Surgery for Parkinson Disease

A Critical Evaluation of the State of the Art

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There has been a marked resurgence of interest in surgical therapies for Parkinson disease (PD) in the past decade. This has been driven by the inexorable progression of the disorder that has been unaltered by available pharmacological therapy and the consistent occurrence of disabling motor complications, including fluctuations and dyskinesias, stemming from this treatment.

Many claims have been made regarding the efficacy of surgery for PD, but remarkably little evidence comes from properly designed controlled clinical trials. In this review, the available evidence for efficacy of the various surgical treatments offered to patients with PD (emphasizing lesions and deep brain stimulation [DBS]) will be summarized and the remaining uncertainties and unmet therapeutic needs will be discussed. A recent report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluates surgery for PD.

Table 1 lists present and possible future surgical therapies for PD. Notably absent from this list is adrenal medullary transplantation, which initiated the resurgence of interest in surgery for PD. Initial case reports of striking benefit were followed by several uncontrolled clinical trials from experienced research centers, but more important, by widespread application of the procedure outside any formal trial setting. Hundreds of patients underwent the treatment despite the complete lack of convincing evidence for efficacy (indeed, there has been some concern raised that 1 of the 2 originally described patients who obtained a striking response may have had psychogenic parkinsonism). Subsequently, the high morbidity and mortality and at best modest efficacy, along with postmortem evidence that few transplanted cells actually survived, eventually resulted in the abandonment of the procedure. This experience highlights an important problem in the application of new surgical therapies for PD: in contrast to the intensive assessment required before a new drug is established as sufficiently safe and efficacious for widespread use, no such standards exist for surgery. As long as there are willing neurologists and surgeons and desperate patients, this problem will persist until the professional community decides to regulate the practice of its members or until external regulations are imposed. In a fashion, this already exists. Sadly, however, it is often not the burden of evidence that permits the application of a surgical procedure but what third party payers will support.

Positive developments in the study of neurosurgical therapies for PD are the widespread formation of movement disorders clinics and the recognition of the need for a team approach combining various specialties, including neurology, neurosurgery, neurophysiology, neuropsychology, and movement disorders nursing. It is generally acknowledged that modern neurosurgical therapy is best provided in such a setting, and certainly for the proper scientific study of surgical treatments, this approach is mandatory.

GENERAL COMMENTS ON STUDY DESIGN ISSUES

There are several inherent problems or issues unique to trials of surgical treatments for PD that should be discussed be-
fore reviewing our state of knowledge. Patients participating in such trials typically have late-stage disease complicated by several difficulties, including motor fluctuations, dyskinesias, motor symptoms that are unresponsive to dopaminergic medication (freezing, postural instability, and dysarthria persistent in the “on” periods), and, finally, cognitive and psychiatric problems. Recognizing these issues, most studies of surgical therapies have used some form of the Core Assessment Program for Intracerebral Transplantations (CAPIT).ُ Recently, an updated version, the Core Assessment Program for Surgical Interventional Therapies in PD, or CAPSIT-PD, has been proposed.ُ The CAPIT and CAPSIT-PD examine patients in a “practically defined off state” after overnight 12-hour drug withdrawal and again in the on state after their usual morning dose of levodopa. However, overnight drug withdrawal clearly does not represent the baseline severity of the disease and is strongly affected by the extent of the “long-duration response” to levodopa (a sustained improvement in motor disability that results from prolonged levodopa administration that is independent of the peripheral pharmacokinetics of the drugُ) and the half-lives of other dopaminergic drugs the patient happens to be taking. The response to the first dose of medication is often strongly influenced by when it is taken, and if there is a long delay required by extensive or prolonged assessments, patients often have considerable difficulty “going on” with their usual morning dosage. To evaluate the effect of the intervention on fluctuations, some form of home diary assessment is usually incorporated in which the patient and caregiver rate the clinical state (usually every 30-60 minutes) as on, on with dyskinesias, off, or asleep. However, in the absence of proper training in the use of such diaries,accuracy may be problematic. Ideally, in defining the effects of surgical interventions, a differentiation between the presence of mild or nondisabling dyskinesias and those that are bothersome or disabling to the patient would be useful. To my knowledge, no published study has attempted to make this distinction, which would require an even higher level of patient training before implementing.

To my knowledge, there are no published trials of any form of surgery for PD comparing patients randomized to surgery with those randomized to best medical management. This is obviously a critical first step given the acknowledged efficacy of pharmacological treatments for PD. As previously mentioned, most patients enrolled in surgical studies are described as having “refractory” symptoms; however, there have been no established definitions of what constitutes this state. There are obvious problems with randomizing patients to surgical and nonsurgical arms. Patients are unblinded to their therapy and, therefore, subjective evaluations of disability (eg, in the performance of activities of daily living [ADL]) are clearly influenced by this bias. The more “objective” evaluation of the motor examination is often performed by assessors who are blinded to the treatment arm (who only examine the patient at baseline and at the end point of the study, having no contact between and having no spoken contact during the evaluations) or includes “blinded” assessments of videotapes of clinical examinations. However, these too are hampered by the unblinded status of the patient. In addition, there is a risk that observation of one clinical state (eg, on) will unblind the assessor and influence the scoring of other clinical features. Possibly the best example of this pitfall relates to the marked ameliorative effect of unilateral pallidotomy on contralateral dyskinesias. Observing such a patient with pronounced asymmetry of dyskinesias postoperatively might well unblind the assessor to the side of the procedure and could easily influence interpretation of the “off period” motor evaluation. In cases in which bilateral procedures are performed in different brain sites (eg, DBS in the internal globus pallidus [GPi] or subthalamic nucleus [STN]), patients and evaluators could be kept blinded to the site of surgery, although the nature of the adverse effects or concomitant drug changes could threaten to unblind the study; also, this approach still lacks a placebo control.

For these reasons, sham procedures are an important consideration in studying the true efficacy of surgery for PD. However, surgical therapies that require detailed invasive physiological mapping with the patient awake and participating in the procedure, such as stereotactic lesioning and deep brain electrode implantation, could not be accomplished in a sham fashion without an elaborate intraoperative staged performance by the surgical team. The practicalities of this approach would probably be insurmountable. On the other hand, when the procedure is done under general anesthesia or is relatively brief, sham procedures are feasible and important in establishing the efficacy of new experimental surgical therapies.ُ The evaluation of efficacy of gamma knife procedures could easily include a sham treatment arm. However, most investigators involved in functional neurosurgery for PD believe that the safety and accuracy of this technique are not adequate to justify large-scale application. Recent and ongoing trials of fetal mesencephalic transplantation have successfully incorporated sham control methods. However, it has been argued that this sham surgery is ethically unacceptable, particularly since, like any surgery with accompanying anesthesia, it poses additional risks that the patient would not have otherwise been exposed to in the placebo arm of a research study.ُ There has also been a reluctance on the part of some experienced academic neurosurgeons to include a sham surgery arm in trials because it is believed to constitute “deceit” of the patient and risks com-

**Table 1. Surgical Options for Parkinson Disease**

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<th>Category</th>
<th>Options</th>
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<td>Ablative lesions or deep brain stimulation</td>
<td>Thalamus, Internal globus pallidus, Subthalamic nucleus</td>
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<td>Transplantation</td>
<td>Human fetal mesencephalon, Porcine fetal mesencephalon</td>
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<td>Other source (stem cells or the carotid body) with or without trophic factors (future)</td>
<td>Polymeric encapsulated cells, Gene therapy</td>
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<td>Other (future)</td>
<td>Direct central nervous system application of trophic factors</td>
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promising the patient-physician relationship. Recent lay press coverage of the revelation of a patient’s involvement in the sham arm of a fetal transplantation study supports this concern and highlights the responsibility that neuroscientists working in this field have in educating the public on the importance of properly designed and controlled clinical trials. The risks of not studying new procedures with appropriate scientific rigor need to be emphasized, including the premature acceptance of treatments that are eventually found to be ineffective or even harmful.9

A unique advantage of DBS for the evaluation of safety and efficacy is the ability to turn the pulse generator on and off, maintaining the patient and the evaluator blind to the status of stimulation. However, this too is not without problems, including the common unblinding of the patient due to the occurrence of non-motor effects, such as paresthesias and visual phosphenes, and the unblinding of patient and evaluator due to motor adverse effects, such as dyskinesias or motor benefit (the latter, obviously, would be the preferred source of unblinding). In addition, it remains unknown how long the full effect of stimulation takes to wear off and so “off stimulation” evaluations performed after long-term use may not adequately represent the baseline untreated state. This off stimulation state is also possibly influenced by the “microlesion” effect of the electrophysiologic mapping and implantation of the stimulating electrode. To adequately evaluate this effect, a randomized delay in turning on the stimulators in the postoperative period could be incorporated into the study design (ie, under blinded conditions, some patients would be randomized to have the stimulators turned on immediately and others would undergo a delay [eg, 3 months] before the stimulators were actually turned on). However, patient blinding would not be possible given the need for complicated and time-consuming postoperative programming to optimize DBS (especially of the GPI and STN), which could not be feigned by the study team.

Another major issue in surgical study design that must be considered is the variability of surgical technique. Surgical methods for all procedures applied to PD vary greatly, including the exact choice of the target of interest (eg, subtargets within the thalamus or globus pallidus); preoperative and intraoperative imaging methods; microelectrode vs macroelectrode recording techniques; intraoperative techniques of defining safety and efficacy of DBS electrode placement; the type of electrode used (shorter or wider interelectrode distances); and multiple unique issues related to transplantation, including the source, amount, preparation, sites, and methods of placement of the transplanted tissue and the use of immunosuppressant therapy. These considerations become critical when interpreting results of surgical therapies and comparing reports from different centers. They are especially important to consider in the design and analysis of multi-institutional studies in which not only are a participating center’s operative morbidity and mortality important concerns but such variability in surgical technique could also readily influence the outcome.

For the reasons outlined, conducting randomized, controlled, clinical trials of surgical therapies for PD is challenging but not impossible. To my knowledge, none of the available procedures have been evaluated in this fashion. In general, the support for efficacy, at best, rests on series with nonrandomized historical controls or no controls and, at worst, on isolated case reports. With this in mind, the various surgical options being used in the management of PD will be discussed, reviewing what is clearly known or established and emphasizing what is still unknown and what studies are still needed to address the outstanding uncertainties. It is not my purpose to provide an in-depth review of the efficacy of surgery for PD. For adverse effects, an important aspect of surgical therapy is operative morbidity and mortality. However, the older literature in this field is derived from an era when modern stereotactic techniques were not available, and recent studies often represent the earliest experiences from centers that are just beginning to acquire new technical, anatomical, physiological, and neurosurgical skills and knowledge. For these reasons, little will be said about surgical complications except where important to the state of clinical equipoise.11

One important related issue that should be considered with respect to the safety of DBS is the fact that late or long-term complications are possible with this technique that have not been addressed in the short-term efficacy studies available to date. These include such problems as erosion of the lead through the skin, infections, lead fractures, and the inevitable battery failure with the accompanying need for surgical replacement. It will be extremely important that the incidence and nature of these problems be addressed in order that comparisons between DBS and other surgical approaches (eg, lesions) are complete and accurate.

**ABLATIVE LESIONS OR DBS**

**Thalamus**

**Thalamotomy.** Thalamotomy has been used in the management of PD for 40 years. There is little disagreement that thalamic lesions, usually targeting the ventral intermediate nucleus, can markedly reduce tremor but have little effect on other parkinsonian symptoms. Generally, a good to marked effect on contralateral resting tremor is reported in 75% to 85% of patients.12 A significant long-term benefit (mean, 11 years) has been demonstrated in the only blinded analysis13 of response to thalamotomy performed to date. Complications are not uncommon, including persistent paresthesias, dystonia, dysarthria, and cognitive changes, and the latter 2 are more frequent following bilateral procedures.

**Thalamic DBS.** The principal theoretical advantages of DBS are that it is titratable (based on efficacy and adverse effects) and that the permanent complications of lesions are less common, particularly when bilateral procedures are performed. The similarity in the clinical effects of lesioning and “stimulation” suggests that DBS somehow blocks the activity of the region in question. However, the exact mechanism(s) of action remains a question for further study (Table 2). The widespread application of DBS to the thalamus makes it unlikely that any better evidence for efficacy of thalamotomy will be forthcoming from further studies. However, the advan-
tages of DBS are mostly theoretical or generally based on historical experience rather than on the results of prospective, randomized studies with blinded evaluations. Recently, a group from the Netherlands reported a comparison between thalamic DBS and thalamotomy in patients with PD, essential tremor, and multiple sclerosis randomly assigned to either treatment. Although both surgical therapies were effective in reducing tremor at the 6-month follow-up, thalamic stimulation resulted in a greater improvement in functional disability and in significantly fewer adverse effects than thalamotomy.14

As with thalamotomy, there are no randomized, controlled trials of thalamic DBS. Open evaluations have indicated that 80% to 90% of patients obtain a marked benefit for tremor (many with complete tremor suppression). This degree of benefit has been confirmed in the trials15,16 that used randomized, blinded evaluations of stimulation on and off. However, despite this improvement, disability was either unchanged or only modestly improved in patients with PD in contrast to the experience of patients with essential tremor described in the same studies. This is probably explained by the important fact that tremor is not the primary source of disability for most patients with PD, and thalamic procedures have little impact on other more important features, such as bradykinesia and gait disturbances. Other studies,17,18 however, have reported some improvement in disability and even significant reductions in rigidity and akinesia scores. The effect of thalamic DBS on levodopa-induced dyskinesias has been quite variable and probably relates to the exact location of electrode placement, with electrodes having antikinesiogenic effects being more posterior, medial, and deeper than the ventral intermediate nucleus, possibly closer to the center median-parafascicular nuclear complex of the thalamus.19 There is a clear need for further studies evaluating the efficacy of thalamic DBS in patients with PD. However, in view of the modest and unpredictable effects on all features other than tremor, these may not be forthcoming, and thalamic stimulation will probably be restricted to a rather small subsegment of the population of patients with PD.

**Globus Pallidus**

**Pallidotomy.** Pallidotomy is probably the most common surgical procedure offered to patients with PD. It was “reintroduced” by Laitinen et al20 in 1992 and further encouraged by the prevailing model of basal ganglia physiological features, which proposes the presence of several parallel cortical-striatal-pallidal-thalamic circuits; the idea that the sensorimotor circuit passes from the putamen through the ventral globus pallidus; and the finding that the internal segment of the globus pallidus (GPi) is overactive in nonhuman primates with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced parkinsonism, resulting in excessive inhibition of downstream targets such as the motor thalamus. Despite the satisfying logic that supports the application of pallidotomy to patients with PD to reduce this excessive inhibitory efferent basal ganglia activity, several controversies or uncertainties persist, including the basic issue of exactly where the lesion should be made: most have concentrated on the posteroverentral

**Table 2. Some Important Questions to Be Answered in Future Trials of Surgical Therapies for Parkinson Disease**

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<thead>
<tr>
<th>General issues</th>
<th>Who are the best surgical candidates (ie, what correlates with good and bad surgical outcomes)?</th>
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<td>Are specific surgical targets and surgical techniques more appropriate for certain symptoms (ie, should surgery be tailored to the specific clinical features)?</td>
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<td>When in the disease should surgery be considered? Should surgery be applied earlier, before disability results in any degree of dependency?</td>
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<tr>
<td>Surgery vs best medical management</td>
<td>Are surgical therapies more effective than best medical management (including newer drugs as they become available, such as selective D, dopamine receptor agonists and glutamate antagonists)?</td>
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<td>Are any of the available surgical therapies effective in improving levodopa-resistant motor symptoms? (This is distinct from improvement in “on” period scores, which are often compromised by limitations to medication doses [eg, dyskinesias and psychiatric effects]).</td>
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**Pallidotomy**

- What is the impact of previous lesion therapy on the response to a subsequent surgical intervention (DBS or transplantation)?
- How do the safety and efficacy (short- and long-term) of microelectrode- vs macroelectrode-guided surgery compare?
- Is DBS safer, especially for bilateral procedures?
- Is a staged approach with a lesion (eg, GPi) followed at a later date necessary by contralateral DBS as effective as bilateral simultaneous application of DBS (GPi or STN)?

**DBS**

- Which is the more effective target, the STN or the GPi?
- How does DBS work? Does it work differently in different targets?
- Why does STN stimulation allow reduction in dopaminergic medication while GPi stimulation generally does not?

**Transplantation**

- Multiple outstanding issues (See “General Comments on Study Design Issues” and “Transplantation” sections in the text.)

DBS indicates deep brain stimulation; GPi, internal globus pallidus; and STN, subthalamic nucleus.

GPi; others on the ansa lenticularis as well (“pallidoan- sotomy”); and Laitinen,21 the founder of modern pallidotomy, subsequently targeted the external segment of the globus pallidus (he moved laterally to avoid the optic tract, which was damaged in a proportion of his early patients). Some of the most vociferous arguments have been made in the absence of any well-documented outcome data. It is rather difficult to accept that this surgical variability does not contribute to variability of outcome. In fact, data have been presented in support of differing responses dependent on where within the ventral GPi the lesion is made.22 As mentioned earlier, the influence of several other surgical methodological factors is completely unknown. For example, a highly contentious and controversial issue is the safety and efficacy of microelectrode vs macroelectrode mapping techniques. Some23–26 suggest that the data obtained from the former clearly improve successful targeting of the GPi, while others27–29 argue that this technique adds unnecessary risk without improving outcome. A trial that is sorely lacking is one that would randomize patients to undergo surgery using one or the other of these approaches. However, most groups using mi-
Microrecording are convinced of its utility, and those who only use macrorecording and stimulation do not have the equipment or expertise to apply microrecording. Thus, it is highly unlikely that a satisfactory resolution to this debate will be forthcoming.

Despite its widespread application, support for the use of pallidotomy in patients with PD is almost exclusively based on evidence derived from uncontrolled case series. Recently, De Brie et al reported the first randomized, single-blind, multicenter trial of unilateral pallidotomy confirming significant benefits in off period PD and levodopa-induced dyskinesias (31% and 50% improvement, respectively). The preliminary results of a National Institutes of Health–funded study from Emory University, Atlanta, Ga, randomizing patients to pallidotomy or best medical management, have also suggested better outcome in the surgical arm (J. Vitek, MD, oral communication, 1999). Of the earlier reported studies, only 1 provided the results of blinded videotape ratings of PD motor scores; only 2 compared results with medically treated groups (however, patients were not randomized to these arms and evaluations were not blinded); and the remainder involved open evaluations of relatively few patients (Lang et al provide a review), with the largest case series reporting inconsistent or uninterpretable data. When the results of studies that provide sufficient comparable raw data are combined, some results are consistent: contralateral drug-induced dyskinesias are improved by 80% to 95% and ipsilateral dyskinesias by 40% to 50%; total off period motor and ADL scores improve by 25% to 30%, with reductions in contralateral PD, including tremor, rigidity, and bradykinesia, accounting for much of this change; and on period scores (motor or ADL scores) change little except as explained by reduction in disabling dyskinesias (ie, as manifest in improvement in ADL scores). These benefits do not come without potential risks. The optic tract and internal capsule are the major neighboring structures that can be damaged at the time of lesioning. However, with experience and careful use of stereotactic and electrophysiologic techniques, persistent visual field deficits and hemiparesis are uncommon. Neuropsychologic dysfunction following medial pallidotomy is variably recognized. One consistent feature is persistent deterioration of verbal fluency, especially following left-sided lesions. Behavioral changes are also evident to a variable extent. The extent and nature of the neuropsychologic changes following pallidotomy are related to where in the ventral GPi the lesion is made.

There are several important issues that remain to be resolved regarding the effects of pallidotomy. Benefit may be sustained for up to 2 years; however, there are little reliable published data available to support efficacy beyond that point. The results of the previously mentioned study at 2 years were generally better than those reported in the only other study providing this duration of follow-up. One possible explanation that needs to be explored relates to differing surgical methods; although the University of British Columbia group originally emphasized that the use of microrecording was unnecessary and provided little additional advantage, the better long-term outcome results in the other study serve as further evidence that this method does improve the accuracy of optimal target localization. Recently, the more extended long-term outcome of 20 patients followed up for up to 51⁄2 years (mean, 41⁄2 years) was analyzed. Total Unified Parkinson’s Disease Rating Scale motor scores and contralateral bradykinesia scores remained significantly improved compared with baseline; however, there was significant decline in these scores compared with the 6-month postoperative scores. Contralateral tremor, rigidity, and dyskinesias maintained their significant initial responses. Despite these persistent benefits, ADL scores were no longer significantly improved compared with baseline.

The effects of pallidotomy on symptoms that are relatively resistant to levodopa are somewhat controversial; generally, it is believed that such features as freezing and postural instability persisting in the on period are not affected. There are no reliable data to support the safety and efficacy of bilateral pallidotomy; claims vary from pronounced benefit beyond that obtained with a unilateral procedure with little risk to variable additional benefit but a high complication rate, especially for speech, cognition, and behavior.

**Globus Pallidus DBS.** Although preliminary results for DBS of the globus pallidus are promising, the available supportive data are extremely limited. The numbers of patients treated have been small, and blinded evaluations have been performed in only one small pilot study that mainly involved patients who had previously undergone a contralateral pallidotomy. A large multi-institutional study that evaluated response to pallidal stimulation blindly at 3 months is in the final stages of data analysis and reporting. Preliminary reports suggest the following results, which need to be confirmed in future studies: pallidal stimulation may improve all off period parkinsonian features, dyskinesias may be markedly suppressed, bilateral pallidal stimulation can be applied safely and effectively, patients continue to require preoperative anti-PD medication dosages, and responses may vary dependent on where in the globus pallidus stimulation is provided. Preliminary studies claim that ventral stimulation blocks dyskinesias but may have a prokinetic effect (which may account for the results reported in one study that questioned the value of GPI DBS), while dorsal stimulation may ameliorate akinesia but aggravate dyskinesias. The exact location of the electrodes in these studies is uncertain, and so these intriguing observations require further careful evaluation with additional anatomic definition using microelectrode and imaging confirmation. There is also a claim that stimulation in the anteromedial globus pallidus may provide substantial benefit. These studies suggest that optimizing GPI stimulation may be an extremely complex task and might also support the future need for development of distinct or unique DBS technologies for application in different brain sites. Despite the widespread belief that DBS is equally effective but safer than lesioning techniques, to my knowledge, the only study available that attempted to address this issue for the GPI involved a total of only 13 patients and, although patients were randomized to the 2 treatment arms and followed up prospectively, the rat-
ings were obtained in an unblinded fashion. Although bilateral GPi DBS has been reported to have little effect on memory or executive function, one study reported that 30% of patients (generally older and taking higher doses of levodopa) undergoing unilateral pallidal stimulation showed some degree of cognitive decline.

**Subthalamic Nucleus**

**Subthalamic Nucleotomy.** The recognition that the STN is overactive in N-methyl-D-aspartate-induced parkinsonism in monkeys, and that the resulting excessive excitatory glutamatergic drive from this region to basal ganglia outflow sites accounts for many of the clinical features, has resulted in recent surgical attempts to block the activity of this nucleus in humans with PD. Surgeons have been understandably reluctant to lesion this area for fear of inducing disabling hemiballismus. However, there have been recent reports suggesting that subthalamic nucleotomy can be performed safely and successfully without inducing ballismus. Although intriguing, this is an experimental technique that requires extremely cautious further study.

**STN DBS.** Deep brain stimulation of the STN has been more widely applied; however, supportive data are quite limited. All aspects of off period PD can respond to bilateral STN stimulation, with reduction in motor and ADL scores of approximately 60%. On period improvements may also be seen; however, it remains uncertain whether STN stimulation is capable of improving truly levodopa-resistant symptoms. Responses of tremor are often striking, and this has encouraged the suggestion that the STN should replace the thalamus as the primary target in the treatment of drug-resistant tremor in view of the more global effects on all other features of PD. Dyskinesias may improve significantly; however, it is believed that this is largely explained by the reduction in anti-PD medication made possible by STN stimulation. To date, only 1 study has provided a double-blind assessment of the effects of STN DBS, confirming the results of reports from unblinded studies. A larger, multi-institutional study assessing 3-month postoperative blinded evaluations is under analysis. As with bilateral GPi DBS, early studies indicate that bilateral STN stimulation does not significantly impair overall cognitive performance; however, a few older patients have experienced notable neuropsychologic decline, especially those with premorbid cognitive dysfunction.

There are no studies available that allow an accurate comparison of the results of GPi and STN stimulation. Preliminary studies have suggested that DBS of the STN may be more effective than GPi DBS with the additional advantages of allowing lower doses of anti-PD medications and lower voltages of stimulation (resulting in longer battery life). However, to date, there has been only 1 small pilot study comparing patients randomized to GPi (n = 4) with those randomized to STN (n = 5) stimulation (patients and evaluators blinded to the site; little difference was found in response between the 2 sites. Clearly, this remains one of the most important surgical issues to be resolved by further randomized, controlled, blinded studies involving larger number of patients. It will also be important for future studies to compare the effects of STN or GPi DBS with the more widely available and less costly pallidotomy (or thalamotomy in the case of tremor-dominant disease) and to assess the efficacy of STN stimulation in patients who have previously undergone a unilateral pallidotomy.

**TRANSPLANTATION**

Transplantation of human fetal mesencephalic tissue into the striatum of patients with PD is an encouraging but highly experimental therapy. Preliminary reports of small numbers of patients have provided open-label evidence of clinical efficacy, positron emission tomographic evidence for increased fluorodopa F-18 activity in the region of the implants, and postmortem evidence of survival of the transplanted cells with extensive reinnervation of the striatum. A recent single case report has demonstrated evidence of persistent graft function (including dopamine storage and release) 10 years after implantation.

As mentioned previously, there are numerous technical issues related to tissue preparation, implantation techniques, and use of immunosuppressive drugs that have to be resolved as this field advances. Two prospective clinical trials attempting to control for either the effects of surgery (using a sham procedure) or the quantity of tissue implanted (varying the number of donors used) have received funding from the National Institutes of Health. Preliminary results from the first of these have indicated a modest benefit in patients 60 years of age and younger but no improvement in those older than 60 years (S. Fahn, MD, oral communication, 1999). One extremely concerning observation from this study has been the development of severe spontaneous dyskinesias independent of dopaminergic therapy, occurring in 1 of 3 patients to date.

Given the belief that 6 to 8 or more fetuses may be required to fully reinnervate both striata of a patient with PD, there is considerable interest in alternative sources of tissue for transplantation, including autologous carotid body cells and fetal porcine mesencephalic cells. These and other techniques attempting to encourage regeneration or reinnervation (eg, using genetically modified cells, polymeric encapsulated cells, stem cells, or trophic factors) are of great interest but either remain highly experimental or are still theoretical prospects. Unfortunately, despite promising preclinical data, a phase 1 to 2 clinical trial of intracerebroventricular glial-derived neurotrophic factor in patients with late-stage PD was terminated due to lack of efficacy and a high incidence of important adverse effects. Direct intraparenchymal application of this and other neurotrophic factors is an alternative for future study. Finally, it will be important to assess the influence of previous surgical interventions (especially lesions such as pallidotomy) on the potential responses to regenerative therapies as they become a reality. For example, theoretically,
the response to successful reinnervation of the striatum might be adversely affected by a previous lesion in the GPi.

**CONCLUSIONS**

Despite numerous claims, the evidence for benefit from surgical therapies in patients with PD is relatively weak by today's scientific standards. This does not detract from the striking benefits that can be obtained from these treatments. However, it does emphasize the importance of critical assessment of the available data and the need for randomized, controlled, clinical trials designed to address important outstanding issues before these treatments are widely applied. Table 2 lists some of the important questions that need to be addressed in future studies of surgical therapies for PD.

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