that our work has been recently duplicated by Guthrie et al. (3), who find that ozone production in air is much less efficient than in 1000 torr O_2.

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Fetal Brain Grafts and Parkinson's Disease

I have reservations about the enthusiastic tone of the report by Lindvall et al. (1) and the accompanying Research News article (2 Feb., p. 529) on the effects of fetal brain tissue transplantation in a single human patient. Lindvall et al. imply that the changes seen were caused by survival of the transplanted cells and the resultant reinnervation of the host brain. The Research News article implies that the effects were qualitatively different from the effects that have so far been seen with adrenal medulla grafts. Compelling alternative possibilities were not discussed. First, the role of patient expectations may not be trivial. The patient could not possibly have been naïve with respect to the expectations associated with the procedure. In addition to the obvious pitfalls of a study based on a single human subject, the interest and attention accorded this procedure may have contributed to the clinical changes.

The magnitude of the clinical changes seen is impressive, although not necessarily more impressive than the changes seen after adrenal medulla transplantation in some studies. For example, in the study of Goetz et al. (2), in which 18 patients received adrenal medulla grafts by means of the Madrazo et al. (3) procedure, an average decrease in "off" time from 52% of the waking day before surgery to 22% 3 months after transplantation was seen. This is almost identical to the change seen by Lindvall et al. (1).

Also, increased fluorodopa uptake seen on a positron emission tomography scan is not entirely equivalent to cell survival. Improvement in the patient for other reasons, including recovery of dopaminergic terminals around the graft site, might result in such a change. There is some evidence, in fact, that recovery of endogenous dopaminergic terminals can contribute to the effects of brain grafts under certain circumstances (4).

Lindvall et al. conclude that the time course of the patient's improvement was "consistent with the slow development of a growing graft" (1, p. 576), but the time course was not entirely consistent with what would be expected for growth of human fetal tissue grafts in situ. In previous experiments by Brundin, Lindvall, and their colleagues in rats (5), effects of human fetal tissue grafts implanted in essentially the same way did not appear until after at least 3 months, and generally not until 4 to 5 months after transplantation. In their Science report (1), substantial improvement was seen as soon as 2 months and was maximal by 3 months. Thus the improvement was almost twice as rapid as in animal studies. In the previous clinical trials of adrenal medulla grafting by Goetz et al. (2), improvement was minimal after 1 month, while near-maximal improvement was seen by 3 months. This exactly matches the time course of improvement seen by Lindvall et al. (1).

Lindvall et al. also conclude that the effects were not due to tissue damage, in part because no improvement was seen in earlier studies where a larger cannula was used. In their most recent experiment, however, the procedure was improved so that more tissue could be implanted. "Virtually all" of the tissue from the ventral mesencephalon of four fetuses was used. Tissue implantation per se produces damage to the host brain; thus the possibility that the present trial produced greater tissue damage than previous trials cannot be ruled out.

An unfortunate consequence of excessive publicity about brain tissue transplantation has been the application of tissue transplantation as though it were a therapeutic procedure. In some cases, tissue transplantation has even been used for diseases other than Parkinson's disease, including schizophrenia, Huntington's chorea, and progressive supranuclear palsy. Tissue transplantation remains an experimental technique and should be applied to humans only in the course of carefully planned therapeutic trials.

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Lindvall et al. (1) are to be congratulated for their demonstration that transplantation of fetal tissue may be therapeutic in patients with neurodegenerative and neurotraumatic disorders. Positron emission tomography (PET) with 6-[F18]fluoro-L-dopa (6FD) revealed a 130% increase in the operated putamen's influx constant. The interpretation of Lindvall et al. is that this represented reinnervation of the putamen by surviving functional graft. However, another explanation is also consistent with their observations, namely, that the surgical procedure induced sprouting of fibers from endogenous, residual, surviving dopaminergic neurons. That dopaminergic fibers from which sprouting could occur are present pre-operatively is evident from the PET scan presented in figure 3 of their report.

We have conducted a series of experiments grafting different tissues into the basal ganglia of primates with hemiparkinsonian symptoms induced by methyl(phenyl)tetrahydropyridine. We have witnessed the capability of PET with 6FD to detect surviving, viable fetal mesencephalic allografts (2). However, we have seen similar alterations of 6FD-derived radioactivity in the area of graft placement that histologically proved to be secondary to neurite sprouting from host dopaminergic neurons (3, 4). The changes in the authors' stereotactic technique, which they hypothesize as contributing to a greater survival of the implanted fetal cells (dopaminergic or nondopaminergic) (4) could also have resulted in greater stimulus for neurite-promoting factor release or could have created a more favorable balance between neurotrophic and neurotoxic influences. Conceivably, both mechanisms could simultaneously be operating.

PET with 6FD provides an in vivo tool for assessing biochemical changes resulting from grafting procedures. Through histologic correlation, the exact interpretation of changes in measured 6FD-derived activity can be obtained. Although Lindvall et al. measured a 130% increase in the operated putamen's influx constant, from the data presented it is not clear to what extent this finding was influenced by the 6FD dose difference between the pre- and postoperative studies. Without information about ra-

diochemical or chemical purity, specific activity, or how the presence of 3-methoxy-6-fluoro-tyrosine (a 6FD metabolite that crosses the blood-brain barrier) was corrected for, we can only speculate as to the quantitative meaning of the PET post-operative changes.

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Response: We welcome the thoughtful comments of Freed and Miletich *et al.*, which attest to the range of important scientific issues that need to be clarified in order to understand the mechanisms by which intracerebral neural implants can promote functional recovery in patients with Parkinson's disease (PD). It is important to emphasize that intracerebral neural grafting is still a highly experimental procedure and we fully agree with Freed that application to patients should be strictly limited to thoroughly evaluated clinical trials, carried out within the framework of carefully planned scientific programs. We appreciate the cautious support of the National Institutes of Health (NIH) researchers in this regard. Intracerebral implantation techniques have an interesting potential for the development of new therapeutic approaches to neurodegenerative conditions and to repair of the central nervous system. This approach is, however, still in its infancy and it could easily become discredited unless it retains a solid scientific base.

Our current strategy is based on the idea of improving dopamine neurotransmission in the dopamine-depleted striatum of patients severely affected with PD. It is important to demonstrate that, as in animals with neurotoxin-induced experimental parkinsonism, neural grafts can improve parameters of dopaminergic neurotransmission in the striatum in PD and that such changes can be correlated with therapeutically significant neurological improvements. The patient described in our report is interesting because he is the first case in which such a correlation has been seen.

Positron emission tomography (PET) is probably the only noninvasive technique available today with which to obtain direct information about dopamine synthesis and handling in the striatum in PD patients. The limitations of this technique are primarily related to sensitivity (we have estimated that the variance between measurements amounts to up to 30%) and spatial resolution (which is about 8.5 × 8.5 mm with the present equipment). With these limitations in mind, PET scanning, with the use of ^{18}F-fluorodopa as a tracer, should allow not only the detection of marked improvements in dopamine formation and retention, but also the observation of where in the striatal complex this change has taken place. As Miletich *et al.* point out, an increased fluorodopa uptake detected by PET does not, by itself, provide information on the biological mechanism(s) behind it. However, the design of our study, in which we focused all implant material in one area (putamen) on one side, made it possible to establish that the increase in fluorodopa uptake was confined to the area surrounding the implantation sites and to see that there were no measurable increases in the nongrafted striatal regions. Our interpretation of this change rests mainly on the experimental data in 6-hydroxydopamine–lesioned rats, where functional recovery has been correlated with the degree of dopaminergic fiber outgrowth from the implanted dopaminergic neurons into the adjacent host striatum [see our original references (*1–3*)]. The suggestion that trophic stimulation of sprouting from the residual surviving dopamine neurons could contribute to the observed improvements is an interesting one, and both the NIH team (*2*) and the Rochester group (*3*) have provided some intriguing new data in mice and monkeys treated with methyl(phenyl)tetrahydropyridine (MPTP) that support this idea. Bankiewicz *et al.* (*2*) have pointed out that the improvement was graft induced, that is, induced by the implanted fetal mesencephalic tissue, and that the damage associated with the grafting procedure (which in this case was a cavity technique) was not sufficient to induce the effect. This raises the possibility that in MPTP–lesioned monkeys, at least, the efficacy of fetal mesencephalic tissue to improve striatal dopaminergic transmission could be due to a combination of two different beneficial effects—host reinnervation by the grafted neurons and trophic stimulation of host fiber sprouting. It remains unclear, however, whether the severely damaged dopamine system in the Parkinson-diseased brain can undergo this type of sprouting response, and if so whether such a response might be aborted by the ongoing disease process. It should also be pointed out that in our study the graft was placed in the most severely affected area of the striatum, where little residual dopamine innervation may remain.

Dose difference between the two PET scans is unlikely to have played a role in the interpretation of the result. Radiochemical purity of 6-L-(^{18}F) fluorodopa was 98.9% for the preoperative study and 97.1% for the postoperative study. Chemical purities were 99.6% and 98.8%, respectively. Specific activities were 14.22 Mbq/μM and 6.19 Mbq/μM. The graphical approach used to calculate the influx constant normalizes for activity injected. The 3-methoxy metabolite of fluorodopa does indeed cross the blood-brain barrier; although the concentration of this metabolite was not assayed, there is no a priori reason to suppose that a major change in the peripheral metabolism of fluorodopa occurred as a result of stereotactic neurosurgery.

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