

Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis

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Article abstract—We enrolled 55 patients in a double-blind, placebo-controlled, parallel design study of the effectiveness of botulinum toxin (Botox) injections for the treatment of spasmodic torticollis. Patients received a standard series of injections, either placebo or Botox. We determined the sites of injection and dose per muscle by the nature of head deviation. Compared with placebo, Botox produced statistically significant improvement in the severity of torticollis, disability, pain, and degree of head turning. There were no serious side effects. During the double-blind phase, 61% of patients injected with Botox improved; 74% of patients subsequently improved during a later open phase at a higher dose of Botox. Direction of head turning, severity of torticollis, and presence or absence of jerky movements did not significantly influence the response rate. We conclude that Botox is a valuable treatment for spasmodic torticollis.

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In 1980, Scott¹ began using injections of botulinum toxin type A (Botox) for the treatment of strabismus, and in 1984, Fruen et al² reported the use of Botox for the focal dystonia blepharospasm. In the subsequent years, Botox injection became the treatment of choice for blepharospasm, resulting in dramatic improvement in over 80% of patients injected.³ In 1986, we reported the results of open trials of Botox injections for the focal dystonia torticollis in patients who had failed to respond to extensive medical trials and who were, in general, severely affected.⁴ These trials indicated that Botox injections are useful in the treatment of torticollis but differ in significant ways from its use in blepharospasm: (1) The muscles involved in torticollis are considerably larger than those in blepharospasm and require much larger doses of Botox. The potential for side effects is greater. (2) Torticollis involves a greater number of muscles than blepharospasm. The correct dose for each muscle must be determined independently. (3) The dose of Botox necessary to see a clinical change in torticollis was found to vary considerably from person to person. This is not the case in blepharospasm.

We now have carried out a double-blind, placebo-controlled study of Botox injections in the treatment of torticollis to document the effectiveness of the injections, and also to address the following issues: (1) the response rate to Botox, (2) the magnitude of the response to Botox, (3) the duration of benefit from Botox injections, (4) the relationship between dose and re-

sponse, (5) the response of pain to the injections, (6) side effects from Botox injections, and (7) whether subgroups of patients with torticollis (eg, pure retrocollis or tilt, patients with tonic vs. jerky torticollis, etc) have a significantly different response to the injections.

Methods. Patients with idiopathic torticollis who had failed to get substantial response from at least 2 drug trials (including at least 1 trial of anticholinergics to tolerance) were enrolled in the study. We excluded patients with a known or suspected cause for the torticollis, a prior thalamotomy or peripheral (nerve or muscle) operation, and patients who had previously received Botox injections. All patients who met these inclusion and exclusion criteria were invited to participate in the study, which was approved by the Institutional Review Board. Fifty-five patients signed consents and were enrolled between March 1987 and August 1988. Two blinded physicians gave the injections, determined the degree of head turning and disability, and videotaped the patients; but they did not examine the strength or size of the neck muscles, so that the presence of muscle atrophy would not identify patients receiving active injection. Two unblinded physicians drew up Botox or saline into syringes for injection, examined the patients for strength and size of neck muscles, evaluated them for adverse effects and subjective responses, and were available to answer questions in case of emergencies.

Each patient had 5 scheduled visits to the Dystonia Clinical Research Center at Columbia-Presbyterian Medical Center, and all were encouraged to make a final 6th visit. During the initial visit, patients were examined by the unblinded physicians and questions about the severity of their torticollis. They were divided into 3 cells (A, pure rotational torticollis; B, tor-

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Table 1. Doses, injection sites, and number of patients enrolled in each cell

	Total dose (units)	No. of Injection sites
Cell A: pure rotational torticollis (N = 26)		
Contralateral sternocleidomastoid	40	8
Ipsilateral trapezius	55	11
Contralateral trapezius	45	9
Cell B: torticollis plus retrocollis (N = 9)		
Contralateral sternocleidomastoid	40	8
Ipsilateral trapezius	55	11
Contralateral trapezius	55	11
Cell C: head tilt ± torticollis and retrocollis (N = 20)		
Contralateral sternocleidomastoid	40	8
Ipsilateral trapezius	55	11
Contralateral trapezius	55	11
Splenius capitis ipsilateral to direction of tilt	15	3

Directions relative to direction of chin turning except where indicated.

torticollis plus retrocollis; and C, head tilt with or without torticollis and retrocollis). In order to ensure reasonable balance of Botox and placebo injections in each cell, randomization was stratified by cell type, which was completed for blocks of 4 sequentially enrolled patients in each cell type. The blinded physicians then rated them according to the Columbia torticollis rating form.⁵ They were videotaped according to a standard protocol: seated with eyes closed while instructed to relax completely, turning maximally toward and opposite to the direction of torticollis, and walking back and forth. They were also asked to attempt to keep their head facing forward for up to 30 seconds. The blinded physicians then injected them with Botox or saline, using syringes filled by the unblinded physicians according to the protocol for cells A, B, or C. Botox was provided by Dr. A. Scott (San Francisco, CA) and dissolved in normal saline to a concentration of 2.5 units per 0.1 ml. The doses per muscle for each cell are shown in table 1. The injection sites were distributed evenly over the respective muscles. The muscles, distribution of injection sites over each muscle, and total dose per muscle were derived empirically during prior open-label injections of Botox in 36 patients with various forms of torticollis. Mean calculated doses were then cut by half because of safety concerns by the FDA.

Subjects returned in 2 weeks (visit 2), 6 weeks (visit 3), and 12 weeks (visit 4). During each of these visits, the unblinded physicians examined them to grade the size and strength of the right and left sternocleidomastoids and trapezii, and asked about possible adverse effects. The subjects were asked by the unblinded physicians to evaluate change in the torticollis relative to baseline according to 3 scales:

(1) Res scale (results of injection): +3 = markedly improved, very happy with results; +2 = moderately improved, happy with results; +1 = slightly improved, but not significantly; 0 = no change; -1 = slightly worse, but not significantly; -2 = definitely worse.

(2) Cap scale (functional capacity): from 0% = completely disabled to 100% = fully functional.⁵

(3) Pain scale: from 0% = no difference in pain from before injections to 100% = complete pain relief.

The blinded physicians completed the Columbia Torticollis Rating Scale and repeated the standard videotaping. The videotapes for all visits were rated by the blinded observers who recorded degree of head turning at rest, degree of head turning while walking, maximum degree of head turning opposite to direction of torticollis, and duration of time in seconds that the head could be kept straight. Head turning was rated as the degree of rotation except in a small number of patients who had essentially pure tilt or retrocollis; in these patients, the degree of tilt or retrocollis was scored.

The double-blind phase was completed at week 12, the code was broken to the patients, and the open phase began. All patients received active (Botox) injections at the same doses assigned to the cell they were in. They returned in 2 weeks for visit 5. At visit 5, all patients had the option of receiving extra injections if they had not received satisfactory benefit from the injections at visit 4. The dose and location of these optional injections was at the discretion of the injecting physician based on the patient's complaints and examination at that time. The total dose of the optional injections varied from 30 to 250 units (mean of 118 units). Those patients who received the booster injections were urged to return in 2 weeks for visit 6 to be examined and videotaped.

All patients completed visits 1 through 3, but 3 missed visit 4. One experienced swallowing difficulty and did not want to continue with the program. A 2nd patient was discouraged that he had not received benefit. A 3rd patient fell and suffered a broken leg and was unable to make her number 4 visit. All had received Botox. In addition, there were some lost data, including videotape segments that were inadvertently destroyed. Pain data were not obtained for visit 2 and were obtained for visit 3 by phone after the visit. The amount of missing data for visits 1 through 3 varied from 5.5% to 10.9% of the total amount of data. From visit 4, 12.7% of the total data were missing. We present mean scores for placebo and Botox patients at each visit, and all statements of statistical significance are based on comparisons of matched pairs.

Videotapes of each patient visit were rated by the 2 blinded observers independently, and the mean of the 2 values was used for analysis. For degree of head turning at rest and walking, and maximum degree of head turning opposite to direction of torticollis, ratings of the 2 observers were correlated ($r = 0.74$ to 0.89). The duration of time the head could be kept straight was difficult to score reproducibly, even for the same observer (especially in the presence of tremor), and was not used in the analysis.

All patients received single-fiber EMG studies performed by a physician who was blinded to what the patients had received. The studies were performed at visit 1 before Botox or saline injections and at visits 2 (week 2) and 4 (week 12). These results will be reported separately.

Data were entered into the Clinfo computer system and analyzed using the SAS statistical software program.

Results. Age at entry into study, sex ratio, duration of torticollis, severity of torticollis, and percentage of patients with pain were comparable in the Botox and placebo groups (table 2).

Double-blind phase. Benefit. Maximum benefit was seen at visit 3 (6 weeks after the injections). Analyses of covariance were done on the results at that time adjusting for baseline measures where appropriate. The subjects had a significant improvement in Cap, Pain, and Res scores compared with the control group. Head turning at rest and with walking were also significantly improved in the subjects compared with the controls. Ability to turn the head in the direction opposite to

Table 2. Patient characteristics

	Botox (N = 28)	Placebo (N = 27)
Male	11 (39%)	9 (33%)
Female	17 (61%)	18 (67%)
	NS by chi-square	
Mean age when injected	46.8 yrs	52.6 yrs
	NS by t test	
Mean duration of disease	6.6 yrs	9.8 yrs
	NS by t test	
Severity		
Mild	2	3
Moderate	20	13
Severe	6	11
	NS by chi-square combining mild and moderate	
Jerks		
Absent	8	9
Mild	13	12
Moderate	6	3
Severe	1	3
	NS by chi-square combining moderate and severe	
Presence of pain	20 (71%)	18 (67%)
	NS by chi-square	

direction of involuntary head turning was not significantly different in subject and control groups. When the Bonferroni correction for multiple tests was applied, all analyses except for functional capacity (Cap) remained significant at the $p < 0.05$ level. The results are shown in table 3.

Time course of benefit. The time course of improvement after the injections is obtained by comparing the responses at visits 2, 3, and 4. This is best appreciated in the curves shown in figures 1 through 4. Although we had initially expected to see maximum benefit at 2 weeks after injection, some patients did not achieve maximum benefit until later.

Amount of improvement. At visit 2, 11 subjects receiving Botox (41%) reported no improvement, 5 (19%) reported minimal improvement (Res score, 1), 5 (19%) reported moderate improvement (Res score, 1.5 to 2), and 2 (7%) reported marked improvement (Res score, 2.5 to 3). Four subjects (14%) reported worsening. By visit 3, 3 (11%) were worse than before injections, 8 (29%) had no improvement, 6 (21%) had minimal improvement, 8 (29%) had moderate improvement, and 3 (11%) had marked improvement.

The amount of improvement due to Botox injections can best be estimated by examining those patients who responded to the Botox. For this analysis, we will consider only patients who received Botox during the double blind phase. We defined responders to be those 17 of 28 (61%) patients with a Res score of 1 or more at visit 3 (mean Res score for this group was 1.8). These patients reported a mean improvement in Cap score of 14%. They experienced a mean change of 17 degrees in head turning at rest, and 22 degrees in head turning while

Table 3. Response to injections

Response (scale)	p value	Group	Baseline	Visit 3	Improvement
Cap (0-100)	0.0097	Botox	39.4	49.1	9.7
		Placebo	47.3	43.4	-3.9
Opp (0-90)	NS	Botox	59.8	62.8	3.0
		Placebo	69.6	66.3	-3.3
Rest (0-90)	0.0001	Botox	63.3	50.7	12.6
		Placebo	71.1	73.7	-2.6
Walk (0-90)	0.0016	Botox	54.8	39.0	15.8
		Placebo	44.1	42.1	2.0
Pain (0-100)	0.0029	Botox		39.5	39.5
		Placebo		4.7	4.7
Res (-3-+3)	0.0001	Botox		0.9	0.9
		Placebo		-0.5	-0.5

When the Bonferroni correction for multiple tests is used, everything but Cap retains significance at the 0.05 level.

Cap Functional capacity scale, percent of normal functioning.
 Opp Maximum extent of head turning opposite to direction of head turning measured in degrees.
 Rest Extent of head turning at rest measured in degrees.
 Walk Extent of head turning while walking measured in degrees.
 Pain Percent improvement in pain.
 Res Result scale.

walking. The mean improvement in pain for 11 patients with pain was 63%.

Subgroup analysis. We analyzed outcome of injections against the following subgroups of patients: (1) type of torticollis: pure retrocollis, pure tilt, all others ("typical torticollis"); (2) severity of head turning: mild, moderate, severe; (3) jerkiness of torticollis: absent, mild, moderate, severe; (4) sex: men, women; (5) age at time of injection; (6) duration of symptoms at the time of injection.

Analyses of covariance were performed with the subgroups as covariates. No subgroup was consistently different in response from the group as a whole (some subgroups differed in 1 outcome measure at some visit). In particular, patients with severe torticollis and patients with jerky torticollis did as well with Botox injections as the group as a whole. We analyzed the subgroups with pure tilt and pure retrocollis separately. There was no significant difference between placebo and Botox treated patients in either subgroup, but the numbers were small.

Side effects. Side effects can be divided into immediate side effects (within 24 hours) and delayed side effects.

Immediate side effects. Five people complained of severe local pain at the time of injection (3 subjects, 2 controls). Eleven people complained of persistent pain lasting at least 24 hours in the area of the injections (5 patients, 6 controls).

Delayed side effects. Three patients who received Botox had swallowing difficulty or a sensation of choking after the injections. These symptoms lasted 4 weeks for 1 patient and 6 weeks for the other 2, and were mild in 2 cases and moderate in the 3rd case.

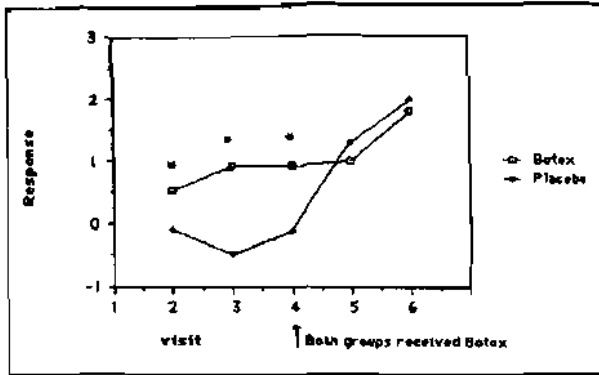


Figure 1. Results of injection. * $p < 0.05$ by paired t test.

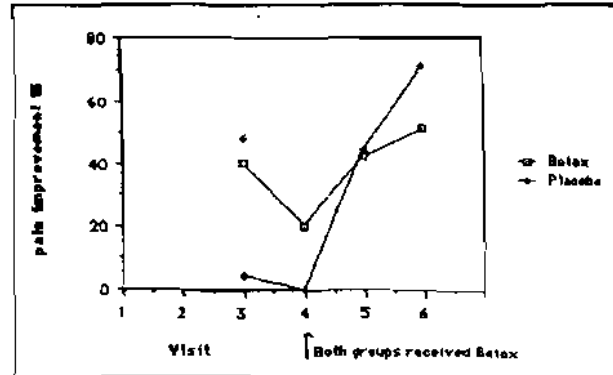


Figure 3. Improvement of pain over time. * $p < 0.05$ by paired t test.

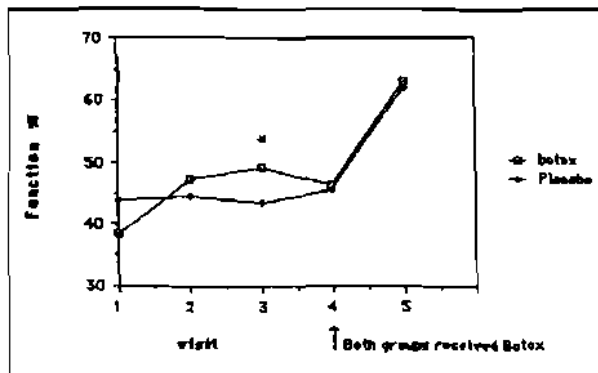


Figure 2. Functional capacity. * $p < 0.05$ by paired t test.

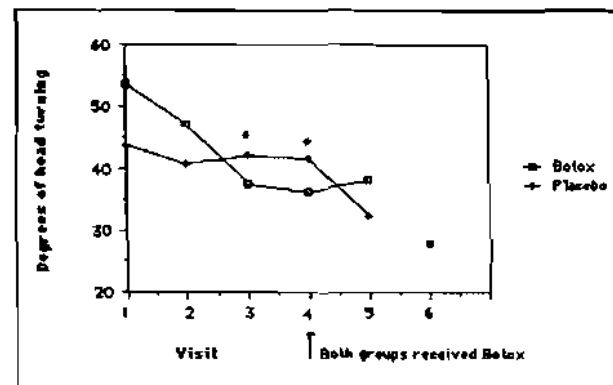


Figure 4. Degree of head turning while walking. * $p < 0.05$ by paired t test. * Botex and placebo groups combined.

Two patients who received Botox complained of generalized weakness lasting 2 weeks for 1 and 3 days for the other. Both were examined 2 weeks after the injections and neither had limb weakness. Both had moderate weakness of neck extension and rotation. Another patient receiving Botox experienced neck weakness without generalized weakness.

Five patients experienced fatigue, lasting 1 to 6 weeks in 4 patients receiving Botox and 2 days in 1 patient who received placebo.

Three patients receiving Botox experienced headache or nausea lasting hours to days.

Four patients experienced increased spasms after the injections (1 receiving placebo and 3 receiving Botox). One of the patients receiving Botox had right turning torticollis. She developed severe spasms in the right trapezius and had to receive an extra 55 units injected into that muscle 5 days after the initial injections. This reduced the spasms by visit 2, and she ultimately had subjective and objective benefit from the injections. The other 2 patients receiving Botox had increased spasms lasting 2 days and 2 weeks, respectively, and both ultimately benefitted from the injections.

In addition to the delayed side effects already listed, patients receiving Botox experienced transient paresthesias (2 patients), episodes of "lightning pains" (1), and hives (1). One patient receiving placebo had hand swelling and 1 developed a boil on the abdomen.

Open phase. The subjective and objective measures of torticollis examined during the double-blind phase can also be examined after the injections at visit 4 (same doses as visit 1) and after the larger cumulative dose given at visits 4 and 5 (2 weeks apart). Of course, these assessments were no longer blind.

Evaluation at visit 5 demonstrated that the subject group appeared to benefit more from the injections at visit 4 than the injections at visit 1 (figures 1 through 4), even though the same injection schedule was used. We suspect that this represents residual effect of the Botox remaining at 12 weeks after the injection. The group that originally received placebo experienced improvement 2 weeks after their 12-week injections that was comparable to the change in the double-blind subject group 2 weeks after their 1st injections.

Thirty-four patients were examined at visit 6, ie, 2 weeks after their 2nd injection (visit 5). There is a suggestion that they experienced greater improvement after this larger dose of Botox (approximately 240 units per patient) than after their Botox injections at the lower dose (approximately 145 units per patient). Mean improvement in pain went from 40% at the lower dose to 61% at the higher dose ($p = 0.003$); mean Res score went from 0.9 at the lower dose to 1.9 at the higher dose ($p = 0.005$). Objective measures were not significantly

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different at the higher dose, possibly because of the small number of patients compared. This is seen graphically in figures 1 through 4.

Discussion. A large, uncontrolled study of the use of Botox injections for treating torticollis found a 70.7% improvement rate.⁶ There have been 3 other double-blind studies of Botox injections in torticollis.⁷⁻⁹ Gelb et al⁷ injected 20 patients with placebo, low doses (50 to 70 units), intermediate doses (100 to 140 units), or higher doses (200 to 280 units) of Botox. They found no statistically significant improvement in an objective torticollis rating score at any dose (compared with placebo), but did find substantial subjective improvement in 16 of 20 patients.

Tsui et al⁸ injected 21 patients with 100 units of Botox—50 units in each of 2 muscles. They used the same rating score and found a statistically significant improvement in objective and subjective measures. They did not estimate the amount of subjective improvement, but the objective score improved a mean 2/11 (18%) in Botox-treated patients compared with a mean improvement of 0.3/11 (3%) in controls.

Jankovic and Orman⁹ injected 7 patients with torticollis during the double-blind phase of their study. Although significantly more patients improved with Botox than with placebo, the degree of improvement was not significant. In addition, some of these patients had injections for oromandibular dystonia. They did not analyze separately the patients injected for torticollis alone.

The objective rating score used by the 1st 2 groups^{7,8} is not particularly sensitive. They used a composite objective score T:

$$T = [(R + L + E) \times DS] + [U \times DU]$$

where R equals rotation (0, absent; 1, <15 degrees; 2, 15 to 30 degrees; 3, >30 degrees); L equals tilt (0, absent; 1, mild; 2, moderate; 3, severe); E equals shoulder elevation (0, absent; 1, mild; 2, severe); DS equals duration of R, L, and E (1, intermittent; 2, continuous); U equals tremor or jerks (0, absent; 1, present); and DU equals duration of tremor/jerks (1, intermittent; 2, continuous).

In the plausible case of a patient with 60 degrees of rotation who improves to 15 degrees of rotation without change in tilt, tremor, or shoulder elevation, the score would go from 14 to 12, a change of only 14.3%. This change would have been considered "less than substantial" by the criterion of a 3-point change used by Gelb et al.⁷

We found Botox to be of subjective and objective benefit in the treatment of torticollis. By 6 weeks after the injections, 39% of patients treated with Botox experienced a moderate or marked subjective improvement (11% had a marked improvement) compared with 0% of controls. We found statistically significant improvement in pain, head turning at rest, and head turning while walking. During the open (nonblinded) phase, 2 weeks after injections at a higher dose (visit 6), 25/34 (74%) experienced a moderate or marked improvement (32% had a marked improvement).

For most patients, there was greater improvement at higher doses than at lower doses. Even so, some patients benefit from the lower doses. Our results suggest that there is considerable variation among patients as to the optimal dose. We suggest that patients initially receive modest doses of Botox, and that the dose be gradually increased at subsequent visits to maximize benefit and avoid dose-related side effects. The choice of muscles to inject, the concentration of Botox, and the number and location of sites were determined during prior open label trials. They do not necessarily represent the optimal technique for the treatment of torticollis. Hopefully, further experience with Botox will determine which techniques are the most successful.

Improvement after injections was delayed from 2 to 6 weeks in some patients. Most of our patients request repeat injections approximately every 3 months. Our observations indicated that there was still residual benefit at this time. Examination of muscle bulk confirmed this, since we frequently found that an injected sternocleidomastoid muscle had not returned to normal bulk at 3 months. These observations should be considered when planning injections doses and schedules.

Only 2 patients discontinued Botox injections because of side effects, both with swallowing difficulties. From subsequent experience, we believe that swallowing difficulty arises because of local spread after injections into the lower portion of the sternocleidomastoid or splenius capitus and can probably be avoided.

Three patients experienced a temporary increase in spasms after Botox injections, 1 requiring supplemental injections because of the severity of the spasms. We have subsequently observed this phenomenon after Botox injections in other patients with torticollis. We suspect that in some patients, improvement in head turning un masks the action of less affected muscles or triggers the involvement of new muscles in dystonia.

We consider Botox a valuable treatment for spasmodic torticollis. Anticholinergic therapy, the best single systemic drug therapy for torticollis, may benefit between 40% to 50% of patients treated.¹⁰ The response rate to Botox injections was 74% at an appropriate dose, making it superior to the best drug therapy. Side effects of Botox injections were mild and infrequent compared with the considerable side effects seen with high-dose pharmacotherapy.

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Environmental risk factors in Parkinson's disease

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Article abstract—To investigate possible risk factors for Parkinson's disease (PD) we conducted a case-control study of 150 PD patients and 150 age- and sex-matched controls. We interviewed and examined all 300 subjects. We collected demographic data including lifetime histories of places of residence, source of drinking water, and occupations such as farming. Subjects completed a detailed questionnaire regarding herbicide/pesticide exposure. Rural living and drinking well water were significantly increased in the PD patients. This was observed regardless of age at disease onset. Drinking well water was dependent on rural living. There were no significant differences between cases and controls for farming or any measure of exposure to herbicides or pesticides. These data provide further evidence that an environmental toxin could be involved in the etiology of PD.

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The cause of Parkinson's disease (PD) is unknown. Parkinsonism occurred as a sequela of the epidemic of encephalitis in 1917-1926,¹ but there is no evidence that PD is related to an infectious process.² Studies of monozygotic twins have found a low concordance rate suggesting a limited role for heredity.³⁻⁵ Age-related loss of the nigrostriatal dopamine system occurs but is insufficient to cause parkinsonism.^{6,7} It would therefore appear that PD is acquired. The discovery that the clinical, biochemical, and pathologic features of PD^{8,9} are caused by the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) suggests that a similar neurotoxin may cause PD. A plant-derived excitatory neurotoxin may be responsible for the Guamanian amyotrophic lateral sclerosis-parkinsonism-dementia complex (ALS-PDC).¹⁰ Several investigators hypothesized that exposure to an environmental toxin may be responsible for PD.¹¹⁻¹³ Epidemiologic studies have indicated that living in a rural environment, farming, drinking well water, and occupational herbicide/pesticide exposure may be risk factors for PD.^{14,15} The state of Kansas is a suitable location to study these variables because of its combination of urban and rural agricultural economy. We have therefore investigated these factors in a case-control study.

Methods. One hundred fifty patients with PD and an equal number of age- (± 2 years) and sex-matched controls were studied. PD patients were randomly selected from the Movement Disorder Clinic (University of Kansas Medical Center) and control subjects were attending neurologic and medical clinics (University of Kansas Medical Center). These clinics are university based and receive referrals from the entire state of Kansas. The diagnosis of PD was based on the presence of 2 or more of the cardinal signs of the disease (tremor, rigidity, bradykinesia, and postural instability) and responsiveness to levodopa therapy. All patients were examined by the same neurologist (W.C.K.). Age at disease onset was defined as the age at which the 1st symptom became evident. Patients with atypical features suggesting a multiple system atrophy or postencephalitic or other forms of secondary parkinsonism were excluded. All control subjects were examined, and those with any parkinsonian signs were excluded. Individuals with exposure to neuroleptics and severe dementia were not included in the study. Information was collected by means of a questionnaire administered by a trained interviewer in a face-to-face interview with the subject and family, if available. Sociodemographic data were obtained including the number of years spent in rural versus urban living, number of years spent farming, number of years drinking well water, and exposure to herbicides or pesticides. Rural living was defined as residing in a town with a population less than 2,500 people (U.S. Bureau of Census criterion). The population of cities in

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