	M	—	Father	Brother	Sister

* Family history of PD-affected first- and/or second-degree blood relatives in two successive generations.
† Family history of a sibship where two or more siblings in the family were reported to have PD.
‡ Cousin on the respondent's mother's side of the family.

affected relatives (first-degree and/or second-degree) in two successive generations of their families, 10 cases reported sibships in which two or more siblings in the family were reported to have PD, and seven cases had families in which both a parent and one or more children were reported to have PD. The family of the control who reported having three relatives with PD included one PD-affected sibship, involving a brother and a sister and three affected first-degree relatives (the control's father, a brother, and a sister) spanning two consecutive generations. None of the cases and only one control reported having a grandparent with PD.

Thirty-one cases (23.8%) and 25 controls (9.7%) reported that they had a serious head injury in the past. Eighteen (58.1%) of the cases and 19 (76.0%) of the controls who reported a previous serious head injury also reported that they had sought medical attention for the head injury. Among those respondents who had sought medical attention for a head injury, there was no significant difference in the reported age at the time of head injury between the cases and the controls (cases: mean age, 19.1 ± 12.9 years; range, 3 to 52 years; controls: mean age, 28.8 ± 16.2 years; range, 8 to 62 years; $t = -1.87$; df 30; $p = 0.075$).

Compared with the initial results (table 1), using the more conservative definition of the variable previous head trauma (history of head injury for which medical attention was sought) resulted in a slight decrease in the crude (crude odds ratio, 1.98; 95% confidence limits, 1.01, 3.86; $p = 0.048$) and adjusted (controlling for family history of PD and occupational herbicide use, adjusted odds ratio, 2.23, 95% confidence limits, 1.08, 4.59; $p = 0.030$) PD risk estimates associated with a history of head trauma. There was also a concomitant decrease in the adjusted PD risk estimates associated with a family history of PD (adjusted odds ratio, 4.93; 95% confidence limits, 2.18, 11.15; $p < 0.001$) and previous occupational herbicide use (adjusted odds ratio, 3.14; 95% confidence limits, 1.31, 7.52; $p = 0.01$). However, regardless of which definition of head trauma was used, in the conditional logistic model that included the three variables history of head injury, family history of PD, and previous occupational herbicide use, each of the three exposure factors resulted in a significantly increased risk for PD, estimated at twofold or greater.

On review of the pesticide exposure histories of the herbicide-exposed cases, only 41% of those exposed could recall the chemical or trade names of the herbicides used.[23] Of these, all but one had used compounds in the chlorophenoxy and thiocarbamate chemical groups, exclusively, and primarily in grain farming. A single case reported having worked with the pyridylium compound paraquat between the ages of 26 and 31 years. He was the only herbicide-exposed case whose onset of symptoms occurred before age 40.

Discussion. In this study, a family history of PD was a very strong positive predictor of PD risk, explaining 22% of the cases and associated with a significant increase in PD risk, with risk estimates ranging from 2.23 to 5.76 (depending on whether only first-degree relatives; only first- and second-degree relatives; or first-, second-, and third-degree relatives were included). There is a documented tendency for PD to occur in families.[26] Although not confirmed, the observed clustering of PD in families may relate to genetic factors[27,28] and to an increased vulnerability to causal environmental factors.[29]

In this study there were 10 sibships where two or more siblings were reported to have PD among the families of the cases and one PD-affected sibship among the families of the controls. Seven of the case families and one control family included both a parent and one or more children with a diagnosis of PD. While the reported PD-affected sibships and parent-child pairs might reflect the involvement of genetic factors, these familial clusters might also be the result of shared environmental exposures or the combination of both genetic and environmental factors, that is, a genetic susceptibility to and subsequent exposure to an environmental neurotoxin. Of particular interest are the 10 case families reported to have one or more second-degree relatives (aunts, uncles) with PD and the seven case families in which two cousins were reported to have PD. Second-degree and third-degree relatives share fewer common genes than do first-degree relatives. However, compared to first-degree relatives, second-degree and third-degree relatives are also less likely to share common environmental exposures. Second-degree relatives do not share the same childhood or adult environments because each relative is of a different generation and time. Cousins generally grow up and live in different homes and geographic locations and, hence, are also less likely than first-degree relatives to share common childhood and adult environments. Thus, if PD is caused solely by environmental factors, one would *not* expect the relative risk for PD to increase if the definition of family history of PD is broadened to include second- and third-degree relatives. Nevertheless, in this study the estimated relative risk for PD associated with having a family history of PD increased markedly from an increased risk of 2.36 associated with having one or more first-degree relatives with PD, to an increased risk of 3.73 associated with a history of one or more PD-affected first- or second-degree relatives, to an increased risk of 5.76 associated with one or more affected first-, second-, or third-degree relatives. These findings suggest that (1) the observed familial clusters of PD cannot be explained entirely by common environmental exposures to a neurotoxic agent, and (2) there is a high likelihood that a significant genetic component is involved in the etiology of PD. However, the existence of a recall bias in the data, ie, biased reporting of a positive family history of PD by the cases,

cannot be ruled out. The extent to which genetic factors were involved in the familial clustering of PD in this study cannot be estimated as we did not record complete genograms for the respondents' families and, hence, cannot estimate the attack rate (proportion of family members affected) for PD in each generation. Another limitation is that the family history data are self-report data and may be subject to recall bias; that is, the cases might have been more inclined to recall having a relative with PD than the controls. Finally, we did not validate (by medical chart review, for example) the diagnosis of PD among family members. It is possible that some family members reported to have PD actually did not have the disease while others with the disease were missed. None of the cases and only one control reported having a grandparent with PD. Given the older age (mean age of approximately 68 years) of the sample studied and the knowledge that most cases of PD are diagnosed after the age of 60, three possible explanations for this observation are that during the respondents' grandparents' lifetime (1) PD did not exist; (2) the disease was less prevalent, as the majority of the population died before reaching the age of 60 and hence before the disease could be diagnosed; or (3) recognition of PD, first described by James Parkinson in 1817, did not exist.

The fact that 78% of the cases in this study did not give a positive family history of PD indicates a high likelihood that other nongenetic factors are also involved in PD. A history of head trauma was also a significant predictor of PD risk, explaining 22% of the cases in the study, and resulting in an estimated relative risk for PD of 3.10 (crude estimate) and 4.23 (adjusted for family history of PD and previous occupational herbicide use) for a history of a serious head injury and 1.98 (crude estimate) and 3.91 (adjusted for family history of PD and previous occupational herbicide use) for a history of a serious head injury for which medical attention had been sought.

Our finding of a significant increase in PD risk associated with a history of head trauma concurs with the results of three previous case-control studies.[3,30,31] In their case-control study of 149 PD patients and 149 age- and sex-matched controls, Stern et al[3] found a significant 2.7-fold increase in PD risk associated with at least one head injury "severe enough to cause vertigo, dizziness, blurred or double vision, seizures or convulsions, transient memory loss, personality changes, or paralysis." Godwin-Austen et al[30] studied 350 case-control pairs (individually matched by age, sex, and attending physician) and found that cases were more likely than controls to have had a head injury causing concussion. In their study of 97 PD patients and 64 spouse controls, Factor and Weiner[31] found that compared with nonparkinsonian control subjects, PD patients reported a significantly higher frequency of both total head trauma and head injury associated with alteration of consciousness. In a previous twin study, Ward et al[32] observed that "head injuries of all severity had occurred about twice as often in the affected as in the unaffected co-twins of the 40 discordant pairs during the period before the onset of PD." However, Tanner et al[33] found no significant difference in the frequency of head trauma between 100 PD patients and 200 age- (±3 years) and sex-matched neurologic controls. In their 39-year follow-up study of 821 Olmsted County residents with head trauma and presumed brain injury, Williams et al[34] estimated the standardized morbidity ratio for PD following head trauma with brain injury at 0.94 (95% confidence limit, 0.38, 1.94) for the seven identified PD cases. Inadequate statistical power, due to small sample size, was a plausible explanation for the nonsignificant results in all three negative studies. Thus, the majority of the case-control studies conducted to date support the hypothesis that head trauma is a risk factor for PD. Although these results might reflect the effect of a recall bias, the consistency of the evidence across studies and between different populations support the conclusion of an etiologic relationship between head trauma and PD.

An interesting finding of this study concerns the relative etiologic importance of occupational herbicide exposure as a risk factor for PD compared with other nonagricultural exposure factors. To our surprise, the results of this analysis parallel the results of our previous analysis[23] in which we only considered agricultural exposure factors. In the current analysis, having a history of occupational herbicide use accounted for approximately 10% of the cases and, consistently, resulted in a significantly increased PD risk of approximately threefold, even after controlling for the effects of the other potential risk factors, including family history of PD and previous head trauma. These data concur with the results of previous case-control studies of PD[14-18] in very different populations and with case reports of chronic central and peripheral nervous system dysfunction in herbicide-exposed agricultural workers[4-11] and, hence, provide further support for the hypothesis that the occupational use of herbicide chemicals results in an increased risk for PD.

Two variables, smoking history and family history of essential tremor, that were statistically significant in the univariate analysis were not significant predictors of PD risk in the multivariate analysis once we controlled for the effects of family history of PD, history of serious head trauma, and previous occupational herbicide use. The results of previous studies are inconclusive with respect to the involvement of smoking in the etiology of PD. While four previous case-control studies[14,15,35,36] and one large prospective study[37] have not found a significant decrease or increase in PD risk associated with a history of smoking, the results of six previous case-control studies[30,38-42] suggest that smoking protects against developing PD. However, in five[38-42] of the

six positive studies, the analyses were restricted only to univariate analyses and the reported PD risk estimates were crude risk estimates; that is, there was no control for potential confounding between the smoking variables and other potential risk factors for PD. The single study[30] that estimated both the crude and adjusted PD risk associated with smoking (ever smoked, smoked at disease onset, smoked 20 years prior to disease onset) also found that smoking was associated with a significantly decreased crude PD risk estimate in the univariate analysis. However, after controlling for previous head injury causing concussion or for family history of PD, the adjusted PD risk estimates associated with smoking did not achieve statistical significance. Thus, our findings concur with the results of all six previous positive studies, which indicate that although smoking may appear to act as a negative predictor of PD risk when considered in isolation, after controlling for the effects of other potential risk factors for PD including family history of PD, history of serious head trauma, and previous occupational herbicide use, smoking has no significant protective effect against the development of PD. Therefore, we conclude that smoking is probably not a protective factor, but might act as an intermediary factor in the relationship between a sative agent and PD. Our observations under- e the limited usefulness of the crude PD risk estimates yielded by the previous studies and the importance of using multivariate statistical methods in risk estimation in etiologic studies of diseases like PD that are believed to result from a combination of factors.

Previous research suggests that some individuals with a family history of essential tremor may have an increased likelihood of developing PD, possibly because of a genetic predisposition to PD.[43,44] However, because of the clinical difficulty in distinguishing cases of essential tremor and PD[45] and since neuropathologic study has revealed no abnormality that could be regarded as specific for essential tremor,[46] the association between essential tremor and PD remains controversial. In our study, family history of essential tremor was not a significant predictor of PD risk when we controlled for family history of PD or for any combination of the other four factors that were significant in the univariate analysis. The consistent strong association between family history of PD and PD risk in our study, and the possibility that a number of the family members reported to have had essential tremor may actually have had PD, leads us to conclude that the significant univariate association between family history of essential tremor and PD risk is likely the result of artifact. Thus, the relationship between familial tremor and PD still requires further investigation.

conclusion, the results of our population-based case-control study of PD in Alberta residents support the hypothesis of a multifactorial etiology for PD, probably involving genetic, environmental, trauma, and possibly other factors. Caution should be taken, however, in generalizing the results of this study to PD cases with dementia, since it is not known to what extent the distribution of exposures differed between the excluded demented cases and the cases studied. This study identified three probable risk factors for PD: (1) family history of PD, (2) history of a serious head trauma, and (3) history of occupational herbicide use. Although not previously considered together, each of these three factors was associated with a significantly increased PD risk in other well-conducted case-control studies of very different populations. Other diseases and conditions (arteriosclerosis, chicken pox, encephalitis, familial tremor, hypertension, hypotension, measles, mumps, rubella, and Spanish flu) did not appear to be important risk factors for PD in this study of Alberta residents. These results also lead us to question the postulated protective effect of smoking on the development of PD. Further research is now needed to identify the specific causative gene or agent involved in the development of PD and the biologic mechanisms and to clearly delineate the nature of any ecogenetic[47] or other interrelationships between the identified etiologic factors (for example, a predisposed susceptibility to a particular neurotoxin commonly found in agricultural herbicides due to a trauma-related inherited liver enzyme deficiency resulting in an inability to metabolize the toxin[47]). However, in consideration of the hypothesized multifactorial etiology of PD, future etiologic research on PD should be multidisciplinary and use multivariate statistical methods to assess the relative etiologic importance of the various putative risk factors and control for confounding and interaction among factors.

References

1. Calne DB, Langston JW. Aetiology of Parkinson's disease. Lancet 1983;2:1457-1459.
2. Kondo L. Epidemiological evaluations of risk factors in Parkinson's disease. In: Yahr MD, Bergmann KJ, eds. Parkinson's disease. Advances in neurology, vol 45. New York: Raven Press, 1986:289-293.
3. Stern M, Dulaney E, Gruber SB, et al. The epidemiology of Parkinson's disease: a case-control study of young-onset and old-onset patients. Arch Neurol 1991;48:903-907.
4. Grcevic N, Jadro-Santel D, Jukic S. Cerebral changes in paraquat poisoning. In: Roizin L, Shiraki H, Grcevic N, eds. Neurotoxicology. New York: Raven Press, 1977:469-484.
5. Grant HC, Lantos PL. Cerebral damage in paraquat poisoning. Histopathology 1980;4:185-195.
6. Bocchetta A, Corsini GU. Parkinson's disease and pesticides. Lancet 1986;2:1163.
7. Sanchez-Ramos JR, Hefti F, Weiner WJ. Paraquat and Parkinson's disease [letter]. Neurology 1987;37:728.
8. Peters HA, Levine RL, Matthews CG, Chapman LJ. Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. Arch Neurol 1988;45:537-540.
9. Ferraz HB, Bertolucci PHF, Pereira JS, Lima JGC, Andrade LAF. Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication. Neurology 1988;38:550-553.
10. Chapman LJ, Sauter SL, Henning RA, Levine RL, Matthews CG, Peters HA. Finger tremor after carbon disulfide-based

pesticide exposures. Arch Neurol 1991;48:866-870.
11. Sechi GP, Agnetti V, Piredda M, et al. Acute and persistent parkinsonism after use of diquat. Neurology 1992;42:261-263.
12. Barbeau A, Roy M, Cloutier T, Plasse T, Paris S. Environmental and genetic factors in the etiology of Parkinson's disease. In: Yahr MD, Bergmann KJ, eds. Parkinson's disease. Advances in neurology, vol 45. New York: Raven Press, 1986:299-306.
13. Barbeau A, Roy M, Bernier G, Campanella G, Paris S. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. Can J Neurol Sci 1987;14:36-41.
14. Tanner CM, Chen B, Wang W, et al. Environmental factors and Parkinson's disease: a case-control study in China. Neurology 1989;39:660-664.
15. Ho SC, Woo J, Lee GM. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology 1989;39:1314-1318.
16. Tanner CM, Grabler P, Goetz CG. Occupation and the risk of Parkinson's disease (PD): a case-control study in young-onset patients [abstract]. Neurology 1990;40(suppl 1):422.
17. Golbe LI, Farrell TM, Davis PH. Follow-up study of early life protective and risk factors in PD. Mov Disord 1990;5:66-70.
18. Hertzman C, Wiens M, Bowering D, Snow B, Calne D. Parkinson's disease: a case-control study of occupational environmental risk factors. Am J Ind Med 1990;17:349-355.
19. Ohlson CG, Hogstedt C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury: a case-referent study. Scand J Work Environ Health 1981;7:252-256.
20. Koller W, Vetere-Overfield B, Gray C, et al. Environmental risk factors in Parkinson's disease. Neurology 1990;40:1218-1221.
21. Zayed J, Ducic S, Campanella G, et al. Facteurs environnementaux dans l'étiologie de la maladie de Parkinson. Can J Neurol Sci 1990;17:286-291.
22. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to rural environmental factors: a population based case control study. Can J Neurol Sci 1991;18:279-286.
23. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 1992;42:1328-1335.
24. Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40-46.
25. Breslow NE, Day NE. Statistical methods in cancer research, vol I. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer 1980, 1989:161-190.
26. Golbe LI. The genetics of Parkinson's disease: a reconsideration. Neurology 1990;40(suppl 3):7-14.
27. Muenter MD, Howard FM Jr, Okazaki H, Forno LS, Kish SJ, Hornykiewicz O. A familial parkinson-dementia syndrome [abstract]. Neurology 1986;36(suppl 1):115.
28. Golbe LI, Di Iorio G, Bonavita V. A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 1990;27:276-282.
29. Rajput AH. Frequency and cause of Parkinson's disease. Can J Neurol Sci 1992;19:103-107.
30. Godwin-Austen RB, Lee PN, Marmot MG, Stern GM. Smoking and Parkinson's disease. J Neurol Neurosurg Psychiatry 1982;45:577-581.
31. Factor SA, Weiner W. Prior history of head trauma in Parkinson's disease. Mov Disord 1991;6:225-229.
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 1983;33:815-824.
33. Tanner CM, Chen B, Wang WZ, et al. Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci 1987;14:419-423.
34. Williams DB, Annegers JF, Kokmen E, O'Brien PC, Kurland LT. Brain injury and neurologic sequelae: a cohort study of dementia, parkinsonism, and amyotrophic lateral sclerosis. Neurology 1991;41:1554-1557.
35. Rajput AH, Offord KP, Beard CM, Kurland LT. A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. Neurology 1987;37:226-232.
36. Sasco AJ, Paffenbarger RS. Smoking and Parkinson's disease. Epidemiology 1990;1:460-465.
37. Golbe LI, Cody RA, Duvoisin RC. Smoking and Parkinson's disease. Arch Neurol 1986;43:774-778.
38. Nefzger MD, Quadfasel FA, Karl VC. A retrospective study of smoking in Parkinson's disease. Am J Epidemiol 1968;88:149-168.
39. Kessler II, Diamond EL. Epidemiologic studies of Parkinson's disease. 1. Smoking and Parkinson's disease: a survey and explanatory hypothesis. Am J Epidemiol 1971;94:16-25.
40. Baumann RJ, Jameson HD, McKean HE, Haack DG, Weisberg LM. Cigarette smoking and Parkinson's disease: 1. A comparison of cases with matched neighbors. Neurology 1980;30:839-843.
41. Marttila RJ, Rinne UK. Smoking and Parkinson's disease. Acta Neurol Scand 1980;62:322-325.
42. Bharucha NE, Stokes L, Schoenberg BS, et al. A case-control study of twin pairs discordant for Parkinson's disease: a search for environmental risk factors. Neurology 1986;36:284-288.
43. Geraghty JJ, Jankovic J, Zetusky WJ. Association between essential tremor and Parkinson's disease. Ann Neurol 1985;17:329-333.
44. Lang AE, Kierans C, Blair RDG. Family history of tremor in Parkinson's disease compared with those of controls and patients with idiopathic dystonia. Adv Neurol 1986;45:313-316.
45. Salisachs P, Findley LJ. Problems in the differential diagnosis of essential tremor. In: Findley LJ, Capildeo R, eds. Movement disorders: tremor. London: MacMillan Press. 1984:219-224.
46. Rajput AH, Rozdilsky B, Ang L, Rajput A. Clinicopathologic observations in essential tremor: report of six cases Neurology 1991;41:1422-1424.
47. Barbeau A, Roy M, Paris S, Cloutier T, Plasse L, Poirier J Ecogenetics of Parkinson's disease: 4-hydroxylation of debrisoquine. Lancet 1985;2:1213-1216.