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A COMPARISON OF CONTINUOUS THALAMIC STIMULATION AND THALAMOTOMY FOR SUPPRESSION OF SEVERE TREMOR

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ABSTRACT

Background Deep-brain stimulation through an electrode implanted in the thalamus was developed as an alternative to thalamotomy for the treatment of drug-resistant tremor. Stimulation is thought to be as effective as thalamotomy but to have fewer complications. We examined the effects of these two procedures on the functional abilities of patients with drug-resistant tremor due to Parkinson's disease, essential tremor, or multiple sclerosis.

Methods Sixty-eight patients (45 with Parkinson's disease, 13 with essential tremor, and 10 with multiple sclerosis) were randomly assigned to undergo thalamotomy or thalamic stimulation. The primary outcome measure was the change in functional abilities six months after surgery, as measured by the Frenchay Activities Index. Scores for this index can range from 0 to 60, with higher scores indicating better function. Secondary outcome measures were the severity of tremor, the number of adverse effects, and patients' assessment of the outcome.

Results Functional status improved more in the thalamic-stimulation group than in the thalamotomy group, as indicated by increases in the score for the Frenchay Activities Index (from 31.4 to 36.3 and from 32.0 to 32.5, respectively; difference between groups, 4.4 points; 95 percent confidence interval, 2.0 to 6.9). After adjustment for base-line characteristics, multivariate analysis also showed that the thalamic-stimulation group had greater improvement (difference between groups, 5.1 points; 95 percent confidence interval, 2.3 to 7.9). Tremor was suppressed completely or almost completely in 27 of 34 patients in the thalamotomy group and in 30 of 33 patients in the thalamic-stimulation group. One patient in the thalamic-stimulation group died perioperatively after an intracerebral hemorrhage. With the exception of this incident, thalamic stimulation was associated with significantly fewer adverse effects than thalamotomy. Functional status was reported as improved by 8 patients in the thalamotomy group, as compared with 18 patients in the thalamic-stimulation group ($P=0.01$).

Conclusions Thalamic stimulation and thalamotomy are equally effective for the suppression of drug-resistant tremor, but thalamic stimulation has fewer adverse effects and results in a greater improvement in function. (N Engl J Med 2000;342:461-8.)

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TREMOR can be an incapacitating symptom that leads to functional impairment. In patients with Parkinson's disease and in those with essential tremor, pharmacologic treatment often does not adequately control tremor. In patients with multiple sclerosis, intention tremor can add considerably to their disability.

Neurosurgical thalamotomy is effective in 73 to 93 percent of patients with incapacitating tremor that is refractory to drug therapy.¹⁻⁶ However, this procedure is accompanied by permanent complications in 9 to 23 percent of patients with Parkinson's disease or essential tremor^{1,2,5-8} and in 16 to 41 percent of patients with multiple sclerosis.^{7,9,10} Bilateral thalamotomy carries an even higher risk¹¹⁻¹³ and is no longer recommended.¹⁴

Continuous deep-brain stimulation through an electrode implanted in the thalamus is an alternative to ablative surgery.¹⁵ Thalamic stimulation has been adopted by many centers, and clinical studies suggest that this approach is as effective as thalamotomy and has fewer complications, allowing bilateral treatment.¹⁴⁻²⁴

To test the hypothesis that thalamic stimulation produces greater functional improvement than thalamotomy because of its lower rate of complications, we conducted a randomized comparison of thalamic stimulation and thalamotomy in patients with unilateral or bilateral tremor due to Parkinson's disease, essential tremor, or multiple sclerosis.

METHODS**Patients**

Eligible patients had had severe unilateral or bilateral tremor of the arms due to Parkinson's disease, essential tremor, or multiple sclerosis for at least one year despite pharmacotherapy. The severity of tremor was defined with the use of disease-specific clinical scales: the tremor item of the Unified Parkinson's Disease Rating Scale²⁵ in the case of patients with Parkinson's disease, the Essential Tremor Rating Scale²⁶ in the case of patients with essential tremor, and the Modified Tremor Scale²⁷ in the case of patients with multiple sclerosis. Patients were not eligible for the study if they were younger than 18 years of age; had cognitive dysfunction,

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as defined by a score of less than 24 on the Mini-Mental State Examination²⁸; had contraindications to surgery (unstable cardiac or pulmonary disease or coagulation disorders); had evidence of advanced cerebral atrophy on computed tomographic scans; or had previously undergone thalamotomy. At base line, the stage of disease was assessed with the Hoehn and Yahr²⁹ staging system and the Unified Parkinson's Disease Rating Scale in patients with Parkinson's disease (range of activity subscores, 0 to 52; range of motor subscores, 0 to 108), the Essential Tremor Rating Scale in patients with essential tremor (range of scores, 0 to 144), and the Kurtzke Expanded Disability Status Scale³⁰ in patients with multiple sclerosis (range of scores, 0 to 10). For all three scales, lower scores indicate better function. All patients provided written informed consent, and the study was approved by the medical ethics committee of the hospital. Randomization was performed according to a computer-generated code, with adjustment for the cause and extent of tremor (unilateral vs. bilateral).

Surgical Treatment

Within one month after randomization, patients underwent surgery under local anesthesia. Patients with unilateral tremor either had an electrode implanted or underwent unilateral thalamotomy. Patients with bilateral tremor either had bilateral implantation of electrodes in one session or underwent unilateral thalamotomy directed at the hand with the most severe tremor, followed six months later by contralateral implantation of an electrode.

The position of the nucleus ventralis intermedius thalami relative to the intercommissural line was identified by positive contrast ventriculography, according to the stereotactic atlas of Schaltenbrand and Wahren.³¹ Intraoperatively, we applied macroelectrodes to identify the optimal position for the lesion or the electrode; the same position was used for both. The site selected was the one in which the effect of the lowest-threshold high-frequency stimulation (130 Hz) was maximal and in which neither high-frequency stimulation nor low-frequency stimulation (2 Hz) produced side effects. We did not use microelectrode recordings. Once the site was selected, either a lesion was produced by applying the bare tip of a 1.5-by-3.8-mm macroelectrode at a temperature of 80°C for 60 seconds, or a four-contact electrode (model 3387DBS, Medtronic, Minneapolis) was implanted, with the second distal contact placed at the target site. After several days of testing, the electrodes were connected to an implantable pulse generator (Itrell II, Medtronic) with the patient under general anesthesia. The surgical technique was not changed during the course of the study.

Outcome Measures

The patients were assessed preoperatively and at three-month intervals for two years after surgery. The results of thalamotomy six months after surgery have been shown to be predictive of its long-term effect,^{13,32} and these outcomes were used for the main analyses. The primary outcome measure was the change from base line in functional status, as measured by the Frenchay Activities Index,³³ for which a validated Dutch version is available.³⁴ This index assesses 15 activities of daily life involving domestic tasks (preparing meals, washing up, washing clothes, doing light housework, and doing heavy housework), leisure or work-related activities (attending social events, pursuing hobbies, going on outings, performing household or car maintenance, reading, and working), and other or outdoor activities (shopping, walking, traveling, and gardening). The items are measured on a four-point scale, and scores can range from 0 to 60. An increase of four points in the score indicates an improvement in the patient's ability to perform at least two of these activities. In earlier research an increase of five points was associated with a clinically relevant improvement in the ability to perform the activities of daily life.³⁴ We used the Frenchay Activities Index rather than disease-specific scales of functional status because this instrument could be used for the entire study population.

Secondary outcome measures were tremor of the arm, adverse effects (including changes in cognitive status), and the patient's

opinion of the surgical outcome. Tremor was assessed from videotaped recordings made at base line and six months after surgery (with patients wearing surgical caps to conceal changes in hairstyle after surgery) according to the items on tremor in the Unified Parkinson's Disease Rating Scale, Essential Tremor Rating Scale, and Modified Tremor Scale. The videotapes were played in random order and analyzed by an independent neurologist who was unaware of the patient's condition or treatment. Videotapes were made of the patients during drug therapy and during thalamic stimulation in patients who received electrodes. A list of possible complications was devised and used to record adverse effects at each follow-up assessment, after a full neurologic examination. Cognitive status was assessed by neuropsychological evaluation both preoperatively and at six months. The patients were asked to rate the change in their ability to perform complex activities using a nine-point ordinal scale in which a score of 0 indicated that their ability to function was "much worse" and a score of 8 that it was "much better."

Statistical Analysis

The difference in the changes in the Frenchay Activities Index score from base line to six months after surgery between the treatment groups was analyzed with Student's *t*-test. In addition, we performed a conditional, multivariable analysis, using general linear modeling and adjusting for the base-line variables of age, sex, diagnosis, duration of disease, extent of tremor (unilateral vs. bilateral), severity of disease, and base-line Frenchay Activities Index scores. For this purpose, severity of disease was calculated as the patient's score divided by the maximal score on the disease-specific clinical scales.

The change in the tremor score from base line to the six-month follow-up visit was compared with use of Mann-Whitney *U* tests. In patients with bilateral stimulation, only the score of the hand with the more severe tremor was used in the primary analysis, since this was the hand targeted in the patients who had undergone thalamotomy. The proportions of patients with complications in each group were compared with use of a chi-square test. The difference between groups in the patients' assessment of functional status at six months was also analyzed with the use of Mann-Whitney *U* tests. Subgroup analyses were performed according to the cause and extent of tremor. The analyses were performed on an intention-to-treat basis. Two-sided *P* values of less than 0.05 were considered to indicate statistically significant differences.

Assuming a standard deviation of 7 points, an alpha level of 0.05, and a beta level of 0.20, we estimated that 32 patients would be needed in each treatment group for the study to have the power to detect a 5-point difference in scores on the Frenchay Activities Index. A target of 70 patients was set.

RESULTS

Characteristics of the Patients

Between June 1995 and October 1998, 175 patients were referred by neurologists throughout the Netherlands. Of these patients, 105 were excluded for the following reasons: further pharmacologic options were available (28 patients), there was evidence of cognitive deterioration (8) or surgical contraindications (22), parkinsonism was part of multiple-system atrophy (4), mild tremor did not interfere with normal physical or social functioning (20), there was an indication for pallidal rather than thalamic surgery (19), the patient had previously undergone thalamotomy (1), and the patient declined to participate (3). The remaining 70 patients underwent randomization. Two patients were not treated: one withdrew after contracting an unrelated disease, and the other

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

CHARACTERISTIC	THALAMOTOMY (N=34)	THALAMIC STIMULATION (N=34)
Age — yr	64±11.0	59±14.2
Patients with Parkinson's disease	68±7.6	63±8.9
Patients with essential tremor	64±7.6	62±17.0
Patients with multiple sclerosis	44±5.4	36±6.6
Sex — no. of patients		
Male	17	27
Female	17	7
Duration of disease — yr	12.6±12.5	10.9±7.4
Extent of tremor — no. of patients		
Unilateral	21	17
Right-sided tremor	12	11
Left-sided tremor	9	6
Bilateral	13	17
Severity of disease		
Patient's with Parkinson's disease — no. of patients	23	22
Hoehn and Yahr stage of disease†		
Median	2.0	2.0
Range	1.0–3.0	1.0–3.0
Mean UPDRS score		
Part II (activities of daily life)	13.2±4.7	15.5±5.0
Part III (motor function)	28.7±11.7	37.9±15.1
Patients with essential tremor — no. of patients	6	7
Mean ETRS score	50.5±25.4	45.7±19.9
Patients with multiple sclerosis — no. of patients	5	5
EDSS score		
Median	6.5	7.0
Range	4.0–8.5	3.5–8.5
Frenchay Activities Index score		
All patients	32.0±8.2	31.4±10.5
Patients with unilateral tremor	33.4±8.3	34.5±11.9
Patients with bilateral tremor	29.7±7.6	28.2±8.1
Patients with Parkinson's disease	34.5±7.7	32.3±11.5
Patients with essential tremor	30.2±6.2	36.1±3.2
Patients with multiple sclerosis	22.6±4.5	20.8±4.3

*Plus–minus values are means ±SD. UPDRS denotes the Unified Parkinson's Disease Rating Scale, ETRS Essential Tremor Rating Scale, and EDSS Kurtzke Expanded Disability Status Scale. For all instruments except the Frenchay Activities Index, lower scores indicate better function.

†Stage 1 indicates unilateral disease, and stages 4 and 5 advanced bilateral disease.

was judged to be a more suitable candidate for pallidotomy after prolonged clinical observation.

Two patients with Parkinson's disease and bilateral tremor who were randomly assigned to thalamic stimulation died before follow-up was complete. One died of complications after implantation of the test electrode. A small intracerebral hematoma caused decreased consciousness and was followed by aspiration pneumonia and, ultimately, by respiratory failure. Since postoperative values could not be assessed, this patient was assigned the lowest score of the study population on the primary outcome measure at follow-up. The other patient had no complications postoperatively or at the three-month follow-up visit but died of a myocardial infarction five months after surgery. This patient's values for the three-month follow-

up assessment were carried forward for the analyses. Data on 68 patients were thus available for analysis.

Table 1 lists the base-line characteristics of the patients. The thalamic-stimulation group had significantly more men than women. Among the patients with Parkinson's disease, the motor-function score for the Unified Parkinson's Disease Rating Scale (part III) was significantly higher in the thalamic-stimulation group; this difference was attributable to differences in overall rigidity and agility of the leg.

Scores for the Frenchay Activities Index

Patients with unilateral tremor had higher Frenchay Activities Index scores at base line than patients with bilateral tremor (Table 1). The average base-line scores were similar in patients with Parkinson's dis-

ease and in those with essential tremor and lowest in those with multiple sclerosis. The mean score in the thalamic-stimulation group increased from 31.4 at base line to 36.3 at six months. The mean score in the thalamotomy group increased from 32.0 to 32.5. In Figure 1, the individual scores for the Frenchay Activities Index at the six-month follow-up visit are plotted against base-line scores.

Table 2 shows the changes in the scores for the Frenchay Activities Index from base line to the six-month follow-up visit for all patients as well as for the various subgroups. There was a significant difference of 4.4 points (95 percent confidence interval, 2.0 to 6.9) in the extent of improvement after surgery between the thalamotomy group and the thalamic-stimulation group, with greater improvement in the latter group. Thalamic stimulation also resulted in greater improvement than did thalamotomy in patients with bilateral tremor, those with unilateral tremor, those with Parkinson's disease, and those with essential tremor, but not in patients with multiple sclerosis.

The results of multivariate analysis, after adjustment for the base-line characteristics of age, sex, cause of the tremor, severity of disease, and scores on the Frenchay Activities Index, were similar to those of the unconditional univariate analysis. Patients assigned to receive thalamic stimulation had greater improvements in scores than patients assigned to undergo thalamotomy (a difference between groups of 5.1 points; 95 percent confidence interval, 2.3 to 7.9).

Tremor

Tremor grades at base line and at the six-month follow-up visit are listed in Table 3. There was no significant difference between the two groups at base line or at the six-month follow-up visit. Total suppression of tremor (grade 0) or almost complete suppression (grade 1, defined as occasional, slight tremor)

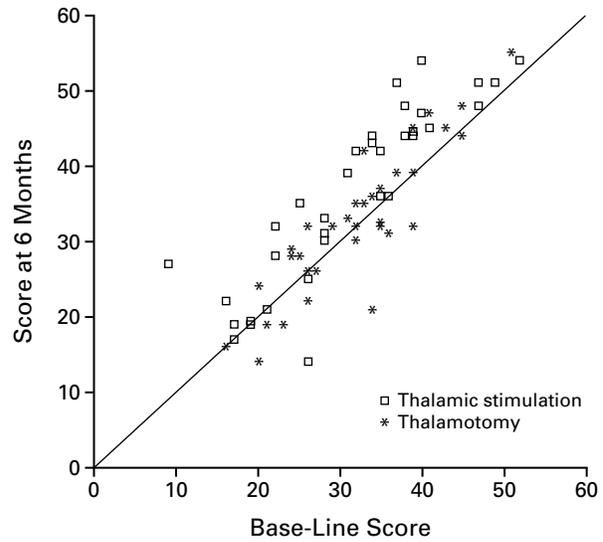


Figure 1. Scores on the Frenchay Activities Index at Base Line and at the Six-Month Follow-up Visit, According to Treatment. Base-line values are plotted against values obtained at the six-month follow-up visit. Higher scores indicate better function. The extent of change for individual patients corresponds to the distance of the symbol from the diagonal line.

was achieved in 27 of 34 patients in the thalamotomy group and in 30 of 33 patients in the thalamic-stimulation group. Data on tremor were not available for the patient with Parkinson's disease who died of complications of electrode implantation. Treatment reduced or eliminated tremor more successfully in patients with Parkinson's disease and in patients with essential tremor than in those with multiple sclerosis. Directly after thalamotomy, tremor disappeared in all patients, but at six months six patients had mild tremor and one had moderate tremor. Tremor

TABLE 2. CHANGES IN THE SCORES FOR THE FRENCHAY ACTIVITIES INDEX FROM BASE LINE TO THE SIX-MONTH FOLLOW-UP VISIT.*

GROUP	THALAMOTOMY		THALAMIC STIMULATION		DIFFERENCE BETWEEN GROUPS (95% CI)
	CHANGE IN SCORE	NO. OF PATIENTS	CHANGE IN SCORE	NO. OF PATIENTS	
All patients					
Univariate analysis	0.5±4.4	34	4.9±5.5	34	4.4 (2.0 to 6.9)
Multivariate analysis	0.2±5.4	34	5.3±5.4	34	5.1 (2.3 to 7.9)
Patients with unilateral tremor	1.0±4.4	21	5.6±5.4	17	4.6 (1.3 to 7.9)
Patients with bilateral tremor	-0.3±4.6	13	4.2±5.8	17	4.5 (0.7 to 8.4)
Patients with Parkinson's disease	0.8±4.9	23	5.5±6.3	22	4.7 (1.2 to 8.0)
Patients with essential tremor	-0.2±3.3	6	6.4±3.4	7	6.6 (2.5 to 10.7)
Patients with multiple sclerosis	-0.2±3.8	5	0.6±1.3	5	0.8 (-3.8 to 5.4)

*Plus-minus values are means ±SD. Positive values indicate an improvement. CI denotes confidence interval.

TABLE 3. SEVERITY OF TREMOR AT BASE LINE AND AT THE SIX-MONTH FOLLOW-UP VISIT.

TREMOR GRADE*	THALAMOTOMY (N=34)		THALAMIC STIMULATION (N=33)†	
	BASE LINE	6 MONTHS	BASE LINE	6 MONTHS
	number of patients			
0	—	26 (20 with Parkinson's disease, 6 with essential tremor)	—	28 (20 with Parkinson's disease, 7 with essential tremor, 1 with multiple sclerosis)
1	—	1 (with Parkinson's disease)	—	2 (1 with Parkinson's disease, 1 with multiple sclerosis)
2	—	6 (2 with Parkinson's disease, 4 with multiple sclerosis)	—	1 (with multiple sclerosis)
3	13 (10 with Parkinson's disease, 3 with essential tremor)	1 (with multiple sclerosis)	13 (8 with Parkinson's disease, 3 with essential tremor, 2 with multiple sclerosis)	2 (with multiple sclerosis)
4	21 (13 with Parkinson's disease, 3 with essential tremor, 5 with multiple sclerosis)	—	20 (13 with Parkinson's disease, 4 with essential tremor, 3 with multiple sclerosis)	—

*The severity of tremor was assessed with use of the disease-specific rating scales. A grade of 0 indicates the absence of tremor; a grade of 1 occasional, slight tremor; a grade of 2 mild tremor; a grade of 3 moderate tremor; and a grade of 4 severe tremor.

†Scores for the patient with Parkinson's disease who died perioperatively were not included.

also disappeared in all patients immediately after thalamic stimulation, but at six months one patient had mild tremor and two had moderate tremor.

Adverse Effects

Table 4 lists the adverse effects that were reported immediately after surgery and at the six-month follow-up visit. Six months after surgery, 16 patients in the thalamotomy group had adverse effects, as did 6 of the patients in the thalamic-stimulation group (P=0.024). The adverse effects in the thalamic-stimulation group at the six-month follow-up visit disappeared once the pulse generators were switched off. Three patients in the thalamotomy group had cognitive deterioration, which was confirmed by neuropsychological testing: one had loss of initiative, one had decreased memory, and one had decreased language fluency. In the thalamic-stimulation group, there were two equipment-related complications: one patient had a hematoma near the pulse generator, and in one the pulse generator became infected and was replaced after antibiotic treatment.

Patients' Assessments of Treatment

After thalamotomy, 8 patients judged their functional status to have improved, 22 patients reported no change in overall functional status, and 4 patients reported that their condition had deteriorated. In the thalamic-stimulation group, 18 patients judged their functional status to have improved, 13 thought that it was unchanged, and 2 thought that it was worse. The results differed significantly between the two groups (P=0.01).

DISCUSSION

Our randomized comparison of deep-brain stimulation and thalamotomy is of one of the few studies that have focused on functional status as a primary outcome measure rather than symptoms of disease.³⁵ Thalamic stimulation resulted in greater improvement in function than thalamotomy, according to both objective and subjective measures. Thalamic stimulation and thalamotomy were equally effective in reducing drug-resistant tremor, whereas stimulation had fewer adverse effects, although one patient in this group died perioperatively.

Patients were aware of which treatment they received, and information provided in the informed-consent form may have led to expectation bias, influencing patients' assessment of the outcome and their responses to questions on the Frenchay Activities Index. The fact that patients in the thalamic-stimulation group required more frequent medical contact for adjustment of the equipment may also have confounded the results. The clinical investigators were also aware of the treatment the patients received, which may have caused surveillance bias with respect to the identification of adverse effects. The assessment of tremor was performed in a single-blind fashion, since the neurologist who reviewed the videotapes was unaware of the patient's treatment assignment and treatment status. Patients were unaware that the Frenchay Activities Index questionnaire was used as the primary outcome measure, since completing the questionnaire took up only a small part of each evaluation.

Patients in the thalamic-stimulation group had a

TABLE 4. INCIDENCE OF ADVERSE EFFECTS IMMEDIATELY AFTER SURGERY AND AT THE SIX-MONTH FOLLOW-UP VISIT.*

ADVERSE EFFECT	THALAMOTOMY (N=34)		THALAMIC STIMULATION (N=34)	
	AFTER SURGERY	AT 6 MONTHS	AFTER SURGERY	AT 6 MONTHS
	number of patients			
Somnolence	3	—	—	—
Cognitive deterioration	3	3 (2 with Parkinson's disease, 1 with essential tremor)	—	—
Dysarthria†				
Mild	8	3 (2 with Parkinson's disease, 1 with essential tremor)	1	2 (1 with Parkinson's disease, 1 with multiple sclerosis)
Severe	3	3 (with Parkinson's disease)	2	2 (1 with Parkinson's disease, 1 with multiple sclerosis)
Dystonia	—	—	2	—
Impaired eye movement	—	—	1	—
Mild facial paresis	6	—	1	—
Mild arm paresis	3	—	2	—
Hypesthesia	2	1 (with Parkinson's disease)	1	—
Gait or balance disturbance‡				
Mild	11	4 (3 with Parkinson's disease, 1 with essential tremor)	2	1 (with essential tremor)
Severe	6	6 (4 with Parkinson's disease, 2 with multiple sclerosis)	1 (with multiple sclerosis)	1 (with multiple sclerosis)
Arm ataxia	6	1 (with Parkinson's disease)	2	1 (with multiple sclerosis)
Death related to surgery	—	—	1 (with Parkinson's disease)	—
Equipment-related effect				
Hematoma near pulse generator	—	—	1	—
Infection of pulse generator	—	—	1	—
Total no. of patients	28	16 (11 with Parkinson's disease, 3 with essential tremor, 2 with multiple sclerosis)	7	6 (2 with Parkinson's disease, 1 with essential tremor, 3 with multiple sclerosis)

*Some patients had more than one adverse effect.

†Patients with mild dysarthria had no difficulty being understood, and patients with severe dysarthria had a speech disturbance that, at a minimum, led to their sometimes being asked to repeat statements.

‡Patients with a mild disturbance of gait or balance had mild difficulty walking, and in some cases required a cane; patients with a severe disturbance could not walk without a walker or were wheelchair-bound.

clinically relevant improvement in their ability to perform the activities of daily life. No such overall improvement was evident in the thalamotomy group, on the basis of either the scores on the Frenchay Activities Index or the patients' assessments. It is conceivable that the adverse functional effects of thalamotomy were underestimated in previous studies because the resulting complications were not assessed. There was a disappointing overall improvement in function after unilateral reduction of tremor with thalamotomy in patients with bilateral tremor.

Our data compare well with the results of other studies that assessed the ability of thalamic stimulation to suppress tremor. In other reports the efficacy ranged from 71 to 94 percent in patients with Parkinson's disease and from 68 to 89 percent in patients with essential tremor.^{14,15,18,23,36,37} Our results for thalamotomy are also similar to those of other studies.¹⁻⁶

Thalamic stimulation was effective in 70 percent

of patients with multiple sclerosis in two small series,^{19,23} but the preliminary results of a prospective evaluation were less favorable.³⁸ Thalamotomy has been reported to result in long-term suppression of tremor in 30 percent³⁹ to 80 percent⁴⁰ of patients with multiple sclerosis, and this wide range probably relates to the varied origins of tremor, which depend on the location of the sclerotic lesions.¹⁷ In our study, the response to surgery of patients with multiple sclerosis was not as good as that of patients with Parkinson's disease or essential tremor. In patients with multiple sclerosis, tremor was less likely to be suppressed, and the unmasking of cerebellar dysmetria might have limited functional gain. Stereotactic treatment of tremor in patients with multiple sclerosis should probably be restricted to patients with stable disease whose tremor does not have a severe ataxic component and who have few other deficits.

Although one patient died perioperatively in the

thalamic-stimulation group, there was a significant difference in the incidence of adverse effects between this group and the thalamotomy group. Sixteen of the patients in the thalamotomy group had complications at the six-month follow-up visit. This rate is higher than the rates in most published series; for example, the rate of permanent complications ranged from 9 to 23 percent in patients with Parkinson's disease,^{1,6} 13 to 38 percent in patients with essential tremor,^{5,8} and 16 to 41 percent in patients with multiple sclerosis.^{7,9} However, surgical studies that included prospective collection of data reported considerably higher rates of adverse events than retrospective studies.^{41,42}

In our study, the use of microelectrode recordings to identify the optimal location for the intervention may have reduced morbidity, although this issue is still controversial. Six of 33 patients in the thalamic-stimulation group had side effects only while the pulse generators were on — suggesting that the adverse effects were reversible. Previously reported side effects of thalamic stimulation have included dysarthria (in 3 to 18 percent of patients),^{16,21} paresthesias (in 6 to 36 percent),^{14,16} dystonia (in 2 to 9 percent),^{14,22} balance disturbance (in 3 to 8 percent),^{16,36} ataxia (in 6 percent),¹⁵ and limb weakness (in 4 to 8 percent).^{14,19} Although these side effects are reversible in practice, many patients leave the stimulator on all the time; therefore, for many patients the benefit derived as a result of tremor control outweighs the side effects of treatment.

The surgery-related death occurred after an intracerebral hemorrhage, which may have been caused by the insertion of the test electrode, a procedure common to both thalamotomy and thalamic stimulation. The risk of intracerebral hemorrhage in stereotactic surgery is 1 to 4 percent^{43,44} and applies to both approaches.

For patients with bilateral tremor, we chose to compare unilateral thalamotomy with bilateral stimulation because bilateral thalamotomy is no longer used in clinical practice^{11,12} and because the results of bilateral stimulation should reflect the full potential of this approach. The average difference in functional gain between the thalamic-stimulation group and the thalamotomy group was similar in the patients with bilateral tremor and in those with unilateral tremor because of the effect on the analysis of the perioperative death of one patient. In patients with bilateral tremor, thalamic stimulation in the dominant hemisphere could be combined with thalamotomy in the nondominant hemisphere, but the morbidity associated with thalamotomy probably outweighs any advantage of this approach.

The long-term effect of thalamic stimulation must be evaluated further, although one center reported that its effectiveness was maintained after eight years of follow-up despite disease progression.¹⁷ A remaining question concerns the optimal location of the

electrodes in view of recent reports of the effects of stimulation of the subthalamic nucleus in patients with Parkinson's disease.⁴⁵⁻⁴⁷ Stimulation of the subthalamic nucleus appears to suppress tremor adequately and to have positive effects on hypokinesia and rigidity. Levodopa-induced dyskinesias diminish as well, because the dose of medication can be reduced and, possibly, as a result of the stimulation itself.⁴⁸ Subthalamic stimulation is therefore probably preferable to thalamic stimulation in patients with Parkinson's disease, although thalamic stimulation remains a therapeutic option in patients with stable Parkinson's disease in whom tremor is the dominant feature and in patients with essential tremor, for whom subthalamic stimulation has not been shown to be effective. Thalamotomy should also remain an option in the treatment of tremor in the case of well-informed patients who decide against stimulation, in economically deprived areas, or in remote areas where mandatory follow-up for adjustments of pulse generators is not possible. In patients with other causes of tremor, such as trauma, the effect of thalamic stimulation remains unknown.

Deep-brain stimulation does not restore normal brain function, and the ultimate goal is to delay or even reverse the neurodegenerative process. For the time being, thalamic stimulation is preferable to thalamotomy as a means of improving function with few adverse effects.

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