ionic flux mechanisms have been suggested, all the models attempt to explain the basis of the oscillations in terms of the dynamics of a single current source having no regenerative characteristics (*2, 5, 10*). Our voltage clamp results suggest, however, that any ionic model must take into account two distinct current sources and incorporate the negative resistance characteristic.

WILKIE A. WILSON*
HOWARD WACHTEL
Departments of Biomedical Engineering and Physiology, Duke University, Durham, North Carolina 27706

References and Notes

1. N. T. Carnevale, thesis, Duke University (1974); H. Wachtel and N. T. Carnevale, paper presented at the 26th International Congress of Physiological Science, New Delhi, India (1974).
2. D. O. Carpenter, in *Neurobiology of Invertebrates*, J. Salanki, Ed. (Plenum, New York, 1973), pp. 35–38.
3. W. R. Frazier, E. R. Kandel, I. Kupferman, R. Waziri, R. E. Coggeshall, *J. Neurophysiol.* **30**, 1288 (1967).
4. W. A. Wilson and H. Wachtel, in *Proceedings of the 23rd Annual Conference on Engineering in Medicine and Biology* (Alliance for Engineering in Medicine and Biology, New York, 1970), abstr. 17.3.
5. D. Junge and C. L. Stephens, *J. Physiol. (Lond.)* **235**, 155 (1973).
6. E. R. Kandel and L. Tauc, *ibid.* **183**, 287 (1966).
7. M. S. Broadwick and D. Junge, *ibid.* **223**, 549 (1972).
8. D. S. Faber and M. R. Klee, *Pfluegers Arch.* **332**, R66 (1972).
9. R. J. David, W. A. Wilson, A. V. Escueta, *Brain Res.* **67**, 549 (1974).
10. S. N. Ayrapetyan, *Biofizika* **14**, 913 (1969); F. Strumwasser, in *The Neurosciences: Third Study Program*, F. O. Schmitt and F. G. Worden, Eds. (MIT Press, Cambridge, Mass., 1974), pp. 459–478.
11. Supported by NIH grants NS 08476 and HE 05716. We thank N. T. Carnevale, L. Mendell, and T. Narahashi for commentary on this report, and E. Kandel for his earlier comments.
* Present address: Epilepsy Center, Veterans Administration Hospital, Durham, N.C. 27705.

28 June 1974; revised 11 September 1974

Lesch-Nyhan Syndrome: Evidence for Abnormal Adrenergic Function

Abstract. *Subjects with the Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase deficiency with self-mutilation) exhibit an apparently unique pattern of adrenergic dysfunction characterized by elevated plasma dopamine β-hydroxylase activity and an absence of pressor response to acute sympathetic stimulation. Patients with a partial deficiency of hypoxanthine-guanine phosphoribosyltransferase without self-mutilation do not exhibit these abnormalities of adrenergic function.*

The Lesch-Nyhan syndrome is an X-linked disorder of purine metabolism characterized by hyperuricemia, an excessive production of uric acid, and profound neurological dysfunction which includes spasticity, mental retardation, choreoathetosis, and a compulsive type of self-mutilation (*1*). These patients have a virtually complete deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) (*2*). Subjects with a less severe deficiency of this enzyme (partial HGPRT deficiency) exhibit a clinical syndrome characterized by hyperuricemia, an excessive production of uric acid, and gout (*3*). Despite occasional neurologic dysfunction in this latter group of patients, self-mutilation does not occur.

The pathogenesis of the neurological and behavioral manifestations in some patients with HGPRT deficiency remains unclear. The development of self-mutilation and "sham rage" in the laboratory animal after administration of caffeine, theophylline, and toxic doses of amphetamine (*4*) led to speculation that the Lesch-Nyhan syndrome might result from a functional alteration in one of the neurologic pathways susceptible to these agents. In the present study we have shown that HGPRT-deficient patients with self-mutilation and severe neurologic dysfunction exhibit a reproducible and apparently unique pattern of adrenergic dysfunction.

The activity of dopamine β-hydroxylase (DBH) in plasma has been proposed as an index of sympathetic nervous system activity (*5*). This enzyme, which catalyzes the conversion of dopamine to norepinephrine, is present in the synaptic vesicles of postganglionic neurons. At the time of discharge, DBH is released into the synaptic cleft along with the neurotransmitter norepinephrine (*6*). Laboratory and clinical data suggest that circulating DBH activity might serve as a quantitative index of adrenergic function (*7*).

Ten children with HGPRT deficiency were studied. Six subjects, 8 to 14 years in age, from five different families manifested the classical Lesch-Nyhan syndrome with choreoathetosis, mental retardation, and self-mutilation. The HGPRT activity in erythrocytes was assayed by a radiochemical method (*3*); a unit is defined as 1 nmole of product per hour per milligram of protein. The HGPRT activity of these six patients ranged from 0.01 to 1.31 units, with a mean and standard deviation (S.D.) of 0.32 ± 0.37 unit. Four subjects ranging in age from 18 months to 16 years exhibited HGPRT deficiency without evidence of self-mutilation. Three of these patients had the partial enzyme defect with no evidence of neurologic dysfunction; erythrocyte HGPRT activity ranged from 0.97 to 1.19 units (mean ± S.D., 1.05 ± 0.10 unit). The fourth patient, whose erythrocyte HGPRT activity was 0.95 unit, a level similar to that of the other patients with the partial enzyme defect, exhibited mental retardation without self-mutilation. Thirty-four controls, without known neurologic disease or neuroblastoma, were randomly selected from the pediatric wards and outpatient clinics. These subjects ranged in age from 1 month to 18 years and had normal HGPRT activity (90 ± 10 units).

Random samples of peripheral venous blood were collected in chilled tubes containing heparin and immediately centrifuged; the plasma was assayed for DBH activity (*8*). The presence of endogenous inhibitors of DBH was excluded (*9*). Since plasma DBH activity is thought to increase progressively with age throughout the developmental years (*10*), the control data were expressed as a 95 percent confidence band for DBH activity with respect to age.

Plasma DBH activity for all groups is depicted in Fig. 1. The four HGPRT-deficient subjects without self-mutilation exhibited plasma DBH activity appropriate for their respective ages. In addition, three randomly selected patients (ages 5 to 14) with cerebral palsy and normal HGPRT activity also exhibited normal plasma DBH activity. In marked contrast, the patients with the Lesch-Nyhan syndrome uniformly exhibited DBH activity well above the 95 percent confidence limit ($P < .001$).

Despite the elevated plasma DBH activity, none of the subjects with the Lesch-Nyhan syndrome exhibited visceral manifestations of adrenergic overactivity such as hypertension, tachycardia, or mydriasis. For this reason we chose to study a clinical index of adrenergic responsiveness. The cold

pressor test, an effective stimulus to sympathetic activation, produces a rapidly perceptible increase in systemic blood pressure and cardiac output (*11*).

Cold pressor tests were performed on ten healthy, normotensive adult volunteers and on six of the HGPRT-deficient subjects. During a 15-minute control period, blood pressure was recorded at 5-minute intervals. One hand was then immersed in ice water for 4 minutes while blood pressure was monitored in the contralateral arm. The relative discomfort elicited by the test appeared comparable in all subjects tested. The blood pressure measurements were obtained by one observer (S.R.) and have been expressed as mean arterial pressure (pulse pressure + ⅓ diastolic pressure).

Changes in mean arterial pressure during the cold pressor test are illustrated in Fig. 2. The normal adults exhibited a rapid pressor response, as did HGPRT-deficient patients without self-mutilation. In contrast, patients with self-mutilation (Lesch-Nyhan syndrome) failed to manifest a pressor response. Subjects in each group exhibited variable increases in heart rate, and differences among groups were not significant ($P > .20$). The absence of a pressor response in patients with the Lesch-Nyhan syndrome could not be attributed to the drugs which they were receiving regularly such as allopurinol, diazepam (one patient), phenobarbital (one patient), or haloperidol (one patient), since discontinuation of these agents did not alter the response. In addition, other subjects treated with similar drugs exhibited a normal response.

In the present study we have shown that patients with the Lesch-Nyhan syndrome exhibit elevated DBH activity in plasma as well as an attenuated or absent pressor response to acute sympathetic stimulation; in contrast, HGPRT-deficient subjects without self-mutilation exhibit both normal plasma DBH activity and a normal pressor response. It appears likely that the abnormal pressor response in the patients with the Lesch-Nyhan syndrome is attributable predominantly to inadequate vasoconstriction rather than to a reduction of the central cardiac component, since a normal increase in heart rate was observed in this group of patients. The abnormalities could be due to (i) an altered ratio of soluble DBH to catecholamines in the synaptic vesicle (*12*), (ii) an altered adrenal release of catecholamines, (iii) impaired

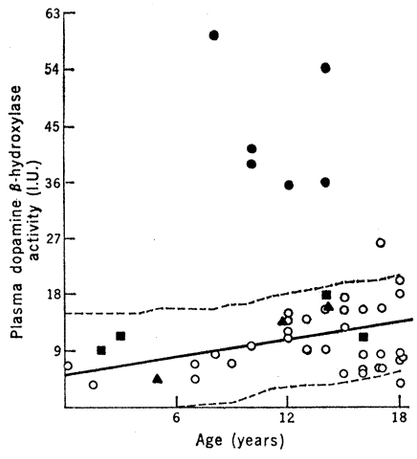

Fig. 1. Plasma dopamine β-hydroxylase activity in HGPRT-deficient subjects. Symbols: ○, normal subjects; ▲, subjects with cerebral palsy; ■, HGPRT-deficient subjects without self-mutilation, (partial HGPRT deficiency); and ●, HGPRT-deficient subjects with self-mutilation (Lesch-Nyhan syndrome). The solid line, $y = 0.5x + 5.4$, represents a regression analysis of age versus plasma dopamine β-hydroxylase; the broken lines represent 95 percent confidence limits; I.U., international unit.

or inhibited binding of catecholamines to the adrenergic receptor, or (iv) unresponsiveness of the adrenergic receptor to catecholamines. We cannot distinguish between these possibilities at the present time. Whatever the mechanism, these observations provide the first reproducible correlation of an experimental variable with the presence of self-mutilation in HGPRT-deficient subjects.

Monoamine pathways in the central nervous system are integrally involved

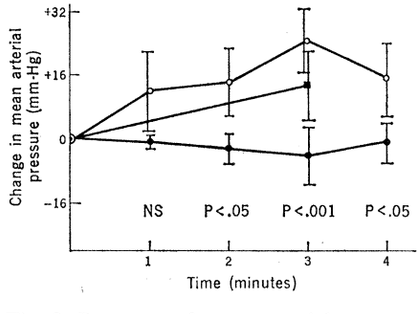

Fig. 2. Response of mean arterial pressure to the cold pressor test. Symbols: ■, normal adults; ○, HGPRT-deficient subjects without self-mutilation (partial HGPRT deficiency); ●, HGPRT-deficient subjects with self-mutilation (Lesch-Nyhan syndrome). Probability values depict the statistical significance of the response of patients with the Lesch-Nyhan syndrome compared to that of the other subject groups; *NS*, not significant ($P > .05$).

in the baroreceptor reflex and the control of systemic arterial pressure (*13*). Thus, one may conjecture that similar or compensatory alterations in the central neural networks might contribute significantly to the bizarre behavioral manifestations of the Lesch-Nyhan syndrome. It is hoped that these findings will not only provide further insight into the pathogenesis of this abnormal behavior but will allow us to design more effective therapeutic maneuvers to avoid its development.

STANLEY ROCKSON, RICHARD STONE
MARTIN VAN DER WEYDEN
WILLIAM N. KELLEY
Departments of Medicine and
Biochemistry, Duke University Medical Center, Durham, North Carolina 27710

References and Notes

1. M. Lesch and W. Nyhan, *Am. J. Med.* **36**, 561 (1964); D. Hoefnagel, E. D. Andrew, N. A. Mireault, W. O. Berndt, *N. Engl. J. Med.* **273**, 130 (1965); W. Nyhan, *Fed. Proc.* **27**, 1027 (1968).
2. J. E. Seegmiller, F. M. Rosenbloom, W. N. Kelley, *Science* **155**, 1682 (1967); W. N. Kelley, *Fed. Proc.* **27**, 1047 (1968); ——— and J. B. Wyngaarden, in *The Metabolic Basis of Inherited Disease*, J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, Eds. (McGraw-Hill, New York, ed. 3, 1972), pp. 969–991.
3. W. N. Kelley, F. M. Rosenbloom, J. F. Henderson, J. E. Seegmiller, *Proc. Natl. Acad. Sci. U.S.A.* **57**, 1735 (1967); W. N. Kelley, M. L. Greene, F. M. Rosenbloom, J. F. Henderson, J. E. Seegmiller, *Ann. Intern. Med.* **70**, 155 (1969); B. T. Emmerson and L. Thompson, *Q. J. Med.* **42**, 423 (1973).
4. E. M. Boyd, M. Dolman, L. N. Knight, *Can. J. Physiol. Pharmacol.* **42**, 995 (1965); D. Hoefnagel, *Fed. Proc.* **27**, 1042 (1968); T. L. Munsat, J. Klinenberg, R. E. Carrel, J. Menkes, *Bull. Los Ang. Neurol. Soc.* **33**, 101 (1968).
5. R. Weinshilboum and J. Axelrod, *Circ. Res.* **28**, 307 (1971); G. F. Wooten, R. Eldridge, J. Axelrod, R. S. Stern, *N. Engl. J. Med.* **288**, 284 (1973).
6. O. H. Viveros, L. Arqueros, N. Kirshner, *Life Sci.* **7**, 609 (1968); L. T. Potter and J. Axelrod, *J. Pharmacol. Exp. Ther.* **142**, 299 (1963); G. P. Gerwirtz and I. Kopin, *Nature (Lond.)* **227**, 406 (1970).
7. R. Weinshilboum and J. Axelrod, *Science* **173**, 931 (1971); P. B. Molinoff, S. Brimijoin, R. Weinshilboum, J. Axelrod, *Proc. Natl. Acad. Sci. U.S.A.* **66**, 453 (1970); F. Lamprecht, R. B. Williams, I. J. Kopin, *Endocrinology* **92**, 953 (1973); A. G. Wooten and P. V. Cardon, *Arch. Neurol.* **28**, 103 (1973).
8. T. Nagatsu and S. Udenfriend, *Clin. Chem.* **18**, 980 (1972).
9. R. A. Stone, J. C. Gunnells, S. M. Schanberg, N. Kirshner, R. R. Robinson, *Circ. Res.* **34–35** (Suppl. 1), I-47 (1974).
10. L. S. Freeman, T. Ohuchi, M. Goldstein, F. Axelrod, I. Fish, J. Dancis, *Nature (Lond.)* **236**, 310 (1972).
11. J. O. Godden, G. M. Roth, E. A. Hines, *Circulation* **12**, 963 (1955); M. A. Greene, A. J. Boltax, G. A. Lustig, E. Rogow, *Am. J. Cardiol.* **16**, 54 (1965).
12. R. A. Rush and L. B. Geffen, *Circ. Res.* **31**, 444 (1972).
13. J. P. Chalmers and R. J. Wurtman, *ibid.* **28**, 480 (1971); J. P. Chalmers and J. L. Reid, *ibid.* **31**, 789 (1972); N. Dohe and D. J. Reis, *ibid.* **34**, 293 (1974).
14. Supported in part by Cerebral Palsy grant R-247-73 and by grant RR-30 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health.

16 May 1974