prophylactic intravenous low-dose heparin therapy, especially on older patients.

Besides the possibility of graft occlusion, the major drawback of the method is the requirement for approximately a 90- to 120-minute period of temporary ICA occlusion. The use of an indwelling intraluminal shunt has been explored in cadavers by us and by Al-Mefty et al. However, the space available is very limited. At present, in patients who are known to have a compromised collateral circulation, we prefer to protect the brain during ICA occlusion with moderate hypothermia and barbiturate or etomidate coma.

Considering the advantages and disadvantages of the technique of SVG bypass of the cavernous ICA, we believe that anastomosis of the superficial temporal or occipital artery to a middle cerebral artery branch is still a better revascularization method when the donor vessel is large. However, a disadvantage is that only a limited amount of flow is available when the ICA has to be acutely occluded. A long venous graft from the external carotid artery to the middle cerebral artery or its branches does not require temporary ICA occlusion, but also has the potential for graft occlusion, even after the immediate perioperative period.

With respect to intracavernous ICA aneurysms, the indications for treatment are controversial. Since many aneurysms arising from the posterior two-thirds of the intracavernous ICA are less dangerous than those originating more anteriorly, and may not progress symptomatically, surgeons should be cautious in recommending treatment. Of course, at the present time, balloon occlusion of the ICA or of the aneurysm alone is available as an alternative treatment. These techniques also have the potential for mortality or major morbidity, and long-term results are not known after such treatment.

We are thankful to Drs. Tabatabai and Khan for bringing to the attention of the readers of the Journal of Neurosurgery the controversies regarding the technique of SVG bypass of the cavernous ICA.

References

Tissue Grafting and Immunosuppression

TO THE EDITOR: The recent article by Bankiewicz, et al., describing implantation of fetal neural tissue into adult rhesus monkeys to alleviate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism showed encouraging results in three of four recipients (Bankiewicz KS, Plunkett RJ, Jacobowitz DM, et al: The effect of fetal mesencephalon implants on primale MPTP-induced parkinsonism. Histochemical and behavioral studies. J Neurosurg 72:231–244, February, 1990). While the paper provides interesting technical and clinical data on this type of transplantation procedure, we are concerned that the authors only superficially addressed the important question of immunological rejection.

The problem of rejection was raised in relation to only one animal which showed graft rejection after receiving tissue from two fetal donors. As a result of this observation, the authors suggest that the use of a single donor source should be the normal protocol until the immunological aspects are further understood, giving the impression that such a grafting procedure would alleviate the risk of immunological rejection. We would argue that the immunology of neural tissue grafting is only beginning to be understood, and that the acceptance of allografts is the exception rather than the rule. Although allogeneic tissue has been reported to survive in the short term,most reports of allogeneic transplantation in which the grafts have been identified have described immunological rejection. Thus, the mammalian brain is no longer believed to be an immunologically privileged site for grafting. Glial cells express major histocompatibility complex (MHC) antigens both in vitro with cytokines and in vivo when grafted, and probably have a major role along with endothelial cells and microglia in initiating immune responsiveness in the brain. It has been further shown that grafting of embryonic neural cells also leads to the expression of MHC antigens on the graft and ultimately causes immune rejection.

The explanation as to why the three animals reported in this study had viable grafts at 5 to 7 months postgrafting is most probably related to the degree of mismatch at the major and minor histocompatibility gene loci. It may well be that this is a highly inbred monkey colony which differs little at these loci, and thus the grafting procedures are more representative of isografts than allografts. It would be important to tissue-type these monkeys if conclusions are to be drawn as to the efficacy of such procedures. It has previously been shown that the degree of mismatch of MHC and non-MHC antigens plays an important part in neural graft survival in rats. It may also relate to the site of
placement and degree of gliosis in the walls of the prepared cavity.

We agree with Gill and Lund that more experimental work must be done before fetal neural grafting can be undertaken clinically. If allografting is to be performed, we believe immunosuppression is required for long-term graft survival. Madrazo, et al., reported cases of human fetal neural grafting. The only alternative to long-term immunosuppression appears to be the technique of immunoselection, in vitro, of embryonic neural cells incapable of MHC expression in the presence of gamma interferon. These cells are used as the source of graft material. This procedure has been shown to be effective in the mouse.

References


RESPONSE: We agree that immunological rejection is an important question in relation to tissue grafting into the brains of primates. We raised the problem of rejection in relation to the animal which showed histological rejection; no such evidence was seen in the animals receiving tissue from a single fetus. The study was not designed to specifically assess the immunogenicity of fetal mesencephalic grafts, but rather to determine the survival capability and behavioral consequences of such grafts. There are at least nine studies in which parkinsonian nonhuman primates received infrastriatal graft of fetal mesencephalon.

Immunosuppression was used in only one of the studies (when a xenograft of human fetal tissue was implanted into monkeys). However, survival of fetal neurons was demonstrated in each study. Furthermore, in another report in which rejection of fetal allografts occurred, placement of the grafts was separated in time and it is quite possible that the recipient was immunized by the first graft and that both were rejected upon placement of the second. We did not tissue-type the recipient monkeys, the parents of the fetus, or the fetal tissue. The recipients and the parents were culled at different times from a colony of rhesus monkeys maintained by the National Institutes of Health on an island off Puerto Rico. This colony was begun with 125 monkeys and was 900 in number when the animals used in this study were obtained. The possibility that these were isografts remains but seems unlikely.

As clearly documented by others, and mentioned by Drs. Rosenfeld, Bartlett, and Kerr, allograft rejection is seen in rodents. This situation in nonhuman primates, as described above, is much less clear. Although Fianada and his colleagues did not observe any significant humoral or immune responses to fetal mesencephalic allografts in rhesus monkeys at 18 months after transplantation, they were concerned about the possibility of slow rejection. Thus, immunological rejection remains a question in primates; investigators performing fetal mesencephalic implants in parkinsonian patients are divided between using and avoiding immunosuppression. There is not yet any clear difference in behavioral outcome in immune-suppressed versus nonimmun suppresses patients, and there is not yet any histological demonstration of fetal dopaminergic neuronal survival. Thus, as we suggested in our paper, current published data imply avoiding multiple fetal donors or sequential fetal grafts. The nonhuman primate has not been a favored model for immunological studies, but the answer to the question of rejection of brain grafts in primates requires that it become one.

In summary, implantation of fetal tissue obtained from a single donor into parkinsonian monkeys results in clinical improvement regardless of the use of im-
munosuppression. Tissue used from multiple fetuses is rejected when immunosuppression is not used, but with immunosuppression may survive and lead to clinical improvement.²

KRZYSZTOF BANKIEWICZ, M.D.
ROBERT J. PLUNKETT, M.D.
EDWARD H. OLDFIELD, M.D.
CNS Implantation Unit
Surgical Neurology Branch, NINDS
Bethesda, Maryland

References