7. This ionophore carries divalent rather than monovalent cations across membranes, probably as a cation-ionophore complex [P. W. Reed and H. A. Lardy, *J. Biol. Chem.* **247**, 6970 (1972); D. T. Wong, J. R. Wilkinson, R. L. Hamill, J. S. Horig, *Arch. Biochem. Biophys.* **156**, 578 (1973); G. D. Case, J. M. Vanderkooi, A. Scarpa, *ibid.* **162**, 174 (1974)]. I thank R. Hamill (Eli Lilly and Co.) for supplying the ionophore.
8. R. D. Feinman and T. C. Detweiler *Nature (Lond.)* **249**, 172 (1974); M. Kogayama and W. W. Douglas, *J. Cell Biol.* **62**, 519 (1974); T. C. Schroeder and D. L. Strickland, *Exp. Cell Res.* **83**, 139 (1974). M. F. J. Holwill and J. L. McGregor [*Nature (Lond.)* **255**, 157 (1975)] suggest that the direction of flagellar wave propagation in *Crithidia* may be controlled by Ca^{2+}, since the majority of organisms propagate waves in a reverse direction in the presence of Ca^{2+} and ionophore.
9. P. Satir, *J. Cell Biol.* **18**, 345 (1963).
10. F. R. Hayes and D. Pellvet, *J. Mar. Biol. Assoc. U.K.* **26**, 580 (1947).
11. I thank P. Setzer for expert technical assistance. Supported by PHS grant HL13849 and the University of California Committee on Research.

26 June 1975

Dyskinesias Elicited by Methamphetamine: Susceptibility of Former Methadone-Consuming Monkeys

Abstract. *Rhesus monkeys with a history of drinking methadone but currently drug-free and control monkeys with no drug history were injected with methamphetamine hydrochloride (2 to 5 milligrams per kilogram of body weight). In six of seven monkeys which had consumed methadone the lowest dose immediately elicited pronounced oral dyskinesias virtually identical to those of human tardive dyskinesia. The control monkeys did not exhibit oral dyskinesias even after prolonged treatment with the highest dose. The clinical implications may be related to the functioning of brain dopaminergic systems.*

The use of methadone hydrochloride in maintenance regimens of former heroin abusers is now firmly established (*1*). Daily oral administration of methadone prevents craving for other narcotic drugs but leaves untouched the potential for abuse of nonnarcotic drugs. Urinalysis of patients taking methadone often reveals significant use of barbiturates and amphetamines (*2*). Chronic use of methadone combined with abuse of nonnarcotic drugs represents a potentially serious but well-recognized clinical problem. Less attention has been directed toward altered sensitivity to a drug after chronic administration of another drug has ceased. We have found that monkeys with a history of oral methadone self-administration are highly sensitive to methamphetamine administered long after methadone treatment was terminated.

Amphetamines elicit repetitive stereotyped movements in many species, including man (*3*). Ellinwood (*4*) has described, for the monkey, development of various stereotyped behaviors during long-term intoxication with methamphetamine hydrochloride (MA). Low and moderate doses (2 to 10 mg/kg) initially produce biting and chewing, searching motions, grooming, picking at the skin, and hand examining. After several months of intoxication, higher doses (10 to 20 mg/kg) elicit a more intense form of stereotyped behavior, buccolingual dyskinesias. These are virtually identical to the oral behaviors seen in tardive dyskinesia in humans and consist of repetitive mouth movements such as tongue protrusion and rolling, wide opening of the mouth, and lateral jaw displacement.

In the present study, seven male rhesus monkeys had previously drunk sub-dependence-producing doses of methadone hydrochloride once daily, for varying periods of time determined by their participation in discrimination learning experiments (*5*). Their methadone histories and duration of subsequent drug-free period are summarized in Table 1. A control group of seven males, similar in age, had never received any narcotic or amphetamine.

We administered daily intramuscular injections of MA (50 mg/ml) on a cyclic schedule of four injection days followed by three rest days (mimicking human "spree" abuse), for up to 12 weeks. Each monkey's dosage was gradually increased within the range specified in Table 2. All monkeys were observed periodically for a minimum of 6 hours after injection in their home cages on all injection days. In addition, on at least one injection day every monkey was observed continuously for 6 hours after injection in another room, where video tape recordings of representative behaviors were made.

Both experimenters independently assessed the behavioral response to MA. Although we knew each monkey's drug history, the presence or absence of criterion oral behaviors was so obvious as to minimize observational bias. These behaviors were (i) tongue protrusion, (ii) widely open mouth with lateral jaw displacement, (iii) widely open mouth with tongue rotation inside cheek, (iv) sucking the inside of cheek, (v) copious salivation probably resulting from the above movements, and (vi) expulsion of air from lungs with a loud frog-like sound. In addition, we required a criterion behavior to persist for a minimum of 4 hours after injection to be considered a dyskinesia. Lip smacking and rapid chewing or teeth-chattering movements, which are characteristic of nondrugged monkeys and are frequently elicited by low doses of MA, were not considered evidence of buccolingual dyskinesia.

Table 1. Drug history of monkeys that had been treated with methadone. Subjects are arranged in order of decreasing sensitivity to methamphetamine.

Subject	Methadone		Drug-free period (months)
	Dose (mg/kg)	Duration (months)	
M1	2.5	10	2
M2	2.0	10	2
M3	1.5	22	6
M4	3.0	12	5
M5	3.0	10	2
M6	1.0	12	17
M7	2.5	10	2

Pronounced buccolingual dyskinesias were elicited almost immediately in six of the former methadone-consuming monkeys by an MA dose of only 2.0 mg/kg. Four monkeys were affected on the very first day on which that dose was administered, and only four injection days were required for the others to develop dyskinesias. The oral dyskinesias occurred at a rate of 25 to 60 per minute. Subsequent injections of MA continued to elicit dyskinesias in these monkeys; several were tested 30 to 40 times, and the same oral behaviors were elicited on each occasion. Increasing the MA dosage prolonged the effect; at 2.0 mg/kg, dyskinesias were obvious 36 hours after injection, whereas at 4.0 mg/kg they were observed for as long as 72 hours. The monkeys did not seem to be distressed by their oral behaviors and gave no appearance of greater hyperactivity or arousal than control monkeys.

Conversely, doses of 2.0 mg/kg did not produce dyskinesias in any of the control animals, nor did these behaviors develop after lengthy treatment with doses up to 5.0 mg/kg. Some of the control monkeys would probably have exhibited oral dyskinesias eventually had we given them higher (10 to 20 mg/kg) doses (*4*). Some oral behaviors were elicited in three control monkeys late in the intoxication schedule (*6*); however, they were mild chewing movements that persisted for only 15 to 30 minutes, at which time they were replaced by other stereotyped behavior peculiar to each monkey.

Tardive dyskinesia in humans is manifested not only in the oral behaviors discussed but throughout the musculature, for example, in peculiar limb movements and abnormal postures (*7*). Three of the monkeys showing buccolingual dyskinesias also exhibited choreiform limb movements after 1 to 2 days at 2.0 mg/kg. This behavior consisted of rhythmic flailing of the up-

per and lower limbs when the monkey was in a sitting or reclining position. In the control monkeys, choreiform movements did not appear at that dose (*8*).

It is not surprising that one former methadone-consuming monkey did not exhibit oral dyskinesias, given the wide range of possible stereotyped behaviors and the fact that not every normal monkey progresses to oral dyskinesias during chronic MA intoxication (*4*). Further, drugs that can produce tardive dyskinesias in humans are by no means universally effective in producing these symptoms (*7*).

The delayed interaction indicates that continual methadone consumption can effect a long-lasting change in brain function. This alteration is manifested in MA-elicited symptoms virtually identical in form, intensity, and frequency to those of tardive dyskinesia produced by lengthy use and withdrawal of neuroleptic agents (such as phenothiazines and butyrophenones) in humans (*7*) and in rhesus monkeys (*9*). Moreover, as has been described in humans (*7*) stress can exacerbate dyskinesias in these monkeys; for example, a sudden loud noise temporarily increases the frequency of their oral behaviors.

Although we are not aware of any such reports, our data suggest that methadone-maintenance patients might be highly sensitive to the effects of amphetamines taken after methadone is withdrawn. In addition, the use and withdrawal of methadone itself might result in the spontaneous appearance of oral dyskinesias, particularly in patients of advanced age, who are most susceptible to dyskinesias induced by neuroleptic agents (*7*), or in patients with a long history of high-dose methadone treatment. Although our monkeys exhibited no spontaneous dyskinesias during methadone administration or thereafter, they were clearly predisposed to the elicitation of dyskinesias by MA. The monkeys' methadone doses were functionally much lower than those employed in methadone-maintenance programs, however, as evidenced by the absence of abstinence symptoms to naloxone challenge and during abrupt drug withdrawal. Thus, it is possible that human patients, maintained at higher methadone doses, might be susceptible to the spontaneous appearance of dyskinesias in addition to possibly being hypersensitive to the effects of amphetamines.

We suggest that the delayed interaction of methadone with MA, which produces symptoms of tardive dyskinesia similar to that which often follow therapy with neuroleptic agents, may be explicable in terms of known effects of these drugs on brain dopaminergic systems. Fog *et al.* suggest that amphetamine causes the release of the neurotransmitter dopamine in the striatum, where consequent receptor activation produces stereotyped behaviors (*10*). It is possible for the striatal receptors to become supersensitive to the release of dopamine. For example, destruction of dopaminergic cell bodies results in a lack of normal dopamine activation of receptor sites in the striatum; after a period of such inactivation, the receptors become supersensitive—less dopamine is then required to activate the receptors (*11*). Inactivation of dopamine receptors may also result from chronic chemical blocking of the receptors by the phenothiazine or butyrophenone neuroleptic drugs (*12*). When long-term treatment with these drugs is halted or the dosage reduced, normal amounts of dopamine are thought to activate supersensitive receptors, producing the symptoms of tardive dyskinesia (*7*). Similarly, the striatal receptors that mediate stereotyped behaviors can become supersensitive to the release of dopamine caused by amphetamine. For example, when animals are treated over a long term with the phenothiazine chlorpromazine (which blocks dopamine receptors), an enhanced sensitivity to amphetamine develops; after cessation of chlorpromazine treatment, less amphetamine is required to produce stereotyped behaviors (*13*). Moreover, a supersensitivity to apomorphine, a direct dopaminergic receptor activator (*14*), develops following cessation of long-term neuroleptic treatment (*15*).

Methadone, too, is known to block dopamine receptors (*16*). Our study strongly implies that chronic blockage leads to the development of receptor supersensitivity, since we found that prior methadone treatment produced a marked decrease in the dose and number of days of MA intoxication required to produce buccolingual dyskinesias in the rhesus monkey. In addition, we have found that long-term methadone treatment enhances sensitivity to subsequent MA administration in the guinea pig. In animals that had been treated with methadone, less MA is required to produce stereotyped behavior, and a low dose of MA induces more open-field activity (*17*). We suggest, therefore, that the oral dyskinesias resulted from MA-induced stimulation of striatal receptors which had been made supersensitive by long-term methadone administration.

Table 2. Results of methamphetamine administration. Subjects M1 through M7 are former methadone-consuming monkeys, and subjects C1 through C7 are control monkeys. Doses of methamphetamine are specified in column 2. The presence or absence (+ or 0) of oral dyskinesias (Dys) is indicated in the third column. For subjects exhibiting oral dyskinesias, column 4 (Day) indicates the day of injection (2.0 mg/kg) on which the dyskinesias were first observed. For the other subjects, column 4 indicates the total number of injection days covering dosage range specified in column 2.

Subject	Dose (mg/kg)	Dys	Day	Principal behaviors
M1	2.0	+	1	Tongue rolling, choreiform limb movements
M2	2.0	+	1	Tongue rolling
M3	2.0	+	1	Jaw displacement, frog sound, choreiform limb movements
M4	1.0 → 2.0	+	1	Sucking and blowing out cheek
M5	2.0	+	4	Wide mouth opening, choreiform limb movements
M6	0.5 → 2.0	+	4	Tongue protrusion
M7	2.0 → 7.5	0	57	Lip and hand grooming, chewing movements
C1	1.0 → 2.0	0	8	Chewing movements
C2	1.0 → 2.0	0	8	Body jerk
C3	2.0 → 5.0	0	31	Shuffling movements
C4	2.0 → 5.0	0	45	Body jerk
C5	2.0 → 5.0	0	40	Facial grimace*, writhing
C6	2.0 → 5.0	0	40	Biting finger, vocalization
C7	2.0 → 5.0	0	44	Body jerk

*Although this behavior may be seen occasionally in human tardive dyskinesia, it was not considered a dyskinesia for this monkey, inasmuch as the same behavior was observed prior to methamphetamine administration. No other monkey displayed behaviors resembling dyskinesias before being given the drug.

ROBERT D. EIBERGEN*
Psychobiology Program, Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania 15261
KRISTIN R. CARLSON
Department of Pharmacology, School of Medicine, University of Pittsburgh

References and Notes

1. V. P. Dole and M. E. Nyswander. *J. Am. Med. Assoc.* **193**, 80 (1965); ———, A. Warner, *ibid.* **206**, 2708 (1968).
2. C. D. Chambers and W. J. R. Taylor, in *Methadone Experiences and Issues*, C. D. Chambers and L. Brill, Eds. (Behavioral Publications, New York, 1973), pp. 121–129; ———, P. V. Walter, *ibid.*, pp. 203–213.
3. A. Randrup and I. Munkvad, *Psychopharmacologia* **11**, 300 (1967).
4. E. H. Ellinwood, *Biol. Psychiatr.* **3**, 25 (1970).
5. K. R. Carlson and M. Pavsek, *Physiol. Psychol.* **2**, 383 (1974); ———, F. Agisim, J. Teplitz, in preparation.
6. These behaviors occurred in subjects C4, C5, and C6 on days 33, 29, and 31, respectively, of MA administration when they had been receiving 5.0 mg/kg for several weeks.
7. G. E. Crane, *Science* **181**, 124 (1973); H. L. Klawans, *Am. J. Psychiatry* **130**, 82 (1973); J. Gerlach, N. Reisberg, A. Randrup, *Psychopharmacologia* **34**, 21 (1974).
8. A 15- to 30-minute episode of mild choreiform limb movements was observed in subjects C6 and C7 on days 31 and 35, respectively, of MA administration when they had been receiving 5.0 mg/kg for several weeks.

9. F. S. Messiha, *Arch. Int. Pharmacodyn. Ther.* **209**, 5 (1974); G. W. Paulson, *Adv. Neurol.* **1**, 647 (1973).
10. R. L. Fog, A. Randrup, H. Pakkenberg, *Psychopharmacologia* **10**, 179 (1967).
11. U. Ungerstedt, *Acta Physiol. Scand. Suppl.* **367**, 69 (1971).
12. A. Carlsson and M. Lindqvist, *Acta Pharmacol. Toxicol.* **20**, 140 (1963); H. Corrodi, K. Fuxe, T. Hokfelt, *Life Sci.* **6**, 767 (19[illegible] N.-E. Anden, S. C. Butcher, H. Corrodi, K. Fuxe, U. Ungerstedt, *Eur. J. Pharmacol.* **11**, 303 (1970).
13. R. Rubovits, B. C. Patel, H. L. Klawans, *Adv. Neurol.* **1**, 671 (1973).
14. N.-E. Anden, A. Rubenson, K. Fuxe, T. Hokfelt, *J. Pharm. Pharmacol.* **19**, 627 (1967); B. Ross, *ibid.* **21**, 263 (1969).
D. Tarsy and R. J. Baldessarini, *Neuropharmacology* **13**, 927 (1974).
16. H. A. Sasame, J. Perez-Cruet, G. Di Chiara, A. Tagliamonte, P. Tagliamonte, G. L. Gessa, *J. Neurochem.* **19**, 1953 (1972); L. Ahtee and I. Kaariainen, *Eur. J. Pharmacol.* **22**, 206 (1973).
17. R. D. Eibergen and K. R. Carlson, in preparation.
18. Supported in part by PHS grant MH20121 to K.R.C. We thank J. Petruzzi for assistance.
* Present address: Department of Psychiatry, Duke University Medical Center, Durham, N.C. 27704.

7 February 1975; revised 24 June 1975

Blockade of Morphine Abstinence by Δ^9-Tetrahydrocannabinol

Hine *et al.* (*1*) reported that Δ^9-*trans*-tetrahydrocannabinol (THC) suppresses certain symptoms of naloxone-precipitated morphine abstinence in rats. However, the title of their report, "Morphine-dependent rats: Blockade of precipitated abstinence by tetrahydrocannabinol," is quite misleading since three important abstinence signs, including ear blanching, ptosis, and vocalization, were not significantly reduced even by the highest dose of THC (two were induced by THC alone). Thus, the most that can be claimed is that THC reduced two of the symptoms of precipitated abstinence, wet shakes and defecation.

At the doses of THC that were effective in suppressing abstinence symptoms in the study, THC has a substantial sedative effect (*2*) (although the authors state that doses of 5 mg/kg or less did not produce sedation in their rats). It is not surprising that THC might suppress a variety of behavioral symptoms of precipitated abstinence because of its general sedative properties. Unfortunately, the study failed to include controls that were treated with other sedative drugs such as benzodiazepines or barbiturates, which do not exhibit cross dependence with narcotics. It is possible that these drugs would be as effective as THC in suppressing certain signs of precipitated abstinence.

Finally, the authors propose that their data suggest that further exploration of the therapeutic utility of THC in narcotic detoxification is warranted. They argue that THC, if it were effective in suppressing abstinence signs, would be preferred to drugs such as methadone since the latter produces physical dependence, while the former does not. However, the doses of THC required for effective suppression of abstinence symptoms in their study, 5 to 10 mg/kg, were far beyond the range of doses required to produce intoxication in human subjects (about 0.02 mg/kg) (*3*). I am not familiar with any other reports of doses in this range administered to human subjects. If such extremely high doses of THC are required to suppress abstinence signs in humans, there is no strong reason to believe that THC would be desirable as an agent for detoxification.

BROOKS CARDER
Department of Psychology,
University of California,
Los Angeles, California 90024

References and Notes

1. B. Hine, E. Friedman, M. Torrelio, S. Gershon, *Science* **187**, 443 (1975).
2. E. F. Domino, *Ann. N.Y. Acad. Sci.* **191**, 166 (1971); W. G. Drew, L. L. Miller, A. Wikler, *Psychopharmacologia* **23**, 289 (1972).
3. M. Perez-Reyes, M. C. Timmons, M. A. Lipton, K. H. Davis, M. E. Wall, *Science* **177**, 633 (1972).
4. Supported by PHS grant DA 00288.

21 February 1975; revised 25 July 1975

The only agents capable of specifically suppressing all components of a narcotic abstinence syndrome are opiates or their derivatives (*1*). At sedative doses, barbiturates may not block or even attenuate narcotic abstinence signs in humans (*2*) or rodents (*3*). Benzodiazepines, clinically effective in controlling seizure activity (*4*), also do not suppress all abstinence signs when used to treat neonatal or adolescent narcotic withdrawal (*5*), notwithstanding evidence of effective suppression by low doses of benzodiazepines of naloxone-induced jumping in morphine-pelleted mice (*6*). Thus, the question of which abstinence signs in animals dependent on narcotics are most "important" is a complex one which cannot be easily answered.

The purpose of our report was to determine the effect of pharmacologically active doses of Δ^9-*trans*-tetrahydrocannabinol (THC) in the rat on nine (by no means exhaustive) components of a precipitated abstinence syndrome in this species. When abstinence scores for each animal were determined from the total number of the nine signs present, the data clearly indicated a THC dose-dependent decrease in number of signs displayed, statistically significant at doses of 2 mg per kilogram of body weight and at higher doses. Moreover, wet shakes, one abstinence sign in the rat elicited at moderate (*7*) to high (*8*) degrees of dependence only with high naloxone doses (*8*), was the sign most affected by THC. Our conservative statistical presentation did not emphasize the fact that, even at 1 mg/kg (the lowest dose used), prior treatment with THC resulted in significantly ($P = .048$, one-tailed Fisher test) fewer rats exhibiting wet shakes compared to control animals. Frequencies of occurrence of two other signs (not one, as Carder suggests), presence of diarrhea at 30 minutes and an elevated fecal bolus count at 15 minutes, were also significantly reduced—to zero in some cases.

Finally, there are two problems with Carder's extrapolation of appropriate THC doses for humans and rodents on a milligram per kilogram basis. There is at least a tenfold difference in doses required for psychopharmacological effects in these species, attributable, in part, to differences in absorption and distribution with different routes of administration. This difference is illustrated in acute toxicity studies in the rat and mouse by a median lethal dose (MLD) after intraperitoneal administration that is 10 to 13 times higher than the MLD after intravenous administration (*9*), since most of the drug remains at the injection site after intraperitoneal injection and relatively little enters the brain or is converted to active metabolites (*10*). Second, 0.02 mg/kg was the approximate average intravenous dose at which autonomic and subjective effects of THC were first perceived by the subjects of the study cited in Carder's reference 3, whereas "intoxicating" human doses generally range from 100 to 250 μg/kg for the inhalation route (*11*). This route is at least as effective as the intravenous one for producing psychoactive and toxic effects (*12*), although impaired performance on some cognitive tasks may not occur even at these doses (*13*). Thus, doses of THC found effective in our study are within a reasonable range for extrapolation to clinical use.

B. HINE
E. FRIEDMAN
M. TORRELIO
S. GERSHON
Neuropsychopharmacology Research Unit, Department of Psychiatry,
New York University School of Medicine,
New York 10016

References

1. H. F. Fraser, *Annu. Rev. Med.* **8**, 430 (1957); H. O. J. Collier, D. L. Francis, C. Schneider, *Nature (Lond.)* **237**, 220 (1972).
2. C. K. Himmelsbach and H. L. Andrews, *J. Pharmacol. Exp. Ther.* **77**, 17 (1943); R. W. Cobrinik, R. T. Hood, E. Chusid, *Pediatrics* **24**, 288 (1959).
3. E. L. Way, H. H. Loh, F. Shen, *J. Pharmacol. Exp. Ther.* **167**, 1 (1969); E. Wei, *Life Sci.* **12**, 385 (1973).
4. W. Schalleck, W. Schlosser, L. O. Randall, *Adv. Pharmacol.* **10**, 120 (1972).
5. I. F. Litt, A. S. Colli, M. I. Cohen, *J. Pediatr.* **78**,