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Utilization of Unilateral and Bilateral Stereotactically Placed Adrenomedullary-Striatal Autografts in Parkinsonian Humans: Rationale, Techniques, and Observations

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A limited clinical pilot study involving an amalgam of specialized disciplines including neurology, neuropharmacology, neuropsychology, neurosurgery, neuroanesthesia, neuroradiology, surgical pathology, neuropathology, and urological surgery was organized to clarify issues related to patient selection, optimization of grafting materials, design of a safe, effective, standardized, and reproducible surgical technique, and possible modification of clinical patterns. After initial assessment of 82 Parkinsonian patients for periods of 6 to 20 months, 10 (age, 39–68 years) were selected for unilateral or bilateral adrenomedullary autografts to the caudate nucleus with ependymal and cerebrospinal fluid contact, employing image-directed stereotactic methods. Selection was made only after clear definition of clinical pattern and optimization of medication responses. Adrenal glands were harvested by a retroperitoneal approach (mean estimated blood loss < 75 ml). Care was taken to maximize the graft content of medullary tissue. Stereotactic methods afforded standardized, reproducible, precise targeting and transit trajectory with unilateral or bilateral placement of materials within the striatum (tissue volume, 80 mm^3) with access to the ventricular fluid of the frontal horn. Considerable variability in satisfactory donor medullary tissue was encountered. One patient did not undergo grafting because of unsatisfactory medullary tissue. No significant surgical complications were noted and all patients were ready for discharge 7 days after surgery. One patient who manifested no apparent clinical change died 6 weeks after bilateral grafting of unrelated causes during a lithotripsy procedure. Postmortem examination disclosed precise graft placement with a paucity of structurally preserved medullary cells. Postoperative observations, including parameters of clinical observation, medication schedules and records, patient and family commentaries, and imaging studies (computed tomograms and single photon emission computed tomograms), have been made for periods from 16 to 20 months. Sustained improvement in preexisting clinical patterns and reduction in drug requirements were observed in 4 of 8 patients. No increased benefit could be ascribed to bilateral graft placement. These observations would indicate a primary role for stereotactic methodology for cerebral graft placement, as it affords a minimally invasive but precise, safe, and reproducible surgical method. In addition, the clinical observations indicate favorable alterations in the established pattern of the disorder, which would justify further cautious exploration of alternate donor sources or refinements of biological graft site manipulations. (*Neurosurgery* 26:746–757, 1990)

Key words: Adrenal medullary graft, Autograft, Brain graft, Neural transplantation, Parkinsonism, Stereotaxy

INTRODUCTION

The prospect for restoration of cerebral function through grafting has initiated both excitement and skepticism for more than half a century (3, 15, 40, 46). The culmination of a number of scientific developments over the past two decades have provided increased impetus and plausibility to the clinical application of this concept (1, 5, 14, 18–23, 33, 47, and Backlund E-O, personal communication, April 1989). Based on over 90 years of periodic laboratory observations and increased sophistication in areas of immunohistology, experimental models, and molecular biochemistry, initial steps were undertaken in Sweden, and two Parkinsonian humans received stereotactically placed adrenal medullary autografts resulting in modest transient alterations in their clinical courses (4). Subsequently, Mexican investigators employing an open technique published more dramatic and sustained alterations of Parkinsonian syndromes in a small series of younger patients (34). These publications provided the impetus for the initiation of the studies transmitted in this report. While clinical investigations are underway in this important area, with several early clinical studies having been reported, a number of issues require further clarification, including those related to patient selection, optimization of surgical techniques, defining and reducing surgical complications, procedural impact on established clinical courses, type and volume of grafted material, graft viability, and expectations of any procedure (4, 6, 24, 32, 35, and personal communications: Backlund E-O, April 1989, and Madrazo I, April 1989). This report presents observations in a modest number of patients in an effort to add further perspective and definition to this complex and largely ill-defined area of study (27, 30, 36, 40–43).

METHODS AND RATIONALE

General considerations and study design

With consideration of the multitude of difficulties attendant on the development of any clinical study, but, in particular, one as complex and variable as Parkinson's disease, it was considered that strict definition of the preoperative patient clinical patterns was essential. Therefore, the initial objective of the study was to identify a group of patients in whom a clinical pattern was clearly established, with absolute optimization of the medication response.

Second, a standardized, precise, and reproducible operation was devised that would reduce the variables attendant on the surgical procedure. Strict observation postoperatively for alteration of established clinical patterns was the final part of the protocol.

A study group was assembled comprised of members of the following divisions and departments: neurological surgery, neurology, neuropharmacology, neuropsychology, neuroradiology, neuroanesthesia, urology, surgical pathology and neuropathology.

Patient selection

After consideration of available data and study goals, criteria for inclusion in the study were established. These were as follows:

1. An unsatisfactory response to medical management with either significant disease progression, unsatisfactory side effects, or complications of drug administration.
2. A problem with response to dopamine.
3. Good general health.
4. No clinical evidence of dementia.
5. A well-established and relatively predictable clinical pattern.
6. A psychosocially stable individual and family.
7. The presence of bilateral adrenal glands on imaging studies.
8. No significant cerebral atrophy on imaging studies.

Preoperative evaluation

Patients were evaluated for 6 months with recording of "on" and "off" functional ratings according to the Hoehn and Yahr scale (25) as well as the Unified Rating Scale for Parkinson's disease (URSP) (29). Evaluations were conducted with care to ensure uniformity of time of day, time elapsed since administration of medication, and other recognized variables in the evaluation of Parkinsonian syndromes. The URSP is a 4-point scale that consists of the following subcategories: 1) mentation, behavior and mood; 2) activities of daily living; 3) motor examination; and 4) complications of therapy. The Hoehn and Yahr scale stages the severity of Parkinsonism, with 0 being no sign of disease and 5 being wheelchair-bound or bedridden. For the purposes of this study, motor examination scores that represented a defined objective performance measure of 14 individual parameters were totalled and the results of 2 to 3 visits averaged to provide a mean motor score. "Off" can be defined as status prior to the first morning dose or at the end of the dose. Scores were obtained in "on" and "off" conditions. "On" represented the peak dose effect and "off" data was at the end of dose assessment. Strict recording of medication dosages and schedules were made. Efforts were made to optimize medication schedules during this period.

Individuals who were considered to be candidates for grafting underwent formal neuropsychological assessment that included the Wechsler Adult Intelligence Scale–Revised, the Mini-Mental Status Examination, the Wechsler Memory Scale, grocery list learning, the Minnesota Paper Form Board, the Purdue Pegboard, finger tapping, star tracing and reaction time tasks. Imaging assessments included magnetic resonance imaging (MRI), computed tomography (CT), and single photon emission computed tomography (SPECT). A video tape record of "on" and "off" function was made for all patients. A record of lumbar fluid examination for catecholamines and metabolites was also kept for all patients. The purpose of videotape recording was to document pre- and postoperative clinical findings in relation to time and dose of medication. A specific examination protocol was followed.

Surgical procedure

General Method. The objectives of the procedure were to place a viable adrenal medullary autograft of consistent volume in an appropriate brain region with minimum risk to the patient and minimization of ancillary neural trauma that could effect clinical observations. Therefore, an image-directed stereotactic method was adopted (2). The stereotactic method offered the advantage of standardization of experimentation with reproducibility of targeting and tissue placement in consecutive patients. Additionally, because craniotomy was not performed, overall operative trauma was minimized. Therefore, harvesting of the patient's adrenal gland, even by a retroperitoneal approach (deemed optimal by our genitourinary surgeons) constituted the major operative procedure in these physiologically impaired patients.

Graft. A key objective was to deliver a viable graft of maximum medullary content. In preparation, cadaver adrenals were dissected by members of the surgical team and examined by a pathologist to gain experience in harvesting methods and definition of adrenal medullary cells. At surgery, glands were immersed in Eagle's minimum essential medium at 42°F and sectioned in 3-mm slices in "bread-loaf" fashion. Individual slices were dissected in chilled Eagle's minimum essential medium under the operating microscope, and fragments were evaluated by the pathologist at frequent intervals. A delivery device was developed that allowed placement of a reproducible volume of tissue in consecutive patients. This consisted of a surgical stainless steel coil (Radionics, Inc., Burlington, Massachusetts) measuring 2.5 mm in diameter and 20 mm in length (100 mm^3) that could be loaded with medullary fragments after microscopic dissection and histological assessment. The volume of the coil was arbitrarily selected to double that described by Backlund et al. in their initial studies (4). During pathological assessment, care was taken to minimize the introduction of cortical tissue, which has been demonstrated to affect plasticity toward neuronal morphology (12, 13, 48). Estimated purity was considered to reach 90% with pathological review, and 10 to 15 fragments of medullary tissue were loaded into the coil by microscopic technique.

Procedure. In consideration of available data and experiences with the open surgical technique introduced by Madrazo et al. (34) the caudate head was selected as the target for grafting within the striatum. This target was selected in spite of data suggesting some advantage for placement in the putamen, since caudate targeting allowed ependymal and cerebrospinal fluid contact (26, 28, 39, 45, 46). Image-directed stereotactic methods employing either a Brown-Roberts-Wells (BRW) (2) or Cosman-Roberts-Wells (CRW) (11) stereotactic system allowed for placement of the graft delivery device in the caudate head and adjacent striatum in a reproducible fashion with approximately 16 mm of the device within the striatal parenchyma of the caudate head and 4 mm in the ventricular fluid of the frontal horn. Therefore, approximately 80 mm^3 of medullary tissue was placed within the parenchyma. Transits and trajectories were predetermined by imaging reconstructive methods. To minimize trauma further, only a 0.25-inch twist drill entry was required. Tissue delivery was performed through a graduated cannula system once initial penetration of the caudate striatum had been achieved in the line of trajectory of the graft. With this method, unilateral or bilateral grafting could be achieved within 3.5 hours of the initiation of the entire procedure. It was considered that minimization of time from harvesting the adrenal to graft placement should be achieved; however, proper dissection and verification of tissue required a minimum of 45 minutes, during which other members of the surgical team prepared stereotactic transit trajectories and instrumentation for immediate placement once dissection, verification, and loading of the device were completed. In general, whether grafting was undertaken in a unilateral or a bilateral technique, the completion time from harvesting to grafting was less than 1 hour (Table 1).

Postoperative Management and Evaluation. In the immediate postoperative period, patients were transferred to the neurosurgical intensive care unit. At that time, initial clinical observations were begun by the neurologists on the study team. In an effort to reduce problems associated with decreases in patient mobility and other neurological dysfunction that could preclude a successful and uncomplicated recovery, medications were initiated immediately in the postoperative period, with adjustments being made as recovery progressed. The following evaluations were carried out:

1. *Clinical evaluation.* The assessments—performed weekly for the first month and thereafter at monthly intervals—included the URSP, the Hoehn and Yahr scale, the Schwab and England scale, medication schedules, patient communications and family communications. Care was taken to assure that assessments were undertaken during uniformly defined periods with respect to time of day and medication administration. Videotape assessment was conducted at 3-month intervals. Patients were evaluated at a defined time before and after their medication on each visit. It was decided that clinically improved status could be conferred on those individuals who satisfied the following criteria 12 months after surgery: *a)* a sustained reduction of preoperative medication requirements; *b)* a sustained improvement in mean motor score (URSP); and *c)* a subjective impression of improvement.
2. *Imaging studies.* These included CT and SPECT at intervals of 1, 3, 6, and 12 months.
3. *Cerebrospinal fluid examination.* Cerebrospinal fluid from lumbar sampling was examined first at 1 week and then at 4, 12, and 24 weeks. Examination included assays of homovanillic acid, 5-hyroxy-indoleacetic acid, and 3-methoxy-4-hydroxy phenylethylene glycol (15).

TABLE 1
Adrenomedullary-Striatal Autograft: Stereotactic Technique

	Time Required (min)
1. Apply base ring (local)	10
2. Scan for target(s)	10
3. Determine transits	10
4. Intubation/prone positioning	30
5. Adrenalectomy (L) (retroperitoneal)	60
6. Gland dissection	60
7. Stereotactic grafting[a]	30
Total time required:	±3 h 30 min

[a] See Reference 2.

CASE MATERIAL AND OPERATIVE OBSERVATIONS

Population profile

After 82 Parkinsonian patients underwent initial assessment for periods of 6 to 20 months throughout a 24-month period, 10 patients were selected who were felt to meet the criteria for inclusion (Table 2). This group included 6 men and 4 women who ranged in age from 39 to 68 years (mean, 53 years). The mean duration of disease was 10.9 years, with a range of 6 to 17 years. The rating on the Hoehn and Yahr scale ranged from 2 to 4, with a mean of 3 while "on" and a mean of 2 to 5 while "off." The mean dose of levodopa (Sinemet, Merck Sharp & Dohme, West Point, Pennsylvania) was 825 mg per day, with a range of 700 to 1250 mg per day. All patients had had frequent increases in their dose of the drug and severe side effects from medications. At the time of surgery, 3 patients were using bromocriptine (Patients 5–7) at an average dose of 15 mg. All the patients except one (Patient 1) had in the past experienced either no benefit or troublesome side effects when given a trial of bromocriptine. One patient had been treated with pergolide and took amitriptyline for sleep (Patient 9). The protocol established that the first 5 patients would be treated with unilateral grafts and the second 5 with bilateral grafts.

Operative procedures

Surgical procedures were undertaken during a 12-month period (July 1987 to June 1988). Adrenal harvesting was uneventful, with a mean blood loss of 75 ml (range, 25–150 ml); however, at dissection, 2 of the 10 glands were observed to have hemorrhage in the medullary region, which made identification of graft material difficult. Of importance, considerable variability was noted in the volume of medullary tissue available for the graft (Table 2). In one case, no graft was undertaken because the combination of hemorrhage and paucity of available material precluded grafting. Stereotactic placement was uneventful, with successful placement achieved unilaterally in 5 patients and bilaterally in 4 (Figs. 1

TABLE 2
Adrenomedullary-Striatal Autograft: Clinical Data

Patient	Sex[a]	Age[b]	Duration of symptoms[c] (yr)	Neurological Profile[d]	H & Y Rating[e]	Medication (mg L-Dopa)[f]	Date of Surgery (mo/yr)	Adrenal Tissue (mm)[g]	Graft[h]	Complications	Outcome[i]
1	M	43	9	B, R, P	3	700	7/87	3⁻	L	0	Nonresponder
2	F	39	8	T, B, R, P	3	1000	8/87	4⁻	R	Vivid dreams	Responder
3	M	57	13	T, R	2	1250	9/87	3⁻	R	0	Responder
4	F	49	5	(R) R, T, B	2	750	11/87	3⁺	R	0	Nonresponder
5	M	44	11	R, B, P	3	500	11/87	4⁺	R, L	0	Responder
6	M	65	8	B, R, P	4	1000	12/87	(H) 2⁺	R	Psychosis	Responder
7	M	68	17	R, B	3	1250	2/88	(H) 1⁺	0	0	Nonresponder
8	F	58	12	R, B	3	500	5/88	4⁺	R, L	0	Nonresponder
9	F	60	15	R, B, T	3	800	5/88	2⁺	R, L	0	Nonresponder
10	M	50	11	B, R	4	500	6/88	1⁺	R, L	0	Death (6 Wks)

[a] Total: 6 men, 4 women.
[b] Average: 53 years.
[c] Average: 10.5 years.
[d] B, bradykinesia; R, rigidity; P, postural instability; T, tremor; (R), right-sided. Profile listed in order of severity.
[e] Hoehn and Yahr scale. Average rating, 3.
[f] Daily requirement of L-Dopa. Average, 825 mg.
[g] Width of medullary ribbon of available donor tissue on sections. (H), hemorrhage.
[h] Site of graft: L, left striatum; R, right striatum; 0, none.
[i] Status at 1 year after surgery.

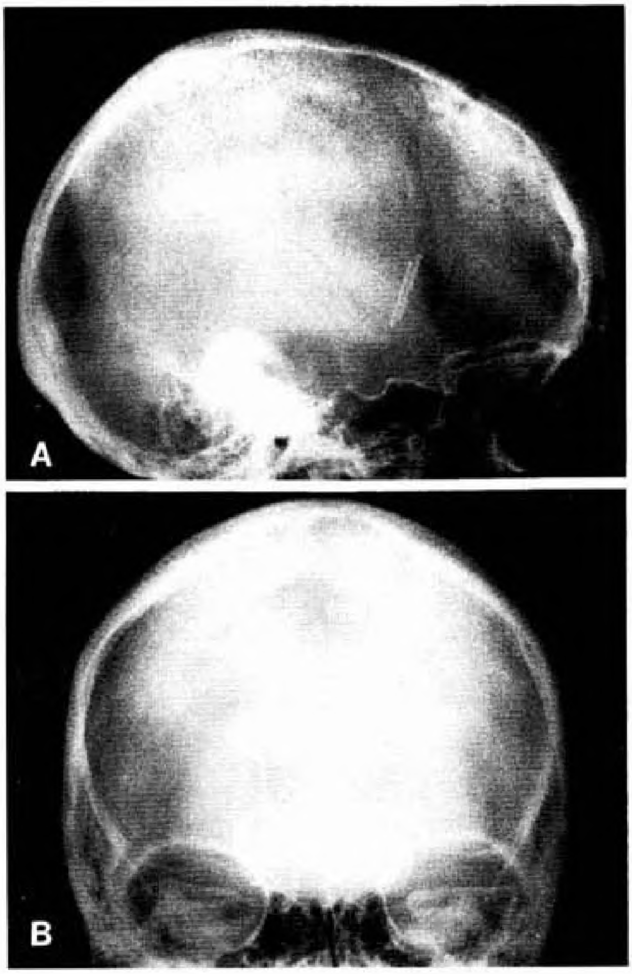

FIG. 1. Lateral (*A*) and posteroanterior (*B*) radiographs demonstrating bilateral coil position.

and 2). Because of the impressive character of bilateral clinical findings, the fifth patient was treated with bilateral caudate grafts. All procedures were concluded in a total of 3.5 to 4 hours of operating time, and the time from adrenal harvesting to graft placement never exceeded 1 hour. No unusual intraoperative events were encountered.

OPERATIVE COMPLICATIONS

No threatening complications occurred in the early postoperative period (Table 2). One elderly patient suffered 48 hours of hallucinatory experiences; however, he was discharged from the intensive care unit at 72 hours and was subsequently discharged from the hospital at 10 days. Emergence from anesthesia was uneventful in all patients; no unusual alteration in analgesic requirement was noted by the urological team.

OBSERVATIONS

Of the 10 patients enrolled in the protocol, 1 had an adrenalectomy without grafting and 1 died 6 weeks after surgery during general anesthesia for a lithotripsy procedure, leaving 8 patients with postoperative follow-up ranging from 16 to 20 months.

Clinical patterns A: Entire patient group

When all the patients are considered as a group, they appear to demonstrate a modest reduction in medication requirements and improvement in motor function from 3 to 5 months after surgery. This initial response was followed by an apparent stabilization of medication requirements at levels not significantly different from preoperative levels. Motor function appeared to deteriorate slightly from 8 to 12 months after surgery, but the patients followed up for 16 to 20 months demonstrated persistent improvements in motor scores on the average of 30 to 40% (Fig. 3).

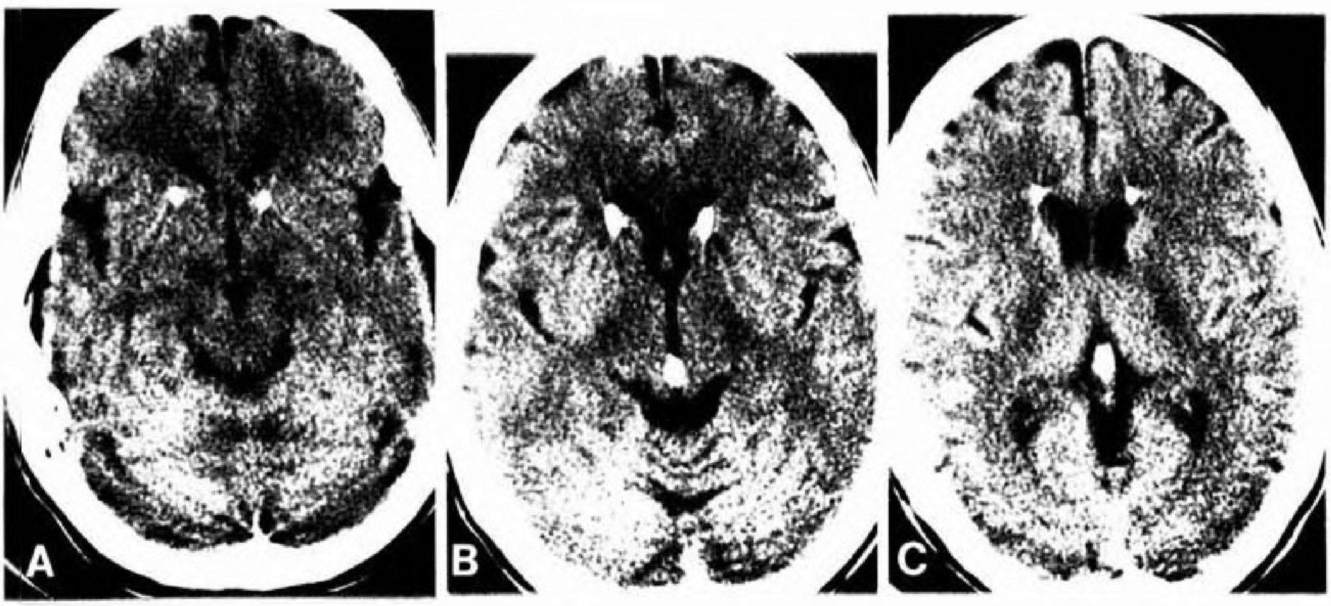

FIG. 2. Computed tomogram demonstrating coil position in the caudate-striatum (*A* and *B*) and frontal horn (*C*) on successive 5-mm slices.

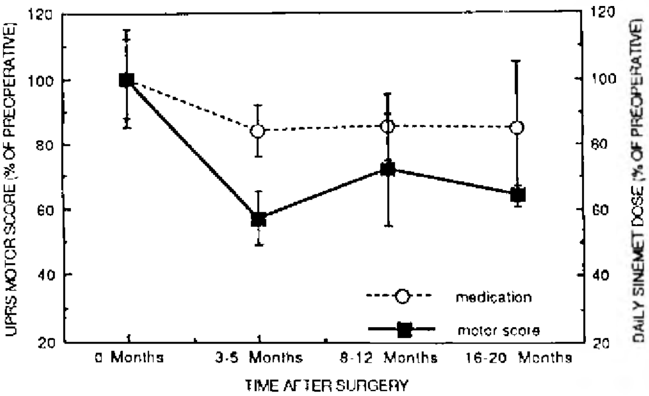

FIG. 3. Medication requirements and motor scores for all patients after surgery.

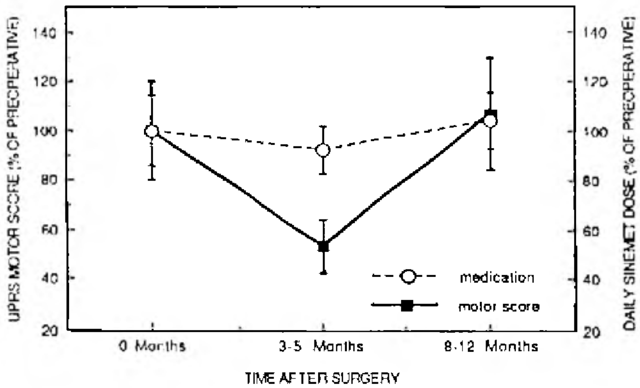

FIG. 4. Nonresponder group. Transient improvement in the motor score is followed by a return to the baseline.

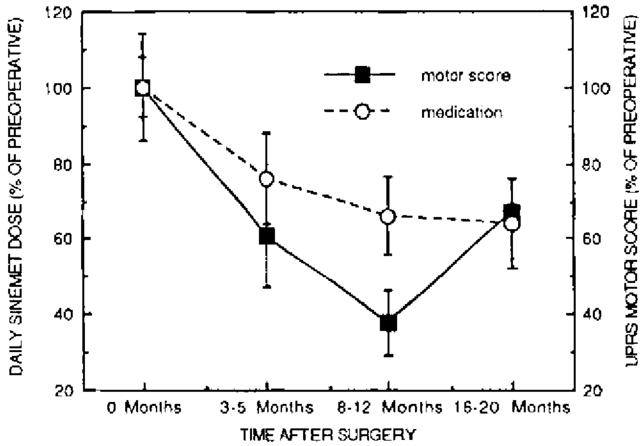

FIG. 5. Responder group. Reduction in medication parallels improved motor scores during the first 12 months after surgery.

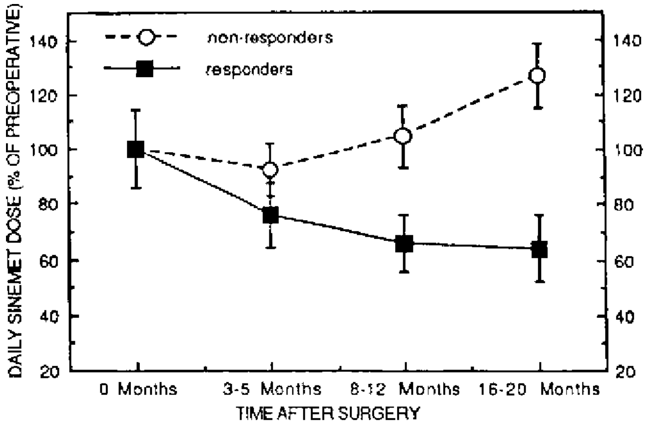

FIG. 6. Patterns of medication requirements after surgery: Responders versus nonresponders.

Clinical patterns B: Nonresponders (no sustained improvement)

When the patients are stratified into responders and nonresponders, postoperative changes become more striking than when the group is considered as a whole. Figure 4 illustrates the trends in medication requirements and motor function in the nonresponder patients. While medication requirements remained unchanged after surgery, an improvement in motor function was observed 3 to 5 months after surgery; however, a return to baseline levels was seen at approximately 12 months. The one nonresponder whose progress was followed out to 20 months after surgery is slightly worse compared with his baseline motor score.

Clinical patterns C: Responders (sustained improvement)

The responder group demonstrated progressive persistent reduction in medication requirements up to 16 to 20 months after surgery. The rate of reduction in medication was most marked during the first 3 to 5 months after surgery, and then remained at approximately two-thirds of the preoperative dosage for the next 12 months.

Motor scores while "on" improved, with peak improvement occurring at 8 to 12 months. As the follow-up period extended to 16 to 20 months, the patients showed a trend toward baseline motor function, but still demonstrated approximately one-third less motor disability as compared with the baseline level (Fig. 5). No change in motor scores while "off" was observed.

Clinical patterns D: Responders versus nonresponders

Figures 6 and 7 emphasize the two apparently distinct patterns of response to the grafting procedure observed in responders and nonresponders. Nonresponders demonstrated an insignificant reduction medication requirements at 3 to 5 months after surgery, followed by progressive escalation in medication requirements from 5 to 20 months. Responders, in contrast, showed the opposite pattern, with sustained reduction in medication requirements up to 20 months after surgery (Fig. 6).

The motor scores of both groups while "on" improved during the 3- to 5-month postoperative period. Nonresponder patients, however, returned to baseline by 12 months after surgery, while responders showed persistent improvement up to 20 months (Fig. 7).

Hoehn and Yahr ratings

No significant changes in the Hoehn and Yahr rating were observed.

Percentage of time "off"

One patient experienced a significant (50%) reduction in the percentage of time "off" at 6 months after surgery, but then deteriorated somewhat at 12 months. Two nonresponder patients (Patients 1 and 9) had modest reductions in time "off" (25%), while the other two nonresponder patients (Patients 4 and 8) had increases in time "off." The remaining 3 patients (all responders) were unchanged with respect to time "off" (Table 3).

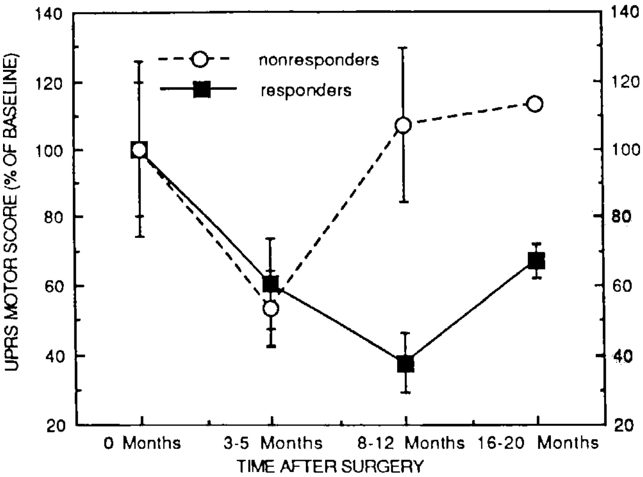

FIG. 7. Patterns of motor response after surgery: Responders versus nonresponders.

TABLE 3
Percentage of Time "Off"[a]

Patient	Preoperative Time "Off" (%)	Postoperative Time "Off" (%) (6 Months)	Postoperative Time "Off" (%) (12 Months)
1	26–50	1–25	1–25
2	76–100	1–25	1–25
3	1–25	1–25	1–25
4	1–25	26–50	26–50
5	1–25	1–25	1–25
6	1–25	1–25	26–50
7	NA		
8	1–25	26–50	26–50
9	25–50	1–25	1–25
10	Died		

[a] As measured by the Unified Rating Scale for Parkinson's disease.

TABLE 4
Patients' Impression of Response to Surgery

Patient[a]	Impression
1	Increased Function (not persistent)
2*	Improved walking (persistent)
3*	Overall improvement in function (persistent)
4	Worsening of Underlying Disease
5*	Greatly improved function (persistent) Medication dosage markedly reduced
6*	Much improvement in walking (persistent)
7	Not applicable
8	Improved balance
9	No change
10	(Patient died.)

[a] * Responders (at 12 months after surgery).

TABLE 5
Characteristics of Responders Versus Non-responders[a]

Characteristic at Time of Surgery	Responders	Nonresponders
Age (yr)	51.2 ± 5.9	51.5 ± 3.4
Duration of disease (yr)	10.0 ± 1.2	10.2 ± 2.2
Hoehn and Yahr rating	3 ± 0.4	2.8 ± 0.3
Daily medication (mg L-Dopa)[b]	1088 ± 153	700 ± 0
Motor score while "on" (Unified Rating Scale for Parkinson's disease	17.0 ± 8.7	16.0 ± 6.7
Percentage of time "off"	32.2 ± 18.8	31.2 ± 12.0
Adrenal gland quality (mm)[c]	3.25 ± 0.48	3.0 ± 0.41
Unilateral graft "success rate"	3/5 (60%)	
Bilateral graft "success rate"	1/3 (33%)	

[a] All values are mean ± SE.
[b] Difference in medication was the only suggestive factor.
[c] Width of medullary ribbon.

Patient impressions

A summary of patient impressions of their overall response to the surgery 1 year later is shown in Table 4. Patients who were considered improved presented a sustained impression of a sense of improved function that correlated with objective motor findings and reduction in medication requirements.

Predictive factors: Response versus nonresponse

In attempting to determine whether responders and nonresponders could be differentiated preoperatively, a number of variables were compared between the two groups, including age, duration of disease, Hoehn and Yahr rating, medication requirements, UPRS motor score, percentage of time "off," and quality of the adrenal gland. There were no significant differences in any of these categories, with the exception of preoperative medication. Nonresponders were receiving less preoperative medication than responders (Table 5).

Unilateral versus bilateral grafting

Although the number of cases was small, no trend indicating an advantage to bilateral grafting was found. In fact, unilateral grafting demonstrated a higher success rate (60%) than bilateral grafting (33%). In order to rule out preoperative factors accounting for this difference in success rate, the characteristics of the unilateral and bilateral graft recipients were compared (Table 6). No significant differences were noted, except that bilateral graft recipients were receiving less medication preoperatively.

Imaging and spinal fluid assessments

Imaging assessment with the position of the coils maintained consistently for up to 18 months of follow-up showed no unusual alteration in structure. In particular, no alteration in dye contrast studies was noted.

SPECT studies were performed on the initial 5 patients during the postoperative period. All studies were negative, with the exception of that of Patient 5, who showed transient activity indicative of blood-brain barrier alteration in the region of his right basal ganglia 1 month after surgery.

Periodic assessment of lumbar spinal fluid catecholamines failed to disclose a pattern of alteration.

Neuropsychological testing

No patterns of improvement or worsening could be demonstrated in the neuropsychological test battery. The two patients (Patients 4 and 6) who felt subjectively improved in their cognitive function did show the greatest improvement across all their test scores; however, this was not statistically significant.

TABLE 6
Characteristics of Patients with Unilateral versus Those with Bilateral Grafts[a]

	Unilateral	Bilateral
Age (yr)	50.6	52.7 ± 3.7
Duration of Symptoms (yr)	8.6 ± 1.5	12.7 ± 1.1
Hoehn and Yahr rating	2.8 ± 0.42	3.0 ± 0
Medication (mg L-Dopa)[b]	1010 ± 159	700 ± 0
Motor score while "on" (Unified Rating Scale for Parkinson's disease)	16.2 ± 4.0	17.0 ± 3.5
Percentage of time "off"	32.5 ± 16.3	29.2 ± 14.5
Adrenal gland quality (mm)[c]	3.0 ± 0.3	3.3 ± 0.7

[a] All values are mean ± SE.
[b] Difference in medication was the only suggestive factor.
[c] Width of medullary ribbon.

REPRESENTATIVE CASE HISTORIES

Patient 1 (Nonresponder)

This 43-year-old, right-handed man developed neurological symptoms at the age of 33. He was previously employed as a carpet layer but stopped working at age 37 because of the progression of his disease despite increasing doses of medication. His initial symptoms were tremor and rigidity of his right arm. Several years later, he developed bradykinesia and tremor on the left side. His symptoms progressed to involve both lower extremities, with rigidity and slowness of movement being the prominent complaints. More recently, he developed difficulties with hypophonia.

During the year prior to surgery, he took Sinemet 25-100 (7 pills per day) and amantadine (100 mg per day). The therapeutic window of his medication was approximately 2.0 hours. During his peak function after medication, he was independently ambulatory but suffered from dyskinesia involving involuntary head movements. At the end of his effective medication period he suffered from rapid wearing off of the medication, during which time his bradykinesia and tremor would return over a period of approximately 15 minutes. During his "off" periods, his voice was reduced to a barely audible whisper and his walking was impaired.

Neurological examination preoperatively during the "off" period was notable for severe bradykinesia, hypophonia, moderate rigidity, and mild tremor. His signs were worse on the right than on the left side. He also demonstrated postural instability.

In July 1987, the patient underwent left adrenalectomy and left caudate adrenostriatal autograft. The left caudate was chosen as a target because of predominantly right-sided symptoms. A preoperative medication schedule was prescribed, but on the second day after surgery, the patient was noted to have choreiform movements of the hands and head. On the third day after surgery, his medication schedule was reduced to two 25-100 tablets per day because of dystonic movements. His medication was gradually increased as his activity increased, reaching his preoperative level on the eleventh day after surgery. His response to Sinemet and his neurological examination was comparable to his preoperative baseline status.

Subsequently, the patient showed transitory improvement in terms of rigidity, bradykinesia, and normal postural reflexes. Mild dyskinesia necessitated a reduction in Sinemet, which was further reduced in the first 4 to 6 months. The symptoms and signs worsened at 6 months, but then showed a period of improvement. At 20 months after surgery, he was found to be independent in all activities of daily living, but had independently escalated his dosage of Sinemet to 5 25-250 tablets per day with "on" periods lasting 3 hours. At this time he felt that his overall level of function was worse than his preoperative level.

Patient 3 (responder)

The patient is a 57-year-old, right-handed businessman in whom tremor in the left arm and leg developed at age 44. One year later, after tremor developed in his right arm, his symptoms were diagnosed as Parkinsonism. Levodopa therapy was prescribed, and then Sinemet therapy, but his symptoms progressed over the next 5 years. In 1983, he had a drug "holiday" without apparent benefit. Bromocriptine was tried and discontinued because of side effects. For the 2 years prior to surgery, the patient's medication regimen had been stable, consisting of Sinemet 25-250 (5 tablets per day) and trihexyphenidyl (Artane; Lederle, Wayne, New Jersey) (2-mg tablets, 3 times per day). The patient's main complaint continued to be tremor, which was significantly reduced to 45–60 minutes after he took Sinemet. The effect of the drug was variable, ranging from 15 minutes to 2 hours. At the peak effect time, tremor was absent, dyskinesia was prominent, and hallucinations were occasionally present.

Neurological examination revealed high-amplitude, low-frequency rest tremor present bilaterally. Only mild cogwheeling and rigidity were present, and the postural reflexes were intact.

The patient underwent left adrenalectomy with grafting of adrenal medullary tissue into the right striatum in September 1987. Immediately after surgery, he demonstrated no tremor, and he required no medication during the first day after surgery. His medication was gradually increased, and he was discharged on the sixth day after surgery with a prescription for the preoperative medication dosage. Three weeks after surgery he again noted subjective improvement, in that the medication seemed to be taking effect more rapidly and with a longer duration action. His drug dosage and the results of examination remained unchanged at that time. By 6 weeks after surgery, Sinemet took effect 15 to 45 minutes after the medication was taken and lasted for 3 to 5 hours (preoperative duration, 1–2 hours). The dosage of Sinemet was gradually reduced. At 4 months after surgery he was taking a total of 800 mg of levodopa, as compared with 1250 mg before surgery. Artane therapy was discontinued for a time. Artane was later retried without success, and ethopropazine (Parsidol; Parke-Davis, Morris Plains, New Jersey) has been given, with good tremor reduction. At 18 months after surgery, the patient's Sinemet requirements reached a plateau at 1000 mg of levodopa per day.

Patient 5 (responder)

The patient is a 44-year-old, right-handed carpenter whose symptoms began 11 years before admission. His first symptom was difficulty in initiating movement with his right hand. His symptoms progressed. Seven years before surgery, his symptoms were diagnosed as Parkinson's disease, and he began taking Sinemet. He had a progressive increase in his bradykinesia, with postural instability and frequent falls, but without tremor. Medication became decreasingly effective, with sudden "off" episodes alternating with severe dyskinesia. At the time of surgery, he was taking Sinemet 25-100 (5.5 tablets per day), bromocriptine (2.5 mg 4 times per day), and benztropine (Cogentin; Merck Sharp & Dohme) (1 tablet 3 times per day). The medication effect lasted 2 hours. When "on," he was able to ambulate independently but slowly. When "off," he could not rise from a chair or bed and was unable to stand or walk.

In November 1987, he underwent left adrenalectomy and placement of bilateral adrenostriatal autografts. (Bilateral grafting was chosen because of the bilateral nature of his symptoms.) His general postoperative course was uneventful. He was discharged on the fifth day after surgery with a prescription of 4 tablets of Sinemet 25-100 per day, but bromocriptine therapy was stopped. His neurological function at the time was subjectively unchanged and, with regard to motor performance, equal to his preoperative condition.

At 4 weeks after surgery, he reported walking 2 to 3 miles per day, compared with one-quarter mile per day before surgery. His freezing episodes and falling had abated. He was able to carry on activities that were impossible during the previous 2 years. Dyskinesia was a prominent finding at his follow-up examination, and therefore, the dosage of Sinemet was reduced. The 3-month follow-up revealed improved postural stability. Medication requirements were reduced further, and at 16 months after surgery, he required 2 Sinemet 10-100 tablets per day. Each dose was effective for 3 to 4 hours and dyskinesia was minimal.

Patient 6 (responder)

This 65-year-old right-handed, retired finance executive developed Parkinson's disease 7 years before surgery. Tremor of the left hand and dragging of the left foot were the initial symptoms. Bradykinesia progressed, in spite of multiple medication changes, and he experienced frequent falls. A drug holiday temporarily improved his symptoms. Immediately before surgery, he was taking up to 1000 mg of levodopa and 10 mg of bromocriptine per day. Additionally, he took clonazepam for insomnia. He was wheelchair dependent, and required assistance in all his activities. Neurological examination revealed significant hypophonia, masklike facies, rigidity, and bradykinesia. His postural reflexes were completely absent.

The patient underwent adrenal medullary grafting to the right caudate nucleus in December 1987. Two days after surgery, he experienced severe paranoia, visual hallucinations, and agitation. All dopaminergic agents were discontinued, and he experienced severe rigidity. The hallucinations abated after 48 hours and had completely disappeared by the fifth day. Sinemet 10-100 was slowly reintroduced, but on 4 doses per day he could not turn at night and slept only 1 to 2 hours. Sinemet 25-250 was started, and bromocriptine was cautiously added, but was then discontinued because of priapism. He was discharged on the tenth day after surgery.

Four weeks after surgery, the patient was taking Sinemet 25-100 4 times per day. His walking was improved. He used a walker, and on one occasion walked independently. His ability to sleep was impaired, necessitating the continued use of clonazepam.

Eight weeks after surgery, he was more mobile and independent in self-care, and was able to turn in bed at night. His postural reflexes had normalized, and he stopped using a walker. His Sinemet requirements gradually increased, however. Depression ensued and amitriptyline was added. He continued to function well until 11 months after surgery, when he developed a reactive depression and took an overdose of clonazepam and amitriptyline. Sinemet was withheld in the intensive care unit for 1 week, and then restarted at 25-250 3 times per day, along with bromocriptine. His examination 16 months after surgery continued to show improvement in bradykinesia, postural reflexes and gait. Falls and freezing had returned, however, and he resumed the use of a walker. He is being treated with fluoxetene (Prozac; Lilly, Indianapolis, Indiana) and amitriptyline for his depression and sleep disorder.

Patient 10 (Death)

A 50-year-old, right-handed, Korean man developed Parkinson's disease at age 37. He had a degree in English from a Korean University and operated a health food store in the United States until his disease developed.

In 1978, he began taking Sinemet, with good results. After his symptoms progressed, a drug holiday was tried, with some effect. Bromocriptine therapy has been tried and discontinued because of lack of benefit. The patient's Sinemet requirements before surgery were 900 mg of levodopa. He had significant peak dose dyskinesia that was very uncomfortable after taking each pill. He was unable to turn at night. Freezing episodes and falls were troublesome, and he was wheelchair bound while "off." He spent most of the day "off," with only 3 to 4 hours of "on" time per day. His examination revealed severe rigidity and bradykinesia, but no tremor. He was unable to walk unassisted.

He underwent left adrenalectomy and bilateral grafting of adrenal medulla into the corpus striatum in May 1988. Postoperatively, he was "off" most of the time and bedridden. At the time of adrenalectomy, he was found to have renal stones with hydronephrosis. A lithotripsy procedure was planned after discharge.

He was discharged with a prescription of Sinemet 25-100 (8 tablets per day). Four weeks after surgery, the family felt that he was very depressed and unmotivated. His examination, which showed no changes from his baseline, revealed severe hypophonia and bradykinesia and moderately increased tone. The patient was confined to a wheelchair. There was no tremor.

Six weeks after surgery, he underwent lithotripsy under general anesthesia. Cardiac arrest occurred during the procedure. Efforts at resuscitation failed. Examination of the patient's brain demonstrated both gross and histological findings of Parkinson's disease, and showed that the coils had entered the caudate head near the lateral angle of the lateral ventricle (Fig. 8). Tissue harvested from the coils showed minute foci of closely aggregated cells with dusky cytoplasm and relatively large round and regular nuclei, numbering no more than 50 cells per cluster, having the appearance of adrenal medulla. These areas formed a small percentage (5–10%) of the tissue having the appearance of adrenal gland (Fig. 9).

DISCUSSION

The concept of grafting tissue into the nervous system will celebrate its centennial in 1990 (46). One of the earliest experimental landmarks, and of considerable relevance to recent events in clinical neuroscience, was the study reported by Elizabeth Dunn in 1917 (46). She grafted cerebral cortex from embryonic rats into cavities of litter-mate hosts and noted that the hosts survived whenever the grafts were juxtaposed to the choroid plexus of the lateral ventricles. She also noted retention of the organotypic appearance of the grafted cortex, which, along with observed survival, remains one of the hallmark principles in the field. In 1957, Flerko and Szentagothai (17) reconfirmed these observations in neuroen-

FIG. 8. Coronal section of the cerebral hemispheres through the anterior striatum with the corpus callosum and medial hemispheres removed. Note placement of the coils and the clean immediate surrounding area.

FIG. 9. *A*, low-power view of tissues from the middle portion of the coil. Sharply marginated clear zones are collapsed profiles created by the wire. Organized fibrous connective tissues surround these areas. *Arrowhead* points to a small island of dark-staining surviving medullary cells. The immediately adjacent paler-staining tissues on both sides are remnants of adrenal cortex (Verhoeff's elastic tissue stain and van Gieson stain, ×33). *B*, cluster of surviving darker-staining medullary cells surrounded by remnants of adrenal cortex (Verhoeff's elastic tissue stain and van Gieson stain, ×450).

docrinological experiments in which tissues were placed in the third ventricle, where excellent survival was noted. Restoration of endocrine function has subsequently been shown, thus demonstrating the first evidence of functional interaction between grafted tissue and host brain (46). Experimentation progressed to demonstrate viability of cells, integration into host brain, and evidence of functional restoration in several rodent and primate models through the past two decades (3, 7, 8, 18, 46). These reports have stimulated exploration into the clinical sector initially by Backlund et al. (4) and then by Madrazo et al. (34), in efforts to apply key and promising observations in the laboratory sector to Parkinsonian humans. These reports have initiated many parallel investigations, several recent reports, and intense discussion.

The study reported here was designed to combine concepts elaborated during established laboratory observations and an amalgam of surgical techniques described by both the Backlund and Madrazo groups. A consistent volume of histologically defined adrenal medullary tissue was stereotactically placed in the caudate head and striatum with periependymal and cerebrospinal fluid access. Early reports and more recent experiences of other investigators using conventional craniotomy for striatal exposures called for caution regarding frequent multiple complications related to the central nervous, cardiac, pulmonary, and gastrointestinal systems (24; personal communications: Bakay R, April 1989; Madrazo I, April 1989; Robertson J, June 1988). Our approach was to select a group of patients by a rigorous screening technique to assure minimum surgical risk and to minimize the trauma of the procedure. Safety and standardization of the procedure were achieved in two respects: first, by employing a retroperitoneal surgical method for harvesting the adrenal tissue, visceral retraction and handling was reduced; second, by employing a stereotactic method for tissue grafting, important advantages over craniotomy were gained, because virtually any intracranial location could be accessed, trauma was minimized, and standardization of reproducible placement with reduction of secondary "lesion" effects could be achieved. Our experiences with intraventricular surgery convinced us that surgical variables and potential ancillary trauma would not only increase the risk and surgical magnitude of graft placement, but might also complicate interpretation of functional outcome. In addition, bilateral graft placement could be accomplished with little added risk to the patient. In concert with this approach, gland handling and tissue dissection were undertaken with care to insure maximum purity and viability of grafted tissue. An effort was made to separate adrenal cortical tissue, in part because in vitro studies have indicated that the presence of cortisol may suppress the tendency of adrenal medullary cells to assume neuronal morphology and function when exposed to endogenous central nervous system substances such as nerve growth factor (12, 13, 48).

Patient selection proved to be a difficult and tedious, with only one in eight Parkinsonian individuals considered to meet the criteria established for candidacy. Of particular concern was identification of the psychosocially stable individual who would be reliable in follow-up, despite potentially difficult emotional periods. Care was taken to afford patients' anonymity in relation to local and national news media, which provided a potential for exacerbation of secondary placebo effects on clinical courses, particularly during early periods of observation.

Although our initial laboratory dissections of postmortem medullary tissue indicated that variability in donor tissues would be a problem, this provided significant difficulty in one case, which precluded grafting. There was no absolute relationship between the patient's age and adrenal tissue quality. We feel that the inconsistency of donor tissue and risk of the adrenalectomy should encourage efforts to investigate alternate donor sources. Such sources include: autologous paraneurons, cadaver adrenal or paraneurons, fetal mesencephalon or adrenal, as well as altered neuroblastoma or genetically engineered cells, all in banked form (46, 49). Aside from ethical and certain scientific difficulties, fetal tissue would appear to be the current logical choice. Genetically engineered and immortalized cell lines represent possible future considerations (44). Cell dispersion techniques may increase ultimate sustained viability of grafted tissues.

Although the low morbidity associated with our procedure was an outcome related to numerous factors, the advantages of stereotactic methods for cerebral grafting are readily apparent, as they enhance the precision, safety, reproducibility and options of graft placement (24, 43, and personal communications: Backlund E-O, April 1989; Bakay R, April 1989; Madrazo I, April 1989). The availability of banked tissue when combined with stereotactic techniques would significantly reduce morbidity and increase options with respect to graft-host interactions. It is our belief that the standardization afforded by the stereotactic method clearly reduced variables attendant on outcome in comparison with the open surgical method.

Postoperative observations indicated both objective and subjective initial improvement in 4 of the 8 patients who received grafts. Although any definition of response short of cure may be arguable, 4 of the 8 patients demonstrated sustained reduction of medication requirements combined with improvement in motor performance scores for periods of 16 to 20 months, and stated that they considered to have benefited from the procedure. Placebo effect may be operant during the early postoperative period; however, it is doubtful that a placebo effect would be sustained for more than 12 months. This data would indicate a need for further study of variations of this procedure, including alternative graft tissue sources, studies of graft-host interactions, and local environmental factors such as growth factors (e.g., nerve growth factor, fibroblast growth factor, etc.) and endogenous toxins (e.g., excitatory amino acids) (31, 37, 44, 48). It is important that improvement in techniques and methods be applied to individuals who have participated in these early exploratory studies and, therefore, they will not be excluded from further developments in the field.

Issues of mechanisms of effect and patient selection remain enigmatic areas. No clear-cut "responder profile" was apparent, nor was benefit from bilateral placement of graft tissue noted. From the experiences of others, it would appear that end-stage Parkinsonian patients are not candidates for this approach (personal communications: Backlund E-O, April 1989; Bakay R, April 1989; Madrazo I, April 1989; Robertson J, June 1988); however, our group of moderately to severely disabled patients indicates that the approach may be applicable to a significant number of Parkinsonian patients, and that our inclusion criteria may be excluding individuals who could experience benefit.

A number of potential mechanisms could theoretically contribute to the clinical changes observed in these patients (9, 10, 16, 38):

1. The *production and release of dopamine by chromaffin cells* into the surrounding striatum. Potential arguments against this mechanism include:

a. The 3- to 5-month delay in maximal clinical improvement. Animal models indicate that stable medullary cells should produce usable catecholamines during the period immediately after transplantation.
b. No increase in cerebrospinal fluid catecholamine levels were observed; however, this does not necessarily exclude local effects within the striatum.
c. The paucity of viable medullary cells on postmortem examination.
d. The observation that unilateral grafts are followed by bilateral functional improvements.

2. The effect of the *surgical lesion* on the striatum. In primates treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, placement of a silver tissue carrier into the striatum alone without tissue has been shown to result in increased sprouting of host fiber (18). Neurite-promoting activity has been shown to peak 1 to 2 weeks after brain injury (41). Such sprouting in response to injury and release of trophic factor could then lead to enhanced activity of physiological circuits within the striatum.

3. The *inductive effect* of grafted tissue. Adrenal medullary grafts have been shown to enhance recovery of striatal dopamine fibers after injury (12). The reasons for these regenerative effects are not known, but we might speculate that grafted tissue may induce recovery by providing or releasing trophic influences on damaged host neurons. Sprouting by host neurons in response to grafted cells has been shown in animals to occur over a longer period of time, which could correlate with the improvement observed over several months in our patients.

4. *Vascular alternatives.* Breakdown of the blood-brain barrier could lead to more effective delivery of therapeutic drugs to the striatum. Arguments against this mechanism include:

a. The integrity of the blood-brain barrier in the region of the graft in all but 1 patient, as shown postoperatively on SPECT scanning.
b. The delay in onset of improvement. It would be expected that the blood-brain barrier would be maximally disrupted immediately after surgery, although delayed alterations in blood-brain barrier could also occur.

5. A *placebo effect.*

6. The *complexity of grafted tissue.* The adrenal tissue transplanted is not homogenous: a variety of cell types, including corticotrophs, chromaffin cells, and connective and vascular elements are present in the adrenal tissue. Studies in primates indicate that there is minimal survival of adrenal chromaffin cells 1 month after transplantation (18). There are, however, large numbers of macrophages. The potential effects of these cells in the brain is unknown. In our postmortem examination, a mixed population of cells including corticotrophs and chromaffin cells was seen.

Our findings and other data would appear to indicate that the biological "pump" concept is most likely a simplification of a complex concatenation of biological events attendant on clinical changes in primate models and responder patients. The definition of these complex mechanisms and elucidation of the reality of the potential for grafting as a therapeutic mode for restoration of central nervous function will require many careful studies in both the laboratory and clinical sectors.

OBSERVATION SUMMARY

The primary observations of this study were as follows:

1. The available adrenal medullary donor material was of variable quality and occasionally inadequate.
2. Stereotactic placement of graft donor tissue was reliably and safely accomplished in a consistent and reproducible fashion.
3. Surgical complications were minimal, provided that care in selection and technique as described herein were followed.
4. Seven of eight showed evidence of clinical improvement during early (6 months) periods of observation.
5. Four of eight patients demonstrated sustained (>1 year) alterations in the patterns of their clinical disorders, with improvement in clinical parameters being observed over a period of 16 to 20 months.
6. The onset of these favorable patterns varied within 12 weeks after surgery.
7. No characterization of a responder profile was evident.
8. No advantage to bilateral grafting was noted.
9. Autopsy findings in a clinical nonresponder 6 weeks after surgery demonstrated a mixed cellular population in which 5% of the cells at the graft site consisted of structurally preserved medullary cells.

CONCLUSIONS

Primary conclusions based on the observations, experiences, and data of this study are as follows:

1. Stereotactic technique offers a consistently uniform, reproducible, minimally invasive, safe method for cerebral grafting and requires consideration in future clinical studies related to this concept.
2. Sustained modest clinical improvement may be expected in a some Parkinsonian patients when this method is employed.
3. The mechanisms responsible for these changes are not clearly apparent, but may not relate to the biological quality or quantity of grafted tissue.
4. Further clinical studies to evaluate the impact of grafts on central nervous system function are indicated.
5. Studies related to the employment of banked forms of tissue are indicated, and aside from reducing the overall trauma attendant on such surgery, may provide improvement in patient response.

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COMMENT

Standing alone, this study of adrenal transplantation does not settle any of the major issues in the field. No statistical analysis of the results of surgery is provided, and patients are grouped retrospectively into responders and nonresponders, a dubious procedure. When the results of this study by Apuzzo et al. are added to those of other clinical studies, however, a number of important observations can be made:

1. The response is variable. Some patients show moderate improvement, a few, dramatic improvement (Madrazo's initial two cases, Apuzzo's Case 5), and others, little to no change.
2. The improvement, when it occurs, is weeks to months after the operation and lasts at least a year in most patients.
3. Unilateral operations implanting a graft in only one caudate may result in bilateral motor improvement.
4. The morbidity and mortality of the operations are substantial in some series, but are less when stereotaxic implants and a retroperitoneal approach are used.

The authors' thoughtfully designed and carefully executed study using uniform and well-accepted measures of Parkinson's disease leads to similar observations. There was no significant morbidity and mortality using the stereotaxic and retroperitoneal approaches; motor responses occur several months after the operation and are sustained up to 16 months; and a unilateral implant has the same bilateral motor effects as a bilateral implant.

Although a pattern of change after adrenal implant appears to be established, which operative procedure is best remains undecided. Apuzzo et al. argue that the stereotaxic approach is advantageous. Certainly, there is no denying that it is easier and safer, but we simply do not have evidence that it is more effective. A study comparing open and stereotaxic procedures has yet to be performed. Until this is done, doubt about the effectiveness of the stereotaxic procedure remains. The initial Swedish implants were done stereotactically and were without significant clinical effect. The Madrazo open procedure, in which there was more transplanted tissue, an injury to the caudate, and exposure of the graft to cerebrospinal fluid, provided the first positive results. These results have been confirmed by a multicenter study, although the changes were much less dramatic. Is the the open procedure's greater injury to the cortex and caudate important in creating the improvements?

This raises the pivotal question: Why does the procedure have any effect whatsoever? The authors mention the current theories. Biological pumps for dopamine are unlikely, and neurotrophic factors induced by the trauma of surgery, the metal carrier, inflammatory cells, or other non-medullary cells are all possibilities. Which factor or factors are important will be difficult to resolve because of the difference between animal models and human disease. Animal models have already been misleading. Extrapolation from animal implants suggested that dopamine could be replaced by grafting, and led to the first transplants. Now we know most of the adrenal medullary cells in humans die, no increase in dopamine production is found, and the effects are bilateral, so other factors must account for clinical changes. Until we have some solid clues about these factors, new operations will be difficult to design rationally. For the present, the best that can be done is to report results in a clear and standardized manner, as Apuzzo et al. have done, so that, gradually, an empirically proven procedure will evolve. The science will then have to catch up with the clinical procedures.

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