The regenerative capacity of damaged adult CNS neurons is limited (*11*). Although regenerative sprouting of severed axons has been observed by many investigators, the formation of appropriate and functional synaptic connections has not been demonstrated and may be rare. The formation of dense connective tissue and neuroglial scars after CNS damage has been regarded as a significant barrier to neural regeneration (*12*). On the other hand, there is evidence that lesioned neonatal CNS neurons can regenerate in a functionally useful way (*13*). In an earlier study (*5*), we found that axons from transplanted vasopressin neurons coursed from the graft into the median eminence of the host. In normal animals, vasopressin is released into the circulation by axons terminating at capillaries in the median eminence and neural lobe (*14*). The presence of vasopressin in the hypothalamic grafts and the increased ability of some of the host animals to conserve water suggest that the axons of the grafted fetal neurons made appropriate and functional connections. Glial scarring in the host brain, resulting from our stereotaxic transplantation procedures, did not prevent functional development.

This study demonstrated that symptoms resulting from a congenital defect in the CNS of an adult mammal can be ameliorated by transplanted neurons. Additional evidence that brain grafts may function in the adult host was recently provided by Perlow *et al.* (*15*). Transplants of fetal dopamine neurons were found to reduce motor abnormalities resulting from lesions of the substantia nigra. The development of the ability to transplant neurons to correct CNS deficiencies, whether due to genetic defects, disease, or trauma, has extraordinary theoretical and clinical implications.

DON GASH
JOHN R. SLADEK, JR.
Department of Anatomy and *Center for Brain Research, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642*
CELIA D. SLADEK
Departments of Anatomy and *Neurology, University of Rochester School of Medicine and Dentistry*

References and Notes

1. U. Stenevi, A. Björklund, N. A. Svengaard, *Brain Res.* **114**, 1 (1976); Å. Seiger and L. Olson, *Cell Tissue Res.* **179**, 285 (1977); R. D. Lund and S. D. Hauschka, *Science* **193**, 582 (1976); C. B. Jaeger and R. D. Lund, *Brain Res.* **165**, 338 (1979); B. K. Beebe, K. Møllgård, A. Björklund, U. Stenevi, *ibid.* **167**, 391 (1979).
2. A. Björklund, M. Segal, U. Stenevi, *Brain Res.* **170**, 409 (1979).
3. H. Sokol, E. A. Zimmerman, W. Sawyer, A. G. Robinson, *Endocrinology* **98**, 1176 (1976).
4. H. Valtin, *Am. J. Med.* **42**, 314 (1967).
5. D. Gash and J. R. Sladek, Jr., *Peptides* **1**, 11 (1980).
6. U. Stenevi, A. Björklund, L. F. Kromer, C. M. Paden, J. L. Gerlach, B. S. McEwen, A. J. Silverman, *Cell Tissue Res.* **205**, 217 (1980); S. R. Henderson, C. L. Bethea, S. E. Monroe, *61st Annu. Meet. Endocr. Soc.* (1979) (Abstr.), p. 464.
7. The animals were decapitated and their brains were quickly removed, frozen on dry ice, and sectioned at approximately 1000-μm intervals. The periventricular region of the hypothalamus was dissected out and homogenized in 1 ml of 0.25 percent acetic acid or phosphate-buffered saline. The homogenizer was rinsed once with 1 ml of the homogenizing solution, and the rinse and homogenate solutions were combined and centrifuged for 5 minutes at 100*g*. The resulting supernatant was heat-treated for 90 seconds in boiling water to inactivate any enzymes and then frozen. Corresponding areas of the diencephalon were removed from the controls. The supernatants were then assayed for vasopressin [D. Gash *et al.*, *Brain Res.* **181**, 345 (1980)]. The vasopressin antiserum used had an affinity for vasopressin 100 times greater than its affinity for oxytocin. Since high levels of oxytocin (relative to vasopressin) would interfere with the vasopressin assay, and since oxytocin was present in the periventricular areas taken for homogenization, homogenates from the periventricular region of the controls were used to establish a baseline of oxytocin interference. The baseline was set at 2 standard deviations above the mean value for the controls—a conservative criterion that probably underestimated the actual vasopressin content of the grafts.
8. T. H. McNeill and J. R. Sladek, Jr., *Science* **200**, 72 (1978).
9. J. Buggy and A. K. Johnson, *Am. J. Physiol.* **233**, R44 (1977); A. K. Johnson and J. Buggy, *ibid.* **234**, R122 (1978).
10. M. Gellai, B. R. Edwards, H. Valtin, *ibid.* **237**, F100 (1979).
11. R. Y. Moore, in *Dynamics of Degeneration and Growth in Neurons*, K. Fuxe, L. Olson, Y. Zotterman, Eds. (Pergamon, Oxford, 1974), p. 379; L. Guth, *Exp. Neurol.* **48**, 3 (1975).
12. C. D. Clemente, in *Regeneration in the Central Nervous System*, W. F. Windel, Ed. (Thomas, Springfield, Ill., 1955), p. 147.
13. K. Kalil and T. Reh, *Science* **205**, 1158 (1979).
14. R. Defendini and E. A. Zimmerman, in *The Hypothalamus*, S. Reichlin, R. J. Baldessarini, J. B. Martin, Eds. (Raven, New York, 1979), p. 137.
15. M. J. Perlow, W. J. Freed, B. J. Hoffer, A. Seiger, L. Olson, R. J. Wyatt, *Science* **204**, 643 (1979).
16. We are indebted to J. Lyness, L. Dick, J. Hasbrouck, and P. Reydel for their technical assistance. We thank C. L. Odoroff for helpful discussions on the statistical analysis, A. G. Robinson for the neurophysin antiserum (provided under PHS grant AM 16166), and T. B. van Wismersma Greidanus for the vasopressin antiserum. This research was supported by PHS grant NS 15109.

20 June 1980; revised 8 September 1980

Mental Symptoms in Huntington's Disease and a Possible Primary Aminergic Neuron Lesion

Abstract. *Monoamine oxidase activity was higher in the cerebral cortex and basal ganglia of patients dying from Huntington's disease than in controls. Enzyme kinetics and multiple substrate studies indicated that the increased activity was due to elevated concentrations of monoamine oxidase type B. Concentrations of homovanillic acid were increased in the cerebral cortex but not in the basal ganglia of brains of patients with Huntington's disease. These changes may represent a primary aminergic lesion that could underlie some of the mental symptoms of this disease.*

Huntington's disease (HD) is an autosomal dominant degenerative disease characterized clinically by mental symptoms including a schizophreniform psychosis and dementia, and the neurological signs of chorea (*1*). The pathophysiology of this disease has some bearing on understanding that of schizophrenia and the primary dementias.

The pathology of the basal ganglia (*1*) includes marked neuronal loss in the caudate nucleus, putamen, and globus pallidus; and relative sparing of the substantia nigra. A reduction in the basal ganglia of the activity of choline acetyltransferase (CAT) and glutamic acid decarboxylase (GAD) (*2, 3*) reflects these morphological changes. Muscarinic cholinergic, γ-aminobutyric acid (GABA), and serotonergic receptor densities are reduced in the basal ganglia (*4*). In contrast, the concentrations in the basal ganglia of norepinephrine, dopamine, and tyrosine hydroxylase are normal (*2, 5*). Drugs that block dopamine receptors, deplete dopamine, or increase acetycholine improve the choreiform movements, while L-dopa and anticholinergics aggravate them (*6*). Work on animals suggests that GABA modulates dopaminergic function in the basal ganglia (*6*). Thus, it is postulated that dopaminergic overactivity, secondary to the loss of the inhibitory restraint of GABA and cholinergic neurons, is responsible for the choreiform movements.

While it is reasonable to assume that the pathology seen in the basal ganglia is responsible for the motor disturbances associated with this disease, the mental symptoms are more likely to be related to changes in the cerebral cortex where degeneration of the third, fifth, and sixth layers occurs (*1*). In contrast to the basal ganglia, the cortex appears to lack a neurochemical counterpart to these histological changes, and pharmacological manipulations aimed at improving cognitive function have been preliminary and desultory. No significant alterations in GAD or CAT activity or in the concentrations of muscarinic or GABA receptors are found in the cerebral cortex (*2, 3, 7*). Decreased [^{3}H]spiroperidol binding is reported in the cerebral cortex of choreics

0036-8075/80/1219-1369$00.50/0

(*8*), a finding consistent with reduced dopamine or serotonin receptor density, but the significance of this observation requires further investigation.

In experiments in which human blood platelets were used as models of some aminergic neuron functions, increased dopamine uptake and monoamine oxidase (MAO) activity have been reported in HD (*9, 10*). These findings may represent a systemic genetic effect on aminergic neurons. Dopaminergic overactivity has been postulated both as part of the cause of the choreiform movements of HD and the symptoms of schizophrenia (*11*). Increased platelet and brain MAO activity has been reported in the primary dementia of Alzheimer's disease (*12*). Perhaps cortical aminergic neuronal dysfunction occurs in HD and is related to some of the mental symptoms of HD, particularly the schizophreniform psychosis and the dementia. We therefore examined MAO activity and homovanillic acid (HVA) concentration in both the basal ganglia and cerebral cortex of patients dying from HD compared to controls.

Brain samples were obtained from HD patients and unmedicated controls dying from nonneurological causes as confirmed by neuropathology. Control and HD samples were handled in the same way (*13*), and were matched for time both to refrigerator (4°C) and freezer (−70°C). The brain areas studied were frontal cortex (Brodman's area 8), parietal cortex (Brodman's area 7), head of the caudate nucleus, lateral segment of the globus pallidus, and a composite of the pars compacta and reticulata of the substantia nigra. MAO activity was measured in duplicate with ^{14}C-labeled phenylethylamine hydrochloride, ^{14}C-labeled tyramine hydrochloride, and ^{14}C-labeled serotonin binoxolate (New England Nuclear) as substrates. The activity was expressed as nanomoles of product formed per milligram of protein of crude brain homogenate per hour (*14*). Enzyme kinetics were measured by ^{14}C-labeled phenylethylamine (PEA). Homovanillic acid was measured by a gas chromatographic technique (*15*). Brain MAO may increase with age (*16*), but the HD specimens did not differ significantly in age from controls with the exception of the samples from the substantia nigra where the controls were 9.7 years older. About half the HD patients were on neuroleptics, but none were on MAO inhibitors. The controls were drug-free. Neuroleptics do not appear to alter MAO activity, but can elevate HVA levels although tolerance may develop to this effect (*17*). Compared to that of controls, the mean MAO activity was significantly elevated in both cerebral cortex and basal ganglia of HD brains (see Table 1). The values for parietal and frontal cortical MAO activity did not differ significantly in either the HD group or controls, and cortical values were therefore combined for intergroup contrasts and intragroup correlations (*18*). Differences in cortical MAO activity were greater with tyramine and PEA (39 and 41 percent, respectively) than with serotonin (10 percent and statistically nonsignificant). There was insufficient tissue to permit a similar multisubstrate study in the basal ganglia. Human MAO can be functionally divided into type A that preferentially deaminates serotonin and type B that preferentially deaminates dopamine and PEA (*19*). Tyramine is a substrate for both types. Thus, the data suggested that the increased MAO activity was largely of type B. The enzyme kinetics (Table 1) demonstrated a significant increase in V_{max} without an overall significant alteration in Michaelis constant (K_m). This was consistent with an increase in concentration of MAO type B rather than an alteration in the enzyme. There was no significant correlation (Pearson product moment) between MAO activity and time to refrigerator or freezer, age, or duration of illness. No differences were found in cortical MAO activity between patients on neuroleptics compared to those without neuroleptics, or between males and females. Studies in human platelets and animals show no clear effect upon MAO activity of neuroleptics (*20*). Thus, the

Table 1. Monoamine oxidase activity and enzyme kinetics in the cerebral cortex and basal ganglia of patients dying from Huntington's disease contrasted with controls dying from nonneurological causes. The substrates used were phenylethylamine (PEA), tyramine, and serotonin (used in the cortex only because of lack of tissue elsewhere). The significance of the differences between groups was calculated by a conventional two-tail *t*-test unless the variance differed significantly between the two groups (significant *F* value), in which case a modified *t*-test was performed; S.E.M., standard error of the mean.

Substrate	Brain MAO activity (nmole mg^{-1} hour^{-1}) or kinetics					
	Control group			Huntington's group		
	Mean	S.E.M.	*N*	Mean	S.E.M.	*N*
			Cerebral cortex			
Tyramine	63.7	4.0	19	88.0*	3.4	18
PEA V_{max}	84.1	6.6	19	118.0*	10.0	18
K_m	5.8	0.5	19	6.1	0.7	18
Serotonin	31.0	1.3	15	33.9	0.6	14
			Substantia nigra			
Tyramine	88.3	10.3	8	134.7†	8.5	9
PEA V_{max}	129.8	24.6	8	235.3†	30.3	9
K_m	4.9	0.5	8	8.4	1.8	9
			Caudate nucleus			
Tyramine	117.9	13.2	10	211.5†	32.0	10
PEA V_{max}	189.0	20.2	10	326.4†	47.8	10
K_m	4.4	0.4	10	5.5	0.4	10
			Globus pallidus			
Tyramine	69.8	11.0	10	184.6*	16.6	10
PEA V_{max}	123.1	20.0	10	324.5*	29.2	10
K_m	4.3	0.4	10	5.9†	0.4	10

*$P < .01$. †$P < .05$.

Table 2. Homovanillic acid concentrations in the cerebral cortex and basal ganglia of patients dying from Huntington's disease, both on and off neuroleptics, compared to controls dying from nonneurological causes. The significance of the differences was calculated by means of a conventional two-tail *t*-test unless the variances of the two groups differed significantly (*F* value) in which case a modified *t*-test was performed; S.E.M., standard error of the mean.

Brain region	Homovanillic acid (ng/mg, wet weight)					
	Control group			Huntington's group		
	Mean	S.E.M.	*N*	Mean	S.E.M.	*N*
Cerebral cortex	0.20	0.06	19	0.29*	0.04	19
Cortex (off neuroleptics)				0.29	0.04	9
Cortex (on neuroleptics)				0.28	0.04	9
Substantia nigra	3.10	0.5	9	4.06	0.04	9
Caudate nucleus	4.27	0.6	10	4.29	1.06	10
Globus pallidus	6.90	0.5	9	5.61	0.4	9

*$P < .02$.

large differences in MAO activity appeared disease-related and were present in both cortex and basal ganglia.

Concentrations of HVA in the HD cerebral cortex, compared to that of controls, were significantly increased, in contrast to normal levels in the basal ganglia (see Table 2). No differences were found in cortical HVA concentration in patients on neuroleptics compared to those without neuroleptics. None of the HD patients had the rigid form of the disease that is associated with increased concentrations of dopamine in the putamen (*21*). Cortical HVA levels did not correlate significantly (Pearson product moment) with time to refrigerator or freezer, age, or duration of illness. Thus, the increased cortical HVA concentrations also appeared disease related.

The changes in MAO activity and HVA concentration cannot be readily explained as secondary to changes in the GABA and cholinergic systems since neurochemical deficits in these two systems appear to spare the cerebral cortex. [^{3}H]Spiroperidol binding is reported to be reduced by 72 percent in the cortex of HD brains and 42 percent in the basal ganglia (*8*), a finding consistent with our finding of elevated HVA concentrations in the cortex, which may be primary or secondary to reduced dopaminergic receptor density.

Increased MAO type B activity has also been reported in the brains of patients dying from Alzheimer's disease compared to age-matched controls, as well as in rat brain after monoaminergic degeneration resulting from hemitransection (*12*). Therefore the increased MAO type B activity in HD and Alzheimer's disease may reflect primary monoaminergic neuron degeneration and secondary gliosis. The lack of a concomitant change in the choreic brains of MAO type A activity in the same cortical areas as MAO type B, combined with the magnitude of the increase in MAO type B activity, suggests these changes are not the nonspecific results of global neuronal degeneration but, as animal data suggest (*12*), are secondary to monoaminergic degeneration. Although the increased MAO type B activity may not directly contribute to the dementia of HD, it may be a marker of monoaminergic neuron degeneration. Both animal and human data suggest a role for aminergic transmitters in cognitive function (*22*) that could thereby explain the dementia of HD through cortical aminergic neuron degeneration. This process may be separate from that causing elevated cortical HVA concentrations and, if so, would be consistent with the lack of significant correlation between MAO activity and HVA levels in both the cortex and basal ganglia (for example, for tyramine in the cortex, $r = -.06$ for the HD group and $r = -.12$ for controls).

That increases in HVA occur in the cerebral cortex, but not in the basal ganglia, of patients dying with schizophrenia, was attributed to the differential effect of neuroleptics on cortex compared to basal ganglia (*21*). Neuroleptics cause elevation of HVA concentrations secondary to dopamine blockade and tolerance develops to this effect more rapidly and at lower dosages in the basal ganglia than the cerebral cortex (*17*). However, an equally valid explanation of this finding in schizophrenia is that the increased cortical concentrations of HVA may be directly related to the primary disease process itself. This latter interpretation would be consistent with the dopamine hypothesis of schizophrenia (*11*). Such a finding in schizophrenia would be more likely located in the cerebral cortex with sparing of the basal ganglia. Equally, our finding of increased HVA concentrations in the cerebral cortex of HD patients may be related to the schizophreniform psychosis that can complicate that disease. The absence of detectable altered HVA concentrations in the basal ganglia of HD patients may be due to the multiple neuron system pathology of that area. Thus, alterations in brain MAO activity and HVA concentrations in HD may represent a primary aminergic lesion in this disease that could underlie some of its mental symptoms.

J. JOHN MANN

Department of Psychiatry, New York Hospital-Cornell Medical Center, New York 10021

MICHAEL STANLEY

Department of Psychiatry, New York University Medical Center, New York 10016

SAMUEL GERSHON

Department of Psychiatry, Wayne State University, Detroit, Michigan 48202

M. ROSSOR

MRC Brain Bank, Addenbrook's Hospital, Hills Road, Cambridge CB22QQ, England

References and Notes

1. G. W. Bruyn, in *Handbook of Clinical Neurology*, P. J. Vinken and G. W. Bruyn, Eds. (Raven, New York, 1973), pp. 298-378; L. S. Forno and C. Jose, *Adv. Neurol.* **1**, 453 (1973).
2. E. D. Bird and L. L. Iversen, *Brain* **97**, 457 (1974).
3. P. L. McGeer and E. G. McGeer, *J. Neurochem.* **26**, 65 (1976).
4. H. I. Yamamura, G. J. Wastek, P. C. Johnson, L. Z. Stern, *Adv. Behav. Biol.* **24**, 35 (1978); K. Lloyd, personal communication; T. D. Reisine, J. Z. Fields, E. D. Bird, E. Spokes, H. I. Yamamura, *Life Sci.* **2**, 79 (1978).
5. O. Hornykiewicz, *Pharmacol. Rev.* **18**, 925 (1966); H. Ehringer and O. Hornykiewicz, *Klin. Wochenschr.* **38**, 1236 (1960).
6. H. L. Klawans and R. Rubovits, *Neurology* **22**, 107 (1972); H. L. Klawans, G. W. Paulson, S. P. Ringel, A. Barbeau, *N. Engl. J. Med.* **286**, 1332 (1972); M. G. Palfreyman, S. Huot, B. Lippert, P. J. Schecter, *Eur. J. Pharmacol.* **50**, 325 (1978).
7. G. J. Wastek, L. Z. Stern, P. C. Johnson, H. I. Yamamura, *Life Sci.* **19**, 1033 (1976); N. Urquhart, T. L. Perry, S. Hansen, J. Kennedy, *J. Neurochem.* **24**, 1071 (1975).
8. T. D. Reisine, J. Z. Fields, E. D. Bird, E. Spokes, H. I. Yamamura, *Commun. Psychopharmacol.* **2**, 79 (1978).
9. M. J. Aminoff, A. Trenchard, P. Turner, W. G. Wood, M. Hills, *Lancet* **1974-II**, 1115 (1974).
10. J. J. Mann and E. Chiu, *J. Neurol. Neurosurg. Psychiatry* **41**, 809 (1978).
11. S. M. Matthysse and S. S. Kety, Eds., *Catecholamines and Schizophrenia* (Pergamon, Oxford, 1975); S. H. Snyder, *Am. J. Psychiatry* **133**, 197 (1976).
12. L. Oreland, C. J. Fowler, A. Carlsson, T. Magnusson, *Life Sci.* **26**, 139 (1980).
13. Corpses were placed in a 4°C refrigerator within 4 hours, and the brains were removed within 96 hours and placed in a deep freezer. The samples were collected by the MRC Brain Bank within 4 days of the patients' dying and frozen at −70°C until dissection at −10°C, and then frozen again at −70°C. Samples were shipped by air to New York University Medical Center in dry ice and collected at the airport; they were still frozen when placed in a −70°C freezer in the laboratory.
14. The method for measuring MAO activity was modified for each substrate from that described (*10*). PEA products were extracted in 2 ml of toluene and serotonin in 0.5 ml of toluene ethyl acetate (1:1). Water blanks were used to save tissue. The tissue was homogenized in saline while on ice, the homogenate contained about 5 mg of crude brain per milliliter. A sample (50 μl) of homogenate was incubated with 30 μl of distilled water and 20 μl of substrate. The final substrate concentrations were: tyramine, 0.4 m*M*; PEA, 0.5, 1, 4, and 16 μ*M*; and serotonin, 0.5 m*M*. Reaction rates were linear over the incubation period. Duplicates were performed for each area and substrate concentration. Protein concentrations were measured according to the method of O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall [*J. Biol. Chem.* **193**, 265 (1951)].
15. E. Watson, B. Travis, S. Wilk, *Life Sci.* **15**, 2167 (1974).
16. D. S. Robinson, T. L. Sourkes, A. Nies, L. S. Harris, S. Spector, D. L. Bartlett, I. S. Kaye, *Arch. Gen. Psychiatry* **34**, 89 (1977).
17. B. Scatton, *Eur. J. Pharmacol.* **46**, 363 (1977).
18. Values of MAO activity and kinetics and HVA concentrations did not differ between frontal and parietal cerebral cortical areas in either the HD or control groups; for example, in the HD group, MAO activity with PEA was 110.6 ± 17.1 nmole mg^{-1} hour^{-1} in the frontal cortex and 125.7 ± 10.9 nmole mg^{-1} hour^{-1} in the parietal cortex. Corresponding figures in the control group were 84.5 ± 9.6 and 83.5 ± 9.5 nmole mg^{-1} hour^{-1}.
19. J. P. Johnston, *Biochem. Pharmacol.* **17**, 1285 (1968); V. Glover, M. Sandler, F. Owens, G. J. Riley, *Nature (London)* **265**, 80 (1977).
20. D. L. Murphy, R. Belmaker, R. J. Wyatt, *J. Psychiatr. Res.* **11**, 221 (1974); J. Mann and K. M. Thomas, *Br. J. Psychiatry* **134**, 366 (1974).
21. E. D. Bird and L. L. Iversen, *Brain* **97**, 457 (1974).
22. R. Adolfson, C. G. Gottfries, L. Oreland, B. E. Roos, B. Winblad, in *Alzheimer's Disease: Senile Dementia and Related Disorders*, R. Katzman, R. D. Terry, K. L. Bick, Eds. (Raven, New York, 1978), vol. 7, pp. 441-451; G. M. Anlezark, T. J. Crow, A. P. Greenway, *Science* **181**, 682 (1973); D. A. Drachman and S. Stahl, *Lancet* **1975-I**, 809 (1975); C. T. Randt, D. Quartermain, M. Goldstein, B. Anagnoste, *Science* **172**, 498 (1971); R. B. Roberts, J. B. Flexner, L. B. Flexner, *Proc. Natl. Acad. Sci. U.S.A.* **66**, 310 (1970).
23. N. C. Bacopoulos, E. G. Spokes, E. D. Bird, R. H. Roth, *Science* **205**, 1405 (1979).
24. Technical assistance was provided by J. Kuster and F. Iohan. Brain samples were provided from the MRC Brain Bank through the permission of L. L. Iversen.

2 April 1980; revised 13 August 1980