

POSTEROVENTRAL MEDIAL PALLIDOTOMY IN ADVANCED  
PARKINSON'S DISEASE

ANTHONY E. LANG, M.D., ANDRES M. LOZANO, M.D., ERWIN MONTGOMERY, M.D., JAN DUFF, R.N.,  
RONALD TASKER, M.D., AND WILLIAM HUTCHINSON, PH.D.

**ABSTRACT**

*Background* Posteroventral medial pallidotomy sometimes produces striking improvement in patients with advanced Parkinson's disease, but the studies to date have involved small numbers of patients and short-term follow-up.

*Methods* Forty patients with Parkinson's disease underwent serial, detailed assessments both after drug withdrawal ("off" period) and while taking their optimal medical regimens ("on" period). All patients were examined preoperatively, and 39 were examined at six months; 27 of the patients were also examined at one year, and 11 at two years.

*Results* The percent improvements at six months were as follows: off-period score for overall motor function, 28 percent (95 percent confidence interval, 19 to 38 percent), with most of the improvement in the contralateral limbs; off-period score for activities of daily living, 29 percent (95 percent confidence interval, 19 to 39 percent); on-period score for contralateral dyskinesias, 82 percent (95 percent confidence interval, 72 to 91 percent); and on-period score for ipsilateral dyskinesias, 44 percent (95 percent confidence interval, 29 to 59 percent). The improvements in dyskinesias and the total scores for off-period parkinsonism, contralateral bradykinesia, and rigidity were sustained in the 11 patients examined at two years. The improvement in ipsilateral dyskinesias was lost after one year, and the improvements in postural stability and gait lasted only three to six months. Approximately half the patients who had been dependent on assistance in activities of daily living in the off period before surgery became independent after surgery. The complications of surgery were generally well tolerated, and there were no significant changes in the use of medication.

*Conclusions* In late-stage Parkinson's disease, pallidotomy significantly reduces levodopa-induced dyskinesias and off-period disability. Much of the benefit is sustained at two years, although some improvements, such as those on the ipsilateral side and in axial symptoms, wane within the first year. The on-period symptoms that are resistant to dopaminergic therapy do not respond to pallidotomy. (N Engl J Med 1997;337:1036-42.)

©1997, Massachusetts Medical Society.

**D**ESPITE the introduction of several new medical therapies, patients with advanced Parkinson's disease continue to have fluctuations between pronounced increases in parkinsonism ("off" periods) and episodes of improved mobility ("on" periods), which are often complicated by choreoathetotic movements (dyskinesias). For this reason, there has been a resurgence of interest in neurosurgical interventions, particularly posteroventral medial pallidotomy. Defining the role of such an invasive therapy requires a long-term prospective study of a large number of patients using methods of evaluation with established sensitivity during off and on periods. To date, none of the few reports describing the effects of posteroventral medial pallidotomy have met these criteria. We performed a follow-up study of 40 patients undergoing pallidotomy, with evaluations at six months, one year, and two years.

METHODS

**Patients**

Forty patients with idiopathic Parkinson's disease underwent posteroventral medial pallidotomy between June 1993 and January 1996 (Table 1). All the patients had initially had good responses to levodopa with the subsequent development of marked disability due to off-period immobility, disabling levodopa-induced dyskinesias, and increasing disability during the on period primarily from ambulatory disturbances, despite an optimal regimen of available antiparkinsonian drugs. Exclusion criteria included marked cognitive dysfunction, active psychiatric symptoms, concurrent neurologic or other, uncontrolled medical disorders, or previous brain surgery. Four additional patients underwent surgery but no lesions were made; these patients are not included in the analysis. Complications in these four patients included intracerebral hemorrhage requiring surgical evacuation (in one patient), unsuccessful microelectrode mappings (in two), and an exacerbation of paranoia (in one).

**Evaluations**

Patients were evaluated clinically as reported previously,<sup>2</sup> with the use of a modified<sup>3</sup> Core Assessment Program for Intracerebral Transplantation.<sup>4</sup> Follow-up evaluations were performed at 1 week in the first 27 patients and at 3, 6, 12, and 24 months in 39, 39, 27, and 11 patients, respectively. When possible, postoperative doses of antiparkinsonian medications were maintained at the

From the Divisions of Neurology (A.E.L., J.D.) and Neurosurgery (A.M.L., R.T., W.H.), Toronto Hospital, Toronto, and the Department of Neurology, University of Arizona, College of Medicine, Tucson (E.M.). Address reprint requests to Dr. Lang at Toronto Hospital Movement Disorders Centre, 399 Bathurst St., MP 11-306, Toronto, ON M5T 2S8, Canada.

preoperative levels. Many patients, however, changed their medication doses because of reduced needs, particularly in the immediate postoperative period.

During the follow-up period, nine patients underwent additional surgical procedures. A repeated ipsilateral lesion was made in one patient after three months of follow-up. The initial lesion had been placed suboptimally, in a more anterior and dorsal position than usual, for fear of creating a visual deficit, because the optic tract could not be identified with certainty (the patient did not report seeing phosphenes in response to electrical stimulation at the location of the optic tract predicted by microrecording). In the second procedure, the optic tract was identified unequivocally with the use of light-flash-evoked action-potential microrecording, and the lesion was placed ventrally in a more appropriate location. After this operation, there was a marked improvement, especially in the patient's incapacitating dyskinesias. The other eight patients underwent contralateral procedures: pallidotomies in two patients (at 6 and 18 months), and implantation of deep brain stimulators in six (at 9 to 18 months). All eight patients had had improvement after unilateral pallidotomy and had requested a second procedure for persistent and disabling ipsilateral symptoms. These patients had further improvement after the second procedure, as reported elsewhere.<sup>5,7</sup> For each of these nine patients, data on efficacy are included only to the last follow-up examination before the second surgical procedure, because including the subsequent follow-up data would have biased the results in favor of the initial procedure.

**Surgical Procedure**

The methods we used for microelectrode-guided posteroventral medial pallidotomy have been described in detail elsewhere.<sup>2,8</sup> Microelectrode recordings and stimulation were used to identify the sensorimotor territory of the internal segment of the globus pallidus, the optic tract, and the internal capsule. One or two largely overlapping radiofrequency lesions, 6 mm in diameter, were produced with the use of a thermistor-coupled probe, 1 mm in diameter, with a 3-mm exposed tip. The temperature of the tissue at the lesion reached 60°C, 70°C, 80°C, and finally, 90°C for 60 seconds.

**Statistical Analysis**

Follow-up evaluations were performed at three and six months in 39 patients. The evaluation at six months was chosen for the assessment of early efficacy in the hope of reducing the influence of the placebo response, which should have been larger at three months than at six months. For the analysis of long-term efficacy, the patients were divided into two groups, those followed for one year (27 patients) and those followed for two years (11 patients), who were also included in the one-year group.

The primary measure of efficacy was the overall score on the Unified Parkinson's Disease Rating Scale<sup>1</sup> (defined as the combined scores for activities of daily living and motor function, Parts II and III of the scale) in the off and on periods. The range of possible scores was 0 to 52 for activities of daily living and 0 to 108 for motor function, with a range of 0 to 160 for the combined score. Lower scores indicate better function. Secondary measures included the Schwab and England Activities of Daily Living Scale and subscores of the Unified Parkinson's Disease Rating Scale for tremor, rigidity, bradykinesia, postural instability and gait disorder, and dyskinesias, as defined previously.<sup>2</sup> Pairwise comparisons between the results of the base-line evaluation and the results of the follow-up evaluations were made with Student's t-test or the Wilcoxon signed-rank test, as appropriate.

For the long-term groups, we used an analysis of variance with repeated measures or a nonparametric Friedman's analysis of variance with repeated measures on ranks. If no significant difference was found, a power analysis was performed. A correlational analysis was also used to detect any trend in loss of improvement over time (with a slope of zero indicating sustained improvement). In view of the number of repeated analyses, a P value of 0.005 was

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.**

CHARACTERISTIC	VALUE
Sex (no. of patients)	
Male	26
Female	14
Age (yr)	
Mean ±SD	58.8±8.2
Range	44-72
Duration of disease (yr)	
Mean ±SD	12.9±4.8
Range	4-25
Schwab and England ADL score (%)*	
On period	
Mean	78
Range	35-100
Off period	
Mean	39
Range	10-70
Hoehn and Yahr stage†	
On period	
Median	2.5
Range	1.5-5.0
Off period	
Median	3.5
Range	2.0-5.0
Side of surgery (no. of patients)	
Right	26
Left	14
Medications‡	
Levodopa and PDCI	
No. of patients	40
Mean dose (mg)	1096
Range	300-2600
Bromocriptine	
No. of patients	10
Mean dose (mg)	23.1
Range	5-47.5
Pergolide	
No. of patients	19
Mean dose (mg)	3.2
Range	0.2-11.25
Total levodopa equivalents	
No. of patients	40
Mean dose (mg)	1153
Range	300-2250

\*The Schwab and England score for activities of daily living (ADL) is based on a scale from 0 to 100, with a higher score indicating better function.<sup>1</sup>

†The Hoehn and Yahr stage of parkinsonism is based on a scale from 0 to 5, with a lower stage indicating higher function.<sup>1</sup>

‡PDCI denotes peripheral decarboxylase inhibitor. The total levodopa equivalent was calculated as the regular dose of levodopa plus carbidopa (or benserazide) + (0.75 × the dose of controlled-release levodopa plus carbidopa) + (10 × the dose of bromocriptine) + (100 × the dose of pergolide).

considered to indicate statistical significance, in order to avoid a type I error. To provide 95 percent confidence intervals, the mean of the percent change in scores for individual patients was used rather than the percent change in mean total scores.

A secondary hypothesis of the study was that pallidotomy would result in clinically significant improvement. This hypothesis was tested by examining the effects of pallidotomy on specific test items in the activities-of-daily-living scale that represent impor-

**TABLE 2.** MEAN ( $\pm$ SD) OFF-PERIOD AND ON-PERIOD SCORES BEFORE AND SIX MONTHS AFTER UNILATERAL PALLIDOTOMY IN 39 PATIENTS.\*

DISABILITY	SCORE RANGE	OFF-PERIOD SCORE			ON-PERIOD SCORE		
		BASE LINE	6 MONTHS	P VALUE	BASE LINE	6 MONTHS	P VALUE
Overall	0-160	68.8 $\pm$ 13.3	47.9 $\pm$ 17.0	<0.001	27.6 $\pm$ 11.7	23.6 $\pm$ 13.5	0.043
ADL	0-52	24.6 $\pm$ 5.1	17.2 $\pm$ 7.0	<0.001	10.3 $\pm$ 5.0	7.2 $\pm$ 5.3	0.004
Motor	0-108	44.4 $\pm$ 11.2	30.7 $\pm$ 11.5	<0.001	17.4 $\pm$ 8.7	16.5 $\pm$ 9.3	0.6
Schwab and England ADL	0-100	39.0 $\pm$ 17.5	65.1 $\pm$ 15.8	<0.001	78.2 $\pm$ 14.3	85.2 $\pm$ 9.3	0.007
PIGD	0-20	10.3 $\pm$ 3.9	7.1 $\pm$ 4.1	<0.001	4.7 $\pm$ 3.6	3.7 $\pm$ 3.6	0.024
Gait	0-4	2.3 $\pm$ 0.9	1.8 $\pm$ 1.1	0.006	1.0 $\pm$ 0.7	0.9 $\pm$ 0.9	0.61
Postural stability	0-4	2.1 $\pm$ 0.9	1.4 $\pm$ 1.0	<0.001	1.2 $\pm$ 0.9	1.0 $\pm$ 1.0	0.1
Freezing	0-4	2.3 $\pm$ 1.0	1.4 $\pm$ 1.1	<0.001	0.7 $\pm$ 0.8	0.5 $\pm$ 0.8	0.098
Ipsilateral side							
Bradykinesia	0-16	7.3 $\pm$ 2.9	5.9 $\pm$ 3.1	0.001	3.2 $\pm$ 2.1	3.4 $\pm$ 2.6	0.74
Tapping†		13.5 $\pm$ 6.0	11.1 $\pm$ 2.8	0.003	10.1 $\pm$ 2.5	9.1 $\pm$ 2.5	0.006
Contralateral side							
Bradykinesia	0-16	9.4 $\pm$ 2.7	5.5 $\pm$ 3.1	<0.001	3.9 $\pm$ 2.4	4.1 $\pm$ 2.7	0.67
Tremor	0-12	2.9 $\pm$ 2.7	1.3 $\pm$ 1.8	<0.001	0.4 $\pm$ 0.9	0.2 $\pm$ 0.6	0.47
Rigidity	0-8	3.7 $\pm$ 2.2	1.7 $\pm$ 1.4	<0.001	1.4 $\pm$ 1.3	1.0 $\pm$ 1.3	0.098
Tapping†		17.8 $\pm$ 14.3	12.1 $\pm$ 8.5	0.003	11.0 $\pm$ 5.8	9.4 $\pm$ 3.8	0.002

\*ADL denotes activities of daily living, and PIGD postural instability-gait disorder. Lower scores indicate better function for all items except the Schwab and England ADL score. Scores are described in detail in Lozano et al.<sup>2</sup>

†The score for tapping was calculated as the time (in seconds) required to complete a simple tapping test.

tant daily self-care functions (feeding, dressing, and personal hygiene), two components of the motor section of the scale that are related to ambulatory ability (gait and postural stability), and the severity of contralateral dyskinesias as scored on the dyskinesia rating scale. For each of these items, a score of 2 or higher (out of 4) generally indicates some degree of dependence on others for care or a major interference in function. With the exception of the analysis of dyskinesias, this evaluation was applied only to the worst off period, since there were insufficient numbers of patients who were dependent on others in the on period to permit conclusions. Evaluations were performed at 6 and 12 months in the one-year group and at 12 and 24 months in the two-year group.

## RESULTS

### Early Response

All 40 patients were followed for at least three months, and data were available at six months for all but 1 patient, who underwent a second procedure. Improvements in the off-period motor and activities-of-daily-living scores were in the range of 30 percent (Table 2). All off-period features of parkinsonism improved significantly on the side contralateral to the side on which surgery was performed. Ipsilateral tremor and rigidity did not change, but bradykinesia improved significantly. In the on period, there was a significant improvement only in the total activities-of-daily-living score (Schwab and England on-period scores showed a trend toward improvement [ $P=0.007$ ]). None of the motor subscores on the Unified Parkinson's Disease Rating

Scale changed significantly in the on period. Tapping scores, a measure of bradykinesia, improved significantly on both the contralateral and ipsilateral sides in the off period and to a lesser but still significant extent in the on period. Mean ( $\pm$ SD) scores for contralateral dyskinesias were dramatically reduced (from  $2.3\pm 0.9$  to  $0.4\pm 0.6$ ,  $P<0.001$ ), and scores for ipsilateral dyskinesias were reduced by 42 percent (95 percent confidence interval, 25 to 50 percent) (from  $2.0\pm 1.0$  to  $1.1\pm 0.7$ ,  $P<0.001$ ).

The effect of age at the time of surgery on the outcome was evaluated by comparing the 22 patients who were 60 years old or younger (mean age,  $53.2\pm 4.5$ ) with the 11 who were 65 or older (mean age,  $68.5\pm 2.5$ ). Overall off-period scores did not differ significantly at base line between the two groups (younger group,  $66.7\pm 13.2$ ; older group,  $69.5\pm 14.4$ ). At six months, there was a 36 percent improvement (95 percent confidence interval, 25 to 47 percent) in the younger group and a 16 percent improvement (95 percent confidence interval, 1 to 31 percent) in the older group ( $P=0.024$ ). Dyskinesias responded similarly in the two age groups.

### Long-Term Response

#### Primary Measure

The off-period scores at each of the follow-up evaluations differed significantly from the base-line

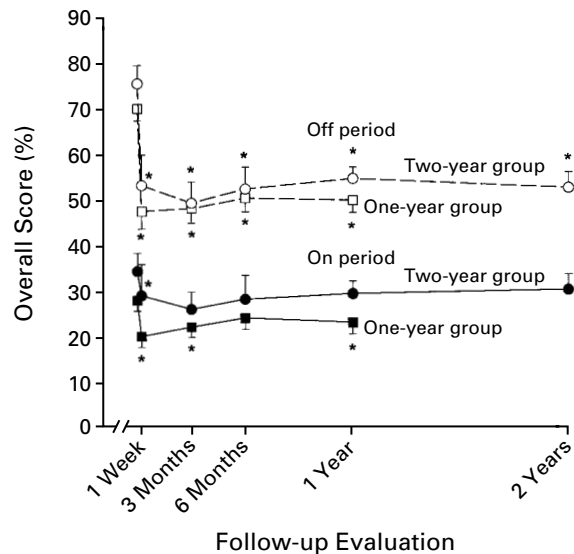
scores by an analysis of variance with repeated measures. There was no significant difference in the degree of improvement (the difference between scores at base line and each evaluation) over time (by an analysis of variance with repeated measures), suggesting sustained improvement, and the analysis demonstrated sufficient power. Regression analysis also demonstrated no significant change in the off-period scores over the follow-up period in either the one-year or the two-year group (mean regression slope, 0.065 [95 percent confidence interval,  $-0.047$  to  $0.117$ ] at one year and  $0.018$  [95 percent confidence interval,  $-0.055$  to  $0.074$ ] at two years). Three patients in the one-year group and one patient in the two-year group had slopes higher than the upper limit of the 95 percent confidence interval, suggesting some worsening of symptoms over time.

In the one-year group, the on-period scores at each postoperative evaluation were significantly different from the base-line score, with the exception of the score at six months (Fig. 1). The analysis of variance with repeated measures showed no differences in improvement at different evaluations, and the analysis showed sufficient power. The mean regression slope was  $0.009$  (95 percent confidence interval,  $-0.075$  to  $0.151$ ), indicating no change over time and a stable improvement in the on-period scores (approximately a 19 percent change). As shown in Figure 1, the improvement in the on-period scores was not sustained in the group of 11 patients followed for two years.

#### Secondary Measures

The significant improvements in off-period contralateral bradykinesia at one week (36 percent change; 95 percent confidence interval, 23 to 49 percent) and rigidity (51 percent change; 95 percent confidence interval, 32 to 68 percent) were sustained in both the one-year and the two-year groups. Improvement in tremor was sustained in the one-year group (53 percent change; 95 percent confidence interval, 35 to 71 percent). There was a tendency toward sustained improvement in the two-year group, but the changes in the scores were not statistically significant, because of the correction for multiple comparisons and the small number of patients (10) with tremor in this group. Significant improvement in the off-period composite score for postural instability and gait disorder was lost between 6 and 12 months in the one-year group and between 3 and 6 months in the two-year group.

Improvement in off-period ipsilateral bradykinesia was not sustained for more than three months in either group, and changes in the scores for other ipsilateral symptoms were not significant. As seen in the group of 39 patients at six months (Table 2), changes in the on-period scores were generally not significant or were unsustained.



**Figure 1.** Overall Scores for Activities of Daily Living and Motor Function during Off and On Periods in Patients with Parkinson's Disease Treated with Pallidotomy and Followed for One Year (27 Patients) or Two Years (11 Patients).

The overall score (on a scale of 0 to 160) was calculated as the score for activities of daily living (on a scale of 0 to 52) plus the score for motor function (on a scale of 0 to 108), with lower scores indicating better function. Analysis of variance with repeated measures showed no significant differences in scores from one week to one year (in the one- and two-year groups) or two years (in the two-year group) for the off and on periods. For all four lines, the mean regression slope did not differ from zero, indicating that the initial effect was sustained over time. The asterisks indicate scores that differed significantly from the base-line values ( $P < 0.005$ ). The bars indicate standard errors.

Improvement in contralateral dyskinesias was sustained in both the one-year and the two-year groups. Trend analysis showed a slight worsening of contralateral dyskinesias between one and two years. The improvement in ipsilateral dyskinesias was sustained in both groups at one year, but the benefit was lost by the second year.

#### Level of Dependence

Between 44 and 52 percent of the patients who were dependent on help with activities of daily living (feeding, dressing, and hygiene) in the off period preoperatively were independent at the six-month follow-up (Table 3). This level of improvement was maintained at two years for feeding and dressing but was reduced at one and two years for hygiene. Improvements in gait and postural stability occurred in a smaller proportion of patients. In approximately 75 percent of the patients, on-period contralateral dyskinesias were reduced from a level of serious interference with function to a level that posed no in-

**TABLE 3.** CHANGE FROM BASE-LINE FUNCTIONAL STATUS AT 6, 12, AND 24 MONTHS.

CHANGE FROM BASE LINE*	6 MONTHS (N=27)	12 MONTHS (N=27)		24 MONTHS (N=11)
		1-YR GROUP (N=27)	2-YR GROUP (N=11)	
		no. of patients (%)		
Feeding				
Dependence to independence	12 (44)	11 (41)	5 (45)	6 (55)
Independence to dependence	1 (4)	1 (4)	1 (9)	2 (18)
Dressing				
Dependence to independence	14 (52)	12 (44)	5 (45)	5 (45)
Independence to dependence	1 (4)	2 (7)	1 (9)	1 (9)
Hygiene				
Dependence to independence	12 (44)	7 (26)	2 (18)	2 (18)
Independence to dependence	3 (11)	2 (7)	0	0
Gait				
Dependence to independence	8 (30)	4 (15)	1 (9)	4 (36)
Independence to dependence	1 (4)	1 (4)	0	0
Postural stability				
Dependence to independence	6 (22)	10 (37)	4 (36)	2 (18)
Independence to dependence	1 (4)	1 (4)	0	0
Contralateral dyskinesias				
Serious interference to no interference	22 (81)	21 (78)	8 (73)	8 (73)
No interference to serious interference	0	0	0	0

\*Dependence or serious interference was defined as a score of 2 or higher, and independence or no interference as a score of less than 2. All data are for the off period, except for the data on contralateral dyskinesias.

terference. Additional data on outcome measures are available elsewhere.\*

#### Medications

There were no statistically significant changes in doses of individual antiparkinsonian medications or in the total dose of levodopa equivalents (Table 1) during the follow-up period.

#### Complications

Table 4 shows the complications of pallidotomy in the 40 patients. The one patient with mild pre-

\*See NAPS document no. 05424 for 17 pages of supplementary material. Order from NAPS, c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) \$7.75 for photocopies or \$5 for microfiche. Outside the U.S., add postage of \$4.50 for up to 20 pages, and \$1.00 for each 10 pages of material thereafter, or \$1.75 for the first microfiche and \$0.50 for each microfiche thereafter. There is a \$15 invoicing charge on all orders filled before payment.

operative dementia, who was enrolled early in the study period, had acute confusion and hallucinations in the immediate postoperative period. As they resolved, there was a persistent worsening in his level of cognitive dysfunction. This was the only patient in whom the disability from complications outweighed the improvement in motor function obtained from surgery. The persistent complications in the other 13 patients were generally rated as mild, and the patients and their families considered them worth tolerating for the benefit gained from the procedure. Included in this group was one patient who sustained a frontal venous infarct with persistent mild facial weakness, dysarthria, dysphagia with drooling, and behavioral changes. The transient bulbar, facial, and limb complications typically resolved within six weeks and were probably related to edema surrounding the lesion, which sometimes coursed along the internal capsule, as seen on postoperative magnetic resonance imaging scans. The persistent worsening of handwriting (in 4 of 15 patients with dominant-side lesions) was in striking contrast to the substantial improvements in all other manual activities. None of the patients had visual-field defects. Age and the side of the lesion were not correlated with the frequency or persistence of complications. All the patients underwent detailed neuropsychological testing, and many underwent formal behavioral evaluations. The preliminary results of these studies have been presented elsewhere.<sup>9</sup>

#### DISCUSSION

We present the results at six months in 39 patients with advanced Parkinson's disease treated with posteroventral medial pallidotomy, with long-term follow-up data in two overlapping groups: 27 patients followed for one year and 11 followed for two years. In this large prospective series, we used validated rating methods to assess signs and symptoms in both off periods and on periods, as well as on-period dyskinesias. Other studies have been retrospective,<sup>10-12</sup> have used nonvalidated methods of assessment,<sup>10-12</sup> have not obtained scores for defined off and on periods,<sup>10-13</sup> have reported very inconsistent data,<sup>14,15</sup> or have involved relatively small numbers of patients.<sup>16-18</sup> Despite the advantages of our study, it was uncontrolled and unblinded, and the outcome measures derived from even the best clinical rating scales have a major subjective component.

Surgery resulted in a pronounced reduction in the score for levodopa-induced contralateral dyskinesias (82 percent; 95 percent confidence interval, 72 to 91 percent). This benefit persisted during two years of follow-up, although there was a mild worsening between the one-year and two-year evaluations. Ipsilateral dyskinesias improved but to a lesser degree, and this change was sustained for one

year but was lost by the second year of follow-up. Both the activities-of-daily-living and the motor subscores in the off period improved by approximately 30 percent, and this improvement persisted for two years. The off-period subscores for tremor, rigidity, and bradykinesia improved significantly, and this benefit was sustained for two years. These changes were almost exclusively related to improvement in the contralateral limbs, although some short-term improvement in ipsilateral bradykinesia was also seen. On-period subscores showed little change, although the activities-of-daily-living scores did improve by 20 percent, possibly because of the striking reduction in dyskinesias. The off-period composite score for postural instability and gait disorder and subscores for gait, postural stability, and freezing were all significantly improved in the 39 patients followed for six months, but these improvements were not sustained. Smaller initial on-period improvement in these scores was also lost by three to six months. Complications were common but in most cases did not persist, were well tolerated, and were far outweighed by the benefit obtained from surgery. Two important exceptions were persistent dysphasia and hemiplegia due to an intracerebral hemorrhage in one patient without a lesion and permanent worsening of dementia in another patient.

Surgery resulted in an unequivocal clinical benefit. Approximately 50 percent of the patients who before surgery had been dependent on assistance in activities of daily living during the off period were independent six months after surgery, and this improvement was sustained for two years for feeding and dressing and partially declined at one year for hygiene but remained stable between one and two years. Improvements in gait and postural stability were less substantial but still evident in one third or more of the patients. Disability from dyskinesias improved markedly, and the benefit persisted for two years. These observations are particularly striking in view of the fact that the surgery was performed because no further clinical improvement could be obtained with adjustments in medication. As in the study by Baron et al.,<sup>18</sup> age at the time of surgery affected the outcome with respect to off-period parkinsonism; the patients who were 60 years old or younger had a 36 percent improvement overall, whereas those 65 years old or older had only a 16 percent improvement. Although Laitinen et al. report that the dosage of levodopa can be reduced by 50 to 75 percent after surgery,<sup>10</sup> most of our patients who were followed for one year or longer eventually required the same doses as before surgery.

The optimal candidate for pallidotomy remains to be identified. Obviously, patients severely disabled by asymmetric dyskinesias are excellent candidates for the procedure, since this feature appears to respond

**TABLE 4.** ADVERSE EFFECTS OF UNILATERAL PALLIDOTOMY IN 40 PATIENTS.\*

ADVERSE EFFECT	NO. OF PATIENTS	NO. WITH PERSISTENT ADVERSE EFFECT
Acute confusion or somnolence	4†	0
Contralateral facial weakness	14	2‡
Dysarthria	10	3‡
Dysphagia	7	2‡
Impaired memory, concentration, or judgment	5	3
Changes in personality or behavior§	3	2‡
Contralateral-limb weakness (very mild)	3	0
Contralateral hypotonia (for <12 hr)	1	0
Worsening of handwriting	10	4¶
Worsening of balance	2	2
Word-finding difficulties	1	1
Worsening of depression	1	0
Worsening of dementia	1	1
Weight gain (4 to 37 kg [8 to 82 lb] in 6 to 12 mo)	14	—
Total**		
One or more adverse effects	25	—
Two or more adverse effects	15	—
One or more persistent adverse effects	14	14

\*Four other patients were excluded because they did not undergo placement of a lesion (see the Methods section).

†Confusion or somnolence lasted from less than 24 hours to 3 to 4 days in three patients and for 2 to 3 weeks in one patient, who sustained a frontal venous infarction.

‡The one patient with a frontal venous infarction is included.

§Data on changes in personality or behavior were reported by the patients' spouses.

¶These 4 patients (of a total of 15) underwent a dominant-hemisphere procedure.

||Factors contributing to weight gain included greater ease of feeding and increased access to food in nine patients, reduced dyskinesias in six, increased appetite in five, behavioral changes (e.g., foraging) in two, and better control of diabetes in one; in nine patients, weight gain was attributable to two or more of these factors.

\*\*Weight gain is excluded.

to surgery in almost all cases. However, this effect does not seem to be correlated with the degree of improvement obtained in other spheres. In general, the greatest improvement in parkinsonism is in the signs and symptoms that are most responsive to levodopa. Symptoms that persist in the on periods remain relatively unresponsive to surgery. Our group and others have obtained uniformly poor results in patients with other "parkinson-plus" syndromes that are not responsive to levodopa, such as striatonigral degeneration, progressive supranuclear palsy, and cortical basal ganglionic degeneration.<sup>19</sup> Patients with marked preexisting cognitive dysfunction seem to

have poorer responses than others<sup>18</sup> and are at considerable risk for further cognitive decline as a result of the procedure (unpublished observations). We do not perform surgery in patients with impaired baseline neuropsychological function, because we believe there is a substantial risk of further decline to a state of disabling cognitive dysfunction.

It is unknown how long the effects of pallidotomy persist and what the long-term outcome is for patients who have undergone the procedure. A recent report by Fazzini et al. suggests that the benefit may be sustained for up to four years,<sup>20</sup> although our observations of the loss of ipsilateral and axial improvement and the degree of overall improvement are in disagreement with their findings. It is unclear whether patients who have undergone pallidotomy will have a response to new treatments — for example, glutamate antagonists,<sup>21</sup> fetal mesencephalic implantation,<sup>22</sup> or regenerative therapies such as glial-derived neurotrophic factor.<sup>23</sup> If high-frequency stimulation of the globus pallidus<sup>24</sup> or subthalamic nucleus<sup>25</sup> is shown to be at least as safe and effective as pallidotomy, it may make sense to offer this non-destructive approach, especially to younger patients, retaining the potential for a response to new treatments as they become available. However, practical issues, including cost and the large amount of time required to optimize deep brain stimulation (e.g., electrode combinations, frequency, amplitude, and pulse width), will strongly influence the final decision about surgery.

Until these questions are resolved, one can consider the use of pallidotomy in patients with late-stage Parkinson's disease who, despite optimal medical therapy, are disabled by levodopa-responsive off-period symptoms or levodopa-induced dyskinesias. Patients with predominant axial symptoms (freezing and falling), especially those that persist in the on period, with minimal dyskinesias should not be offered the procedure, nor should those with substantial cognitive decline or other levodopa-resistant parkinson-plus disorders.

Supported in part by grants from the Parkinson Foundation of Canada and the National Parkinson's Foundation. Dr. Lozano is a Medical Research Council of Canada Clinician Scientist.

*We are indebted to Drs. J. Miyasaki and N. Galvez-Jimenez for valuable assistance in evaluating and caring for the patients; to Dr. J. Dostrovsky for electrophysiologic guidance; to Dr. A. Harsin for assistance in data analysis; and to Drs. K. Kiebertz, W. Koller, and N. Quinn for helpful comments on the manuscript.*

## REFERENCES

- Lang AET, Fahn S. Assessment of Parkinson's disease. In: Munsat TL, ed. Quantification of neurological deficit. Boston: Butterworths, 1989:285-309.
- Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease. *Lancet* 1995;346:1383-7.
- Lang AE, Benabid A-L, Koller WC, et al. The Core Assessment Program for Intracerebral Transplantation. *Mov Disord* 1995;10:527-8.
- Langston JW, Widner H, Goetz CG, et al. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;7:2-13.
- Gálvez-Jiménez N, Lang AE, Lozano A, et al. Deep brain stimulation in Parkinson's disease: new methods of tailoring functional surgery to patient needs and response. *Neurology* 1996;46:Suppl:A402. abstract.
- Galvez-Jimenez N, Lozano AM, Duff J, Trepanier L, Saint-Cyr JA, Lang AE. Bilateral pallidotomy pronounced amelioration of incapacitating levodopa-induced dyskinesias but accompanying cognitive decline. *Mov Disord* 1996;11:242. abstract.
- Davis KD, Taub E, Houle S, et al. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. *Nat Med* 1997;3:671-4.
- Lozano A, Hutchison W, Kiss Z, Tasker R, Davis K, Dostrovsky J. Methods for microelectrode-guided posteroventral pallidotomy. *J Neurosurg* 1996;84:194-202.
- Saint-Cyr JA, Trepanier LL, Lang AE, Lozano AM. Neuropsychological outcome of posteroventral pallidotomy in parkinsonian patients. *Mov Disord* 1996;11:161. abstract.
- Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 1992;76:53-61.
- Svennilson E, Torvik A, Lowe R, Leksell L. Treatment of parkinsonism by stereotactic thermolesions in the pallidal region: a clinical evaluation of 81 cases. *Acta Psychiatr Neurol Scand* 1960;35:358-77.
- Laitinen LV. Pallidotomy for Parkinson's disease. *Neurosurg Clin North Am* 1995;6:105-12.
- Johansson F, Malm J, Nordh E, Hariz M. Usefulness of pallidotomy in advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;62:125-32.
- Iacono RP, Shima F, Lonser RR, Kuniyoshi S, Maeda G, Yamada S. The results, indications, and physiology of posteroventral pallidotomy for patients with Parkinson's disease. *Neurosurgery* 1995;36:1118-25.
- Iacono RP, Lonser RR, Ulloa JE, Shima F. Postero-ventral pallidotomy in Parkinson's disease. *J Clin Neurosci* 1995;2:140-5.
- Sutton JP, Couldwell W, Lew MF, et al. Ventroposterior medial pallidotomy in patients with advanced Parkinson's disease. *Neurosurgery* 1995;36:1112-6.
- Dogali M, Fazzini E, Kolodny E, et al. Stereotactic ventral pallidotomy for Parkinson's disease. *Neurology* 1995;45:753-61.
- Baron MS, Vitek JL, Bakay RAE, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. *Ann Neurol* 1996;40:355-66.
- Lang AE, Lozano A, Duff J, et al. Medial pallidotomy in late-stage Parkinson's disease and striatonigral degeneration. In: Marsden CD, Obeso JA, Delong M, Ohye C, eds. *Advances in understanding the basal ganglia and new surgical approaches for Parkinson's disease*. New York: Lippincott-Raven (in press).
- Fazzini E, Dogali M, Sterio D, Eidelberg D, Beric A. Stereotactic pallidotomy for Parkinson's disease: a long-term follow-up of unilateral pallidotomy. *Neurology* 1997;48:1273-7.
- Greenamyre JT, O'Brien CF. N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. *Arch Neurol* 1991;48:977-81.
- Kordower JH, Freeman TB, Snow BJ, et al. Neuropathological evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with Parkinson's disease. *N Engl J Med* 1995;332:1118-24.
- Gash DM, Zhang ZM, Ovadia A, et al. Functional recovery in parkinsonian monkeys treated with GDNF. *Nature* 1996;380:252-5.
- Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery* 1994;35:1126-9.
- Limousin P, Pollak P, Benazzouz A, et al. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995;345:91-5.