

- ers. Although r is maximized, the scheme can also work when instead the standard properly scaled crystallographic R factor is minimized.
18. M. Thayer, K. M. Flaherty, D. McKay, *J. Mol. Biol.*, in press.
 19. K. M. Flaherty *et al.*, unpublished results.
 20. A. Mondragon, S. Subbiah, S. C. Almo, M. Drott, S. C. Harrison, *J. Mol. Biol.* **205**, 189 (1989).

21. P. T. Unwin and R. Henderson, *ibid.* **94**, 425 (1975).
22. I am deeply indebted to A. Haykovich, M. Babyonyshev, P. Rosenthal, and T. B. Spott for their irrational faith, G. Petsko for arranging a home for this work, M. Levitt and everyone in his group—M. Steffy, M. Hirschberg, C. Lee, B. Park, D. Hinds, N. Kuhn and V. Daggett—for giving me that home

and more (NIH grant GM-41455), D. McKay and in particular, K. Flaherty, for being exceptionally generous neighbors, R. Kornberg for invaluable help, and the Damon Runyon-Walter Winchell Postdoctoral Fund (DRG-1019) for my stay at Stanford.

3 August 1990; accepted 11 January 1991

Technical Comments

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 cynomolgus 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 vas-

cular 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.

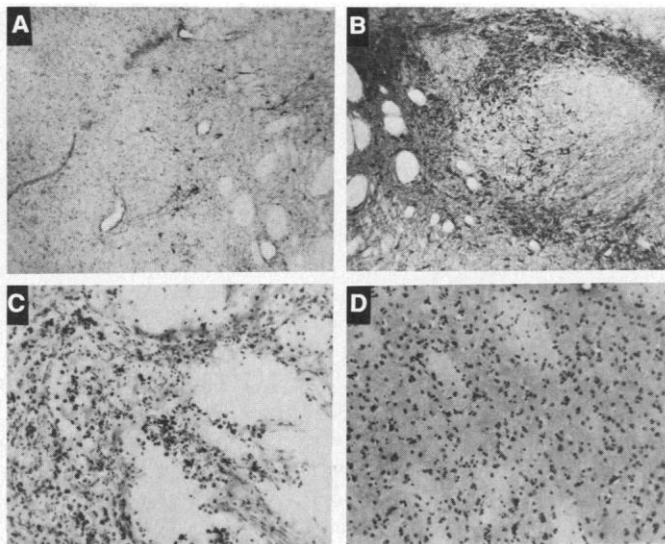
STN lesions could only modify the output of the GPi. Further animal studies should be conducted so that we understand the discrepancy between the results of lesioning the GPi in an MPTP model and the results of thalamotomies or pallidectomies that have been performed for the treatment of human idiopathic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

PATRICK AEBISCHER

MOSES GODDARD

*Division of Biology and Medicine,
Brown University,
Providence, RI 02912*

Fig. 1. Tyrosine hydroxylase (TH) immunostain (Incstar) demonstrate an absence of the dopaminergic pars compacta cells of the SN on the lesioned (A) and the unlesioned (B) sides. Free-floating sections were treated with a monoclonal antibody to TH (Incstar, Stillwater, Minnesota), followed by secondary rabbit antibodies to mouse, and a mouse peroxidase-antiperoxidase complex (Sternberger-Meyer, Jarrettsville, Maryland). The reaction is made visible by enzyme histochemical techniques and counterstaining with cresyl violet. Cresyl violet-stained sections of the GPi show necrosis on the lesioned (C), but not the unlesioned (D) side. Magnification, $\times 100$.



REFERENCES

1. H. Bergman, T. Wichmann, M. R. DeLong, *Science* **249**, 1436 (1990).
2. K. S. Bankiewicz *et al.*, *Life Sci.* **39**, 7 (1986).
3. P. Aebischer *et al.*, *Soc. Neurosci. Abstr.* **16**, 963 (1990).
4. P. Aebischer and W. Schultz, *Neurosci. Lett.* **50**, 24 (1984).
5. R. Meyers, *N.Y. State J. Med.* **42**, 317 (1942); T. Hirai, M. Miyazaki, H. Nakajima, T. Shibasaki, C. Ohye, *Brain* **106**, 1001 (1983); L. V. Laitinen and M. I. Hariz, *Movement Disord.* **5** (suppl. 1), 82 (1990).

18 October 1990; accepted 8 March 1991

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-

case. 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.

HAGAI BERGMAN

Department of Physiology,
Hadassah Medical School,
Hebrew University,
Jerusalem, 91010 Israel
THOMAS WICHMANN

MAHLON R. DELONG*
Department of Neurology,
Emory University,
Atlanta, GA 30322

REFERENCES

1. H. Bergman, T. Wichmann, M. R. DeLong, *Science* **249**, 1436 (1990).
2. R. Hassler, T. Reichert, F. Munding, W. Umbach, J. A. Gangleberger, *Brain* **83**, 337 (1960); H. Narabayashi, in *Stereotaxy of the Human Brain*, G. Schaltenbrand and A. E. Walker, Eds. (Thieme, Stuttgart, West Germany, 1982), pp. 510-514.
3. E. Svendsen, A. Torvik, R. Lowe, L. Leksell, *Acta Psychiat. Neurol. Scand.* **35**, 358 (1960); L. V. Laitinen and M. I. Hariz, *Movement Disord.* **5** (Suppl. 1), 82 (1990).

17 December 1990; accepted 8 March 1991

*To whom correspondence should be addressed.

AAAS-Newcomb Cleveland Prize

To Be Awarded for an Article or a Report Published in *Science*

The AAAS-Newcomb Cleveland Prize is awarded to the author of an outstanding paper published in *Science*. The value of the prize is \$5000; the winner also receives a bronze medal. The current competition period began with the 1 June 1990 issue and ends with the issue of 31 May 1991.

Reports and Articles that include original research data, theories, or syntheses and are fundamental contributions to basic knowledge or technical achievements of far-reaching consequence are eligible for consideration for the prize. The paper must be a first-time publication of the author's own work. Reference to pertinent earlier work by the author may be included to give perspective.

Throughout the competition period, readers are invited to nominate papers appearing in the Reports or Articles sections. Nominations must be typed, and the following information provided: the title of the paper, issue in which it was published, author's name, and a brief statement of justification for nomination. Nominations should be submitted to the AAAS-Newcomb Cleveland Prize, AAAS, Room 924, 1333 H Street, NW, Washington, D.C. 20005, and **must be received on or before 30 June 1991**. Final selection will rest with a panel of distinguished scientists appointed by the editor of *Science*.

The award will be presented at the 1992 AAAS annual meeting. In cases of multiple authorship, the prize will be divided equally between or among the authors.