Possible environmental, occupational, and other etiologic factors for Parkinson's disease:

A case-control study in Germany

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Article abstract—In a case-control study, we investigated the possible etiologic relevance to Parkinson's disease (PD) of rural factors such as farming activity, pesticide exposures, well-water drinking, and animal contacts; toxicologic exposures such as wood preservatives, heavy metals, and solvents; general anesthesia; head trauma; and differences in the intrauterine environment. We recruited 380 patients in nine German clinics, 379 neighborhood control subjects, and 37 regional control subjects in the largest case-control study investigating such factors and collected data in structured personal interviews using conditional logistic regression to control for educational status and cigarette smoking. The latter was strongly inversely associated with PD. There were significantly elevated odds ratios (OR) for pesticide use, in particular, for organochlorines and alkylated phosphates, but no association was present between PD and other rural factors. A significantly elevated OR was present for exposure to wood preservatives. Subjective assessment by the probands indicated that exposure to some heavy metals, solvents, exhaust fumes, and carbon monoxide was significantly more frequent among patients than control subjects, but this was not confirmed by a parallel assessment of job histories according to a job exposure matrix. Patients had undergone general anesthesia and suffered severe head trauma more often than control subjects, but a dose-response gradient was not present. Patients reported a significantly larger number of amalgam-filled teeth before their illness than control subjects. The frequency of premature births and birth order did not differ between patients and control subjects. Patients reported significantly more relatives affected with PD than control subjects. These results support a role for environmental and genetic factors in the etiology of PD.

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The discovery that 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a syndrome that is clinically almost identical to Parkinson's disease (PD)[1] strengthened the hypothesis that PD could be caused by exogenous neurotoxins. Although there is increasing evidence that genetic factors may also play a role in the etiology of PD, at least in some patients,[2-7] this likely involves interaction with environmental factors. For example, defects in enzyme detoxification systems, including debrisoquine hydroxylation,[8-12] sulfur conjugation and oxidation,[13] and thiolmethyltransferase activity,[14] could lead to potentiation of relatively low-level neurotoxic exposures in PD patients. Such environmental-genetic interaction is supported by heritability coefficients for PD as calculated from several genetic studies by Johnson et al.[15] and Kondo et al.[16] Therefore, we conducted a large hospital-based case-control study using neighborhood and regional control groups to examine environmental risk factors in PD patients with a short disease duration in Germany.

Previous studies implicated various environmental factors in PD. Because of the nature of their metabolism, dopaminergic neurons may be more sensitive to certain neurotoxins, such as MPTP,[17] than other cells. Oxidative stress may have a role in the progression of PD.[18-24] Therefore, environmental substances capable of initiating oxidant damage, such as heavy metals, could also be of etiologic importance.

Several studies examined a possible relationship between premorbid exposure to rural factors and PD with conflicting results. Rural living[25-30] or farming[28,31] were associated with PD in case-control studies, and PD patients were found to have lived or to have been raised more frequently in rural areas.[9,32] However, other case-control studies did not support

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these findings[33-37] nor found a negative association.[38] Similarly, some[27,29,30] but not all studies[25,26,30,33,35,38,39] found PD to be associated with a premorbid history of well-water drinking. Wang et al.[37] found a negative association with this factor in China, although they found a positive association with drinking river water. Methodologic differences and small sample sizes, as well as regional differences in agricultural practices, may explain these divergent findings. Our study considers these hypotheses by means of a detailed residential history.

Pesticide exposure may be relevant to the etiology of PD because of the chemical similarity between MPTP and paraquat and similar herbicides. Whether such herbicides can act in a neurochemically identical fashion to MPTP is debated.[40-43] Nonetheless, several studies found an association between PD and pesticide exposure, both with an ecologic[9] and a case-control approach.[26,28,34,44] Again, other case-control studies failed to corroborate such a relationship.[27,29-31,35,45] In this study, we attempt to investigate an association between PD and pesticide exposure with particular attention to the frequent practice of gardening in Germany, even by city dwellers.

Several studies found a link between PD and exposure to industrial chemicals[31,38] and heavy metals,[39,46] as well as working in planar mills,[31] in the printing industry, or in quarries.[38] Our study considers exposure to various potential neurotoxins such as heavy metals, solvents, and wood preservatives. We also considered the number of previous episodes of general anesthesia as a potentially neurotoxic exposure.

There has been a strong negative association between cigarette smoking and PD in prospective studies based on mortality data,[47-50] in one study based on the Honolulu Heart Study cohort,[51] and in retrospective studies,[9,29,31,39,52-62] although other, generally smaller, studies have not found this relationship.[28,35,46,63,64] Therefore, smoking must be considered as an important potential confounder in studies investigating etiologic factors of PD.

Methods. PD patients were recruited in nine German neurologic clinics. These clinics were selected mainly because the involved neurologists had a special interest and expertise in PD. The catchment areas of the clinics cover large parts of northern, southern, western, and eastern Germany. We believed that eastern Germany was especially important, as exposure to environmental neurotoxins may have been higher in former East Germany. All patients with a clinical diagnosis of PD in 1987 or later and 65 years of age or less were identified. Four patients from three clinics up to 67 years of age were included as well. Older patients were not recruited to minimize memory deficits, and patients with a longer disease duration were excluded to minimize recall bias. All patients were under the care of trained neurologists, who were asked to verify inclusion and exclusion criteria according to the U.K. Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[65] Step 1 criteria (bradykinesia and at least one of muscular rigidity, 4 to 6 Hz rest tremor and/or postural instability not caused by primary visual, vestibular cerebellar, or proprioceptive dysfunction) were rigidly applied by all examiners. The suggested step 2 (exclusion criteria) were applied as well, although not all patients had CT and patients with more than one affected relative were not excluded. Step 3 criteria, supportive prospective positive criteria for PD, were applied retrospectively and not as rigidly. As disease duration was under 5 years for the most part, not all step 3 criteria were applicable. Patients with secondary parkinsonian syndromes or PD patients with dementia were specifically excluded. Of 533 PD patients identified, 377 agreed to participate (71%). Of 25 patients who provided reasons for declining an interview, 13 stated poor health. Five additional patients were recruited from neurologic practices affiliated with two of the centers, resulting in 382 participating PD patients. The two former East German clinics referred 93 of these patients.

Two control subjects were recruited for each patient on a random route basis.[66] The first control subject was recruited within the patient's immediate neighborhood and the second control subject from the same urban or rural region. Recruitment of population control subjects would have been prohibitively expensive in Germany, as community registries charge fees for the provision of randomly generated address lists and numerous communities would have had to be approached. The random route scheme instructed interviewers to personally contact every second household starting with the patient's (first control subject) or a predetermined "regional" (second control subject) address to find a person of the same sex and age (±3 years) as the patient. The regional address was selected randomly from a list of all addresses in the patient's voting district. In rural regions, this meant that the control person might be in a nearby small town or village. If the potential control person was not at home at the time the initial contact was made, the interviewer was instructed to ask to be able to return at a mutually convenient time. On average, 21 household contacts were required to find an appropriate neighborhood control subject and 22 contacts to find a regional control subject willing to participate. No control subjects could be found for two cases, no neighborhood control subject could be found for one case, and no regional control subjects could be found for four cases, leaving 380 patients with at least one control subject, 376 neighborhood control subjects, and 379 regional control subjects for the analysis.

Experienced interviewers were contracted with Infratest/Epidemiologische Forschung Berlin, a sociologic and health research institute. These interviewers were professionally trained in standardized interview techniques and a nondifferential approach to patients and control subjects. The interviewers were informed that the study dealt with environmental influences and PD but were unaware of specific hypotheses being investigated. They were given basic information about the clinical manifestations of PD. Patients were not informed of the hypotheses. Control subjects were asked to participate in a "health survey"; they were unaware that the investigation dealt primarily with PD. The same person interviewed the patient and the corresponding control subjects.

A detailed structured interview was developed to ob-

information about a variety of environmental exposures before the diagnosis of the disease. When patients were questioned about variables referring to the period immediately before diagnosis, such as the number of amalgam fillings, control subjects were asked about their situation 1 year before the interview. This meant that on average, control subjects did not have to remember backward in time as far as the patients (illness duration 3.7 ± 1.8 years). However, we believed that this would be offset to some extent by recall bias on the part of the patients and considered this to be less artificial than creating a fictitious "matched" date corresponding to the patient's diagnosis. For most variables in this study, exact dates and thus durations of exposures could be elicited.

The interviewers documented a complete residential history for each participant, including locations (with approximate population number) and dates of residence from early childhood up to the present. For each residence, the following information was elicited: water supply; whether the home was on or adjacent to a farm or farmland; the presence of a garden, whether or not pesticides were applied, and, if so, which ones; and whether wood paneling was present in the home. Further areas covered by the questionnaire included animal contacts; a detailed occupational history; contact with a number of potentially neurotoxic substances, including heavy metals, wood preservatives, and solvents; general anesthesia; premature delivery; birth order; and a smoking history.

Because subjects were not always able to specify names of herbicides and insecticides they had applied, the initial analysis of pesticide exposure was carried out without regard to product names. Responses were categorized according to the number of years of application weighted by the frequency of usage ("dose years"; rarely, factor 1; for special indications, factor 2; and regularly [seasonally], factor 3). A toxicologic expert was then asked to categorize all pesticides named by subjects with regular pesticide usage. Products fell into five groups: organochlorines, alkylated phosphates and carbamates, inhibitors of cellular metabolism (cellular respiration, enzyme activity, membrane excitation), and "other."

Occupational exposures were assessed in two ways. First, the probands' own assessment of "ever" versus "never" exposures to a list of neurotoxic substances was analyzed. Because this type of assessment is prone to recall bias, a job exposure matrix was constructed for the job titles and industries named by the probands in our study with the help of three experts and a doctoral student. This permitted a more objective exposure assessment, although classification at the job title level could not consider all possible task-specific exposures.

Odds ratios (OR) and 95% CIs were calculated using conditional logistic regression.[67] Tests for trend were calculated with the interval-scaled data based on logistic regression. For several interval scaled variables, only ORs calculated for ever versus never categories are presented in addition to the p for trend. All calculations were performed separately for both sets of matched pairs. Missing values (generally <1%) were analyzed as a separate category (not shown here) so as not to reduce the number of case-control pairs unnecessarily in the multivariate analysis. Smoking and educational status were included as covariates in the multivariate analyses to adjust for potential confounding. ORs will be presented in the text with 95% CIs, adjusted for smoking and educational status, for patients versus neighborhood control subjects (N1 versus N2) and for patients versus regional control subjects (N1 versus N3). More detailed results are available from the authors upon request.

Results. The mean age of patients was 56.2 ± 6.6 years, of neighborhood control subjects, 56.2 ± 7.0 years, and of regional control subjects, 56.5 ± 6.8 years. Mean age at diagnosis (as reported by patients) was 52.5 ± 6.6 years. Mean age at symptom onset was 50.5 ± 7.2 years. Disease duration (from date of diagnosis) was 3.7 ± 1.8 years (min < 1, max 8). Of the 380 patients, 251 were men and 129 were women.

Educational level was assessed by years of schooling (including general or academic level) in three categories that took into account differences between East and West German school systems. In general, patients were more highly educated than control subjects, although this difference was not statistically significant (p = 0.07, patients versus neighborhood control subjects; p = 0.08, patients versus regional control subjects, Mann-Whitney test).

Patients smoked for significantly fewer pack years than control subjects (patients, 16.9 ± 15.5 pack years, neighborhood control subjects 23.6 ± 19.4 pack years, regional control subjects, 22.4 ± 17.1 pack years, test for trend for both comparisons, $p < 0.00005$). (A detailed analysis of the smoking history will be published separately.)

The average population density of the probands' places of residence from birth to time of diagnosis or, for control subjects, to 1 year before the interview did not differ between patients and controls (ORs comparing highest to lowest average population density: N1 versus N2-1.2 [0.5 to 2.9], p trend = 0.22; N1 versus N3-0.9 [0.4 to 2.1], p trend = 0.85). There was no difference in the frequency of previous farming activity or employment in agricultural work between patients and control subjects as determined through the occupational history (ORs for N1 versus N2 0.9 [0.6 to 1.4], N1 versus N3 0.7 [0.4 to 1.1]). The residential history revealed nonsignificant ORs for living on a farm (N1 versus N2 0.8 [0.6 to 1.1], N1 versus N3 0.9 [0.6 to 1.2]), farming near the home (N1 versus N2 1.0 [0.7 to 1.4], N1 versus N3 1.1 [0.8 to 1.6]), well-water drinking (N1 versus N2 0.8 [0.6 to 1.2], N1 versus N3 0.9 [0.6 to 1.3]), having a garden (N1 versus N2 1.2 [0.7 to 1.9], N1 versus N3 1.5 [0.9 to 2.5]), contact with farm animals (N1 versus N2 0.8 [0.6 to 1.1], N1 versus N3 0.7 [0.5 to 1.0]), or involvement in slaughter (N1 versus N2 0.9 [0.7 to 1.3], N1 versus N3 1.1 [0.8 to 1.5]). Tests for trend for the duration of these exposures were also nonsignificant.

Duration of insecticide and herbicide use in the past was weighted by frequency of usage for the calculation of "dose years." Table 1 shows the results of this analysis using responses for "any" pesticide use, disregarding whether patients could provide product names or not. Patients were more likely to report herbicide or insecticide use than either control group. A positive trend across the number of dose years can be seen in each case, although ORs and the p for trend are significant only in the comparison with regional control subjects.

Patients provided a higher absolute number of specific product names for pesticides than either of the control groups. However, the proportion of "exposure years" for

Table 1 Pesticide usage

Variable	Dose years	Versus neighbor control subjects N1	N2	Adj. OR*	p for Trend†	Versus regional control subjects N1	N3	Adj. OR*	p for Trend†
Herbicide use	Never	239	273	1.0 —	0.06	238	287	1.0 —	0.001
	1–40	61	46	1.7 (1.0–2.7)		59	44	1.7 (1.0–2.6)	
	41–80	34	27	1.4 (0.8–2.5)		34	15	3.0 (1.5–6.0)	
	>80	20	11	2.2 (0.9–5.2)		20	10	2.4 (1.0–6.0)	
Insecticide use	Never	214	240	1.0 —	0.12	213	258	1.0 —	0.002
	1–40	46	38	1.4 (0.9–2.1)		70	55	1.8 (1.1–2.7)	
	41–80	21	16	1.5 (0.9–2.5)		46	25	2.5 (1.4–4.5)	
	>80	26	24	1.6 (.07–3.4)		21	14	2.1 (0.9–4.8)	
Organochlorines	Never	264	291	1.0 —	0.54‡	262	309	1.0 —	0.26‡
	Ever	7	5	1.6 (0.4–6.2)		7	2	5.8 (1.1–30.4)	
	NPN§	86	61	1.5 (1.0–2.2)		85	45	2.1 (1.4–3.2)	
Alkylated phosphates and carbamates	Never	228	261	1.0 —	0.56‡	227	284	1.0 —	0.03‡
	Ever	43	35	1.8 (0.9–3.3)		42	27	2.5 (1.3–4.6)	
	NPN§	86	61	1.5 (1.0–2.3)		85	45	2.2 (1.4–3.4)	

* Adjusted for smoking and education, with 95% CI enclosed in parentheses.
† Years of exposure duration.
‡ Years of specific exposure duration.
§ NPN, Pesticide exposure, but unable to specify product name.

N1 = number of cases; N2 = number of neighborhood control subjects; N3 = number of regional control subjects.

which specific product names could be given was higher for control subjects (patients, 36%, or 1,745 of 4,836 exposure years; neighborhood controls, 44%, or 1,514 of 3,471 exposure years; regional control subjects, 44%, or 1,268 of 2,868 exposure years). In a further comparison, toxicologic classification was attempted for specific products named by the probands. Exposures for which no product name could be given were classified separately. This led to a rather small number of exposed probands in each toxicologic group. Table 1 shows that patients were more likely than control subjects to have used organochlorines and alkylated phosphates/carbamates (significant only for the comparison with regional control subjects). No difference was found for the categories "inhibitors of cellular metabolism" and "other."

Contact with wood preservatives was assessed in three ways. Patients reported that they had wood paneling in their homes significantly more often than control subjects (table 2). A dose-response gradient is seen with increasing number of years of exposure, although the trend test is not significant. The gradient becomes more pronounced when exposure is considered only for the 15 years before diagnosis (p for trend = 0.02, N1 versus N2; p = 0.07, N1 versus N3).

Patients reported exposure to wood preservatives at work or in their free time significantly more frequently than control subjects (table 2). ORs in this analysis are additionally adjusted for the number of job changes, as a higher number of jobs would tend to increase the chance of any given exposure. On average, patients changed jobs 3.3 ± 2.1 times, neighborhood control subjects 3.0 ± 2.2 times (p = 0.02), and regional control subjects 3.0 ± 2.0 times (p = 0.05).

As this is a rather subjective indication of exposure, a job exposure matrix (JEM) was created for relevant neurotoxicants in the jobs and industries reported by the subjects in this study. With this more objective, but less sensitive, assessment of exposure, no difference could be seen between patients and control subjects for exposure to wood preservatives (table 2). However, when subjects who reported previous free time exposure are placed into a separate category rather than classified as being unexposed in the JEM analysis, the OR for occupational exposure is once again elevated and approaches significance (table 2).

Elevated ORs were found for ever versus never occupational exposure to lead (N1 versus N2 1.2 [0.7 to 2.0], N1 versus N3 1.9 [1.1 to 3.1]), mercury (N1 versus N2 1.3 [0.6 to 2.6], N1 versus N3 2.0 [0.9 to 4.2]), and zinc (N1 versus N2 1.1 [0.7 to 1.7], N1 versus N3 1.5 [0.9 to 2.4]) in the comparison with regional but not neighborhood control subjects; however, these were not significant with the exception of the OR for lead exposure. Exposure to other heavy metals (copper, cadmium, chrome, nickel, arsenic, zinc) did not differ between patients and control subjects. Five patients and one neighborhood but no regional control subjects reported exposure to manganese. Again, the JEM analysis did not reveal an association between PD and any heavy metal. The number of probands reporting exposure in their free time was too small to permit a separate analysis as done for wood preservatives.

To further assess a possible link between heavy metal exposure and PD, probands were asked to state the num-

Table 2 Exposure to wood preservatives

Variable	Category	Versus neighbor control subjects N1	N2	Adj. OR*	p for Trend†	Versus regional control subjects N1	N3	Adj. OR*	p for Trend†
Wood paneling in the home	Never	167	197	1.0 —	0.11	167	193	1.0 —	0.16
	1–15 yr	52	50	1.3 (0.7–2.2)		52	52	1.3 (0.8–2.2)	
	>15 yr	144	116	1.8 (1.2–2.6)		141	112	1.6 (1.1–2.4)	
Contact with wood preservatives	Never	196	239	1.0 —	—	195	249	1.0 —	
	In free time	106	79	1.9 (1.2–3.0)		105	82	2.0 (1.3–3.1)	
	At work	75	60	1.8 (1.1–2.9)		74	43	2.3 (1.4–3.7)	
Wood preservative exposure as assessed by									
JEM only	Never	235	243	1.0 —		233	252	1.0 —	
	Ever	111	108	1.1 (0.7–1.6)		110	101	1.1 (0.8–1.7)	
JEM, taking into account free time exposure	Never	153	176	1.0 —		152	182	1.0 —	
	Ever	111	108	1.3 (0.8–2.0)		110	101	1.4 (0.9–2.2)	
	In free time	82	67	1.6 (1.0–2.6)		81	70	1.7 (1.0–2.7)	

* Adjusted for smoking and education.
† Years of exposure duration.

N1 = number of cases; N2 = number of neighborhood control subjects; N3 = number of regional control subjects.

ber of amalgam fillings they had before illness onset. Patients had a significantly higher number of amalgam-filled teeth before illness onset (patients 7.8 ± 6.1, neighborhood control subjects 6.5 ± 5.9 [$p = 0.0008$], regional control subjects 6.1 ± 5.9 [$p < 0.00005$]). However, patients also had a significantly higher number of remaining natural teeth (patients 23.1 ± 9.4, neighborhood control subjects 18.6 ± 11.4, regional control subjects 18.7 ± 11.4; $p < 0.00005$ for both comparisons). Therefore, a conservative risk estimate was carried out by calculating ORs for "amalgam fillings per remaining number of teeth" (based on quartiles of the values). This showed a positive association with PD, although consistently significant only for the comparison with regional control subjects (ORs for second, third, and highest versus lowest quartile, N1 versus N2 1.3 [0.8 to 2.1], 1.6 [1.0 to 2.6], 1.3 [0.8 to 2.1], p trend = 0.12; N1 versus N3 1.7 [1.0 to 2.7], 2.5 [1.4 to 4.5], 1.9 [1.1 to 3.3], p trend = 0.003). The high proportion of missing values for this variable (15% patients, 21% neighborhood control subjects, and 25% regional control subjects) as compared with other variables (~1%) should be pointed out.

Patients reported occupational or free time exposure to the following additional substances more frequently than control subjects: gases and vapors; solvents; as a group, glues, paints, and lacquers; exhaust fumes; and carbon monoxide (table 3). None of these associations could be confirmed using the JEM for assignment of exposures.

More patients than control subjects reported ever having undergone general anesthesia (ORs for N1 versus N2 1.4 [1.0 to 2.0], N1 versus N3 1.3 [0.9 to 1.9]). However, a dose-response gradient for the number of episodes of anesthesia was not found (p for trend = 0.5 in both comparisons).

To assess a possible role for physical injury, subjects were asked whether they had ever sustained an episode of head trauma "associated with dizziness, blurred vision and/or memory loss." Patients reported such an episode more frequently than control subjects (ORs for N1 versus N2 1.4 [0.9 to 2.3], N1 versus N3 1.5 [1.0 to 2.4], patients versus regional control subjects). The test for trend for the number of episodes is not significant ($p = 0.07$ and 0.11, respectively. However, only 1.7% of patients, 1.4% of neighborhood control subjects, and 0.6% of regional control subjects reported more than one episode of head trauma, making the test for trend less meaningful.

Only 16 patients and eight subjects in each control group reported a premature delivery. This yielded ORs of 2.2 (0.9 to 5.7) versus neighborhood control subjects and 1.6 (0.7 to 3.9) versus regional control subjects. There was no relationship between PD and birth order.

Forty-six of 343 patients but only 5 of 365 neighborhood control subjects (OR 12.6 [4.4 to 36.1]) and 9 of 359 regional control subjects (OR 5.0 [2.4 to 10.7]) reported a history of PD in first- or second-degree relatives. For this variable, there was also a high proportion of missing values; 36 patients, 14 neighborhood control subjects, and 7 regional control subjects did not know whether any relatives were affected. The overall small number of patients reporting a positive family history does not permit a separate analysis of this subgroup to determine whether a different spectrum of risk factors might be relevant.

Discussion. This study reveals a number of statistically significant associations between exogenous factors and PD. The study has several strengths over many existing case-control studies about environmental factors and PD. Being the largest case-con-

Table 3 Potentially neurotoxic exposures

Variable	Category	Versus neighbor control subjects			Versus regional control subjects		
		N1	N2	Adj. OR*	N1	N3	Adj. OR*
Gases and vapors	Never	191	224	1.0 —	190	225	1.0 —
	In free time	11	10	1.2 (0.5–3.1)	11	9	1.4 (0.5–3.5)
	At work†	177	145	1.6 (1.1–2.2)	175	140	1.7 (1.2–2.4)
Solvents	Never	244	278	1.0 —	242	284	1.0 —
	In free time	32	15	2.6 (1.2–5.4)	32	14	3.4 (1.5–7.5)
	At work†	100	79	1.6 (1.1–2.4)	99	73	1.8 (1.2–2.7)
Glues, paints, lacquers	Never	163	198	1.0 —	162	193	1.0 —
	In free time	73	72	1.1 (0.7–1.8)	72	58	1.5 (0.9–2.6)
	At work†	141	108	1.6 (1.1–2.4)	140	124	1.5 (1.0–2.3)
Exhaust fumes	Never	181	210	1.0 —	180	232	1.0 —
	In free time	60	47	1.6 (0.9–2.7)	59	49	1.9 (1.1–3.4)
	At work†	135	119	1.6 (1.1–2.4)	134	94	2.4 (1.5–3.6)
Carbon monoxide	Never	257	275	1.0 —	255	287	1.0 —
	In free time	29	16	2.1 (1.0–4.2)	29	29	1.3 (0.7–2.5)
	At work†	84	81	1.2 (0.8–1.8)	83	55	1.9 (1.2–3.0)

* Adjusted for smoking and education.
† Includes probands exposed only at work as well as those exposed at work and in their free time.

N1 = number of cases; N2 = number of neighborhood control subjects; N3 = number of regional control subjects.

trol study to date, the power to detect significant differences for rare exposures, such as specific pesticide groups, certain occupational exposures, and the occurrence of head trauma, is considerable. An OR of approximately 2 can be detected with a power of 90% for an exposure rate of 10% among the control subjects.[68] Although this was not a study based on newly diagnosed cases, the average disease duration was relatively short, thus reducing the potential for recall bias.

Case-control studies are open to bias.[68] Because this study was not population based, a patient selection bias cannot be ruled out. To minimize such a bias, we included a large number of clinics in different areas of Germany and attempted to recruit all patients under the age of 66 in each clinic. There was no difference in disease duration between patients who participated in the study and those who declined. We obtained reasons for nonparticipation from only 26 patients. Half of these stated deteriorating health as the reason for not participating. Thus, there is some evidence that patients with more severe disease declined to take part.

The largest group of patients (184 of 380) was recruited from a clinic in Kassel specializing in the treatment of PD. Although patients in this clinic were on average slightly less educated (66% versus 60% less than Grade 10 education, 20 versus 21% Grade 10 education, and 14 versus 19% high school education), this difference was not statistically significant ($p = 0.14$, Mann-Whitney test). The employment status at the time of the interview and smoking history did not differ between patients from this clinic and patients from the other clinics.

Our method of control selection is open to selection bias as well. Interviewers attempted to recruit the first matching control subject in the neighborhood or region according to the random route scheme. However, the employment rate of control subjects at the time of the interview was lower than expected compared with the general population. For example, of neighborhood control subjects aged 50 to 60 years, 63.2% of men and 50.6% of women were employed, and of the regional control subjects in this age group, 64.6% of men and 39.5% of women were employed. The national average employment rate for this age group is 82.6% for men and 50.4% for women,[69] suggesting that at least some control subjects were easier to contact at any given time of day. We have partly adjusted for this factor by including educational status in the regression equation. In addition, to determine whether unemployment on the part of control subjects influenced the results, we compared control subjects who were employed or older than 64 years of age (i.e., likely retired) at the time of the interview with those PD patients employed or older than 64 years of age at the time of symptom onset. This left 326 cases, 213 neighborhood control subjects, and 212 regional control subjects (which we analyzed as unmatched data sets, referred to subsequently as the "employed or retired" data sets). This had no substantial effect on the results.

Our results revealed an elevated OR for pest-

usage but failed to show an association between other rural factors and PD. This is in accordance with some studies and contrary to others (see previous results). Although our study is larger than previous studies investigating this association, we may have failed to find an association because we matched for neighborhood/region at the time of the interview (overmatching for location). Subjects are often unable to remember names of products they used. Although patients were able to name a higher absolute number of products, control subjects were able to name a higher proportion of products when considered in relation to the total number of exposure years. This suggests that patients were perhaps more likely to recall "any" exposure but were able to remember less specifically than control subjects. Our results are nonetheless in accordance with other studies that show an elevated OR with pesticide exposure.[26,28,34,44] Semchuk et al.[34] reported that PD patients were most frequently exposed to organochlorines and alkylated phosphates, as we found here. Fleming et al.[71] examined brain tissue of a small series of PD patients and control subjects for organochlorine pesticide residues and found dieldrin to be present significantly more frequently in brains of PD patients. In our study, only one patient (diagnosed at age 33), but no control subjects, reported use of preparations containing paraquat as well as diquat, both structurally similar to MPTP.[40,71]

The data suggest that exposure to wood preservatives may be relevant to the etiology of PD. In Germany, important potentially neurotoxic ingredients of wood preservatives up to the late 1980s were lindane and pentachlorophenol.[72,73] However, in Germany, many people are aware of a possible health hazard due to wood preservatives because of recent lawsuits. Thus, recall bias may have influenced this result.

[redacted] heavy metals (iron, [illegible], lead, [illegible]). Although plausible as neurotoxic exposures, that statistical significance was reached solely for lead exposure and, only in comparison with the regional control group, suggests that heavy metal exposure is not an important risk factor for PD. However, fewer than 10% of control subjects and patients was exposed to several of the heavy metals, reducing the power of the study to detect significant differences. We did not assess aluminum exposure in our interview, but, in agreement with Semchuk et al.,[74] the JEM analysis revealed no association between occupational aluminum exposure and PD.

A possible role for mercury is suggested by the positive association between the number of amalgam fillings before illness onset and PD. This finding is not adequately explained by control subjects having fewer remaining teeth than the patients, because the proportion of filled teeth was also significantly different between patient and control groups. When we reanalyzed the data using the "employed or retired" data set to rule out a control selection bias particularly for this finding (see previous results), the test for trend was no longer significant for the number of fillings per remaining number of teeth, although patients still had a significantly higher absolute number of fillings than control subjects. We had no measure of the length of time the amalgam fillings had been in place.

Whether amalgam fillings contribute significantly to the body burden of mercury remains a controversial issue.[75] Some studies showed a correlation between the number of amalgam fillings and the mercury concentration in various parts of the brain.[76,77] In this study, other sources of mercury exposure do not appear to act as risk factors for PD, but the number of exposed subjects was small. Thus, a role for mercury and possibly other heavy metals in the etiology of PD cannot be ruled out. Dexter et al.[78] suggested that alterations in heavy metal ions in the substantia nigra could facilitate oxidant damage. This group of researchers found increased iron and zinc levels and decreased copper levels in postmortem brain tissue of PD patients as compared with control subjects. Yasui et al.[79] found elevated aluminum and decreased magnesium levels in various regions of PD brains postmortem as compared with control subjects.

A positive association between gases and vapors, solvents, glues, paints and lacquers, exhaust fumes, and carbon monoxide and PD was present with self-reported data, but not when we used the expert ratings in the JEM. This discrepancy illustrates the problems involved in retrospective exposure assessment without the support of on-the-job toxicologic measurements or biological monitoring. JEM assessments can result in misclassification of toxicologic exposure because task-specific exposures cannot be adequately incorporated,[80-83] but they are less prone to errors of recall bias. As illustrated by our results for wood preservatives, the JEM assessment may be refined when nonoccupational exposures are considered separately; this is only feasible when a substantial number of probands are exposed in their free time.

Volatile substances such as paints and solvents have been associated with neuropsychiatric illness in other studies.[84-88] Fuxe et al.[89] found selective reduction of dopamine turnover in various areas of the anterior nucleus caudate of rat by toluene at low concentrations. Uitti et al.[90] reported a patient with acute-onset parkinsonism clinically indistinguishable from PD after abuse of lacquer thinner. The positive association between volatile toxins and PD based on our "subjective" data are somewhat supported by the elevated OR seen for ever having undergone general anesthesia, although statistical significance is not reached. Two previous smaller case-control studies found no association between general anesthetics and PD.[59,61] More frequent episodes of general anesthesia could also be a reflection of enhanced susceptibility to (surgical) illness.

Repeated head trauma can cause secondary post-

traumatic parkinsonism.[91,92] However, only two case-control studies found a significant OR for head trauma and PD.[35,74] Although head trauma was more frequent in patients than control subjects in this study, a causal relationship appears unlikely because statistical significance was not reached and other case-control[54,59,61,93,94] and a prospective study[95] found no association.

To look for differences in the intrauterine environment, as proposed by Eldridge and Ince,[96] we asked subjects whether they were born prematurely or not, recognizing that this may be difficult to answer validly after many years passed. We could not establish a significant relationship between PD and premature birth or birth order. However, questions regarding perinatal factors could be more validly examined in a prospective approach.

In summary, our results suggest that environmental factors may play a role in the etiology of PD, possibly acting through a genetic predisposition. Unfortunately, our study was not designed to adequately account for the concurrent or interactive influence of genetic factors. Thus, it would be relevant to correlate exposure status with genetic markers, including a more detailed and well-documented family history and enzymatic function, such as debrisoquine hydroxylation.[8-12] In addition, there is a need for more precise exposure determination, possibly through biological monitoring in newly diagnosed cases. An incident study on the basis of a population-based PD registry seems the closest achievable approximation to a prospective risk assessment at present.

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Limited usefulness of electroconvulsive therapy in progressive supranuclear palsy

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Article abstract—*Objective:* To perform a pilot study of the efficacy of electroconvulsive therapy (ECT) in improving motor function in progressive supranuclear palsy (PSP). *Background:* Few effective treatments are available for PSP. Tricyclic antidepressants and idazoxan (which increases central norepinephrine) have shown benefits in small clinical trials, and dopaminergic therapy has been reported, anecdotally, to be beneficial. ECT exerts effects on all of these transmitter systems, possibly by inducing increased receptor sensitivity. We postulated that by sensitizing dopaminergic and noradrenergic systems, ECT might improve motor symptoms of PSP. *Methods:* Five patients with clinically diagnosed PSP were evaluated before and after nine ECT treatments using the Unified Parkinson's Disease Rating Scale (UPDRS) and an apomorphine challenge to assess dopaminergic responsiveness. *Results:* No permanent side effects were seen. Transient side effects included confusion in all patients, worsening of speech and swallowing in two, and dystonic posturing of the foot in one. One patient experienced a dramatic response (going from a completely wheelchair-bound state to independent ambulation), two were mildly improved, and two were unchanged. *Conclusions:* Although ECT may ameliorate motor symptoms in PSP, the long hospitalization and the significant treatment-induced confusion limit the usefulness of this technique.

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Progressive supranuclear palsy (PSP) is a relentlessly progressive disorder that is typically unresponsive to therapy.[1,2] Although occasional patients may benefit early in the course of their disease from dopaminergic or anti-cholinergic medications, the response tends to be incomplete and short-lived.[3,4] Tricyclic antidepressants, too, may be partially effective for a short time in some patients, but unfortunately the benefits are usually not dramatic.[5] More recently, idazoxan, which increases central norepinephrine, has shown some promise, but it is not readily available.[6] New therapeutic approaches are clearly needed for this devastating condition.

Electroconvulsive therapy (ECT) has effects on multiple transmitter systems.[7–11] It enhances the synthesis and utilization of norepinephrine centra-

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