

organisms other than the target species. The results of our experiment, together with results of similar promising ones (13), demonstrate that disruption of pest-insect pheromone communication may soon become a useful component of the pest management systems used on a variety of crops.

LYLE K. GASTON, R. S. KAAE  
H. H. SHOREY, D. SELLERS  
*Division of Toxicology and Physiology,  
Department of Entomology,  
University of California,  
Riverside 92521*

#### References and Notes

1. J. P. Tette, in *Pheromones*, M. C. Birch, Ed. (North-Holland, Amsterdam, 1974), p. 399.
2. R. S. Kaae, J. R. McLaughlin, H. H. Shorey, L. K. Gaston, *Environ. Entomol.* 1, 651 (1972); R. S. Kaae and H. H. Shorey, *ibid.* 2, 1081 (1973).
3. H. E. Hummel, L. K. Gaston, H. H. Shorey, R. S. Kaae, K. J. Byrne, R. M. Silverstein, *Science* 181, 873 (1973).
4. H. H. Shorey, L. K. Gaston, R. S. Kaae, in *Pest Management with Sex Attractants*, M. Beroza, Ed. (American Chemical Society, Washington, D.C., 1976), p. 67.
5. Gossypure is a 1:1 mixture of *cis*-7, *cis*-11, and *cis*-7, *trans*-11 synthetic isomers of hexadecadienyl acetates (3).
6. Hollow fibers made from Celcon, a biodegradable polyoxymethylene polymer 0.22 mm inside diameter by 0.45 mm outside diameter, were produced by Conrel, an Albany International Corp. subsidiary, Norwood, Mass. The rate of evaporation of pheromone from a hollow fiber sealed at one end is controlled by diffusion from the open end. The rate of pheromone evaporation from a point source, which probably should be greater than the female rate of evaporation, can be specified by the number of fibers located together constituting a release site; the amount of pheromone evaporated per unit area can be specified by the number of release sites per hectare; the longevity of a fiber can be specified by the length of fiber filled with pheromone [E. Ashare, T. W. Brooks, D. W. Swenson, in *Proceedings of the 1975 International Controlled Release Symposium*, F. W. Harris, Ed. (Wright State University, Dayton, Ohio, 1975), p. 42].
7. One end was sealed and one was open. Each hoop was filled with gossypure containing 1 percent of the antioxidant *N*-2-octyl-*N'*-phenyl-*p*-phenylenediamine (Union Oil Products No. UOP-688) by immersing the hoops in gossypure, reducing the pressure to 6 mm, and then releasing the vacuum.
8. We applied the hoops by hand to ensure a precise 1 by 1 m grid. This degree of precision could not be accomplished with the available commercial equipment used by Conrel for ground and aerial application of 20-mm-long gossypure-filled fibers on a semicommercial experimental basis on 1600 ha of cotton in California and Arizona during 1976. Also, hand application permitted locating the hoops at the most effective location on the foliage, the top of the plant. Hoops were chosen as the method of attachment because they ensured retention on the plant until it was defoliated (4).
9. Traps [described by J. R. McLaughlin, H. H. Shorey, L. K. Gaston, R. S. Kaae, F. D. Stewart, *Environ. Entomol.* 1, 645 (1972)] were baited with a 20-mm-long No. 22 Teflon tube containing a 3-mm length of gossypure. Two traps were placed at the top of the cotton canopy and two at the base of the cotton plants. Traps were examined twice weekly starting 15 May for pink bollworm moths.
10. The experiment was evaluated by weekly examination in the laboratory of 100 randomly selected susceptible bolls from each treated and control field for first-through third-instar larvae. Density of susceptible bolls was determined weekly by counting the number of bolls in four 1-meter segments of row per field. Evaluation was started 1 July and continued until 15 September according to the method of R. A. Van Steenwyk, G. R. Ballmer, and H. T. Reynolds [*J. Econ. Entomol.* 69, 579 (1976)].
11. R. A. Van Steenwyk, V. M. Stern, R. S. Kaae, personal communication.
12. A rate of evaporation from each fiber of 10  $\mu$ g/day was determined in a wind tunnel (0.4 m/sec) with the temperature programmed for a typical hot growing day, 21° to 43°C. This corresponds to about a 2-mm length of gossypure evaporated per week.
13. G. H. L. Rothschild, *Bull. Entomol. Res.* 65, 473 (1975); H. Arn, B. Delley, M. Baggilone, P. J. Charmillot, *Entomol. Exp. Appl.* 19, 139 (1976); M. Beroza, in *Pest Management with Sex Attractants*, M. Beroza, Ed. (American Chemical Society, Washington, D.C., 1976), p. 99.
14. We thank T. W. Brooks and R. Kitterman for bringing to our attention the potential of using hollow fibers as pheromone dispensers, and W. E. Yates for determining the rate evaporation of gossypure for those fibers. Supported by the California State Cotton Pest Advisory Board of the California State Department of Food and Agriculture, Cotton, Inc., and The Rockefeller Foundation.

15 November 1976; revised 17 December 1976

## Lesch-Nyhan Syndrome: Low Dopamine- $\beta$ -Hydroxylase Activity and Diminished Sympathetic Response to Stress and Posture

**Abstract.** *Patients with Lesch-Nyhan syndrome with virtually no hypoxanthine phosphoribosyltransferase activity demonstrate significantly low plasma activity of dopamine- $\beta$ -hydroxylase but normal basal levels of norepinephrine. Under conditions of emotional or postural stress the plasma concentrations of norepinephrine in Lesch-Nyhan patients increased less than in a normal population.*

Lesch-Nyhan syndrome, described in 1964 (1), is an X-linked disorder of purine metabolism and is characterized clinically by automutilation and aggressive and compulsive self-destructive behavior, choreoathetoid cerebral palsy, marked hypertonicity, athetoid dysarthria and dysphagia (2). There is a marked deficit in hypoxanthine phosphoribosyltransferase (HPRT, E.C. 2.4.2.8), hyperuricemia, and excessive uric acid production (3). Increased activity of dopamine- $\beta$ -hydroxylase (DBH, E.C. 1.14.17.1) with an

absence of the pressor response to cold stimulation has been noted (4).

The hypertonicity and involuntary dyskinetic movements in Lesch-Nyhan patients have been likened to symptoms in dystonia (2), and we have found both increased DBH activity and increased concentrations of norepinephrine (NE) in the autosomal dominant form of torsion dystonia (5). Accordingly, we undertook the evaluation of sympathetic function in Lesch-Nyhan syndrome by measuring NE concentrations and DBH activity un-

der various environmental circumstances.

Although plasma activity of DBH has been related to sympathetic nervous system activity (6), measurement of basal levels of NE and its increment with postural stress appear to provide a more direct and sensitive measure of both the basal state and responsivity of the sympathetic nervous system in humans (7).

Fourteen patients with Lesch-Nyhan syndrome with a mean age of  $14 \pm 1$  ( $\pm$  standard error) years (range, 6 to 22 years), all with evidence of severe self-mutilation and virtual absence of erythrocyte HPRT activity (8), were evaluated for possible sympathetic dysfunction after the proper consents had been obtained. A control group consisted of 14 healthy volunteers (mean age of  $23 \pm 2$ ; range, 12 to 44 years). Although plasma concentrations of NE vary with age but not sex (9), there was no significant difference among the basal levels of NE in the present control group, the Lesch-Nyhan patients, and an age-controlled group ( $15 \pm 1$  years; basal NE of  $221 \pm 37$  pg/ml) which did not undergo the same postural change after the basal blood sample was taken for NE determination. Since DBH activity may not increase after the second decade (6, 10), 312 adult volunteers ( $42 \pm 1$  years) also served as controls for DBH activity. All subjects were placed in a supine position after which the needle of a "heparin lock" was inserted into an antecubital vein. Blood (12 ml) was withdrawn immediately from ten Lesch-Nyhan patients, and a blood sample was taken from all subjects (in the resting supine position) after about 15 minutes, by which time normal subjects reach basal levels (7). Pulse rate was measured by radial palpation at the time of blood sampling. Eight patients and all the controls were subsequently allowed to sit upright (two patients were tilted to 60 degrees) and blood was sampled after 10 minutes. In normal subjects these maneuvers (sitting and tilting) increase similarly the plasma concentrations of NE (7). Volunteer subjects were asked to discontinue all medications for 1 week before the test. All Lesch-Nyhan patients were receiving allopurinol; eight of them were also taking diazepam; three, thioridazine; three, dantrolene; two, phenobarbital; and one, diphenylhydantoin. Five patients had their medication discontinued 24 hours before the test.

Blood was collected, centrifuged, and stored as described (7) until assayed for DBH by the method of Weinshilboum and co-workers (6) and for NE by the radioenzymatic method of Henry *et al.* (11) modified as described (7).

Table 1. The concentration of NE, activity of DBH, and the pulse rate in 14 Lesch-Nyhan patients and 14 volunteer subjects. Results are expressed as means  $\pm$  standard error. The basal concentration of NE was determined in supine subjects about 15 minutes after venipuncture. The increment in NE was determined by subtracting the basal NE from the concentration determined after the subjects were allowed to sit upright (two patients were tilted to 60 degrees).

Subject	NE (pg/ml)		Pulse rate		DBH (units of activity)*
	Basal	Increment	Basal	Upright	
Lesch-Nyhan	321 $\pm$ 57	39 $\pm$ 26†	106 $\pm$ 4‡	117 $\pm$ 3‡	344 $\pm$ 72†
Volunteers	248 $\pm$ 28	165 $\pm$ 40	74 $\pm$ 3	80 $\pm$ 3	668 $\pm$ 109

\*One unit equals 1 nmole of phenylethylamine converted to phenylethanolamine per milliliter of plasma per hour. † $P < .02$ , Student's *t*-test. ‡ $P < .001$ .

As expected, the Lesch-Nyhan patients were more agitated than the volunteer group, and restraints were used with several patients. It is likely that these patients did not understand the procedure but were afraid that they were to undergo a painful experience. The basal pulse rate in the patients was significantly higher than controls (Table 1). In normal subjects, pulse rate and plasma levels of NE decline significantly and proportionately between immediate and basal samplings (7). In the present experiments, the pulse rate of the patients declined significantly ( $P < .05$ ; paired *t*-test) by  $10 \pm 4$  beats per minute to  $116 \pm 6$  by about 15 minutes after venipuncture, but the patients did not reach basal state as observed subjectively or objectively by pulse rate at the time the basal samples were obtained. The concentration of NE in the plasma obtained immediately after venipuncture was  $331 \pm 67$  pg/ml, and there was a minimal decrease in this concentration by the time the second (basal) sample was obtained. This decrement was not significant; also, the NE concentrations in the plasma obtained immediately or 15 minutes after venipuncture were not significantly higher than the basal levels of NE from the volunteers, despite the higher anxiety levels of the patients (Table 1). After the postural change the patients maintained their elevated state of anxiety and their pulse rates remained higher than controls ( $P < .001$ ; Table 1). Although the concentrations of NE in the plasma obtained from patients and volunteers in the upright position were similar ( $360 \pm 84$  and  $413 \pm 46$ , respectively), the increment in plasma NE in the Lesch-Nyhan patients was significantly blunted (Table 1). In a normal population the NE concentrations increase by about 65 percent above basal values after the individuals have been sitting or have been tilted to 60 degrees for 10 minutes, regardless of the magnitude of the basal plasma content of NE (7, 9).

In contrast to previous results (4), the present study showed that the DBH activity in 14 Lesch-Nyhan patients was sig-

nificantly lower than that in either the 14 volunteers ( $P < .02$ ; Table 1) or the large adult control group ( $760 \pm 26$  units;  $P < .001$ ). To determine whether Lesch-Nyhan plasma contains an inhibitor of DBH activity, the plasma from nine patients was individually mixed with an equal volume of plasma containing high DBH activity and allowed to stand at room temperature for time periods of 5 and 60 minutes before being assayed for DBH activity. The DBH activities from the mixed plasma samples were found to be additive at both time periods, suggesting that the low activity in Lesch-Nyhan plasma is not secondary to endogenous inhibitors.

Since Lesch-Nyhan patients are not able to stand up unassisted, sitting in their wheelchair is generally the most upright posture they assume with respect to the force of gravity on the circulatory system. A major function of the peripheral noradrenergic nervous system is the maintenance of blood pressure upon standing by increasing peripheral vascular resistance. The activity of DBH has been demonstrated to be lower during sleep (12) compared to the waking hours when posture is often changed and individuals are upright. The present data, showing (i) the absence of an elevation in plasma NE concentrations in patients with Lesch-Nyhan syndrome immediately after venipuncture, (ii) a diminished increment in NE upon postural change, and (iii) low plasma DBH activity, support the

recent report (4) of a diminished autonomic responsiveness to cold in Lesch-Nyhan syndrome.

The explanation for these data in Lesch-Nyhan patients may be the relative disuse from infancy of the sympathetic nervous system because of the lack of demand for noradrenergic responsiveness to standing posture, this resulting in a diminished need for synthesis of NE and its synthetic enzymes. Basal noradrenergic tone is not reflected by plasma DBH activity in Lesch-Nyhan syndrome because basal concentrations of NE are normal. That these patients raised their heart rates under conditions of stress supports the view (13) that the cholinergic nervous system has a dominant role in control of heart rate during stress.

C. RAYMOND LAKE

Laboratory of Clinical Science,  
National Institute of Mental Health,  
Bethesda, Maryland 20014

MICHAEL G. ZIEGLER

Department of Pharmacology,  
University of Texas Medical Center,  
Galveston 77550

#### References and Notes

1. M. Lesch and W. L. Nyhan, *Am. J. Med.* **36**, 561 (1964).
2. W. L. Nyhan, *Arch. Intern. Med.* **130**, 186 (1972).
3. J. E. Seegmiller, F. M. Rosenbloom, W. N. Kelley, *Science* **155**, 1682 (1967).
4. S. Rockson, R. Stone, M. van der Weyden, W. N. Kelley, *ibid.* **186**, 934 (1974).
5. M. G. Ziegler, C. R. Lake, R. Eldridge, I. J. Kopin, *Adv. Neurol.* **14**, 307 (1976).
6. R. M. Weinshilboum and J. Axelrod, *Circ. Res.* **28**, 307 (1971); R. M. Weinshilboum, N. B. Thoa, D. G. Johnson, I. J. Kopin, J. Axelrod, *Science* **174**, 1349 (1971).
7. C. R. Lake, M. G. Ziegler, I. J. Kopin, *Life Sci.* **18**, 1315 (1976).
8. The erythrocytes were prepared and sent frozen to either J. E. Seegmiller at the University of California Medical Center, La Jolla, or to W. N. Kelley at the University of Michigan Medical Center, Ann Arbor, for determination of HPRT activity by a radiochemical method.
9. M. G. Ziegler, C. R. Lake, I. J. Kopin, *Nature (London)* **261**, 333 (1976).
10. R. M. Weinshilboum, F. A. Raymond, L. R. Elveback, W. H. Weidman, *Science* **181**, 943 (1973).
11. D. P. Henry, B. J. Starman, D. G. Johnson, R. H. Williams, *Life Sci.* **16**, 375 (1975).
12. T. Okada, T. Fujita, T. Ohta, T. Kato, K. Ikuta, T. Nagatsu, *Experientia* **30**, 605 (1974).
13. D. F. Leon, J. A. Shaver, J. J. Leonard, *Am. Heart J.* **80**, 729 (1970).

30 November 1976

## Legionnaires' Disease: Nickel Levels

**Abstract.** *Nickel concentrations in lung tissues of nine deceased Legionnaire victims average nine times that of controls. There is a significant correlation between the nickel levels in the lungs of the Legionnaire victims and the weights of the lung specimens. No similar correlation is evident in the study of the victims' kidney tissues or tissues from the controls.*

Since the outbreak of Legionnaires' disease during July and August 1976, medical sleuths have indicated that a toxin may have been the responsible

agent. Suggested toxins included nickel carbonyl, phosgene, paraquat, and others (1). The phosgene and paraquat theories are based on inferences from the