rons, but the distribution pattern did not change. The magnesium distribution pattern was reversed by the application of PTZ; magnesium increased in the axon hillock region and decreased in the cell body. Convulsant drugs other than PTZ, such as strychnine ($1 \times 10^{-2}$ mole) and picrotoxin ($5 \times 10^{-3}$ mole), had little effect, as shown in Fig. 1B. Similarly, PTZ has the greatest effect and strychnine and picrotoxin have only a slight effect on intracellular potential change in the D neuron of *Euhadra*.

Figure 2 shows a more detailed general view of the distribution changes induced by PTZ. Calcium, which was concentrated in the cytoplasm in the normal state (Fig. 2A), became more concentrated in and near the cell membrane and less concentrated in the cytoplasm (Fig. 2B) on PTZ application.

In the *Euhadra* ganglion, the neurons can be classified into three types: D neurons, which are depolarized by acetylcholine (ACh); H neurons, which are hyperpolarized by ACh; and I neurons, which are indifferent to ACh (*3*). The I neurons are slightly depolarized by application of PTZ but never manifest bursting activity. We compared the I and D neurons with respect to calcium distribution changes induced by PTZ. The I neurons [RO-1 or LO-1 according to the classification in (*3*)] were incubated in normal or PTZ-containing Ringer solution, frozen, and thin-sectioned. Freeze-dried specimens of both samples were examined. The results showed that no intracellular calcium distribution change was induced by PTZ in the I neuron.

To determine the origin of the increased calcium more precisely—that is, whether it was extracellular or intracellular—the same procedures were carried out with solutions containing cobalt chloride or lanthanum chloride. Figure 2, C and D, show the maps obtained with PTZ Ringer solution containing 30 m*M* cobalt chloride and 4.5 m*M* lanthanum chloride, respectively. The calcium distribution pattern changes are almost the same as those observed with PTZ only. These results suggest that the calcium concentrated in or near the cell membrane on application of PTZ is mainly of intracellular origin.

In voltage clamping studies, the bursting cell shows negative resistance characteristics; this phenomenon is considered to be caused by influx of calcium (*6*). Calcium influx may occur during the bursting activity, but at the same time as or before it occurs the intracellular calcium, probably bound to some granule, to endoplasmic reticulum, or to mitochondria, is released and moves toward the cell membrane. Binding to the inner or outer surface of the cell membrane may then occur and trigger changes in ion channels, probably for potassium and sometimes for calcium. This could be the intracellular mechanism of PTZ-induced bursting activity. The EPXMA provides a promising technique for the study of intracellular ion movement in relation to ultrastructural changes.

EIICHI SUGAYA
MINORU ONOZUKA
*Department of Physiology, Kanagawa Dental College, Yokosuka, Japan*

**References and Notes**

1. E. Sugaya, S. Goldring, J. L. O'Leary, *Electroencephalogr. Clin. Neurophysiol.* **17**, 661 (1964).
2. N. Chalazonitis and H. Takeuchi, *C. R. Seances Soc. Biol. Paris* **162**, 1552 (1968); D. S. Faber and M. R. Klee, *Pfluegers Arch.* **332**, R66 (1972); E. U. Speckmann and H. Caspers, *Epilepsia* **14**, 397 (1973).
3. A. Sugaya *et al.*, *Jpn. J. Physiol.* **23**, 261 (1973).
4. M. R. Klee and D. S. Faber, *Science* **179**, 1133 (1973); R. J. David, W. A. Wilson, A. V. Escueta, *Brain Res.* **67**, 549 (1974); C. Ducreux and M. Gola, *Pfluegers Arch.* **361**, 43 (1975).
5. J. L. Barker and H. Gainer, *Brain Res.* **84**, 479 (1975).
6. R. Eckert and H. D. Lux, *J. Physiol. (London)* **254**, 129 (1976).
7. We thank S. Okudera and Y. Ono for help in computer programing. Supported in part by a grant from the Japanese Ministry of Education, Science and Culture.

14 October 1977

## Dyskinesias Evoked in Monkeys by Weekly Administration of Haloperidol

Abstract. *In two cebus (*Cebus albifrons*) monkeys given weekly oral doses of 0.25 milligram of haloperidol per kilogram, movement disorders appeared 1 to 8 hours after drug administration following the tenth weekly dose. These disorders included oral movements, peculiar postures, writhing, and stretching. Such reactions faded in intensity after the next two doses. Increasing the dose to 0.5 milligram per kilogram has elicited the disorders reliably after each weekly dose for almost 2 years. Similar reactions also developed in a squirrel monkey (*Saimiri sciurea*) treated weekly with haloperidol and in a third cebus monkey previously maintained for a year on a regimen of 0.25 milligram of haloperidol per kilogram on 5 days per week. These findings suggest an experimental model for determining the etiology of drug-induced movement disorders. They also suggest an unrecognized clinical problem.*

Drug therapy dominates the psychiatric treatment of behavior disorders. Its efficacy is limited, however, by widespread pharmacologic mismanagement (*1*) and by the inherent toxicity of the drugs. These two factors are closely connected because the most prominent toxic manifestations are neurobehavioral, producing on the part of clinicians an understandable confusion between side effects and primary behavioral disturbances. Movement disorders represent the most salient and disturbing toxic reactions (*2*). Such disorders may develop as rapidly as a few hours after a single dose of a drug or develop only after years of treatment. Acute dyskinesias assume a variety of forms, including grimacing, yawning, abnormal tongue excursion, writhing motions of the trunk and limbs, and spasmodic, prolonged tonic contractions. Parkinsonism may occur after several weeks of treatment. Persistent or tardive dyskinesias resemble acute reactions in many ways except that oral-facial movements are more conspicuous, and the syndrome emerges after prolonged therapy. Sometimes it may even develop only after medication is halted or reduced (*3*). Although rarely mentioned, the frequency spectrum of resting finger tremor may also identify tardive dyskinesia (*4*). The tardive dyskinesias arouse the most concern because they develop insidiously, often seem to be irreversible, and, ironically, some-

Fig. 1. Monkey 39 after the tenth weekly dose of haloperidol (0.25 mg/kg). The hind legs remain straight, the forearms stretched backward parallel to the torso. (The tip of the paw lies under the inverted V. The V pointed sideways is aimed just below the elbow.) The open mouth is part of a yawn sequence that appeared several times per minute at its peak frequency.


0036-8075/78/0519-0799$00.50/0  

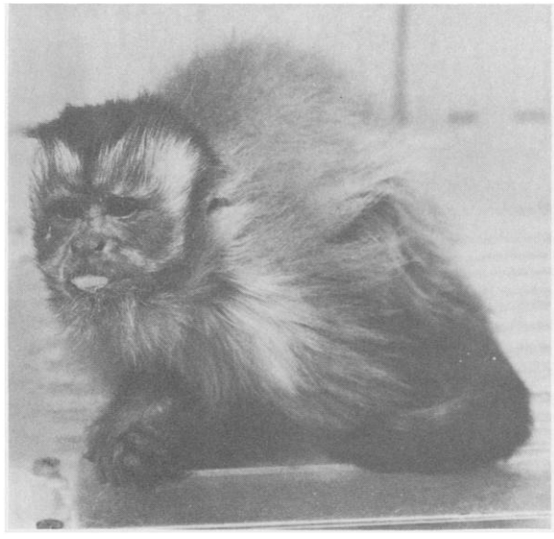

Fig. 2. Monkey 42 after the 90th weekly dose of haloperidol (0.5 mg/kg). During this episode the animal grimaced, yawned, twisted into unusual postures, and, as shown, protruded its tongue as it made incipient chewing movements. Note the slight ptosis of the left eyelid and the peculiar clasped position of the front paws.

times can be treated only by reinstituting drug therapy (*5*).

Since drug-induced movement disorders represent a vexing practical problem (*6*), seem to be related to neurologic diseases such as parkinsonism and Huntington's chorea (*3, 7*), and may provide a basis for understanding the neuropharmacology of movement (*8*), numerous animal models have been proposed and examined. Most such models are based on typical laboratory species such as rodents (*9*). Nonhuman primates, however, seem more accurately to simulate the human syndrome (*10*).

Recently, a dyskinetic syndrome was found (*11*) to occur in New World primates treated with haloperidol, a prominent antipsychotic agent. After several months of being given haloperidol on 5 days per week, both cebus (*Cebus apella* and *C. albifrons*) and squirrel (*Saimiri sciurea*) monkeys exhibited striking dyskinetic episodes after each dose of the drug. Such episodes encompassed limb, trunk, and oral movements and aberrant postures. One of the most provocative findings was an enduring sensitivity to the drug. Even after a drug-free hiatus of 508 days, a single administration of haloperidol triggered a dyskinetic episode as intense as the episodes that earlier had required 6 months to induce. That finding, coupled with our observation (*12*) that low doses of haloperidol administered weekly to squirrel monkeys occasionally produced peculiarities of movement, led us to undertake the present experiment.

Two cebus monkeys (*C. albifrons*) served as the first subjects. Both had served previously as control animals (*11*), receiving only the vehicle (fruit drink). Each had received a single intramuscular injection of haloperidol (1.0 mg/kg) more than a year earlier. Weekly doses began with 0.25 mg (per kilogram of body weight) of haloperidol (Haldol elixir, McNeil) in 10 ml of fruit drink, a quantity consumed in a few minutes. For the first 9 weeks of treatment we detected no significant effects of drug consumption. The tenth weekly dose, however, evoked a striking spectrum of reactions that recurred episodically 1 to 8 hours after drug consumption. We observed flailing of the arms, limb tremors, bizarre postures, and oral manifestions such as lip-smacking, yawning, salivation, and biting (Fig. 1). One monkey was filmed during a typical episode on week 11. A 7-minute segment of the film was selected for time sampling. Every 15 seconds the observer noted the prevailing reaction (or reactions) and obtained the following frequencies: tongue and perioral movements, 9; trunk movements, 11; extremity movements, 7; twitching, crouching, and writhing, 17 (*13*). These dyskinetic episodes decreased in frequency and intensity after 2 weeks, to be replaced mainly by sedation after the drug was ingested. Six weeks after the first appearance of these reactions, we raised the weekly dose to 0.5 mg/kg. The original phenomena appeared in exacerbated form. As drug administration continued, the repertoire of reactions broadened to include rocking movements, vocalization, repetitive circling, and occasional periods of violent movements during which the animal crashed into the cage walls [see (*11*)]. These reactions continue unabated after each of more than 100 weekly treatments with haloperidol (Fig. 2).

A third cebus monkey had undergone a year of drug treatment (5 days per week; 0.25 mg/kg) without overt consequences. It was then assigned to a weekly regimen of 0.5 mg/kg. Two hours after the second weekly dose, it began to writhe on the cage floor, to salivate profusely, and to perform mouth movements. These reactions persisted for over 7 hours. A similar sequence appeared after each dose for the next 7 weeks. Profound sedation prevailed after each dose for the next 23 weeks, until the monkey died of undetermined causes.

A squirrel monkey that received 0.5 mg/kg weekly failed to display any significant consequences after 7 weeks. During the next 2 months it consumed the fruit drink only sporadically. We then discovered that the haloperidol was readily ingested when administered in a banana, and dosing resumed. The second, third, and fourth weekly doses caused sedation and huddling. After the fifth treatment, the monkey crouched on its perch, its limbs trembling, for 5 hours; the sixth dose produced sedation; the seventh dose, and each dose thereafter, evoked a pattern of behavior that includes eye blinking, writhing motions of the trunk and limbs, bizarre postures dominated by standing or walking on three legs, and repetitive circling. Such responses, which were also described earlier (*11*), have been observed after every dose administered during the last ten months.

These observations demonstrate that intermittent administration of haloperidol can induce movement disorders in nonhuman primates. Such disorders are frequently explained by effects attributed to dopamine in extrapyramidal dysfunction. Processes impairing dopaminergic function are believed to foster parkinsonism. Processes amplifying dopaminergic function are believed to promote tardive dyskinesias (*14*). Impairment can progress to facilitation, a progression observed with haloperidol and phenothiazines if, for example, extended receptor blockade induces receptor supersensitivity (*4*) and concurrently increases the rate of dopamine synthesis (*3*). Our results could well be the outcome of just such a joint process. A further explanation of the process might be obtained by experiments with dopamine agonists and antagonists and other compounds. An animal model of this kind might be used to predict the potential of new therapeutic agents to produce movement disorders.

The mechanisms underlying these results warrant further exploration not only because they might reveal the etiology of tardive dyskinesias or other neurolog-

ical disorders arising from disrupted neuropharmacologic function, but also because they might represent an unrecognized therapeutic problem. With the current tendency to shift patients in and out of institutional settings at frequent intervals, and with neuroleptic drug treatment often paralleling such a cycle, clinicians unwittingly may produce effects resembling those reported here, then treat them by raising the dose or adding additional drugs.

BERNARD WEISS
SHIRLEY SANTELLI
*Department of Radiation Biology and Biophysics* and *Environmental Health Sciences Center, University of Rochester Medical Center, Rochester, New York 14642*

### References and Notes

1. Polypharmacy is among the worst problems. See S. Merlis, V. Beyel, D. Fiorentino, J. Fracchia, C. Sheppard, *Curr. Psychiatr. Ther.* **12**, 89 (1972); L. Hollister, *N. Engl. J. Med.* **286**, 984 (1972); D. Greenblatt and R. I. Shader, *Am. J. Psychiatry* **127** (10), 33 (1971).
2. D. X. Freedman, *Arch. Gen. Psychiatry* **28**, 463 (1973). This represents a statement by a task force appointed by the American College of Neuropsychopharmacology.
3. T. N. Chase, in *Neurotransmitters, Research Publications of the Association for Research in Nervous and Mental Disease* (Williams & Wilkins, Baltimore, 1972), pp. 448–471.
4. A. J. Friedhoff, *Compr. Psychiatry* **18**, 309 (1977).
5. R. J. Baldessarini, *Can. Psychiatr. Assoc. J.* **19**, 551 (1974).
6. G. E. Crane, *Science* **181**, 124 (1973).
7. ———, *Adv. Neurol.* **1**, 115 (1973).
8. H. Bernheimer and O. Hornykiewicz, *ibid.*, p. 152.
9. H. L. Klawans, Jr. and R. Rubovits, *J. Neural Transm.* **33**, 235 (1972).
10. G. A. Deneau and G. E. Crane, in *Psychotropic Drugs and Dysfunctions of the Basal Ganglia. A Multidisciplinary Workshop*, G. E. Crane and R. Gardner, Jr., Eds. (Government Printing Office, Washington, D.C., 1969), p. 12; R. D. Eibergen and K. R. Carlson, *Pharmacol. Biochem. Behav.* **5**, 175 (1976); J. F. Sassin, *Adv. Neurol.* **10**, 47 (197➡ L-M Gunne and S. Bárány, *Psychopharmacologia* **50**, 237 (1976).
11. B. Weiss, in *Alcohol, Drugs and Brain Damage*, J. G. Rankin, Ed. (Addiction Research Foundation of Ontario, Toronto, 1975), p. 71; B. Weiss, S. Santelli, G. Lusink, *Psychopharmacologia* **53**, 289 (1977).
12. W. Sette, thesis, University of Rochester (1976).
13. These categories are derived from the Abnormal Involuntary Movement Scale of the National Institute of Mental Health. They represent only illustrative data for one episode. A more detailed, comprehensive assessment is needed, especially one based less on subjective clinical criteria.
14. D. Tarsy and R. J. Baldessarini, *Biol. Psychiatry* **12**, 431 (1977). These authors list an extensive bibliography on the subject. It incorporates the literature on tardive dyskinesias dealing with incidence, neurochemistry, and therapy. See, also, H. L. Klawans, Jr., *Am. J. Psychiatry* **130**, 82 (1973).
15. Supported in part by grants ES-01247 from the National Institute of Environmental Health Sciences, MH-11752 from the National Institute of Mental Health, and by a contract with the U.S. Department of Energy at the University of Rochester (Report No. UR-3490-1258). We thank I. Shoulson for many helpful suggestions.

13 October 1977; revised 24 January 1978

## Reading Disability: Methodological Problems in Information-Processing Analysis

Morrison *et al.* (*1*) present data which they claim indicate that poor readers have a deficit in transferring information from "visual information storage" to "short term storage." Using tachistoscopic presentation, the authors displayed a circular array of a set of eight stimuli (letters, geometric shapes, or abstract shapes). After a variable delay interval of 0 to 2000 msec, a pointer was briefly flashed in one of the eight positions that corresponded with those in the target array. A fixation point preceded the target array and returned after the pointer presentation. Subjects, good and poor readers, were asked to fixate the point and to indicate which stimulus had appeared in the pointer position by selecting the appropriate stimulus from a response card. Correct responses declined for both groups as a function of target array–pointer interval for all three sets of stimuli. Good and poor readers performed about the same for target-pointer intervals of 0 to 300 msec. At intervals of 300 to 2000 msec the poor readers performed consistently worse than the good readers. The authors suggest that memory, rather than perceptual, processes play a role in reading disability.

Three features of the experiment make interpretation difficult:

1) The authors do not report ascertaining eye position before, during, or after target-pointer presentation. Furthermore, the fixation point was apparently not displayed in the interval between the presentation of the target array and the pointer. If the subject's eyes were not in the same position during presentation of the pointer as during presentation of the target array, then detection of the pointer itself, as well as perception of pointer position relative to the target array, would be difficult. Failure to determine eye fixation points at the time of both target and pointer presentation makes it possible that differences in data for the two groups may be caused by differences in ability to maintain constant eye position on a blank visual field for target-pointer intervals of greater than 300 msec.

2) It is not clear whether only one target array card was used throughout the 80 trials for each stimulus set. If only one card was used, some learning of stimulus position on the target array would be expected. The greater the learning of the position of each stimulus element in the array, the less the subject need rely on each presentation of the array in selecting the correct array element indicated by the pointer position; correct responses may no longer reflect short-term visual information storage.

3) No information is provided about the order in which delay intervals were tested over the 80 trials. If the sequence of delay intervals over each set of 80 trials was not randomized or counterbalanced, then delay interval was confounded with the cumulative effects of repeated presentation of the same target array.

STEPHEN ROTHENBERG
KAREN GROSS
*Department of Psychology, McLean Hospital, Belmont Massachusetts 02178* and *Department of Psychiatry, Harvard Medical School, Boston, Massachusetts 02115*

### References

1. F. J. Morrison, B. Giordani, J. Nagy, *Science* **196**, 77 (1977).

6 April 1977; revised 14 September 1977

Morrison *et al.* (*1*) drew two major conclusions from their study of good and poor readers: (i) the basic deficits of poor readers may be related to memory skills rather than to the perception of written symbols, and (ii) this memory deficit affects the poor reader's ability to process not only linguistic but nonlinguistic information. The second claim contradicts the results of several studies (*2*, *3*) in which the poor reader's memory was found to be inferior on tasks employing linguistic stimuli, but equal to that of good readers in tests on nonlinguistic materials.

This apparent contradiction might be caused by the choice of nonlinguistic stimuli used by Morrison *et al.* Many of the "abstract" forms, which they presume to be relatively free from linguistic mediation, probably could not be perceived by sixth graders without some form of labeling. Several of them closely resemble familiar objects (a cup, a flying bird, a cross, a dagger, and so forth). Even if that were not the case, the distinctive configurations of the forms should encourage a strategy of singling out in each a particular labelable characteristic, which could then be sought out on the response card. A set of more nearly nonlabelable stimuli, such as Kimura's nonsense designs (*4*), would be


0036-8075/78/0519-0801$00.50/0 