Neurosurgical forum

tumor itself which inhibits the host’s immune system, thereby allowing the tumors to grow relatively unchallenged. Immunosuppression is not seen in patients with low-grade gliomas, but is consistently found in patients with malignant gliomas. The work of Elliott, et al.,2 indicates that this immunosuppression appears to be modulated by a marked suppression in the functions of the lymphocyte subset, T cells.

Wrann, et al.,4 purified a factor from malignant glial cell lines which inhibited T cell proliferation. The amino acid sequence was found to be similar to that of TGF-β. The same group, this time headed by de Martin,1 determined that the complementary deoxyribonucleic acid (DNA) of this “glioblastoma-derived T cell suppressor factor” had over 70% amino acid homology to TGF-β.

The report of Clark and Bressler, as well as our results, tend to refute the hypothesis that the immunosuppression seen in patients with malignant gliomas is totally mediated by TGF-β or TGF-β subtype. It is possible that the TGF-β detected by bioassay in Clark and Bressler’s laboratory and the TGF-β detected by immunohistochemistry in our laboratory for some reason did not detect the “TGF-β-like” factor described by Wrann, et al., and de Martin, et al.1

VICTORIA SAMUELS-PAKALNIS, M.D., M.S.
Medical College of Georgia
Augusta, Georgia

References


RESPONSE: We thank Dr. Samuels-Pakalnis for her thoughtful comments regarding our recently published work. However, we cannot agree with the statement that this work tends to refute the previously cited studies related to the role of transforming growth factor-β (TGF-β) or TGF-β subtypes in the immunosuppression seen in patients with high-grade malignant gliomas. We cannot comment on the methodology used by Dr. Samuels-Pakalnis, but our assay was performed on cells. The key point here is that the factor reported by both Elliott, et al., and de Martin, et al., was isolated from tissue culture supernatants. We did not assay the supernatants from the cultures we used. As a result, the decreased TGF-β activity observed in the high-grade gliomas we examined might have occurred as a result of the factor being actively secreted from the cells. While we are sure other explanations might exist for the discrepancies in the findings of various studies, we are not so convinced that our work argues against a role for TGF-β in the suppression of the mitogenic capabilities of the T4 subset of cells. In short, our quest continues in an effort to elucidate the complex actions associated with TGF-β in brain-tumor patients.

W. CRAIG CLARK, M.D., PH.D.
University of Tennessee
Memphis, Tennessee

Neural Transplantation for Parkinson’s Disease

To THE EDITOR: The recent article by Sladek and Gash on neural transplantation for Parkinson’s disease is important because it raises the level of consciousness of the neurosurgical community relative to this important experimental neuroscientific procedure (Sladek JR Jr, Gash DM: Nerve-cell grafting in Parkinson’s disease. J Neurosurg 68:337-351, March, 1988). These authors have been outstanding contributors to the discipline of brain-grafting research over a long period of time. There are, however, some areas of controversy we wish to discuss and would appreciate the authors’ comments on them.

First, we hope that the intermixing of discussion about fetal mesencephalic and adrenal medullary grafts did not become confused in the mind of the readers. Unquestionably, great success has been achieved with fetal grafting in rodents and in nonhuman primates. The data on this are very strong. Behavioral improvement using the chromaffin cells has been less successful both in rodents and in nonhuman primates. The best results were achieved by chronic administration of nerve growth factor, which further complicates the procedure. Those of us who have used both types of tissue for grafting in parkinsonian nonhuman primates will attest to the fact that there is a clear and unequivocal difference in the degree of behavioral improvement obtained.

Madrazo, et al.,7 surprised the world with their announcement of successful transplantation of adrenal medullary tissue into the caudate nuclei of patients with Parkinson’s disease. In doing so they bypassed the traditional progression through nonhuman primate studies to man. This has resulted in a serious void in understanding of mechanisms and optimal techniques for grafting. Nevertheless, many in the neurological and neurosurgical communities have enthusiastically endorsed the procedure and clinical investigations are under way. A shroud of controversy surrounds the procedure, as it has not produced the dramatic results originally anticipated and technical problems have re-
sulted in morbidity. There is an expression of concern that the clinical studies have moved too far ahead of the laboratory investigations, and we would wholeheartedly agree with the authors that nonhuman primate studies are imperative to help guide future clinical studies. We believe a review of this subject should focus on these issues. There are many questions about optimal techniques for preparation of the graft, optimal graft volume, and optimal implantation site. Whether the graft is needed or if the lesion alone is sufficient to produce symptomatic improvement is a basic question that has yet to be answered.

Fetal mesencephalic transplantation has the theoretical advantage that the precise neurons that are required for reversal of the neurological deficit can be integrated into the host. Mesencephalic grafts in rodents have demonstrated active neurons which spontaneously fire at rates that are indistinguishable from normal nigral neurons and can be inhibited or activated by the host. The transplanted neurons have also demonstrated the ability to sustain intracranial self-stimulation, suggesting that the transplanted neurons, under certain circumstances, axonally convey specific, temporally organized information to the reinervated striatum. Behavioral recovery is related to the number of dopaminergic neurons in the graft, the extent of axon reinnervation, and the topographic distribution of the graft. Dopaminergic synaptic contacts from the graft onto the host have been observed. However, Bankiewicz, et al., in a paper presented at the American Association of Neurological Surgeons (AANS) meeting in Toronto in 1988, noted that it is unclear whether or not anatomical integration of this degree is needed for optimal behavioral recovery since recovery can be observed with fetal grafts that do not reinnervate the host. A major disadvantage of utilizing fetal neural transplants is the difficulty in acquiring such tissue should this therapy ever be applied to the human situation. The legal and moral debates have already begun. The National Institutes of Health moratorium on the use of therapeutically aborted human fetuses for grafting, although unwelcome from a scientific point of view, nevertheless may help resolve some of the debate preoperatively rather than in the courts postoperatively. The use of cell culture lines might avoid the ethical issues, but it would not avoid the major disadvantage of any allographic technique, which is the risk of immunological rejection and the potential initiation of an autoimmune encephalopathy.

Adrenal medullary transplantation has the advantage of utilizing an autograft with almost no risk of rejection or adverse immunological reactions. The disadvantage is that this tissue does not contain functional neurons. The chromaffin cells are capable of neuronal transformation in primates, but only under certain conditions. Although biochemical differentiation to a state of increased dopamine synthesis and fiber formation can occasionally be seen in intracranial grafts, the chromaffin cells are not integrated into the brain and may simply serve as an "infusion pump." There is disagreement whether infusion of dopamine or a neurotrophic factor is responsible for the effects, or even if chromaffin tissue is required. The adrenal medullary grafts do not appear to work as well as fetal mesencephalic grafts in correcting turning behavior in the rat, especially in older animals. Adrenal grafts in both man and monkey have a poor survival rate and very little differentiation compared to that seen in rats. Because of the advantages of autografts, other tissues such as sympathetic ganglion, retina, and mesenteric ganglion should be further in-

---

**TABLE 1**

Summary of reports of adrenal medullary grafting in nonhuman primates*

<table>
<thead>
<tr>
<th>Authors, Yr. &amp; Reference</th>
<th>No. of Grafted Subjects</th>
<th>Model</th>
<th>Graft Tissue</th>
<th>Graft Site</th>
<th>Operative Technique</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morihisa, et al., 1984†</td>
<td>1</td>
<td>6-OHDA</td>
<td>AA</td>
<td>C</td>
<td>stereotaxic</td>
<td>only with the intraventricular technique was there significant cell survival; no behavioral data</td>
</tr>
<tr>
<td>Bankiewicz, et al., 1988‡</td>
<td>3</td>
<td>6-OHDA</td>
<td>AA</td>
<td>C</td>
<td>intraventricular</td>
<td>allografts without long-term survival of chromaffin cells but some behavioral improvement</td>
</tr>
<tr>
<td>Bakay, et al., 1987†</td>
<td>3</td>
<td>MPTP</td>
<td>AA</td>
<td>C</td>
<td>intraventricular</td>
<td>less than 10% cell survival but long-term behavioral improvement</td>
</tr>
<tr>
<td>Tuck, et al., 1988‡</td>
<td>3</td>
<td>MPTP</td>
<td>AA</td>
<td>C</td>
<td>intraventricular</td>
<td>symptomatic improvement in 2 animals with graft in caudate; no change in animal with graft in white matter</td>
</tr>
<tr>
<td>Fiandra, et al., 1988‡</td>
<td>9</td>
<td>MPTP</td>
<td>AA</td>
<td>C</td>
<td>stereotaxic</td>
<td>very few surviving chromaffin cells; behavioral studies not done</td>
</tr>
<tr>
<td>Plunkett, et al., 1988‡</td>
<td>3</td>
<td>MPTP</td>
<td>AA</td>
<td>C</td>
<td>intraventricular</td>
<td>transient improvement only in intraventricular procedure</td>
</tr>
</tbody>
</table>

*C = caudate; P = putamen.
† This work was supported in papers presented at the Annual Meeting of the American Association of Neurological Surgeons in Toronto, Ontario, Canada, on April 24-28, 1988.
‡ This work was reported in a paper presented at the Annual Meeting of the Southern Neurosurgical Society in Hot Springs, Virginia, on March 30-April 2, 1988.