Long-term improvement in patients with severe Parkinson’s disease after implantation of fetal ventral mesencephalic tissue in a cavity of the caudate nucleus: 5-year follow up in 10 patients

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Different groups worldwide have observed in recent years that stereotactic implantation of fetal tissue can ameliorate the clinical symptoms of Parkinson’s disease. The authors therefore investigated whether implantation of fetal ventral mesencephalic (FVM) tissue via open surgery is also capable of producing an improvement and whether this improvement is transient or long lasting. The authors report their findings in a 5-year follow-up study in 10 patients with Hoehn and Yahr Grade IV or V Parkinson’s disease in whom a single FVM graft was implanted in a cavity created in the right caudate nucleus. The results indicate that the implants improved motor function and that clinical recovery persisted in seven of the 10 patients 5 years after implantation. Amelioration was observed in both the on and off phases and was accompanied by a 64% reduction in the levodopa dose and withdrawal of the dopamine agonist. The on phase was prolonged from 39% of the waking day to 72%, with reduced intensity and duration of dyskinesias. All symptoms that were analyzed showed improvement, although they differed in intensity and time of onset. The course of improvement seemed to be stepwise, with significant improvement between 5 and 7 months postimplantation followed by two waves of progress peaking in Months 15 and 36. Withdrawal of cyclosporine in three patients after more than 2 years of administration produced a decline in the patients’ clinical conditions.

In conclusion, the results indicate that open surgery implantation of FVM tissue in the caudate nucleus improves the clinical condition of parkinsonian patients and that this improvement can persist for at least 5 years. In comparison with two earlier series reported by the authors, which involved implants of perfused adrenal medulla and coimplantation of adrenal medulla and peripheral nerve, the course and pattern of improvement in these implant recipients suggests that their recovery can be attributed to more than one factor.

KEY WORDS • Parkinson’s disease • transplantation • embryonic graft • dopamine • substantia nigra • neurotrophic

The neural tissue implant, initially conceived as a tool for an in vivo study of the development, plasticity, and regeneration of the nervous system, has become an experimental therapeutic alternative in the treatment of degenerative diseases, especially Parkinson’s disease. Studies involving experimental models of this disease have shown that embryonic mesencephalic tissue implanted into the striatum of denervated animals, first in rodents and more recently in nonhuman primates, is capable of surviving, reinnervating host tissue, releasing neurotransmitters, and partially compensating for behavioral and motor deficits.4,5,10,16,25,66 The promising results in experiments using animals have led to human studies.

Eight years after its introduction, intracerebral transplantation for the treatment of Parkinson’s disease has awakened high expectations, fueled first by the attempt to reproduce the widely criticized good results reported in 1987 by Madrazo, et al.,46 after implantation of autologous adrenal medulla and, later, after the publication of initial clinical results in several series of patients who received mesencephalic tissue grafts.1,17,33,42 Clinical trials using embryonic tissue have been undertaken in several research centers around the world, principally in Europe22,31,35,46,52,61,64,67 and America14,18,25,26,45,48,58 where moderate-to-good results have been reported.

The efforts of the groups involved have been marked by disparities in the selection and clinical management of the patients, together with heterogeneity of the surgical procedure and the amount and age of the donor tissue. Two main surgical procedures have been performed: implanta-
tion of blocks or pieces of tissue using an open surgery technique\textsuperscript{14,18,21,25,26,34,35,52,58,61,64,66} and stereotactic implantation of mechanically or mechanically and enzymatically dissociated mesencephalic cells in the striatum.\textsuperscript{14,18,21,25,26,34,35,52,58,61,64,67} In the former procedure, the implantation is unilateral, using tissue from a single embryo deposited into a single cavity created in the caudate nucleus; in the latter procedure, unilateral\textsuperscript{14,20,34,35,52,58,61,66} or bilateral\textsuperscript{18,25,64} implantation in the caudate nucleus\textsuperscript{14,20,58,61,67} or the putamen\textsuperscript{9,52} or both\textsuperscript{14,34,52,64} has been performed at one\textsuperscript{22,61} or more\textsuperscript{14,25,34,35,52,58,64} sites, with tissue from one\textsuperscript{14,22,58,61,66} or more\textsuperscript{14,18,34,35,52,64} embryos.

If we add to all these variables the fact that implant recipients vary with respect to their presurgical clinical condition, disease grade (Hoehn and Yahr\textsuperscript{23} Grade III and IV patients) and complications are presented and discussed. The findings are presented in such a way as to allow comparison of the results in these implants with those in other series reported by our group.\textsuperscript{76–78}

**Clinical Material and Methods**

Between 1988 and the first half of 1989, 10 patients in our center with Parkinson’s disease received implants of FVM procured in legal abortions. The patients consented to participate in the study after being informed of the clinical and surgical risks, the source of the donor tissue, and the need for immunosuppression over an undetermined period of time, as well as the possible lack of improvement and the fact that the study focused more on clinical research than on therapeutic effects. The use of fetal tissue and the experimental procedure were approved by the pregnant women from whom the tissue was obtained and by the human research ethics committees of the participating centers, with the consent of the Spanish National Institute of Health, and followed the guidelines of pertinent Spanish law.\textsuperscript{32} The entire research project was government funded.

**Patient Selection and Preoperative Clinical Features**

The selection criteria for the patients were those used in our previous series of recipients of PAM\textsuperscript{39} or adrenal medulla and peripheral nerve\textsuperscript{33} transplanted in the caudate nucleus: parkinsonian patients in an advanced stage of the disease whose history of disease had lasted several years and who had no pharmaceutical control or a suboptimum response to medication. The patients had been subjected to other clinicopharmaceutical trials with no appreciable clinical results and presented daily fluctuations with severe on–off phenomena and dyskinesias. All patients had responded to levodopa administration at the onset of their disease.

Disqualifying criteria included the existence or presence of endocrine, vascular, cardiac, or pulmonary disease and/or dementia or psychiatric disturbances. Age and sex were not considered exclusion criteria, nor was Grade V Parkinson’s disease. With the exception of the patient in Case 6, the individuals in this study had undergone evaluation and treatment by one of the participating clinicians for at least 2 years prior to enrollment in the program. The patient in Case 6 had been studied and managed previously at another national medical center and had enrolled in this program 6 months before undergoing implantation.

The mean age of the recipients at the time of surgery was $61 \pm 6.84$ years (range 52–72 years); the mean duration of their Parkinson’s disease was $13.5 \pm 3.8$ years (range 7–19 years). The patients had been receiving levodopa/inhibitor for a mean of $12.5 \pm 3.0$ years (range 7–17 years) and all had received dopaminergic agonists. Their disease severity was in the range of Grades IV to V according to the Hoehn and Yahr scale, with four Grade IV patients, three Grade IV to V, and three Grade V patients.

**Evaluation of the Patients and Pharmaceutical Management**

The patients enrolled in this study underwent a general medical examination, with special attention given to cardiac and pulmonary risk factors, and a neurological examination, which included a study of the clinical, physical, and therapeutic conditions.

All patients were assessed pre- and postoperatively during off and on phases with full regular medication and during predefined off and on periods; their status was determined on the basis of internationally accepted rating scales. The patients were evaluated in predefined off and on periods; the predefined off phase corresponded to the
period between 10 and 11 a.m., 2 to 2.5 hours after awaken-
ing and before breakfast, 12 to 14 hours after the last
levodopa administration; the predefined on phase was es-
"abiled as the time of maximum therapeutic benefit, 1 to
1.5 hours after the first regular morning levodopa dose.
From the moment of their enrollment in the program until
hospital admission 1 week before the transplantation pro-
cedure, the patients were evaluated approximately once
per month.
The patients’ disability was classified as Grades I to V
on the basis of the Hoehn–Yahr scale. Their motor func-
tion and normal daily activities were rated according to
the Unified Parkinson’s Disease Rating Scale (UPDRS, ver-
sion 3.0.1)27 and the Northwestern University Dis-
sability Scale (NUDS).24,65 Briefly, the UPDRS, which
was developed by the Parkinson’s study group for use in the
Datatop computer software data bank, takes into account
the mentation, behavior, and mood of the patient (four
items); daily living activities (13 items); physical exam-
nation of motor functions (12 items, rated individually on
a scale of 0 to 4, involving facial expression, tremor, rigid-
ity, speech, rapid alternating hand movements, foot tapp-
ing, finger tapping, rising from a sitting position, gait,
postural stability, axial posture, and bradykinesia); and
therapy-related complications (dyskinesias and clinical
fluctuations) for a total of 42 parameters and a possible
146 points. The NUDS provides the physician with the
patient’s functional disability and degree of social integra-
tion by measuring disturbances in five items—speech,
dress, nutrition, hygiene, and gait—each rated on a scale
of 0 (severe) to 10 (absent). In addition, the patients were
instructed to keep a diary in the form of an hourly self-
evaluation chart.
Patient assessment included blood analyses, electrocar-
diogram, and respiratory function tests. Magnetic reso-
nance imaging of the brain, using complete T1- and T2-
weighted sequences, proton density, and gadolinium
infusion, was performed before surgery and 1, 6, 12, 36,
and 60 months after surgery.

Pharmaceutical Management and Immunosuppressive
Therapy
The patients were maintained with optimum doses of
medication (levodopa, agonists, anticholinergics) until 1
to 2 weeks before surgery, at which time the dopaminerg-
ic agonists and/or amantadine hydrochloride were grad-
ually tapered, to be discontinued the day before implan-
tation.
Immediately after surgery all patients received dexam-
ethasone (4 mg four times daily) and phenytoin at the
usual postoperative dose. Because of the severity of their
parkinsonian symptomatology, four patients received bi-
periden (2 mg administered intravenously three times
daily) until they could tolerate oral medication. Once they
could tolerate oral intake, levodopa/carbidopa treatment
was renewed at the preoperative level. During the period
of analysis (60 months), the dosage was reduced, provid-
ed that sustained psychiatric symptoms were not observed
and dyskinesia/dystonia did not increase in frequency and/
or intensity. Administration of dexamethasone and pheny-
toin was gradually tapered as usual.
All patients were immunosuppressed 1 day prior to
surgery with intravenous administration of cyclosporine
(Sandimmune, 1–1.25 mg/kg two times daily), which was
continued orally to achieve blood levels of 100 to 200
ng/ml, as measured by radioimmunoassay with a monocl-
onal antibody. The mean daily dosage was 168 mg
two times daily (1st month) and 141 mg two times daily
(7th month), in ranges of 140 mg to 220 mg and 120 mg
to 220 mg, all two times daily, respectively. Starting 1 year
postimplantation to the present, the patients’ blood cyclo-
sporine levels have been maintained at 80 to 100 mg/ml.
Immunosuppression had to be discontinued in four pa-
ients because of neurological and systemic complications
that were attributed to the cyclosporine: in Cases 1 and 9,
27 and 30 months after surgery, and in Cases 6 and 2, 35
and 42 months, respectively.

Tissue Preparation and Surgical Procedure
The donor material was obtained by ultrasound-guided
instrumental uterine scraping, as previously described.41
The gestational ages of the embryos/fetuses obtained by
this procedure were 6 to 8 weeks (crown to rump length
14–30 mm, as measured with ultrasound). A microcesare-
an procedure was performed in two cases. This technique
is not habitually used by our group, but was indicated by
the clinical situation of the mother and the gestational age
of the fetus (15 weeks) and was not used simply to facili-
tate removal of the donor tissue.
The fetus or fetal material containing the encephalon
was collected in a sterile petri dish in cold calcium- and
magnesium-free buffer under an operating microscope.
The tissue was rinsed three times before being changed to
a clean petri dish, where the mesencephalon was identi-
fied. After washing, the mesencephalon was dissected out
following routine landmarks. The dissected tissue, free
of meninges, was placed in cold sterile Dulbecco’s modified
Eagle medium containing glucose (4 mg/ml), penicillin
(100 μ/ml), and 5% heat-inactivated fetal serum and was
put into 10 to 20 fragments before being transported to the
transplantation center. The time between tissue prepara-
tion and implantation ranged from 4 to 6 hours in the first
seven patients and was 24 hours in the last three. In the lat-
ter cases, the tissue was cold stored in fresh enriched cul-
ture media until use. To enable us to calculate the viability
of the tissue and to study its in vitro behavior prior to
implantation, a fragment of FVM was dispersed enzym-
atically (in 0.1% trypsin at 37˚C for 15 minutes) and
mechanically (in 0.1% DNase, 70% Hank’s balanced salt
solution, and 20% fetal calf serum, using Pasteur pipettes
of different diameters), according to routine laboratory
techniques.42 The viability, calculated by the trypan blue
extension test, was greater than 73% in the freshly im-
planted tissue and between 71% and 83% in that stored for
24 hours. The cellular suspension obtained was cultured
for at least 7 days for morphological and immunocyto-
chemical studies as an indirect control of the survival of
the implanted cells. The cultures demonstrated tyrosine
hydroxylase–containing neurons in all cases.
Once the viability of the tissue was known, the neu-
rosurgical procedure was undertaken, using the same
methods we previously used with PAM autologous trans-
plants.38,39 After right-sided frontal craniotomy, the right
caudate nucleus was approached through the right lateral
ventricle via a transcortical second frontal circumvolution.
One partially mechanically disrupted FVM was implanted in each patient in a cavity created in the right caudate nucleus in contact with the ventricular cerebrospinal fluid, with the exception of one patient (Case 1) who, because of surgical problems, received the implant in the left caudate nucleus. The cavity was covered with Surgicel and the edges were bound clipped.

**Postsurgical Management**

The patients spent the 1st postoperative night in the intensive care unit and were discharged from the hospital 10 to 21 days after the transplantation procedure. No surgical complications were observed. During the patients’ hospital stay, clinical assessment was performed twice a day. Once home, the patients were evaluated monthly for the 1st year, every 3 months for the 2nd, and two or three times per year thereafter. Evaluation was based on the scales described earlier and on an hourly self-evaluation chart that either the patient or a family member filled out at least 1 week prior to the monthly visit.

**Statistical Analysis**

Changes in parkinsonian symptoms were assessed according to the UPDRS and the NUDS scales over a period of 60 months; Friedman’s nonparametric analysis of variance was applied, followed by Wilcoxon’s paired test, to compare the changes taking place over the entire study period. Values are always expressed in terms of the mean and standard deviation (SD).

**Results**

**Postoperative Course**

There were no surgical complications in our patients. During the immediate postoperative period, one Grade V patient (Case 2) developed pneumonia, probably due to aspiration, which was treated with a broad-spectrum antibiotic medication. During the 5 years of clinical follow up, only moderate complications were observed; these could be grouped according to their systemic, neurological, or psychiatric nature.

**Systemic Complications.** One patient (Case 2) presented with recurrent urinary infections 2 to 3 years postimplantation; the infections were successfully treated with standard antibiotic therapy and required no changes in medication or discontinuance of cyclosporine. This same patient developed recurrent pneumonia 40 to 42 months postsurgery, causing the family to request withdrawal of the cyclosporine. Twenty-three months postsurgery, the patient in Case 6 presented with *Pseudomonas aeruginosa* pneumonia, which was managed with antibiotic medications; the course of cyclosporine was not interrupted. Twelve months later (35 months postsurgery) this patient was admitted to the intensive care unit with a general picture of hemorrhagic sputum, cough, fever, chest pain, and neurological signs of confusion and increased dyskinesias in the on phase. The diagnosis was *P. aerugi- nosa* pneumonia and pulmonary tuberculosis, which were treated with a course of broad-spectrum antibiotic and tuberculostatic medications, and administration of cyclosporine was discontinued.

**Neurological Disorders.** After the first episode of pneumonia the patient in Case 2 presented with a right frontal hematoma in the surgical track 3 to 4 months after implantation; the hematoma did not require drainage. Since then, he has presented with a right frontal syndrome and intensification of his psychiatric symptomatology in the form of spatial and visual illusions and optical hallucinations during the on phase.

Three patients presented with akathisia and muscle cramps: the patient in Case 1, 9 to 12 months after surgery, the patient in Case 2, 26 to 31 months after surgery, and the patient in Case 9, 27 to 30 months after surgery. In the first two cases, there was a temporal relationship with respect to the administration of medication and the symptomatology improved after a reduction in the levodopa dosage.

Two patients (Cases 1 and 9) complained 20 to 24 months after surgery of a feeling of internal tension; a slight, rapid, barely perceptible tremor; and a restless motor activity in their arms and legs that made it impossible for them to remain still, causing them to get up and move nervously around the room—a sensation that alternated with episodes of akathisia and muscle cramps. The situation produced severe distress in both of their families. The patients associated it with the administration of cyclosporine because the symptoms presented 3 to 4 hours after its administration and were not alleviated by reducing the levodopa dosage. In both cases, the patients declined to continue taking the cyclosporine, a step that was taken 27 and 30 months after surgery, respectively. Subsequently, the two patients worsened progressively (clinical details of these cases can be found in Overall Postoperative Course). To rule out the possibility that the improvement observed in these patients was directly due to cyclosporine and that its withdrawal had provoked their deterioration, we administered cyclosporine at starting dosages for 1 to 3 weeks. There were no changes in the patients’ parkinsonian clinical signs and the patients continued to worsen. Of the other two patients in whom cyclosporine administration was stopped, one has shown no decline and the other has deteriorated with respect to the improvement achieved after implantation.

Two patients (Cases 5 and 8) reported postoperative variations in their parkinsonian symptomatology that they considered to be related to changes in the weather and the seasons (May–June); these episodes lasted 3 to 5 days and required no change in the therapeutic regimen. Moreover, one patient (Case 8) believed that these changes coincided with her premenstrual period, an event that she claimed had never occurred prior to surgery.

**Psychiatric Complications.** Five patients experienced postsurgical psychiatric disorders in the form of personality changes, delusions, hallucinations, and vivid dreams. The patient in Case 2 reported somnolence and confusion. Personality changes were observed in three cases (hypomania in one, aggressiveness in one, and sexual disinhibition and/or hypersexuality in two). Hallucinations occurred in five cases (visual in four and visual/auditory in one), delusions in three (spatial disturbances in one and spatial/somatic in two), and vivid dreams in three cases. The mean interval between implantation and the appearance of delusions and hallucinations was 1.5 months in four patients; the exception was the patient in Case 9, in...
TABLE 1

<table>
<thead>
<tr>
<th>Clinical Evaluation Scales</th>
<th>Preop Score</th>
<th>First Statistically Significant Change Postop Mos (score)*</th>
<th>Maximum Improvement Postop Mos (score)</th>
<th>Peak % Change (range)</th>
<th>60-Mo Follow Up Score</th>
<th>Mean % Change (range)</th>
<th>No. of Patients</th>
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<tr>
<td>predefined off period</td>
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<tr>
<td>UPDRS</td>
<td>89.9 ± 13.3</td>
<td>5–7 (67.5 ± 18)</td>
<td>36 (45.9 ± 13.8)</td>
<td>46 (32–60)</td>
<td>56.8 ± 23.3</td>
<td>34 (0–58)</td>
<td>7</td>
</tr>
<tr>
<td>motor subscale</td>
<td>46.1 ± 5.4</td>
<td>5–7 (36.3 ± 7.4)</td>
<td>36 (22.4 ± 5.6)</td>
<td>49 (32–63)</td>
<td>27.2 ± 9.9</td>
<td>39 (17–63)</td>
<td>8</td>
</tr>
<tr>
<td>NUDS</td>
<td>18.5 ± 7.7</td>
<td>7 (25.6 ± 7.9)</td>
<td>30 (35.1 ± 4.7)</td>
<td>75 (24–164)</td>
<td>32.2 ± 8.1</td>
<td>63 (–17 to 174)</td>
<td>8</td>
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<tr>
<td>predefined on period</td>
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<tr>
<td>UPDRS</td>
<td>55.7 ± 17.9</td>
<td>5–7 (43.6 ± 17.5)</td>
<td>36 (26.5 ± 9.4)</td>
<td>45 (37–54)</td>
<td>29 ± 12.8</td>
<td>39.6 (7.2–67.7)</td>
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<tr>
<td>motor subscale</td>
<td>26.8 ± 9.6</td>
<td>5–7 (19.6 ± 9.7)</td>
<td>36 (10 ± 2.5)</td>
<td>50 (35–63)</td>
<td>12.3 ± 4.7</td>
<td>43 (35–74)</td>
<td>10</td>
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<tr>
<td>NUDS</td>
<td>31.4 ± 7.6</td>
<td>7–9 (38.4 ± 5.7)</td>
<td>42 (42.6 ± 4.3)</td>
<td>24 (3–57)</td>
<td>41.3 ± 7</td>
<td>20.6 (–21 to 57)</td>
<td>7</td>
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* Statistically significant at p < 0.01.

Effects of FVM implantation on overall postoperative course in 10 patients with Parkinson’s disease

Fetal tissue implants in caudate nucleus

whom onset occurred 5 days after surgery. The mean resolution time was 5 days once the levodopa dosage was adjusted. Visual hallucinations reappeared in one patient (Case 1) 31 to 33 months after surgery, and the patient in Case 2 experienced visual hallucinations and delusions at regular intervals starting 18 months after surgery and persisting until Month 36. Both patients responded to a decrease in the levodopa dosage.

With the exception of the patient in Case 9, who presented a picture of disinhibition and hypomania 5 days after surgery, personality changes coincided with delusions, with onset at Month 2 and gradual disappearance by transplantation Month 5; they did not seem to be affected by decreases in medication.

Overall Postoperative Course

Table 1 summarizes the overall clinical changes in the parkinsonian symptomatology (UPDRS and NUDS scores) of the 10 patients in predefined off and on phases.

The UPDRS (Fig. 1A) revealed a statistically significant improvement in predefined off and on periods that started in Months 5 to 7 and persisted 60 months after surgery. In the on phase, clinical decline was observed in the 1st month (55.9 ± 19.2; not significant) as a consequence of the deterioration of five patients in the series. In the predefined off phase, the improvement began to be significant beginning in Months 3 to 4, but it was not until Months 5 to 7 that progress was observed in eight of the 10 subjects. Five years after surgery, the clinical improvement persisted in all but three patients; two in whom the decline began in Month 30 were worse than before undergoing implantation. In the predefined off phase, the improvement occurred in waves of improvement. In the predefined off phase, two patients improved by more than 50%, three showed an improvement of 40 to 43%, three improved by 20 to 30%, and two patients worsened by 0.5%. In the on phase, the mean percent improvement was 39.6%.

The motor function subscale in predefined off and on phases (Table 1 and Fig. 1B) also reflected a statistically significant improvement that persisted until the end of the follow-up period 60 months after surgery. The improvement in the group as a whole appeared to commence in Month 4 and became statistically significant 5 to 7 months postsurgery. The time of onset of improvement varied according to the preoperative clinical status of the patients, presenting earlier in Grade IV patients than in Grade V patients (5th vs. 7th month). No progress was observed during the 1st postoperative weeks and the maximum improvement was observed in Month 36. From Month 36 to Month 60, there was a trend toward deterioration (27.3 ± 9.9 points; not significant) owing to the decline of three patients in the series. In the off phase, the mean percentage of improvement at the end of the study period was 39%, ranging from 17 to 63%; with an improvement of more than 60% in two patients, between 40 and 43% in three patients, over 30% in three patients, and a moderate-to-ineptible improvement of 17% in two patients (who had begun to get worse in Month 30 and who were taken off cyclosporine therapy). At the end of the follow up, all the patients were better in the on phase than they had been prior to surgery, despite the fact that three patients had deteriorated in the preceding months. The mean percentage of improvement was 43%, ranging between 35% and 74%.

The patient’s clinical progress (Fig. 1A and B) was not linear but sporadic, occurring in waves of improvement. A comparison of results obtained each month with the clinical situation in subsequent months (Wilcoxon’s test) showed that after the first statistically significant clinical change (5–7 months postsurgery), a second stage of improvement occurred at Months 15 to 18, becoming more marked in Month 36, (p < 0.01 for the 5th and 9th months vs. the 15th and 36th months).

The analysis of data provided by the NUDS scores (Table 1) revealed a clinical improvement in the off stage that commenced 3 to 4 months after surgery; however, it was not until Month 7 that progress was detectable in eight patients. When the postoperative data were compared from 1 month to another, it was seen (Fig. 1C) that 9 months after surgery, there was a statistically significant improvement (Months 1–7 vs. Month 9; p < 0.01; Wilcoxon’s test). Although a second degree of improvement was detected in Month 15, the greatest progress was observed in Month 30. From that time until the end of the study period, there was a moderate deterioration as a consequence of the declines of two patients in the group. At the end of the follow-up period, five patients continued to show an improvement of over 69% and three patients an improvement of between 32% and 40%; the improvement was of little significance in one patient who had declined...
by 56% since Month 36 and one patient was 17% worse than before implantation. The NUDS score in the on phase showed a very moderate but perceptible improvement, especially in those patients with the most severe disorders (Fig. 1C). During the 1st postoperative month, the patients as a group were worse than before implantation. Eight of the 10 patients worsened by 3 to 27%. The improvement began to be statistically significant 7 to 9 months postsurgery (Table 1). After 60 months of follow-up review, seven patients were better than before surgery.

Evaluation of the Parkinsonian Symptoms

Improvement was registered in every symptom studied, appearing at different times and reaching different degrees in each (Table 2). The changes observed were bilateral in all cases.

Rigidity and facies were the symptoms showing the earliest recovery, followed by rising from a sitting position and postural stability; gait and bradykinesia were the slowest to show improvement.

Again, we must point out that the clinical progress observed in the symptoms was not linear. The improvement in the initial months was seen to be slow and progressive, followed by a phase or two of stepwise progress that differed in its pattern of onset from that of the corresponding symptom. As is summarized in Table 2, the maximum improvement in the off phase was obtained sooner for rising from a sitting position, facies, and rigidity than for postural stability, speech, and gait.

Time Spent in On and Off Stages

One of the important aspects of the study was to determine whether this surgical treatment modified the length of time throughout the day that the patients spent in the on or off stage. For the procedure to be beneficial, not only did it have to produce a qualitative amelioration of the symptomatology of the disease; a quantitative improvement in terms of increase in the number of hours in the on phase was also necessary.

Prior to surgery, all the patients presented with on and off periods. The portion of the day spent in the on phase (Fig. 2A) was only 39±6% ranging from 28 to 50%. During the initial postoperative months, no significant changes were observed in the time spent in the on or off phase when the group was taken as a whole, despite the fact that the dosage of levodopa/carbidopa administered had been reduced. The improvement or increase in time spent in the on phase appeared to commence in Month 5 and was statistically significant as of postoperative Month 7 (39±8% of the day spent in the on phase presurgery vs. 65±20% at Month 7; p<0.01). A second peak of improvement was seen at Months 12 to 15 (p<0.01 for Months 7 and 9 vs. Month 15; Wilcoxon’s test). From there the amount of time spent each day in the on phase increased progressively until Month 42 postsurgery (76±15% of the day spent in the on phase, ranging from 57–94%). From that month on (Fig. 2A), there was a

Fig. 1. Graphs displaying overall progress in parkinsonian symptomatology from presurgery to 60 months postsurgery, assessed according to (A) the UPDRS (UPD) score (B) the motor subscale of the UPDRS, and (C) the NUDS (NUD) score during predefined off (lines with closed circles) and on (lines with open circles) periods as compared with the levodopa/inhibitor treatment course (bars). *Significantly different from presurgery values; p<0.01. †Separate “peaks” or stages of improvement postsurgery after comparing clinical results at different postoperative months (p<0.01, for Months 7–9 vs. Month 15 and for Month 15 vs. Month 36; Wilcoxon’s test). Values are mean scores ± SD. Presurgery values represent the mean ± SD of the evaluations performed over the 6 months prior to implantation.
Presence of Dyskinesias

The first of these two patients (Case 9) was also clinically deteriorated, going from 35.7 to 25% of the on time spent with dyskinesias 36 months after surgery four of the five patients were asymptomatic. Twenty-four months after surgery four of the five patients were asymptomatic.

Effects of FVM implantation on parkinsonian symptoms in 10 patients

All patients in the group presented with dyskinesias in their preoperative time, eight of them coinciding with benefit of dose (six at peak of dose and two at peak of dose or square wave) and two at the beginning and in the pre–off phase (diphasic) or at peak of dose, showing irregular daily and monthly patterns. The patients experienced dyskinesias during 67 ± 30% of their daily on time, which represented 30 ± 17% of the entire day. Figure 2B shows that 5 years after surgery, the patients presented a significant decrease in the on time spent with dyskinesias.

TABLE 2

<table>
<thead>
<tr>
<th>Clinical Evaluation Scales</th>
<th>Preop Score</th>
<th>First Statistically Significant Change</th>
<th>Maximum Improvement Postop Mos (score)</th>
<th>Peak % Change (range)</th>
<th>60-Mo Follow-Up Mean % Change (range)</th>
<th>No. of Patients Improved†</th>
</tr>
</thead>
<tbody>
<tr>
<td>predefined off period</td>
<td></td>
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<tr>
<td>rigidity</td>
<td>3 ± 0.5</td>
<td>2–3 (1.78 ± 0.86)</td>
<td>18–24 (1.18 ± 0.83)</td>
<td>60.7 (33.4–100)</td>
<td>54 (83.4–0)</td>
<td>9</td>
</tr>
<tr>
<td>facies</td>
<td>3 ± 0.41</td>
<td>2–3 (2.36 ± 0.48)</td>
<td>18 (1.39 ± 0.64)</td>
<td>53.7 (80–33.4)</td>
<td>35.5 (80 to –16)</td>
<td>7</td>
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<tr>
<td>postural stability</td>
<td>2.86 ± 0.75</td>
<td>5–7 (1.86 ± 1.25)</td>
<td>30 (1.56 ± 0.98)</td>
<td>56.5 (100–28.6)</td>
<td>35.8 (100 to –14.3)</td>
<td>6</td>
</tr>
<tr>
<td>rising from sitting position</td>
<td>2.4 ± 0.9</td>
<td>5 (1.68 ± 1.3)</td>
<td>15 (0.96 ± 0.8)</td>
<td>66.3 (100–33)</td>
<td>54 (100 to –33)</td>
<td>9</td>
</tr>
<tr>
<td>speech</td>
<td>2.78 ± 1.18</td>
<td>7 (1.71 ± 0.69)</td>
<td>30–36 (1.35 ± 1.14)</td>
<td>49.8 (100–25)</td>
<td>45.2 (100 to –16)</td>
<td>7</td>
</tr>
<tr>
<td>bradykinesia</td>
<td>2.96 ± 0.64</td>
<td>7 (2.18 ± 0.66)</td>
<td>18 (1.9 ± 0.87)</td>
<td>35.3 (77.8–0)</td>
<td>25.1 (55.5 to –33)</td>
<td>7</td>
</tr>
<tr>
<td>gait</td>
<td>3.18 ± 0.69</td>
<td>7–9 (2.21 ± 1)</td>
<td>30–36 (1.78 ± 0.85)</td>
<td>44.5 (76.9–14)</td>
<td>32.6 (100 to –20)</td>
<td>6</td>
</tr>
<tr>
<td>tremor</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
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</tr>
<tr>
<td>predefined on period</td>
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</tr>
<tr>
<td>rigidity</td>
<td>1.5 ± 0.69</td>
<td>5 (0.78 ± 0.49)</td>
<td>27 (0.53 ± 0.4)</td>
<td>49 (100–20)</td>
<td>49.4 (100–20)</td>
<td>9</td>
</tr>
<tr>
<td>facies</td>
<td>1.57 ± 0.53</td>
<td>5 (0.64 ± 0.56)</td>
<td>18 (0.6 ± 0.6)</td>
<td>58.9 (100–12.5)</td>
<td>39.3 (75 to –50)</td>
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<td>postural stability‡</td>
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</tr>
<tr>
<td>speech</td>
<td>1.86 ± 0.99</td>
<td>7 (1.07 ± 0.84)</td>
<td>18 (0.93 ± 0.73)</td>
<td>54.1 (66.7–25)</td>
<td>30.4 (100 to –25)</td>
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<tr>
<td>bradykinesia</td>
<td>1.64 ± 0.68</td>
<td>9–12 (1.04 ± 0.65)</td>
<td>30 (0.85 ± 0.44)</td>
<td>40.4 (100–0)</td>
<td>36.9 (100 to –30)</td>
<td>8</td>
</tr>
<tr>
<td>gait</td>
<td>1.68 ± 0.69</td>
<td>7–9 (0.89 ± 0.53)</td>
<td>18–36 (0.67 ± 0.47)</td>
<td>57.6 (100–25)</td>
<td>49.3 (75–0)</td>
<td>7</td>
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<tr>
<td>tremor</td>
<td>†</td>
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</table>

* Seven patients presented with moderate tremor. Individual patients had changes in this symptom in Months 9 to 15, showing 33 to 83% improvement.
† Five patients presented with slight tremor (score 1 ± 0.97). Twenty-four months after surgery four of the five patients were asymptomatic.
‡ No change in on phase (only changes in individual patients).

Table footnote:
- **Effects of FVM implantation on parkinsonian symptoms in 10 patients**
- **Predefined off period**
- **Rigidity**
- **Facies**
- **Postural stability**
- **Rising from sitting position**
- **Speech**
- **Bradykinesia**
- **Gait**
- **Tremor**

The improvement in parkinsonian symptomatology and the increase in time spent in the on phase (Fig. 1) observed in our patients was accompanied by a reduction in the amount of levodopa/inhibitor (from 1038.9 ± 762.2 mg/day presurgery to 370 ± 225 mg/day at Month 60). The postoperative course of levodopa administration in our series could be divided into two separate periods. The first took place during Months 1 to 2 postimplantation. In this period, the amount of levodopa was reduced to 720.8 ± 365.9 mg/day in the 2nd month with no accompanying mitigation of symptomatology, prolongation of on time, or improvement in status in the off phase. The reduction in levodopa during this period was necessary to manage side effects such as dyskinesias and/or psychiatric disorders.

Medication Regimen

The improvement in parkinsonian symptomatology and the increase in time spent in the on phase (Fig. 1) observed in our patients was accompanied by a reduction in the amount of levodopa/inhibitor (from 1038.9 ± 762.2 mg/day presurgery to 370 ± 225 mg/day at Month 60). The postoperative course of levodopa administration in our series could be divided into two separate periods. The first took place during Months 1 to 2 postimplantation. In this period, the amount of levodopa was reduced to 720.8 ± 365.9 mg/day in the 2nd month with no accompanying mitigation of symptomatology, prolongation of on time, or improvement in status in the off phase. The reduction in levodopa during this period was necessary to manage side effects such as dyskinesias and/or psychiatric disorders.

During the second part, levodopa slowly continued to be tapered over a 5-year follow-up period. This was accompanied by waves of clinical progress, followed by periods in which there were only slight improvements or plateaus. This second phase could be divided into two or three subperiods, coinciding with the clinical recovery observed between Months 5 and 7 (622.7 ± 401 mg/day at Month

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Further dissection of the data as a consequence of the clinical decline of two patients (Cases 1 and 9), whereas three patients continued to show gradual progress. At the end of the follow-up period, the time spent in the on phase was 72 ± 27% of the day, ranging from 33 to 94%.

Presence of Dyskinesias

All patients in the group presented with dyskinesias in their preoperative time, eight of them coinciding with benefit of dose (six at peak of dose and two at peak of dose or square wave) and two at the beginning and in the pre–off phase (diphasic) or at peak of dose, showing irregular daily and monthly patterns. The patients experienced dyskinesias during 67 ± 30% of their daily on time, which represented 30 ± 17% of the entire day. Figure 2B shows that 5 years after surgery, the patients presented a significant decrease in the on time spent with dyskinesias. Nevertheless, this reduction was moderate despite the progressive and continuous decrease in the levodopa administered. The improvement was significant from Month 5 on, but it was not until Months 7 to 9 that a reduction was observed in all of the patients. Eighteen months after surgery four of the five patients were asymptomatic.

<table>
<thead>
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<th>No. of Patients Improved†</th>
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<tr>
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Discussion

The results of this study seem to indicate that implantation of FVM in the caudate nucleus did improve the clinical situation of our parkinsonian patients, as exhibited by a lowering of the total Parkinson’s disease score in predefined on and off phases, reduction in the levodopa medication, lengthening of the on periods, and shorter and less frequent dyskinesias. The postoperative improvement is general, periodically following a step-by-step process and persisting at least 5 years after implantation.

All the surgically treated patients progressed until postoperative Month 30, although there were qualitative and quantitative differences from one case to another. At the end of the clinical follow-up period, seven of 10 patients enjoy a better situation than prior to surgery, the status of one patient has declined in recent months, and the remaining two patients are the same and worse, respectively, than before implantation.

The significant clinical findings in our study included improvements in activities of daily living (63%) and in UPDRS scores (43%), which allowed the patients, each to a different degree, to return to their customary social activities.

Course of Clinical Progress

In contrast to the results reported by other authors who observed an improvement in vocalization, autonomic functions, and even parkinsonian symptomatology within minutes or hours after implantation, we detected no immediate clinical change. The first weeks after surgery, a qualitative, but statistically nonsignificant, decline was observed in five patients during the on phase. It was necessary to reduce the amount of medication as a consequence of motor and psychiatric complications and this measure, together with the withdrawal of preoperative dopaminergic agonists, may have been the cause of the deterioration. Nonetheless, other authors have also reported this finding.

There are a number of differences between the clinical course observed in our patients and that reported in other series. In patients undergoing stereotactic implantation, the clinical improvement commences from Months 1 to 3, and from Months 3 to 4, with the maximum improvement occurring in Month 4 or 5, and in Month 6, after which patients stabilize, with exceptions. In our series, the overall mitigation of the symptomatology progressed stepwise and was not statistically significant until Months 5 to 7 after grafting.

Lengthening of the Awake On Period and Decrease in Dyskinesias

Perhaps one of the most noteworthy and widely appreciated findings, as far as patients are concerned, was the significant lengthening of the on time (39–72%), with decreased intensity and duration (67–36%) of dyskinesias. These results coincided qualitatively but not quantitatively with those reported by other groups, whether using stereotactic or open surgery. The University of Birmingham group reported that in nine of 12 patients undergoing stereotactic implantation in the caudate nucleus, the percentage of on time was prolonged from 38.4% pre- to 47.9% postsurgery starting in Months 3 to 12; these researchers observed a reduction in dyskinesias of 65% at 6 months in eight of 12 patients. Freed and colleagues reported a lengthening of the time spent in the on phase of 15% and 40% in two of their seven patients. In the case of the University of Lund group, the onset of recovery occurred earlier (Months 2–4 vs. Months 5–7), did not seem to follow a stepwise process, and, with the exception of one patient (who 3 years after grafting...
Fetal tissue implants in caudate nucleus

is in the on phase almost 100% of the day), the reported clinical improvement was less marked.

The differences between our results and those observed with open surgery and implantation in the caudate nucleus44,45,48 did not involve the percentage of improvement, but the moment of onset. In our experience, the on period was prolonged over the course of the follow up, whereas for Molina and associates48,49 and Madrazo and coworkers44,46 the improvement was more rapid, appearing between 15 and 30 days postsurgery in the case of Molina, et al.49 and at 4 to 8 weeks in that of Madrazo, et al.46 and stabilizing by Months 3 to 6. With all three groups performing open surgery, what was the reason for these differences? Could they have been a consequence of the different types of patients, younger and with a shorter history of medication in the series of both Madrazo, et al.45 and Molina, et al.48 Could there have been additional factors such as the source and the age of the fetal tissue employed (spontaneous abortions in Madrazo’s series vs. therapeutic abortions in our series and that of Molina) or the immunosuppressive regimen (which in Cuba was discontinued in Month 6)? The responses to these questions are still a matter of hypothesis.

Improvement in Parkinsonian Symptoms

The quantification of the progress in individual parkinsonian symptoms has not often been included in reports on implantation procedures. Minor44,48,54,55 to marked34,35,48 improvements have been reported for bradykinesia,14,48,54,55 tremor,34–36,54,58 motor tasks,34–36,54,58 rigidity,34–36,48 facial expression,14 gait,14 and postural stability.14,48 The onset of recovery ranged between 15 days48 and 2 to 3 months postsurgery.34,36,48 In our group, the degree of improvement and the time to onset varied from one symptom to another. Rigidity, facial expression, and rising from a sitting position were the symptoms in which the progress was most pronounced (54–66%) and occurred earliest (Months 2 or 3–5); improvements in speech, body kinet- ics, and gait were slightly less pronounced and occurred later. Less intense tremor and that dependent on levodopa diminished, as did mild postural instability. However, severe cases were not mitigated by this procedure.

Medication Regimen

In our patients, the improvement in parkinsonian symptomatology and the increase in time spent in the on phase was accompanied by a marked reduction (64%) in the amount of levodopa/carbidopa administered and the withdrawal of dopaminergic agonists. Reduction in medication has also been reported by other authors. The reasons for discrepancy concerning this aspect are difficult to pinpoint. According to published results, implantation in the caudate nucleus19,22,45,48,54,58,61 would appear to allow a greater reduction in medication than implantation into the putamen,34,55,57 and open surgery45,48 seems to enhance this gain further. The reasons for this difference are still a matter of speculation. Perhaps, as we will discuss later, there are unknown aspects such as injury to cortical area F, during the approach to the lateral ventricle or to the caudate nucleus; humoral factors liberated by donors or host cells; the sprouting of fibers in the caudate nucleus (which is less affected than the putamen); better absorption of the medication; or a toxic effect of levodopa on the host fibers or on donor viability and fibers, any of which may play an important role in this reduction.

Complications in the Series

In contrast to our first series that involved implants of PAM™ instead of FVM, there have been no deaths, perhaps because of the elimination of the increased morbidity and mortality associated with adrenal gland resection. In contrast to some series,19,22,34 there was no hematoma or hemorrhage surrounding the implanted tissue.

As was to be expected, perhaps the most serious complications observed in our series were pulmonary infections, which led to the withdrawal of immunosuppression in two patients 30 and 42 months postimplantation. Moreover, immunosuppression provoked neurological complications in two patients who developed muscle cramps, restless motor activity in the arms and legs, and/or akathisia. The latter, as far as we know, has not previously been mentioned as a neurological complication in patients receiving cyclosporine for organ transplantation or in the course of immunological or hematological disorders. In our opinion, the role of cyclosporine in triggering this symptomatology was confirmed by the fact that onset always coincided with the peak serum cyclosporine level 3 to 4 hours after morning and evening administration. The symptoms did not remit after reduction of the dopaminergic medication and they disappeared after cyclosporine was withdrawn.

Immunosuppression in Patients With Parkinson’s Disease

The need for immunosuppression in implant recipients with Parkinson’s disease has been widely debated and a definite conclusion has yet to be reached. Some groups maintain long-term immunosuppression.34–36,41,44 The Birmingham team,19,20,22 which employs tissue from older fetuses, bases its arguments against patient immunosuppression on the results obtained in monkey allograft implantation.21 Others, like the Cuban group,48 those at Yale University,52 and the group in Créteil, France,52 administer immunosuppressive therapy to patients until 6 or 7 months postimplantation. Still others, like Freed, et al.,34 provided immunosuppressive therapy to one series but not to another, finding no significant differences between the two groups, albeit with a somewhat lesser improvement in immunocompromised recipients. It could be argued that ABO antigen matching had been performed prior to tissue implantation, a fact that in itself may explain (as in heart transplantation) the decreased risk of rejection. In addition, Freed, et al.,14 administered cyclosporine and steroids for immunosuppression; thus, the less marked recovery observed in the immunocompromised patients could be a consequence of steroid administration, which can provoke a deterioration in the clinical status of parkinsonian patients and which appears to diminish the viability of dopaminergic cells in vitro and in vivo.51,57 Perhaps the difference between the findings reported by Freed and colleagues14,14 and Hitchcock and associates19,22 and our own results lies in the surgical technique selected. Perhaps if ABO antigen matching were to be performed prior to intraparenchymal stereotactic surgery, which involves a less aggressive surgical approach, immunosuppression
would not be strictly necessary or a regimen of a few months would suffice. In our case, the increased surgical damage with rupture of the frontal lobe architecture and exposure of the caudate nucleus to the lateral ventricle, in contact with the cerebrospinal fluid and in the proximity of the choroid plexuses (which contain fenestrated vessels, opening into the general circulation and serving as an antigen exposure site) may make immunosuppression necessary, more so because our implantations were not preceded by antigen matching. The clear deterioration of three of our patients after cessation of cyclosporine therapy indicates that we should consider that the drug is necessary; the fact that the fourth patient whose cyclosporine regimen was terminated did well may indicate that the donor and recipient were an antigenic match and that this condition may effectively eliminate the need for long-term cyclosporine administration. On the other hand, we may be wrong and, perhaps, the improvement does not depend solely on the implanted tissue.

Causes for Improvement

Two separate but complementary sets of causes or mechanisms can be proposed for the recovery seen in this model of implantation. On the one hand are those related to the viability and integration of the implanted cells and, on the other, those resulting from the secondary response of the enhanced striatal cells and/or the activation-repair-modification process of the basal ganglia circuits of the recipient. We could ask the following questions: What mechanism or mechanisms could explain the better results obtained in our patients in comparison with those observed after stereotactic implantation in the putamen? Could it be that open surgery, a procedure that produces cortical damage and requires opening the caudate, provides keys for recovery that do not depend on earlier suppositions? The comparison of the clinical course of the patients in this series with that of our earlier series of PAM recipients allows us to theorize, in our model, as to the causes or factors governing this improvement. In the first place, the reduction in the medication and the amelioration of the psychiatric and motor complications observed in our patients during the 1st week, together with the immediate progress reported by other authors may be due to the effects of the surgical procedure and the release of dopamine and/or other factors by the cells injured during tissue preparation, findings that may be comparable to those of the PAM implants. Further support for this hypothesis is provided by Meyers’ work in extensive caudotomies in the 1940s resulted in immediate, transient, and unilateral improvement, mainly in rigidity, and by the 50% improvement in motor tasks reported after cavitation of the caudate nucleus in nonhuman primates treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Moreover, although the cavitation hypothesis would be supported by the early improvement in rigidity and facial expression in our PAM implant recipients, this would not be the case in our FVM recipients in whom 2 to 3 months were required for these symptoms to be alleviated.

What occurs, then, in the course of the 1st postoperative year in our parkinsonian patients? The improvement observed over the initial 7 months in this series of FVM recipients was less marked and occurred later than that observed during the same period of time for PAM implants. What is the reason for these differences? If we forget the implanted cells for a moment and consider that the recovery could only be due to the stimulus caused by injury to the striatal cells, which in turn provokes through unknown mechanisms (tropic–trophic factors) the sprouting and growth of nigrostriatal fibers from the few neurons remaining in the host (it should not be overlooked that the caudate nucleus in parkinsonian patients has more surviving fibers than the putamen), the same degree of recovery should have been achieved during the initial months in this series of FVM implants. If the difference between the two series lies in the implanted tissues, it appears obvious that the cells must play a role in the recovery. On the one hand, PAM would exert its effect, either through direct action of the cells on the host fibers or through indirect action involving the striatal cells or the fenestrated vessels that it contains. On the other hand, the FVM cells could provoke a tropic–trophic stimulus or become directly integrated with the host. In the first case, the tropic stimulus during the early months would have been less pronounced than that produced by the PAM cells. In the second case, the slowed recovery could be attributed to the technique used—intracavitary implantation rather than intraparenchymal implantation of dissociated tissue—because the fetal cells would require more time to cross the interface between the cavity and the host striatum.

Perhaps the most interesting feature of the course of our FVM transplants is the continuation of improvement after the initial months, occasionally with great advances, especially after the 1st year. This does not occur with PAM transplants. Could these sudden advances, which are accompanied by reduced medication, indicate the involvement of new factors that produce the recovery beyond the 1st year? We consider this a real possibility, arguing that this improvement is not likely to be due to a rearrangement resulting from collateralization of the host fibers and that the implanted FVM cells, mature by that time, and their fibers play a major role. The results published by Kordower et al. support this hypothesis. These authors demonstrate that 18 months after implantation, FVM cells were capable of surviving, emitting projections and reinnervating the striatum of a parkinsonian patient who had received a bilateral implant of FVM tissue in the putamen. Therefore, the second wave of improvement observed in our patients 18 to 24 months postsurgery could be partially related to the reinnervation of the caudate nucleus.

Thus, we conclude that in our implant model there appears to be more than one cause for the improvement. The surgical lesion, caudotomy, and frontal transcortical approach to the lateral ventricle could partly explain the recovery observed; however, the difference between the courses of the FVM transplant series and the PAM series indicates that the implanted cells play a role in the improvement either indirectly, through the release of different factors that provoke the host response of the host, or directly, by modulating circuits of the basal ganglia cells. In our fetal transplant series, this role would be corroborated by the progressive improvement obtained beyond 1 year posttransplantation. Nevertheless, the significant clinical recovery observed in our patients might depend
partly on their pharmaceutical management. Perhaps the progressive decrease in postimplantation levodopa, together with preoperative withdrawal of dopaminergic agonists, permits graft development and the sprouting of host fibers, thus causing collateralizations that would increase the area of the dopaminergic terminals. Whatever the reasons for these encouraging clinical results, we must be cautious because before this experimental procedure can be considered a valid therapeutic alternative in parkinsonian patients, it will be necessary to assess the long-term results of other similar studies.

Acknowledgment

We thank Martha Messman for her editorial assistance.

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