Treating Parkinson’s Disease with Lesions of the Subthalamic Nucleus

We would like to caution against reviving ablation therapies for the treatment of Parkinson’s disease, as was suggested by H. Bergman et al. (1). The authors report that unilateral lesioning of the subthalamic nucleus (STN) with ibotenic acid injection reduced all of the major motor disturbances in the contralateral limbs of two monkeys rendered parkinsonian by systemic treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). They postulate that the motor abnormalities seen in the MPTP model of Parkinson’s disease were the result of excessive activity in the STN, which increased inhibitory output of the internal division of the globus pallidus (GPi). They suggest that surgical or pharmacological inactivation of the STN should be studied as a potential clinical therapy for this movement disorder.

Using the MPTP model in cynomologus monkeys (Macaca fascicularis) (2), we evaluated the role of polymer-encapsulated, dopamine-secreting cells in reversal of experimen-
tal parkinsonism (3). We evaluated tremor and rigidity with qualitative observations of behavior. We quantified akinesia for each upper limb by measuring the time required for a monkey to empty a tray of small wells loaded with food treats (4). Fifteen animals showed the typical parkinsonian akinesia contralateral to the carotid injection. Their ability to pick food from the tray was either completely or significantly impaired. One animal showed nearly complete unilateral loss of dopaminergic cells in the substantia nigra (SN). It did not show the typical parkinsonian symptoms, but demonstrated normal performance at the picking test even after two consecutive MPTP injections (0.6 and 0.3 mg/kg) 7 weeks apart. Ten weeks after the second injection this animal was killed. Tyrosine hydroxylase immunohistochemistry revealed severe lesions in the SN pars compacta comparable to that seen in our hemiparkinsonian animals (Figs. 1, A and B). Macroscopic observation and cresyl violet staining of slides revealed that a vascu-
lar lesion, possibly caused by an air embolism created during the carotid injection of MPTP, also destroyed the GPi (Fig. 1, C and D). In this monkey suppression of the inhibitory output of the GPi apparently prevented the development of typical parkinsonian symptoms, including akinesia.

Coagulative lesions of the GPi or of its thalamic projection targets have reduced tremor and rigidity in human Parkinson’s patients without any effect on akinesia (5). The absence of parkinsonism in a primate with a combined lesion of both the SN and the GPi indicates that the pathophysiology of idiopathic Parkinson’s disease may be more complex than that suggested by the MPTP model, or that the pallidectomies performed in humans were not sufficiently restricted to the GPi.

STN lesions could only modify the output of the GPi. Further animal studies should be conducted so that we understand the discrepancy between the results of lesioning the GPi in an MPTP model and the results of thalamotomies or pallidectomies that have been performed for the treatment of human idiopathic Parkinson’s disease.

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REFERENCES

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Response: Our paper (1) was intended to be a contribution to the understanding of the pathophysiology of parkinsonian motor signs. It was not meant to be a proposal for new surgical treatments for Parkinson’s dis-

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ease. We do not advocate new ablative therapies for parkinsonism, and agree with Aebischer and Goddard that more animal research is needed on the mechanism by which parkinsonian motor signs develop. Nonetheless, possible implications of our findings for future clinical applications cannot be ignored.

The finding of Aebischer and Goddard supports the hypothesis that reducing the output of the globus pallidus (GPi) in monkeys treated with MPTP is sufficient to reduce parkinsonian signs. However, the inconsistencies they perceive between the results of lesions in primates and in humans seem more apparent than real. It is widely accepted that thalamotomy is useful against tremor and rigidity, while it is not effective against akinesia (2); but there are at least two larger, well-documented studies which indicate that pallidectomies in humans reduce all major parkinsonian signs, including akinesia (3). Regarding the effects of lesions, experimentation in animal models lags behind clinical experience with humans. We agree that such therapies of Parkinson's disease need to be explored in animal models before clinical trials are carried out.

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