

ELECTRICAL STIMULATION OF THE SUBTHALAMIC NUCLEUS IN ADVANCED PARKINSON'S DISEASE

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ABSTRACT

Background In many patients with idiopathic Parkinson's disease, treatment with levodopa is complicated by fluctuations between an "off" period (also referred to as "off medication"), when the medication is not working and the motor symptoms of parkinsonism are present, and an "on" period, when the medication is causing improved mobility (also referred to as "on medication"), often accompanied by debilitating dyskinesias. In animal models of Parkinson's disease, there is overactivity in the subthalamic nucleus, and electrical stimulation of the subthalamic nucleus improves parkinsonism. We therefore sought to determine the efficacy and safety of electrical stimulation of the subthalamic nucleus in patients with Parkinson's disease.

Methods We studied 24 patients with idiopathic Parkinson's disease in whom electrodes were implanted bilaterally in the subthalamic nucleus under stereotactic guidance with imaging and electrophysiologic testing of the location. Twenty were followed for at least 12 months. Clinical evaluations included the Unified Parkinson's Disease Rating Scale, a dyskinesia scale, and timed tests conducted before and after surgery, when patients were off and on medications.

Results After one year of electrical stimulation of the subthalamic nucleus, the patients' scores for activities of daily living and motor examination scores (Unified Parkinson's Disease Rating Scale parts II and III, respectively) off medication improved by 60 percent ($P < 0.001$). The subscores improved for limb akinesia, rigidity, tremor, and gait. In the testing done on medication, the scores on part III improved by 10 percent ($P < 0.005$). The mean dose of dopaminergic drugs was reduced by half. The cognitive-performance scores remained unchanged, but one patient had paralysis and aphasia after an intracerebral hematoma during the implantation procedure.

Conclusions Electrical stimulation of the subthalamic nucleus is an effective treatment for advanced Parkinson's disease. The severity of symptoms off medication decreases, and the dose of levodopa can be reduced, with a consequent reduction in dyskinesias. (N Engl J Med 1998;339:1105-11.)

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IN many patients with idiopathic Parkinson's disease, there is an initial satisfactory response to levodopa, but then motor fluctuations develop that are difficult to control. The patients alternate between a state of severe parkinsonism (the "off" period, when the medication is not working, also referred to as "off medication") and a state of

improved mobility, when the medication is working (the "on" period, also referred to as "on medication"), which is often impaired by dyskinesias. Neurosurgery offers additional therapeutic possibilities for these patients. Originally, lesioning procedures (pallidotomy and thalamotomy) were performed.¹⁻¹¹ Subsequently, high-frequency electrical stimulation of implanted electrodes was developed primarily to decrease the morbidity induced by bilateral thalamotomy.^{12,13}

Thalamic stimulation is effective mainly for tremor and therefore is useful to only a small proportion of patients with Parkinson's disease. The problem of motor fluctuations affects a much larger number of patients.¹⁴ Studies performed in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, an animal model of Parkinson's disease,¹⁵ found hyperactivity of the subthalamic nucleus-internal pallidum pathway¹⁶⁻¹⁸ and improvement of parkinsonian symptoms after the creation of lesions¹⁷⁻²¹ or high-frequency stimulation of the subthalamic nucleus.²²

We therefore applied the stimulation procedure to the subthalamic nucleus in patients with Parkinson's disease who had disabling motor fluctuations. Preliminary results in three patients showed a reduction in disability during off periods.²³ We now report long-term follow-up in 24 consecutive patients, 20 of whom have undergone bilateral stimulation of the subthalamic nucleus for at least one year.

METHODS**Patients**

Twenty-four patients (11 men and 13 women) with a mean (\pm SD) age of 56 ± 8 years at the time of surgery and a mean duration of disease of 14 ± 5 years were selected for implantation of electrodes in the subthalamic nucleus. The selection criteria were clinically diagnosed idiopathic Parkinson's disease,²⁴ disabling motor fluctuations despite all drug therapies, age under 70 years, normal magnetic resonance imaging (MRI) studies of the brain, and no severe dementia (score on the Mini-Mental State Examination, ≥ 24 ²⁵). During off periods, all were severely impaired in performing activities of daily living (Table 1 and Fig. 1), and 19 had painful dystonia. During on periods, they could cope with most activities of daily living (Fig. 1 and Table 2) but had levodopa-induced dyskinesias (Table 2). Their Hoehn and Yahr rating, indicating the global stage of the disease, was 4 to 5 during

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TABLE 1. OFF-MEDICATION UPDRS SUBSCORES IN 20 PATIENTS WITH LONG-TERM BILATERAL STIMULATION OF THE SUBTHALAMIC NUCLEUS.*

| SCORE | MAXIMAL VALUE | UPDRS No.† | SCORE BEFORE SURGERY | SCORE 3 Mo AFTER SURGERY | | SCORE 12 Mo AFTER SURGERY | |
|--|---------------|------------|----------------------|--------------------------|----------------|---------------------------|----------------|
| | | | | OFF STIMULATION | ON STIMULATION | OFF STIMULATION | ON STIMULATION |
| Rigidity | | | | | | | |
| Upper limbs | 8 | 22 | 5.5±1.5 | 5.6±2.3 | 2.0±1.7‡§ | 4.4±2.0 | 1.6±1.7‡§ |
| Lower limbs | 8 | 22 | 5.3±1.5 | 4.0±2.1 | 2.1±2.0‡§ | 4.0±2.1 | 1.7±1.7‡§ |
| Neck | 4 | 22 | 3.3±0.6 | 2.7±1.2 | 1.4±1.4‡§ | 2.4±1.2 | 1.3±1.1‡§ |
| Overall | 20 | 22 | 13.9±2.7 | 12.3±4.2 | 5.5±4.0‡§ | 10.8±4.8¶ | 4.5±3.9‡§ |
| Akinesia | | | | | | | |
| Upper limbs | 24 | 23–25 | 12.6±3.9 | 12.5±4.1 | 6.4±4.7‡§ | 12.4±5.2 | 6.0±5.2‡§ |
| Lower limbs | 8 | 26 | 5.2±1.9 | 4.2±2.0 | 1.9±1.5‡§ | 3.9±2.1 | 1.9±1.9‡§ |
| Overall | 32 | 23–26 | 17.9±5.1 | 16.8±5.3 | 8.3±5.7‡§ | 16.3±7.1 | 7.9±6.9‡§ |
| Tremor | 28 | 20, 21 | 5.1±4.2 | 5.0±5.4 | 1.8±2.0§ | 3.7±3.3 | 1.0±1.4‡§ |
| Gait | 4 | 30 | 3.1±0.8 | 2.1±0.9 | 1.1±1.0‡§ | 2.3±0.8 | 1.4±1.1‡§ |
| Arising from chair | 4 | 27 | 2.4±1.4 | 1.4±1.0 | 0.6±0.8‡§ | 1.1±1.1 | 0.8±0.9§ |
| Postural stability | 4 | 29 | 2.8±1.1 | 1.6±1.0 | 1.1±1.0§ | 1.8±1.0 | 1.1±0.9‡§ |
| Speech | 4 | 18 | 1.8±1.0 | 1.6±0.9 | 1.3±0.8 | 1.6±1.0 | 1.4±1.1 |
| Global stage of disease (Hoehn and Yahr)** | 5 | 43 | 4.6±0.5 | NA | 2.9±0.8‡ | NA | 2.8±0.6‡ |
| Global activities of daily living (Schwab and England)** | 100 | 44 | 29.0±14.1 | NA | 74.0±19.0‡ | NA | 73.2±15.3‡ |

*Plus-minus values are means ±SD. For all scales except the Schwab and England scale, a reduction in the score indicates an improvement in function. UPDRS denotes Unified Parkinson's Disease Rating Scale, and NA not applicable.

†The number refers to the number of the item in the Unified Parkinson's Disease Rating Scale. Items 18 to 30 refer to part III of the Unified Parkinson's Disease Rating Scale.

‡P<0.001 for the comparison with the condition before surgery.

§P<0.001 for the comparison with the condition off stimulation.

¶P<0.005 for the comparison with the condition off stimulation.

||P<0.005 for the comparison with the condition before surgery.

**Patients were not evaluated by the Hoehn and Yahr score or the Schwab and England score while off stimulation, because they were never off stimulation while performing activities of daily living.

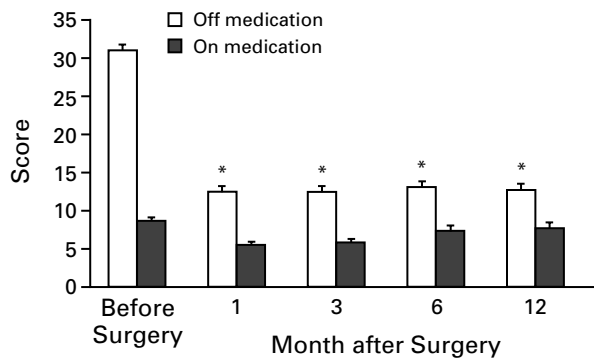


Figure 1. Mean (±SE) Off-Medication and On-Medication Scores for Impairment in the Performance of Activities of Daily Living before and 1, 3, 6, and 12 Months after Surgery.

After surgery, bilateral stimulation was on. The scores are for part II of the Unified Parkinson's Disease Rating Scale. The maximal possible score was 52. A reduction in scores indicates an improvement in function. The asterisks indicate P<0.001 for the comparison with the same condition before surgery.

the off period and 2 to 3 during the on period (a lower score indicates improvement).²⁶ All 24 patients were treated with levodopa plus a peripheral decarboxylase inhibitor. Twenty-one also received an oral dopaminergic agonist, and 12 received subcutaneous apomorphine. The dosage of antiparkinsonian drugs was kept constant during the two months before surgery. The study was approved by the ethics committee of the Grenoble University Hospital, and the patients gave their written informed consent.

Clinical Evaluation

Clinical evaluations were based on the Core Assessment Program for Intracerebral Transplantations, a validated protocol for the study of surgical treatments of idiopathic Parkinson's disease.²⁷ Evaluations were performed at least twice in the month before surgery, once or twice at 1, 3, 6, and 12 months after surgery, and thereafter once a year. Patients were evaluated with use of the Unified Parkinson's Disease Rating Scale,²⁶ a dyskinesia scale, and timed tests. Patients were assessed in two conditions before surgery (off medication and on medication) and in four conditions after surgery (off medication, off stimulation; off medication, on stimulation; on medication, off stimulation; and on medication, on stimulation). The examiner, but not the patient, knew whether the patient was receiving electrical stimulation at the time of the evaluation. The order of the off- and on-stimulation conditions was randomized. Before they were assessed off medication, patients fasted and drugs were withdrawn overnight. The same evaluation was repeated on medication after the admin-

TABLE 2. ON-MEDICATION UPDRS SUBSCORES AND DYSKINESIA SCORE IN 20 PATIENTS WITH LONG-TERM BILATERAL STIMULATION OF THE SUBTHALAMIC NUCLEUS.*

| SCORE | MAXIMAL VALUE | UPDRS No.† | SCORE BEFORE SURGERY | SCORE 3 Mo AFTER SURGERY | | SCORE 12 Mo AFTER SURGERY | |
|---|---------------|------------|----------------------|--------------------------|----------------|---------------------------|----------------|
| | | | | OFF STIMULATION | ON STIMULATION | OFF STIMULATION | ON STIMULATION |
| | | | | Rigidity | 20 | 22 | 5.0±2.9 |
| Akinesia | 32 | 23–26 | 5.1±3.7 | 6.0±4.0 | 5.2±4.7 | 6.7±6.0 | 5.7±5.9 |
| Tremor | 28 | 20, 21 | 0.7±0.9 | 0.8±1.1 | 0.5±0.9 | 0.9±1.4 | 0.4±1.2 |
| Gait | 4 | 30 | 0.6±0.8 | 1.0±0.9 | 0.7±0.9 | 0.8±1.0 | 0.7±0.8 |
| Arising from chair | 4 | 27 | 0.3±0.7 | 0.3±0.7 | 0.3±0.7 | 0.3±0.7 | 0.5±0.8 |
| Postural stability | 4 | 29 | 1.1±0.9 | 0.8±0.9 | 0.9±1.0 | 1.0±1.1 | 0.7±0.9 |
| Speech | 4 | 18 | 0.9±0.9 | 1.1±0.9 | 1.2±0.9 | 1.2±1.0 | 1.3±0.9 |
| Global stage of disease (Hoehn and Yahr)¶ | 5 | | 2.3±0.7 | NA | 2.5±0.4 | NA | 2.2±0.6 |
| Global activities of daily living (Schwab and England)¶ | 100 | | 84.0±9.4 | NA | 86.5±9.9 | NA | 84.7±8.4 |
| Dyskinesia | 24 | | 11.0±5.9 | 7.7±4.6 | 9.2±5.0§ | 7.4±4.6 | 7.7±3.8 |

*Plus–minus values are means ±SD. For all scales except the Schwab and England scale, a reduction in score indicates an improvement in function. UPDRS denotes Unified Parkinson's Disease Rating Scale, and NA not applicable.

†The number refers to the number of the item in the Unified Parkinson's Disease Rating Scale. Items 18 to 30 refer to part III of the Unified Parkinson's Disease Rating Scale.

‡P<0.005 for the comparison with the condition before surgery.

§P<0.005 for the comparison with the condition off stimulation.

¶Patients were not evaluated by the Hoehn and Yahr score or the Schwab and England score while off stimulation, because they were never off stimulation while performing activities of daily living.

istration of 100 to 300 mg of levodopa, according to the usual morning dose, plus benserazide. A subjective dyskinesia scale (maximal score, 24) was used to assess the maximal intensity of dyskinesias during the levodopa challenge.²³ The timed tests included a hand-tapping test and a stand-walk-sit test.²³

We assessed cognitive function in the off-medication period before and after surgery (on stimulation). All the patients followed for 12 months were assessed with a battery of tests sensitive to frontal-lobe dysfunction.²⁸ We calculated a score for frontal-lobe dysfunction adapted from Pillon et al.,²⁹ which rated patients on a 50-point scale according to four subscores: the Wisconsin card-sorting test,³⁰ verbal fluency, two series of motor sequences, and two series of graphic-writing sequences. Patients 7 to 24 were also rated according to the Mattis scale for global cognitive assessment (maximal score, 144).³¹

Surgery

Bilateral surgery was performed under local anesthesia. In the first three patients, the second electrode was implanted from 1 to 12 months after the first. In the remaining patients, both electrodes were implanted in a single operation. The follow-up data for the patients who had two operations were obtained after the second. The surgical procedure was based on that developed for thalamic stimulation.^{12,13} The subthalamic nucleus was located by MRI, contrast ventriculography, and electrophysiologic recordings and stimulation. We used tungsten microelectrodes (impedance, 2 to 8 mΩ; Frederick Haer, Bowdoinham, Me.) to identify areas showing a pattern of electrical activity characteristic of the subthalamic nucleus.^{16–18} Electrical stimulation was performed while a neurologist examined the patient for akinesia, rigidity, tremor, and adverse effects. An electrode for long-term stimulation was inserted at the location where typical activity was recorded and parkinsonian symptoms decreased with the lowest intensity and no adverse effects. The electrodes used for the first six patients had four contacts 1.5 mm long and 1.5 mm apart (DBS-3387 electrode,

Medtronic, Minneapolis). In the electrodes used for subsequent patients, the contacts were separated by 0.5 mm (DBS-3389 electrode), which permitted more contacts in the target area. The average duration of a bilateral operation was 12 hours.

To identify the location of the electrodes and possible brain lesions, a brain MRI was performed after the electrodes had been implanted but before the pulse generators were put in place. One week after implantation, the electrodes were connected to a pulse generator (Itrel II, Medtronic) that was placed subcutaneously in the subclavicular area, like a cardiac pacemaker. The pulse generator could be programmed by telemetry for different variables of stimulation, contact (cathode or anode), voltage (0 to 10.5 V), rate (2 to 185 Hz), pulse width (60 to 450 μsec), and timing (cyclic or continuous stimulation).

Electrical Settings

The neurologists selected electrical settings after surgery and at each follow-up visit. The patients could not modify the stimulation themselves. The effect of different electrical settings was first studied off medication, each contact being successively selected as the cathode, with the pulse-generator case as the anode (monopolar stimulation). A constant pulse width of 60 μsec and a frequency of 130 Hz were initially used, and the voltage was progressively increased. Favorable effects on akinesia, rigidity, and tremor and adverse effects, such as ocular movements, involuntary movements, and muscle contractions, were evaluated. The contact that improved parkinsonian symptoms with the lowest voltage without adverse effects was selected for long-term stimulation. The amplitude of stimulation was progressively increased over the first few days after surgery. In the on-medication condition, we checked the effect of the stimulation on dyskinesias. Bipolar stimulation, with at least one contact selected as the cathode and one as the anode, was used when the effect was more favorable than with monopolar stimulation. In the first 10 patients, we tried not to decrease the dosages of drugs before the three-month follow-

up unless there were adverse effects. For subsequent patients, we decreased the dosages immediately after surgery.

Statistical Analysis

The primary outcome measures were the scores on parts II (activities of daily living) and III (motor examination) of the Unified Parkinson's Disease Rating Scale. The secondary measures were the subscores on part III of the Unified Parkinson's Disease Rating Scale, which evaluated limb akinesia, limb rigidity, limb tremor, and axial symptoms (gait, arising from chair, postural stability, and speech); the dyskinesia scale; the subscores on part IV (complications of therapy) of the Unified Parkinson's Disease Rating Scale; the Hoehn and Yahr global stage and the Schwab and England scores for global activities of daily living; the tapping test; neuropsychological tests; and the dose of levodopa.

Data were analyzed by analysis of variance for repeated measures (with surgery [before or after], time [length of follow-up], stimulation [on or off], and medication [on or off] as variables in individual patients), by the paired Student's *t*-test, or by the paired Wilcoxon signed-rank test. To correct for the number of analyses and to avoid a type I error, a *P* value of 0.005 was considered to indicate statistical significance.

RESULTS

Clinical Results

In the 20 patients followed for at least 12 months, long-term bilateral stimulation greatly improved motor symptoms (Fig. 2 and Table 1). Repeated-measures analysis of variance was used to compare the effect of electrical stimulation on the scores on part III of the Unified Parkinson's Disease Rating Scale at 1, 3, 6, and 12 months after implantation in the off- and on-medication conditions. Stimulation significantly reduced the score on part III of the rating scale ($F_{18,1}=89.4$, $P<0.001$), and the effect was different in the off- and on-medication conditions ($F_{18,1}$ for the interaction between stimulation and drug, 108.5; $P<0.001$). To understand this interaction, we analyzed each condition separately. The effect of the stimulation was significant in both conditions but was greater off medication (60 percent; $F_{19,1}=101.8$, $P<0.001$) than on medication (10 percent; $F_{18,1}=14.6$, $P<0.005$). The off-stimulation score on part III of the Unified Parkinson's Disease Rating Scale was also significantly reduced 12 months after surgery ($P<0.005$) (Fig. 2).

Ten patients were followed for more than 24 months; their mean (\pm SD) off-medication score on part III of the Unified Parkinson's Disease Rating Scale decreased from 59.0 ± 10.1 before surgery to 29.5 ± 13.2 at 3 months, 30.1 ± 16.2 at 12 months, and 25.3 ± 17.7 at 24 months. Five patients were followed for more than 36 months; the treatment had a continuing beneficial effect in all of them.

Long-term stimulation resulted in improved scores for akinesia, rigidity, and tremor of the upper and lower limbs and for impairment in arising from chair, gait, and postural stability, when patients were evaluated off medication (Table 1). When patients were evaluated on medication, scores for limb rigidity were improved but not scores for limb akinesia (Table 2).

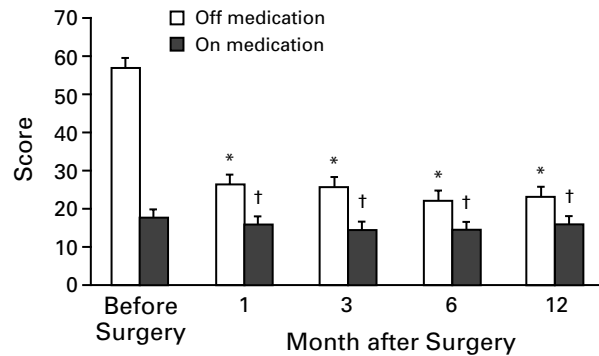


Figure 2. Mean (\pm SE) Off-Medication and On-Medication Scores for Motor Examination before and 1, 3, 6, and 12 Months after Surgery.

After surgery, bilateral stimulation was on. The scores are for part III of the Unified Parkinson's Disease Rating Scale. The maximal possible score was 108. A reduction in scores indicates an improvement in function. The asterisks indicate $P<0.001$ and the daggers $P<0.005$, for the comparison with the same condition before surgery.

The score for the duration of the off period was reduced from 2.2 ± 0.7 to 0.6 ± 1.0 ($P<0.001$) (Unified Parkinson's Disease Rating Scale item 39; range, 0 to 4). The intensity of symptoms was mild during these phases, and 12 patients were totally unaware of them. The score for the duration of the on period was increased correspondingly.

Performance on the hand-tapping test in patients off medication improved from 73 ± 5 per minute before surgery to 117 ± 8 per minute on stimulation after surgery ($P<0.001$). Before surgery, 8 of 20 patients could perform the stand-walk-sit test when off medication, all with freezing. The mean time for this task was 88 ± 64 seconds, with three freezing episodes per test, on average. When tested off medication and on stimulation 12 months after bilateral surgery, 19 patients could perform the stand-walk-sit test, with a mean time of 27 ± 21 seconds, and only 1 patient had freezing.

Before surgery 16 of 20 patients suffered from painful off-period dystonia, which disappeared in 12 patients and decreased in 4 after surgery. Levodopa-induced dyskinesias assessed during the levodopa challenge were nonsignificantly decreased after surgery (Table 2). At three months only, the dyskinesia score was significantly increased during stimulation as compared with the score when stimulation was switched ($P<0.005$). The mean disability related to dyskinesias decreased from 2.2 ± 1.2 before surgery to 0.8 ± 0.9 at 12 months (Unified Parkinson's Disease Rating Scale part IV, item 33; range, 0 to 4). The mean score for the duration of dyskinesias decreased from 2.0 ± 1.0 before surgery to 0.9 ± 0.8 at 12 months (part IV, item 32; range, 0 to 4).

As a result of the clinical improvement, the scores

for activities of daily living were greatly improved in patients on stimulation (Unified Parkinson's Disease Rating Scale part II, $F_{19,1}=41.1$ [$P<0.001$]; Schwab and England, $F_{20,1}=73.6$ [$P<0.001$]) (Fig. 1 and Table 1). The effect of surgery differed according to whether the patient was on or off medication (for the interaction between surgery and medication: part II, $F_{19,1}=103.8$ [$P<0.001$]; Schwab and England, $F_{20,1}=107.6$ [$P<0.001$]). To understand this interaction, we analyzed each drug condition separately and found that the effect of the stimulation was significant only off medication (part II: off medication, $P<0.001$; on medication, $P=0.50$; Schwab and England: off medication, $P<0.001$; on medication, $P=0.75$). The off-medication Hoehn and Yahr score (for global stage of disease) was significantly decreased at 12 months ($P<0.001$) (Table 1) and remained unchanged when the patient was on medication ($P=0.36$) (Table 2). The only scores applicable to the whole group of 24 patients were the Schwab and England score (for global activities of daily living), which improved in patients off medication from 27.5 ± 13.6 before surgery to 68.7 ± 22.7 at six months ($P<0.001$), and the Hoehn and Yahr score, which improved from 4.7 ± 0.5 to 2.9 ± 0.8 ($P<0.001$).

On average, neuropsychological results did not change after surgery. The mean score for frontal-lobe dysfunction was 39.6 ± 6.9 before surgery and 37.4 ± 8.5 12 months after surgery ($P=0.30$). The mean Mattis score was 138.0 ± 4.7 before surgery and 137.0 ± 5.7 12 months after ($P=0.31$).

Medications and Electrical Treatment

At 12 months, the mean dose of levodopa was significantly decreased ($P<0.001$) (Table 3), and one patient had stopped treatment. Apomorphine treatment was stopped in 9 of 10 patients. At 12 months, all the patients were being stimulated continuously. Fourteen patients were receiving bilateral monopolar stimulation, five were receiving bilateral bipolar stimulation, and one was receiving bipolar stimulation on one side and monopolar stimulation on the other. The voltage was adjusted at each follow-up visit according to the clinical effect on parkinsonian symptoms and the adverse effects. The mean voltage was 2.0 ± 0.6 V at 1 month, 2.2 ± 0.7 V at 3 months, 2.4 ± 0.8 V at 6 months, and 2.8 ± 0.6 V at 12 months ($P<0.001$ for the comparison between 12 months and 1 month). The frequency was between 130 and 185 Hz and the pulse width was 60 μ sec for all patients.

Adverse Effects

Four of the 24 patients could not be included in the 12-month follow-up. In one patient, an intracerebral hematoma 8 cm in diameter developed in the corona radiata during surgery, resulting in persistent severe paralysis and aphasia. Another patient lived far

TABLE 3. DOSE OF ANTIPARKINSONIAN MEDICATIONS BEFORE AND 12 MONTHS AFTER SURGERY FOR 20 PATIENTS WITH LONG-TERM BILATERAL STIMULATION OF THE SUBTHALAMIC NUCLEUS.*

| DRUG | BEFORE SURGERY | | 12 MO AFTER SURGERY | |
|-------------------|----------------|-----------------|---------------------|-----------------|
| | DOSE | NO. OF PATIENTS | DOSE | NO. OF PATIENTS |
| | mg/day | | mg/day | |
| Levodopa and DDI† | 1224±723 | 20 | 615±350‡ | 19§ |
| Bromocriptine | 30±12 | 14 | 17±11 | 7 |
| Lisuride | 3 and 5 | 2 | 2 | 1 |
| Pergolide | 3 and 4.5 | 2 | 3 | 1 |
| Cabergoline | 2 | 1 | 3 | 1 |
| Apomorphine | 9–200 | 10 | 6 | 1 |

*Plus-minus values are means \pm SD.

†DDI denotes dopa decarboxylase inhibitor.

‡ $P<0.001$ for the comparison with the value before surgery.

§Levodopa was discontinued in one patient.

away and did not return for the one-year follow-up; however, she reported by telephone that she still benefited from the stimulation. Another patient died of an unrelated cause 11 months after implantation. In another patient, a subcutaneous infection developed at the site of the extension lead; she was treated with antibiotics, and the extension lead and pulse generator were removed for six months, then reimplanted.

In 8 of the other 20 patients, transient adverse effects on mental status developed after surgery, such as confusion, hallucinations, temporospatial disorientation, and abulia. The effects lasted for a few days to two weeks, and the patients recovered without sequelae. In one patient, cognitive performance was impaired before surgery and worsened thereafter (the frontal-lobe score decreased from 16 to 6). In 18 patients, dyskinesias could be induced by increasing the stimulation voltage above the long-term level, which limited the benefit of the stimulation only transiently after surgery. Five patients had difficulty in opening their eyes because of eyelid-opening apraxia that was induced or worsened by the surgery. Four of them were successfully treated by injection of botulinum toxin. Hypophonia and postural instability worsened in one patient after three months. Eighteen patients gained weight after surgery (mean, 4.2 kg; maximum, 10.0 kg).

DISCUSSION

Bilateral stimulation of the subthalamic nucleus greatly improved off-period symptoms in this group of severely disabled patients. Motor fluctuations were attenuated, and patients with sudden on-off fluctuations before surgery had milder fluctuations or none thereafter. All patients became independent in most activities of daily living. Medications could be

decreased after surgery to about half of the initial dosage.

The three cardinal signs of parkinsonism — bradykinesia, rigidity, and tremor — were decreased by stimulation of the subthalamic nucleus when the patients were off medication. The average tremor score was low because few patients had a large-amplitude tremor, but a short report on a different group of patients confirms that tremor is reduced by stimulation of the subthalamic nucleus.³² Neuronal bursts in synchrony with tremor are recorded in the subthalamic nucleus of monkeys given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.¹⁸ Arm, leg, and axial symptoms and signs were equally improved. Unilateral stimulation of the subthalamic nucleus improves mainly contralateral symptoms.²³ The motor score on the Unified Parkinson's Disease Rating Scale was reduced by only 10 percent in patients on medication.

Immediately after surgery, the voltage of the stimulation was limited, because stimulation could induce reversible dyskinesias, probably related to inactivation of the subthalamic nucleus.³³ After the first 10 patients, we reduced the doses of dopaminergic drugs more rapidly after surgery, which allowed a rapid increase in the voltage without inducing dyskinesias. In the long term, levodopa-induced dyskinesias were decreased. The reduction in the doses of dopaminergic drugs is likely to be an important factor in this decrease. Because stimulation of the subthalamic nucleus greatly and rapidly improved dystonia in patients off medication, the mechanisms might be different for dyskinesias in patients on medication.

Patients with severe dementia were excluded from this study. Cognitive functions were on average unchanged after surgery, except in one patient who had frontal-lobe dysfunction before surgery. The outcome in this patient suggests that patients with cognitive deficits may be at risk for further worsening after surgery.

Off-medication and off-stimulation Unified Parkinson's Disease Rating Scale motor scores were also improved after surgery. This improvement could be related either to a microsubthalamotomy effect due to the presence of the electrode on the subthalamic nucleus or to a long-lasting effect of the stimulation. The mechanism of action of stimulation of the subthalamic nucleus is unknown. The frequency and the amplitude of the stimulation are important.²³ Since stimulation of the subthalamic nucleus mimics the effect of lesions in monkeys given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine,²² it is likely that the stimulation inhibits overactivity of the subthalamic nucleus. This inhibition would decrease the inhibitory action of the globus pallidus internus on the ventrolateral thalamus and consequently increase excitatory input to the cortex. The results of two experiments support this hypothesis. A study in rats showed that stimulation of the subthalamic nucleus

inhibited the activity of the entopeduncular nucleus, the equivalent of the globus pallidus internus.³⁴ A positron-emission tomographic study in patients with Parkinson's disease demonstrated an increase in cortical activity of the supplementary motor area, dorsolateral prefrontal cortex, and cingulate when patients performed movements with high-frequency stimulation of the subthalamic nucleus, which is effective in the treatment of parkinsonism.³⁵

The most severe complication was an intracerebral hematoma, an inherent risk in stereotactic neurosurgery that is estimated to occur in 2 to 8 percent of patients.³⁶ The transient confusion observed in some patients may have been related to nonspecific factors, such as the long duration of brain surgery and the withdrawal of dopaminergic drugs. Most patients gained weight, as has been described after pallidotomy.⁷⁻¹⁰ Surgery of the subthalamic nucleus worsened eyelid-opening apraxia. The mechanism of eyelid-opening apraxia is unknown. It is observed in idiopathic Parkinson's disease and other degenerative diseases involving the basal ganglia.³⁷

The alternative target for surgery on the basal ganglia in Parkinson's disease is the globus pallidus internus. The effect of pallidotomy is well established, with a moderate improvement of parkinsonism in off periods and a major decrease in levodopa-induced dyskinesias,⁵⁻¹¹ but the safety of bilateral procedures is still being debated.³⁸ The data so far suggest that stimulation of the globus pallidus internus has effects similar to those of pallidotomy.³⁹⁻⁴² In our study, the voltage was mildly increased over time, and this raises the theoretical risk of partial loss of benefit. The principal improvement in all dopa-sensitive symptoms and dyskinesias was sustained during the follow-up period. Comparative studies, including cost-benefit analysis, are needed to determine the value of each procedure. Because of the risks, this procedure, like all surgical approaches, should be reserved for severely disabled patients with good cognitive and general status.

Supported by Medtronic, INSERM, and the department of Rhône-Alpes, France.

We are indebted to Professor N. Quinn and Dr. R. Brown for their helpful comments on the manuscript.

REFERENCES

1. Meyers R. Surgical interruption of the pallidofugal fibers: its effect on syndrome of paralysis agitans and technical considerations in its applications. *N Y State J Med* 1942;42:317-25.
2. Guiot G, Brion S. Traitement des mouvements anormaux par la coagulation pallidale: technique et résultats. *Rev Neurol* 1953;89:578-80.
3. Hassler R, Riechert T. Indikationen und Lokalisationsmethode der gezielten Hirnoperationen. *Nervenarzt* 1954;25:441-7.
4. Cooper IS, Bravo GJ. Anterior choroidal artery occlusion, chemopallidectomy and chemothalamectomy in parkinsonism: a consecutive series of 700 operations. In: Fields WS, ed. Pathogenesis and treatment of parkinsonism. Springfield, Ill.: Charles C Thomas, 1958:325-63.
5. Svnilson E, Torvik A, Lowe R, Leksell L. Treatment of parkinsonism

- by stereotactic therolesions in the pallidal region: a clinical evaluation of 81 cases. *Acta Psychiatr Scand* 1960;35:358-77.
6. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 1992;76:53-61.
 7. 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. [Erratum, *Lancet* 1996;348:1108.]
 8. Dogali M, Fazzini E, Kolodny E, et al. Stereotactic ventral pallidotomy for Parkinson's disease. *Neurology* 1995;45:753-61.
 9. Baron MS, Vitek JL, Bakay RA, 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.
 10. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W. Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med* 1997;337:1036-42.
 11. Golbe LI. Pallidotomy for Parkinson's disease: hitting the target? *Lancet* 1998;351:998-9.
 12. Benabid AL, Pollak P, Gervason C, et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 1991;337:401-6.
 13. Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg* 1996;84:203-14.
 14. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring levodopa. *Ann Neurol* 1996;39:37-45.
 15. Langston JW, Forno LS, Rebert CS, Irwin I. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Res* 1984;292:390-4.
 16. Miller WC, DeLong MR. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: Carpenter MB, Jayaraman A, eds. *The basal ganglia II: structure and function — current concepts*. Vol. 32 of *Advances in behavioral biology*. New York: Plenum Press, 1987:415-27.
 17. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* 1990;249:1436-8.
 18. Bergman H, Wichmann T, Karmon B, DeLong MR. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J Neurophysiol* 1994;72:507-20.
 19. Aziz TZ, Peggs D, Agarwal E, Sambrook MA, Crossman AR. Subthalamic nucleotomy alleviates parkinsonism in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed primate. *Br J Neurosurg* 1992;6:575-82.
 20. Guridi J, Herrero MT, Luquin MR, et al. Subthalamotomy in parkinsonian monkeys: behavioural and biochemical analysis. *Brain* 1996;119:1717-27.
 21. Wichmann T, Bergman H, DeLong MR. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. *J Neurophysiol* 1994;72:521-30.
 22. Benazzouz A, Gross C, Feger J, Boraud T, Bioulac B. Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *Eur J Neurosci* 1993;5:382-9.
 23. Limousin P, Pollak P, Benazzouz A, et al. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* 1995;345:91-5.
 24. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745-52.
 25. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
 26. Fahn S, Elton RL, UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. *Recent developments in Parkinson's disease*. Vol. 2. Florham Park, N.J.: MacMillan Healthcare Information, 1987:153-63.
 27. Langston JW, Widner H, Goetz CG, et al. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;7:2-13.
 28. Brown RG, Marsden CD. Cognitive function in Parkinson's disease: from description to theory. *Trends Neurosci* 1990;13:21-9.
 29. Pillon B, Dubois B, Lhermitte F, Agid Y. Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. *Neurology* 1986;36:1179-85.
 30. Nelson HE. A modified card sorting test sensitive to frontal lobe defects. *Cortex* 1976;12:313-24.
 31. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karasu TB, eds. *Geriatric psychiatry: a handbook for psychiatrists and primary care physicians*. New York: Grune & Stratton, 1976:77-121.
 32. Krack P, Pollak P, Limousin P, Benazzouz A, Benabid AL. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. *Lancet* 1998;350:1675.
 33. Limousin P, Pollak P, Hoffmann D, Benazzouz A, Perret JE, Benabid AL. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. *Mov Disord* 1996;11:231-5.
 34. Benazzouz A, Piallat B, Pollak P, Benabid AL. Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. *Neurosci Lett* 1995;189:77-80.
 35. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Ann Neurol* 1997;42:283-91.
 36. Obeso JA, Guridi J, Obeso JA, DeLong M. Surgery for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997;62:2-8.
 37. Lepore FE, Duvoisin RC. "Apraxia" of eyelid opening: an involuntary levator inhibition. *Neurology* 1985;35:423-7.
 38. Galvez-Jimenez N, Lozano AM, Duff J, et al. Bilateral pallidotomy: pronounced amelioration of incapacitating levodopa-induced dyskinesias but accompanying cognitive decline. *Mov Disord* 1996;11:Suppl 1:242. abstract.
 39. Siegfried J, Lippitz B. Bilateral chronic electrostimulation of ventro-posterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery* 1994;35:1126-9.
 40. Pahwa R, Wilkinson S, Smith D, Lyons K, Miyawaki E, Koller WC. High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. *Neurology* 1997;49:249-53.
 41. Gross C, Rougier A, Guehl D, Boraud T, Julien J, Bioulac B. High-frequency stimulation of the globus pallidus internalis in Parkinson's disease: a study of seven cases. *J Neurosurg* 1997;87:491-8.
 42. Tronnier VM, Fogel W, Kronenburger M, Steinworth S. Pallidal stimulation: an alternative to pallidotomy? *J Neurosurg* 1997;87:700-5.