Exp. Ther. **179**, 284 (1971); R. F. Ritzmann and B. Tabakoff, *ibid.* **199**, 158 (1976).
16. M. D. Hammond and C. Schneider, *Br. J. Pharmacol.* **47**, 667P (1973).
17. As judged by a qualified veterinarian using subjective gross observation, slight inflammation was noted 1 day after implantation of either ethanol- or saline-filled SERT's, perhaps because of the destruction of tissue by the probe. The inflammation disappeared by the second day. Fourteen days was the maximum time the SERT's were tested in any one mouse.
18. Weight loss for 12 mice given free access to laboratory chow and water averaged 6.8 percent after 7 days of exposure to ethanol-filled SERT's plus twice-daily intraperitoneal injections. However, a group of control mice (no incisions, no injections) in individual cages showed the same weight loss (mean 6.5 percent) 7 days later.
19. A. E. LeBlanc, *Can. J. Physiol. Pharmacol.* **46**, 665 (1968).
20. We thank P. Lange of Dow Corning for a generous supply of Silastic tubing. The work was supported by research grant AA 01417 (to C.K.E.) from the Department of Health, Education and Welfare.
* Present address: College of Pharmacy, University of Texas at Austin, Austin 78712.

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Δ^9-Tetrahydrocannabinol: Antiaggressive Effects in Mice, Rats, and Squirrel Monkeys

Abstract. *Δ^9-Tetrahydrocannabinol, the most active constituent of marihuana, decreased species-specific attack behavior in mice, rats, and squirrel monkeys at doses (0.25 to 2.0 milligram per kilogram of body weight) that have no effects on other elements of the behavioral repertoire. Aggressive behavior was engendered in all three species by confronting a resident animal with an intruder conspecific. The present results contrast with the widely held belief that marihuana increases aggressive behavior.*

The link between cannabis and violence goes back at least to the anecdote that fanatic members of a medieval Ismaili sect, called the Assassins (*hashshashin* in Arabic), drank hashish before slaying Crusaders. Contrary to folklore and historical anecdotes, many experimental studies show that acute administration of cannabis extracts of Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, reduces aggressive behavior in a variety of situations and animal species (*1*). Yet, the large doses required to decrease such behavior in many of these studies raise the question as to how specific this effect is to aggressive behavior. Moreover, under certain experimental conditions, acute administration of THC or cannabis extract is reported to induce indiscriminate biting and bizarre postures in rats, incorrectly referred to as "aggressiveness" (*2*).

Conclusions from laboratory studies on the effects of THC on aggressive behavior in animals have been limited not only because of high doses, but also because of the large variations in test conditions and in behavior patterns which are considered as "aggression." In the present investigation, aggressive behavior was engendered in mice, rats, and squirrel monkeys by the same experimental manipulations; namely, a stranger animal intrudes into the home cage of a conspecific or a group of conspecifics. Fighting between resident and intruder animals has wide species generality (*3*), and results in intense aggressive behavior including neck bites, attack leaps, threat displays, and defensive, submissive, and flight reactions in the three species studied. Concurrent monitoring of agonistic as well as nonagonistic behavioral elements provides information on which elements of the behavioral repertoire are primarily altered by THC. The present experiments demonstrate that THC, in doses that produce marihuana-like effects in humans, specifically and selectively decreases aggressive behavior in mice, rats, and squirrel monkeys subjected to similar experimental conditions.

In the first series of experiments, male Swiss-Webster albino mice (Zivic-Miller Laboratories, Pittsburgh) were housed individually in Plexiglas cages (28 by 18 by 13 cm) with free access to food and water. After 4 to 6 weeks of individual housing, each resident mouse was confronted in the home cage with an intruder mouse. Intruder mice were housed in groups of five. Resident mice that reliably attacked the intruding mouse during at least three consecutive 5-minute tests without drug were assigned to receive THC (*4*). The THC was injected intraperitoneally once a week in the resident mice ($N = 15$) and, on a second weekly test day, in the intruder mice ($N = 15$). The same resident and intruder mice confronted each other throughout all THC and vehicle tests. Each resident and intruder mouse received the different doses of THC (0.25, 0.5, 1.0, 2.0, and 4.0 mg per kilogram of body weight) in a systematically varied sequence following a Latin-square design. Tests with vehicle only were conducted before and after those with THC. An intruder test lasted 5 minutes after the first attack and was terminated when no attack occurred within 5 minutes. Videotape recordings of all 180 drug and vehicle encounters were analyzed by two experienced observers, each focusing on either resident or intruder mouse. The observers were unfamiliar with the drug treatment of the animals. Latency, frequency, and duration of 11 reliably occurring acts and postures of agonistic and nonagonistic nature were measured (*5*).

In a second series of experiments, male rats of the Sprague-Dawley strain (Zivic-Miller) which attacked an intruding rat in their Plexiglas home cage (28 by 28 by 38 cm) in three consecutive tests were selected for THC administration. Individually housed resident rats ($N = 8$) and group-housed intruder rats ($N = 10$) were maintained at 90 percent of their free-feeding weight and paired for intruder tests once a week, 1 to 2 hours before the daily feeding. As in the tests with mice, the same pair of resident and intruder rats confronted each other during all drug tests. The frequency and duration of the resident and intruder rats' agonistic and nonagonistic behaviors were measured for 5 minutes after the initial attack as described (*6*). Resident rats were injected intraperitoneally with one of four THC doses (0.125, 0.25, 0.5, and 1.0 mg/kg) and with vehicle on alternating tests; in a separate series of experiments, treatments were scheduled in identical sequence for intruder rats. Each rat was subjected to a random sequence of doses.

In a third series of experiments, an intruder monkey was introduced into two separate indoor free-ranging colonies each comprising two or three adult male squirrel monkeys, three adult females, and one infant (*7*). The resident subdominant monkeys of one colony served as intruders into the adjacent colony. The THC, contained in a slice of banana, was administered to either the resident male monkey ($N = 2$) that had attacked the intruder first and most in preceding drug-free tests, or to the intruder monkey ($N = 2$). Drug was administered to the resident and intruder monkeys on alternate test days once a week. An ascending and descending sequence of THC doses (0.25, 0.5, 1.0, and 2.0 mg/kg) and vehicle tests was repeated in each of the two resident and two intruder monkeys. Three observers, two focusing on the two resident males and one on the intruder, recorded the frequency of 15 clearly identifiable agonistic and nonagonistic acts, postures, and displays (*8*).

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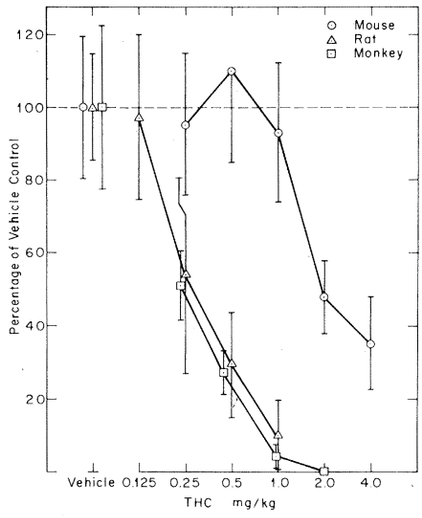

Fig. 1. Effects of THC on attack frequency by resident mice, rats, and squirrel monkeys, expressed as percentage of vehicle control. The 100 percent level refers to the attack frequency during vehicle control tests.

Nonparametric tests of statistical significance were used for analysis because of the heterogeneous distribution of the data (*9*).

In all vehicle control tests, the resident mice, rats, and squirrel monkeys showed intense attack and threat behavior, including attack bites toward the neck and back region of the intruding opponent. There was no significant change in attack frequency during vehicle tests before and after the sequence of THC tests. Administration of THC to the resident animals reduced the frequency of attacks in a dose-dependent manner (Fig. 1). The lowest doses of THC that reliably decreased attacks were 2.0 mg/kg for mice, 0.5 mg/kg for rats, and 0.25 mg/kg for squirrel monkeys. In rats, THC also decreased the frequency of threat behaviors such as offensive sideways postures at the same dose that reduced attack; in squirrel monkeys and mice, however, behavioral elements with threat function such as circling, body straightening, genital display, and tail rattling remained unaffected by THC.

Administration of THC to intruder mice (0.25 to 4.0 mg/kg), rats (0.125 to 1.0 mg/kg), and squirrel monkeys (0.25 to 2.0 mg/kg) did not alter their reactions of defense, submission, and flight when confronted with nontreated attacking resident opponents; the only exception to this general pattern was a small but reliable decrease in the duration of the defensive upright posture shown by intruder rats given the 0.5 mg/kg dose.

Aside from agonistic behavior, resident and intruder animals engage in less intense forms of interactions such as allogrooming and genital investigation as well as self-grooming. Following THC administration, resident rats and mice significantly increased the frequency of grooming and investigating the intruder, but self-grooming was unaffected. When administered to intruder mice, THC decreased autogrooming at all doses.

The drug did not alter locomotor activity in resident and intruder rats and squirrel monkeys in the dose range that effectively reduced attacks. In resident mice, however, THC suppressed locomotion at the same doses (2.0 and 4.0 mg/kg) at which reliable antiaggressive effects were obtained.

Fighting behavior in the resident-intruder situation and under related test conditions is very sensitive to a variety of psychoactive drugs (*10*). Most drugs, including LSD, amphetamine, alcohol, chlordiazepoxide, and morphine, enhance attack behavior at low doses and decrease it at higher doses. The present results show that, unlike these other psychoactive agents, THC reduces attacks even at low doses (0.25 to 2.0 mg/kg).

This pattern of effects agrees with and extends previous evidence suggesting that acutely administered THC or cannabis extract decreases intraspecies aggressive behavior in a variety of animal species (*1*). The attack behavior was decreased by comparatively low THC doses in all three species studied. With a few notable exceptions (*11*), THC doses that produce marihuana-like effects in humans (about 0.2 mg/kg) fail to produce behavioral effects in animals. The fact that the presently observed effects of THC were mostly limited to attack behavior appears to argue against the possibility that the antiaggressive effects of THC are the result of a general depression or incapacitation. Other social interactions such as genital investigation and allogrooming in rats and mice actually increased in frequency at the doses that reduced attacks.

The present results agree with the prevalence of accounts that marihuana does not instigate hostile interactions in humans (*12*). However, human aggression may involve different behavior patterns. Thus, the present results do not necessarily refute accounts of marihuana increasing aggressiveness in humans (*13*).

KLAUS A. MICZEK
Department of Psychology,
Carnegie-Mellon University,
Pittsburgh, Pennsylvania 15213

References and Notes

1. E. L. Abel, *Behav. Biol.* **14**, 1 (1975); *Psychol. Bull.* **84**, 193 (1977); K. A. Miczek, in *Pharmacology of Marihuana*, M. C. Braude and S. Szara, Eds. (Raven, New York, 1976), p. 499; ——— and H. Barry, in *Drug Addiction*, J. Singh and H. Lal, Eds. (Symposia Speciality, Miami, 1974), p. 19; K. A. Miczek and H. Barry, *Behav. Biol.* **11**, 261 (1974); D. R. Cherek and T. Thompson, in *Proceedings, 80th Annual Convention, American Psychological Association* (1972), p. 847; M. Dorr and H. Steinberg, *Psychopharmacology* **47**, 87 (1976); B. Dubinsky, R. C. Robichaud, M. E. Goldberg, *Pharmacology* **9**, 204 (1973); D. Ely, J. P. Henry, C. J. Jarosz, *Behav. Biol.* **13**, 1 (1975); S. Garattini, in *Hashish: Its Chemistry and Pharmacology*, G. E. W. Wolstenholme, Ed. (Churchill, London, 1965), p. 70; M. ten Ham and J. van Noordwijk, *Psychopharmacologia* **29**, 171 (1973); M. M. Kilbey, G. E. Fritchie, D. M. McLendon, K. M. Johnson, *Nature (London)* **238**, 463 (1972); M. Santos, M. R. P. Sampaio, N. S. Fernandes, E. A. Carlini, *Psychopharmacologia* **8**, 437 (1966); E. N. Sassenrath and L. F. Chapman, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **34**, 1666 (1975); R. K. Siegel and J. Poole, *Psychol. Rep.* **25**, 704 (1969).
2. C. N. Alves, A. C. Goyos, E. A. Carlini, *Pharmacol. Biochem. Behav.* **1**, 183 (1973); B. Carder and J. Olson, *Physiol. Behav.* **8**, 599 (1972); E. A. Carlini and C. Gonzales, *Experientia* **28**, 542 (1972); E. A. Carlini and C. J. Lindsey, *Aggressive Behav.* **1**, 81 (1974); ———, S. Tufik, *Ann. N.Y. Acad. Sci.* **281**, 229 (1976).
3. E. O. Wilson, *Sociobiology: The New Synthesis* (Belknap, Cambridge, Mass., 1975).
4. (−)-*trans*-Δ^9-Tetrahydrocannabinol was obtained from the National Institute on Drug Abuse in a 99 percent concentration in dehydrated alcohol. After flash evaporation of the alcohol, the resin was dissolved in 100 percent propylene glycol in a concentration of 50 mg/ml; this stock solution was kept at −4°C. Shortly before drug administration, the appropriate amount of stock solution was removed and diluted with 1 percent Tween 80–saline so that the drug was administered at a constant volume (1 ml per kilogram of body weight for rats and monkeys; 1 ml per 100 g of body weight for mice). The vehicle composition was 5 percent propylene glycol in 1 percent Tween 80–saline. The drug was administered 30 minutes before the intruder test. The schedules of tests and the behavioral analysis of intruder experiments in mice were identical to those described by K. A. Miczek and J. O'Donnell (*Psychopharmacology*, in press).
5. Reliability of the measurements was established by repeated analysis of the videotape records. Variations between repeated measurements were less than 10 percent.
6. E. C. Grant and J. H. Mackintosh, *Behaviour* **21**, 246 (1963); S. A. Barnett, in *Aggressive Behaviour*, S. Garattini and E. B. Sigg, Eds. (Excerpta Medica, Amsterdam, 1969), p. 3; K. A. Miczek, *Psychopharmacologia* **39**, 275 (1974).
7. The indoor monkey colonies were in two adjacent rooms (2.3 by 2.5 by 2.9 m and 2.3 by 2.2 by 2.9 m) with controlled temperature (day, 25° to 26°C; night, 22°C), humidity (40 to 60 percent), and photocycle (12 hours of dark, 12 hours of light). All animals had free access to fresh water and protein-enriched Purina New World Primate Chow with weekly fruit supplements. The colony rooms could be viewed from adjacent rooms through one-way-vision glass.
8. S. Hopf, E. Hartmann-Wiesner, B. Kühlmorgen, S. Mayer, *Folia Primatol.* **21**, 225 (1974); M. Maurus, B. Kühlmorgen, E. Hartmann-Wiesner, H. Pruscha, *ibid.* **23**, 208 (1975).
9. The Mann-Whitney U test was used for comparing separate animals, and the Wilcoxon T test for comparing different tests in the same animals. Because of the small number of subjects, the χ^2 test was applied to the data from the monkey experiments by combining the data from all THC tests and comparing the data from the four THC doses with those from the vehicle control tests. Statistical significance was defined as $P < .05$ using the conservative two-tail criterion. All differences mentioned in the text meet this criterion.
10. K. A. Miczek and H. Barry, in *Behavioral Pharmacology*, S. D. Glick and J. Goldfarb, Eds. (Mosby, St. Louis, 1976), p. 176; *Psychopharmacology* **52**, 231 (1977); M. Krsiak, *ibid.* **51**, 75 (1976); A. P. Silverman, *Psychopharmacologia* **10**, 155 (1966).
11. D. G. Conrad, T. F. Elsmore, F. J. Sodetz, *Science* **175**, 547 (1972); B. Zimmerberg, S. D.

Glick, M. E. Jarvik, *Nature (London)* **233**, 343 (1971); D. P. Ferraro, W. C. Lynch, D. M. Grilly, *Pharmacology* 7, 273 (1972).
12. L. E. Hollister, R. K. Richards, H. K. Gillespie, *Clin. Pharmacol. Ther.* **9**, 783 (1968).
13. Mayor's Committee on Marihuana, *The Marihuana Problem in the City of New York: Sociological, Medical, Psychological, and Pharmacological Studies* (Cattell, Lancaster, Pa., 1944).
14. This work was supported by research grants DA-00722 and DA-01502 from the Public Health Service. I thank C. DeMarco, D. Niehoff, M. Roos, J. Weems, D. Williams, and D. Wilson for technical assistance, and M. Braude for arranging promptly delivered supplies of THC samples.

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Compulsive, Abnormal Walking Caused by Anticholinergics in Akinetic, 6-Hydroxydopamine–Treated Rats

Abstract. *In otherwise profoundly akinetic rats that had been severely depleted of brain catecholamines, anticholinergic drugs caused excessive walking. The effect did not appear until 10 days after surgery and then increased with time, suggesting that a phenomenon analogous to denervation supersensitivity may be involved. If the animals walked into corners, they were unable to turn around or back out. Their gait (extremely short steps) was reminiscent of that of patients with Parkinson's disease. The results are consistent with a mutually antagonistic interaction between cholinergic and dopaminergic brain systems and emphasize certain complexities in this interaction.*

Evidence suggests that destruction of ascending dopamine-containing pathways can produce deficits in locomotion. For instance, when 6-hydroxydopamine (6-OHDA) [a neurotoxin believed to destroy catecholamine systems relatively selectively (*1*)] is applied to the substantia nigra, to the nigrostriatal pathway in the hypothalamus (*2*), or intraventricularly (*3*), it can produce akinesia as well as many of the other symptoms of hypothalamic damage (*4*). Akinesia also can be produced by drugs, such as neuroleptics, which depress the action of catecholamine brain systems (*5*). Furthermore, akinesia is a prominent symptom of parkinsonism, which has been related to the destruction of cells and depletion of catecholamines in the nigrostriatal system (*6*).

Anticholinergic drugs have long been valuable in the treatment of parkinsonism (*7*). However, some evidence, both clinical and in experimental animals, suggests that although anticholinergics are useful in alleviating rigidity, tremor, and catalepsy, they typically do not counteract akinesia (*8*).

Using rats depleted of brain catecholamines by intraventricular application of 6-OHDA (*9*), we have found that short-step locomotion—a form of walking reminiscent of the gait of some patients with parkinsonism—can be temporarily induced by the anticholinergic atropine in otherwise profoundly akinetic rats.

Thirty-two male rats weighing 400 to 500 g (16 experimental and 16 control rats) were treated with pargyline (50 mg/kg) 30 minutes prior to surgery. In ten of the experimental rats, 200 μg of 6-OHDA was injected into each lateral ventricle and 100 μg of 6-OHDA into the third ventricle in a single operation (*10*). In the remaining six experimental rats, 200 μg of 6-OHDA was injected first into one lateral ventricle and 48 hours later into the other. After the initial pargyline treatment, 12 control rats were given no further treatment. In the remaining four control rats, only the vehicle was injected into all three ventricles. Radioenzymatic assays for dopamine (DA) and noradrenaline (NA) confirmed the effectiveness of the 6-OHDA treatment in depleting catecholamines (*11*).

After the injections of 6-OHDA, the animals displayed various degrees of catalepsy and akinesia (*12*). In a test for cataleptic clinging (*13*), each rat was placed with its head and forequarters partway up onto the horizontal surface of an inverted, wire-mesh hanging cage. Its front paws grasped the upper horizontal mesh surface of the cage (that is, the cage bottom which, when inverted, was now on top), whereas its hindpaws

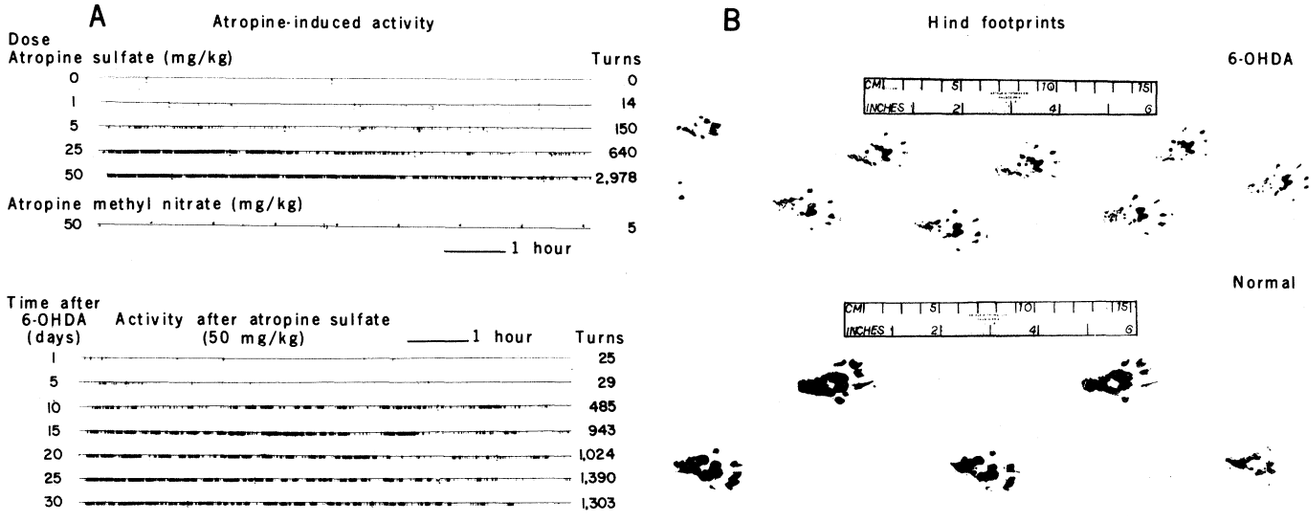

Fig. 1. (A) Top: A record of activity pattern in an otherwise akinetic 6-OHDA–treated rat injected at least 30 days after surgery with various doses of atropine sulfate or atropine methyl nitrate. Actual number of wheel turns are indicated on the right (turns were recorded by a counter on each wheel). Thin vertical slash marks reflect the pattern of activity (these do not always agree exactly with the number of turns because time markers also appear on the record). Bottom: A record of activity pattern after atropine sulfate (50 mg/kg) was injected on various days after surgery in another 6-OHDA–treated rat. Atropine has little or no effect until about 10 days after surgery but becomes increasingly effective in producing excessive walking thereafter. (B) Footprints from the ink-brushed hind feet of a 6-OHDA–treated rat (top) that was induced to walk by an injection of atropine sulfate (25 mg/kg). Rulers were placed next to each set of footprints before photographing and were later retouched for the figure.

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