PHARMACOLOGICAL REVIEWS
Vol. 23, No. 4

Printed in U.S.A.

GENERAL AND BEHAVIORAL PHARMACOLOGY

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l-trans-Δ^9-Tetrahydrocannabinol and its Δ^8-isomer (Δ^8- and Δ^9-THC) represent what are thought to be the active principles of *Cannabis sativa* (29, 30). As is true of the plant materials, marihuana and hashish, the tetrahydrocannabinols produce a state of intoxication in animals and man which is a unique mixture of central nervous system (CNS) stimulation and depression not mimicked by other classes of drugs. In addition to the problems of an adequate supply, poor solubility, and absorption, a major stumbling block to progress in our understanding the effects of these drugs has been the lack of good laboratory models. There are no animal test procedures which adequately reflect many of the major pharmacological properties of cannabis intoxication in man such as euphoria and hallucinations.

For some time now we have been studying the pharmacological properties of Δ^8- and Δ^9-THC as well as various homologues and analogues (9, 11, 21) with the view toward ascertaining how they work and whether their pharmacological properties might suggest therapeutic usefulness. This paper will describe some of our findings and those of others along these lines.

In order to solve the problem of poor water solubility, we have investigated a number of solvent systems for formulating the drugs. All have certain advantages and disadvantages. The use of organic solvents complicates results because of the pharmacological actions of the solvents. This is particularly true in small animals and systems *in vitro*. On the other hand, the use of a variety of suspending agents and oil solutions leads to an unreliable absorption of the THC. We have utilized an albumin suspension in many of our tests (11, 12) although this is far from ideal. For instance, the acute toxicities (table 1) obtained with this vehicle are somewhat less than those reported by Phillips *et al.* (31) with 10% Tween 80 suspensions. Similar differences are reflected in a somewhat lower potency of the THC's in other test procedures with this vehicle. The major virtues of this vehicle are that it allows accurate dilutions, is stable, and control albumin solutions have little or no pharmacological activity. In any case, the toxicities of of Δ^8- and Δ^9-THC are low relative to their pharmacologically active doses. Animals medicated with these agents exhibit a mixture of CNS stimulation and depression. Thus, spontaneous activity is depressed (8, 18, 19, 22) but the animals are markedly hypersensitive to external stimuli such as sound or touch. The THC's potentiate barbiturate sleeping time (8, 18) but also at certain doses, they potentiate the stimulatory effect of amphetamine on spontaneous activity (8, 18).

It has been reported that Δ^8- and Δ^9-THC have potent analgesic activity (2, 5).

[1] The original investigations from the author's laboratory mentioned in this review were supported in part by National Institute of Mental Health research grant MH-17001.

TABLE 1

Acute toxicity of tetrahydrocannabinol (Δ^8 and Δ^9 THC) in albumin suspension

Species	Route of Administration	Acute LD50	
		Δ^8-THC	Δ^9-THC
		mg/kg	
Mouse	i.v.	31 (20.7–46.5)*	60 (46–80.8)
Rat	i.v.	97 (67.8–139)	100 (64–160)
Mouse	i.p.	210 (140–315)	168 (125–225)
Rat	i.p.	560 (479–666)	430 (290–636)
Mouse	p.o.	>2000	1900 (1250–2888)
Rat	p.o.	>2000	>2000

* 95% confidence limits determined by the method of Litchfield and Wilcoxin (26).

In our hands the antinociceptive activity of these compounds has been erratic and highly dependent on the testing method, the species used, the solvent system, the route of administration, and the time of testing. For instance, in the mouse tail-flick test when, albumin preparations of Δ^9-THC were given intraperitoneally and the mice were tested 30 min after medication the drug had little effect at doses below 80 mg/kg. When examined at 60 min significant effects were seen with doses of 20 mg/kg (table 2). Increasing doses, however, produced little additional effect. When given in Triton X-100 more pronounced effects were seen, but inhibitions of the reflex greater than 50% of the maximal possible effect were difficult to attain. With the Triton X-100 solvent system, peak activity appeared to be attained at 30 min.

In the hot plate test ED50 values could be obtained for Δ^8- and Δ^9-THC given intraperitoneally in albumin suspensions (table 3). Δ^9-THC was generally more potent than Δ^8-THC. Peak activity appeared to occur at 1 hr with either isomer and some activity was still appearent 2.5 hrs after medication. Again, the effects seemed more pronounced when Triton X-100 was used as the suspending agent.

In the phenylquinone abdominal-stretching test, subcutaneous doses of Δ^9-THC from 10 to 80 mg/kg produced inhibitions ranging from 43 to 65%. A dose-response relationship was not evident. Similar data were obtained with Δ^8-THC although it was less potent. In our laboratory the dose of morphine necessary to produce a 50% effect is approximately 0.56 mg/kg. However, it should be pointed out that subcutaneous absorption of Δ^9-THC is poor (25) and the use of the intraperitoneal route of administration in this test procedure has inherent difficulties since the phenylquinone is also given by this route. In summary, while Δ^8- and Δ^9-THC have some antinociceptive properties they are inconsistent and have a profile different from that of known clinical analgesics.

It has been reported that a variety of tetrahydrocannabinols have profound actions on the cardiovascular system (9, 10, 13, 20). In man, tachycardia is consistently described (23, 24, 36). In the anesthetized dog, low doses (0.1–0.3 mg/kg) of Δ^8- and Δ^9-THC have little effect on blood pressure, heart rate, or respiration. However, at these doses there is a marked potentiation of the cardio-

vascular and respiratory effects of epinephrine and norepinephrine (9, 10). This is illustrated in figure 1. Similar findings had been reported earlier by Dargirmanjian and Boyd (7) for the synthetic tetrahydrocannabinol DMHP. At higher doses (1.0–10.0 mg/kg) there is a fall in blood pressure, bradycardia and a depression of respiration (9, 10, 13). This is shown in figure 2. The hypotension is relatively slow in onset, has a long duration, and both systolic and diastolic pressures are equally affected (fig. 3). The fall in blood pressure is not blocked by vagotomy or atropine, and tends to eliminate peripheral cholinergic mechanisms as a possible explanation. In addition, the fall in blood pressure produced by Δ^9-THC is not blocked by the *beta*-adrenergic blocking agent propranolol which points to mechanisms other than *beta*-adrenergic stimulation. Δ^8- and Δ^9-THC do not block the cardiovascular responses to acetylcholine, isoproterenol or histamine. With Δ^9-THC there is a fall in cardiac output and a decreased hind-limb peripheral resistance accompanied by an increased femoral blood flow (13).

TABLE 2

The effect of Δ^9-tetrahydrocannabinol in the mouse tail-flick test

N	Time of Test after Injection	Dose	Route	Vehicle	Percent MPE*
	min	*mg/kg*			
6	60	10	i.p.	Albumin	7
12	60	20	i.p.	Albumin	36
12	60	40	i.p.	Albumin	28
6	60	80	i.p.	Albumin	28
24	20	10	i.p.	Triton	28
6	30	10	i.p.	Triton	53
6	60	10	i.p.	Triton	20
12	30	20	i.p.	Triton	55
12	60	20	i.p.	Triton	44

* Percent of the maximum possible effect. In these experiments a 10-sec cut-off time was used and the % MPE calculated by:

$$\% \text{ MPE} = \frac{\text{Test} - \text{control}}{10 - \text{control}} \times 100$$

TABLE 3

Effects of albumin suspensions of tetrahydrocannabinol (Δ^8- and Δ^9-THC) in the mouse hot-plate test

Time after Medication	ED50	
	Δ^8-THC	Δ^9-THC
min	*mg/kg*	
60	48 (30.4-75.8)*	39 (26.5-57.3)
150	94 (37.6-235)	60 (40-90)

* 95% confidence limits determined by the method of Litchfield and Wilcoxin (26).

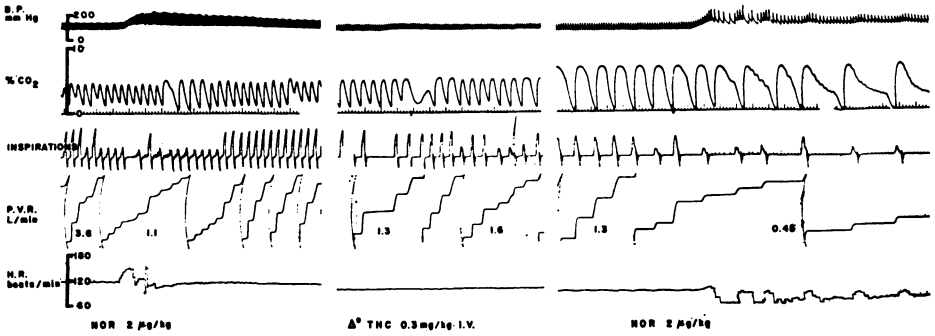

FIG. 1. The effect of an intravenous injection of 0.3 mg/kg Δ^9-tetrahydrocannabinol on cardiovascular and respiratory parameters in the anesthetized dog and its effect on a 2-μg/kg challenge of norepinephrine. Blood pressure was measured by a Statham P-23 transducer; percent of carbon dioxide by a capnograph; inspirations by a pneumotachograph (volume pressure transducer); pulmonary ventilation rate was determined by a Grass integrator; and heart rate was monitored by a Grass 7P4C tachograph. Parameters were recorded on a model P-7 Grass polygraph (W. L. Dewey *et al.*, unpublished data).

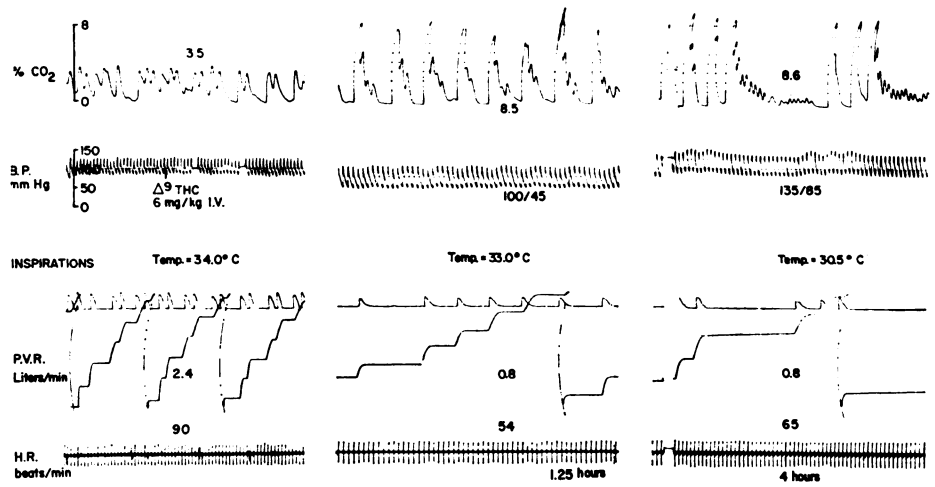

FIG. 2. The effect of an intravenous injection of 6 mg/kg of Δ^9-tetrahydrocannabinol on cardiovascular and respiratory parameters in the anesthetized dog and its effect on a 2-μg/kg challenge of norepinephrine. Blood pressure was measured by a Stathan P-23 transducer; percent of carbon dioxide by a capnograph; inspirations by a pneumotachograph (volume pressure transducer); pulmonary ventilation rate was determined by a Grass integrator; and heart rate was monitored by a Grass 7P4C tachograph. Parameters were recorded on a model P-7 Grass polygraph (W. L. Dewey, *et al.*, unpublished data).

In summary, the THC's produce a fall in blood pressure and bradycardia in the anesthetized dog. This effect is probably not due to *alpha*-adrenergic blockage, *beta*-adrenergic stimulation, or parasympathetic stimulation and the mechanism remains to be elucidated.

The tetrahydrocannabinols have been studied in a number of schedule con-

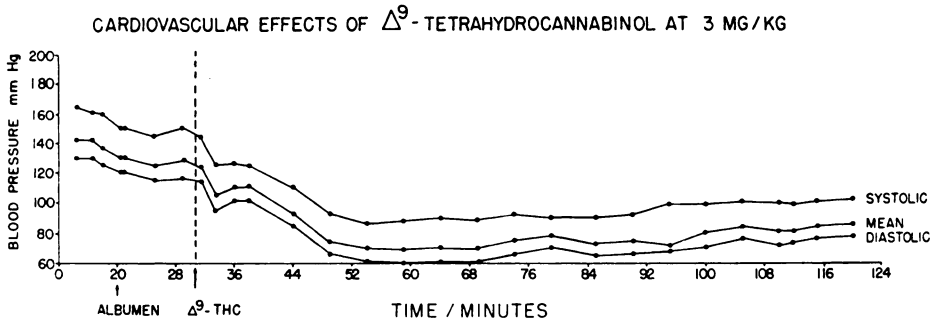

FIG. 3. The effect of the intravenous injection of 3 mg/kg Δ^9-tetrahydrocannabinol on the systolic, diastolic and mean blood pressure of an anesthetized (35 mg/kg pentobarbital, intravenously) dog (W. L. Dewey *et al.*, unpublished data).

trolled behavioral systems (1, 3, 4, 16, 17, 32). In our hands (16, 17, 27) both Δ^8- and Δ^9-THC produced a dose-dependent depression of response in pigeons trained to a multiple fixed-interval 5-min, fixed-ratio 30 responses (mult FI-5, FR-30) schedule of food presentation. This is illustrated in figure 4 for Δ^9-THC. It should be noted that no stimulation was seen and that the depression occurred in both schedules at the same dose levels. Domino and his colleagues (3, 14) have since reported essentially identical results. Δ^8-THC produced the same pattern of effects but to a lesser degree. Thus, it required 5.6 mg/kg of Δ^8-THC to produce a significant depression of response. Similar results were obtained in the rat trained to a mult FI-1, FR-6 schedule of reinforcement. The depressant effects, particularly at the higher doses in the pigeon had a long duration. This is illustrated in figure 5 for 5.6 mg/kg Δ^9-THC in one bird. In this animal the response in the FR component recovered somewhat more rapidly than response in the FI component, but response did not return to control levels until 72 hr after medication.

Earlier reports (6, 10, 33) as well as the difficulties which were encountered in obtaining a good dose-response relationship led us to consider the possibility that tolerance was developing to repeated medication with the tetrahydrocannabinols. This prompted us to carry out more extensive experiments to test this hypothesis.

Two drug naive pigeons were trained under the mult FI-5, FR-30 schedule of reinforcement and then medicated with 1.8 mg/kg of Δ^9-THC (27). This dose essentially eliminated response in these birds. When this dose was given daily the drug effect gradually disappeared and after a week the rate of response was normal. This is illustrated for the FI-component in figure 6 and the FR-component in figure 7. The dose was then gradually increased over the next 3 weeks to 36 mg/kg. This dose given to a drug naive bird produced prostration which lasted for 48 hr and the animal did not eat until 72 hr after medication.

In other experiments (28)[2] we have gradually brought pigeons to a dose level

[2] A complete account of this work has been submitted for publication by McMillan and his colleagues.

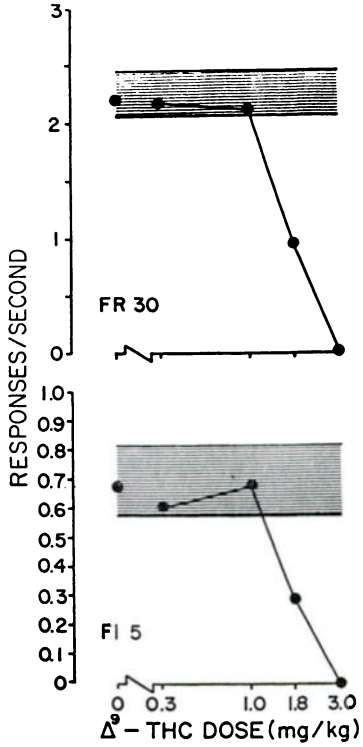

FIG. 4. Effect of Δ^9-tetrahydrocannabinol on rates of key pecking under each component of the multiple fixed-ratio 30 responses, fixed-interval 5-min schedule of food presentation in pigeons. Abscissae: dose, log scale. Ordinates: rates of responding during a complete session. The point at 0 on the dose scale represents the mean rate for the 4 pigeons during the hour-long session beginning 2 hr after the vehicle control injection. The shaded area is the range of the means for 8 non-injection sessions. Each point represents the mean of one observation for that dose in each of the 4 pigeons. (From J. M. Frankenheim, D. E. McMillan, and L. S. Harris, J. Pharmacol. Exp. Ther. **178:** 241–252, 1971. Copyright 1970 by the Williams & Wilkins Co., Baltimore, Md.)

of 180 mg/kg. This dose is lethal in the non-tolerant bird. At this point, cessation of medication produced no observable changes in either overt or operant behavior over a period of several days. Medication was then resumed at 100 mg/kg Δ^9-THC with no obvious loss of tolerance. The birds were then medicated with a high dose of Δ^8-THC with no noticeable effect thus indicating a cross tolerance between the two isomers. Identical experiments were carried out with Δ^8-THC with different pigeons. As was the case with Δ^9-THC, a high level of tolerance was obtained with Δ^8-THC. Cross tolerance to Δ^9-THC was demonstrated and no signs of abstinence were noted on cessation of medication. Similar experiments have been reported by Black and his colleagues (3) with two synthetic tetrahydrocannabinols (synhexyl and DMHP) as well as Δ^9-THC and by Campo (personal communication) with a nitrogen analogue. The work by Black *et al.* (3) indicated that tolerance could be obtained even when the medications were spaced

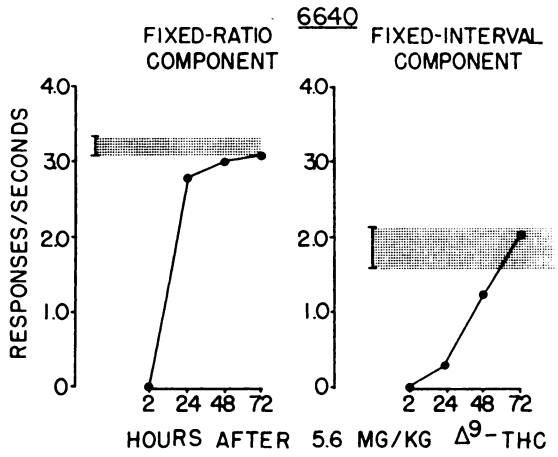

FIG. 5. Effect of 5.6 mg/kg of Δ^9-tetrahydrocannabinol (Δ^9-THC) on rates of key pecking under each component of the multiple fixed-ratio 30 responses, fixed-interval 5-min schedule of food presentation for a pigeon that had not received Δ^9-THC previously. Abscissae: hours after Δ^9-THC injection. Ordninates: rates for response during a complete session. The shaded area is the range of means for 5 non-injection sessions. (Derived from data from D. E. McMillan, L. S. Harris, J. M. Frankenheim, and J. S. Kennedy, Science **169:** 501-503, 1970.)

a week apart. We have noted a long persistence of tolerance. Thirty days after cessation of medication in pigeons there was essentially no loss of tolerance. The time parameters of this phenomena have not as yet been fully delineated.

That this phenomenon is not confined to the pigeon is evidenced by the reports by Carlini and his colleagues (6, 33) and Ford and McMillan (15) of tolerance development to Δ^9-THC in the rat. In the work from our laboratory (15, and footnote[2]) a dose of 10 mg/kg markedly depressed the response of rats trained to a fixed-ratio 10 (FR-10) schedule of water reinforcement. This dose was repeated until tolerance developed and was then gradually increased to 100 mg/kg. Thus a 10-fold tolerance was easily developed to the behavioral effects of Δ^9-THC in the rat. No signs of abstinence were seen when medication was discontinued. Recent reports from the chronic toxicity studies with Δ^9-THC indicate that tolerance also occurs to the lethal effects of this drug in the rat (34).

We have also found that tolerance develops in dogs to most of the behavioral and somatic signs produced by the intravenous administration of Δ^9-THC (10).[3] Δ^9-THC, 2 mg/kg, administered intravenously produced profound behavioral effects in the dog. After the 4th daily administration a marked but not complete tolerance had developed. The dose was then gradually increased to 32 mg/kg. At this point medication was stopped for 10 days. No signs of withdrawal were seen. Medications were then resumed and the dose carried up to 160 mg/kg. This is approximately four times the acute lethal intravenous dose in the dog. Again no observable signs of abstinence were noted on discontinuation of the

[3] A complete account of this work has been submitted for publication by Dewey and his colleagues.

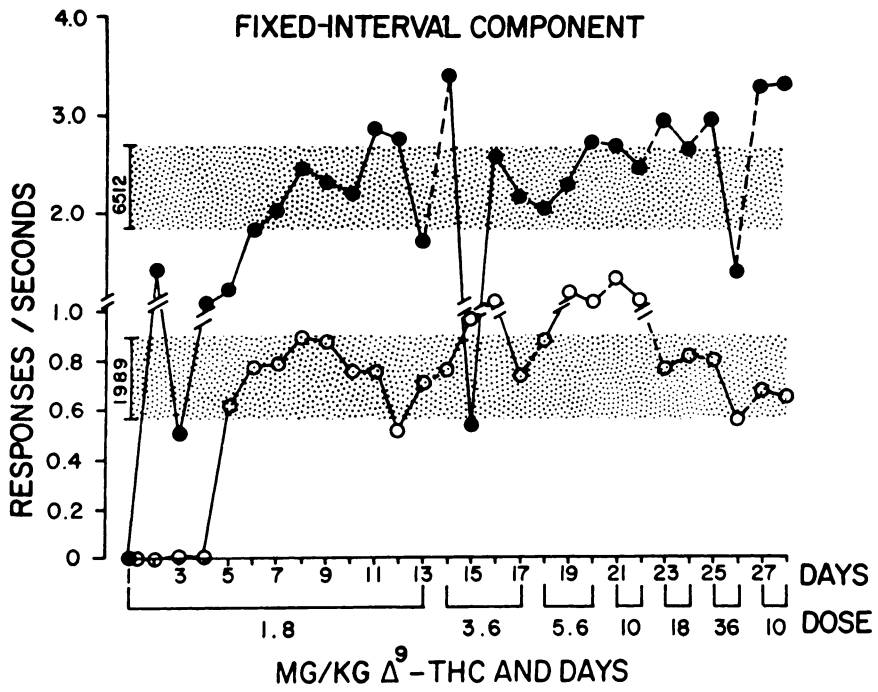

FIG. 6. Effects of long-term administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) on performance under the fixed-interval component of the multiple schedule. The ordinates show the rate of response during a session. The abscissae show consecutive daily sessions and dose (mg/kg) of Δ^9-THC. Open circles, bird 1989; closed circles, bird 6512. The upper shaded area represents the range of values after nine injections of Triton X for bird 6512 and the lower shaded area is the same range for bird 1989. (From D. E. McMillan, L. S. Harris, J. M. Frankenheim, and J. S. Kennedy, Science **169**: 501–503, 1971. Copyright 1970 by the American Association for the Advancement of Science.)

medication and this animal, although emaciated, made an uneventful recovery. Another dog on a similar medication regimen died when the dosage reached 60 mg/kg. On postmortem examination, the gastrointestinal tract was empty, and the only notable gross pathological finding was hemorrhagic lungs. In the chronic toxicity studies with Δ^9-THC in dogs and monkeys, tolerance to the drug has also been noted after oral administration (35). Doses as high as 2 to 3 g/kg per day have been achieved in these experiments.

In our chronic intravenous studies (see footnote[3]) we evaluated certain cardiovascular parameters as well as behavioral effects. Initial injections of Δ^9-THC produced bradycardia which decreased over the first week. It should be noted, however, that the daily premedication heart rates also decreased perhaps indicating a long duration of action or an adaptation to handling. When the dosage reached 16 mg/kg tachycardia was noted. No significant changes occurred in the blood pressure.

In conclusion, Δ^8- and Δ^9-THC have marked effects on the central nervous system. In this regard they are qualitatively the same and have a profile of ac-

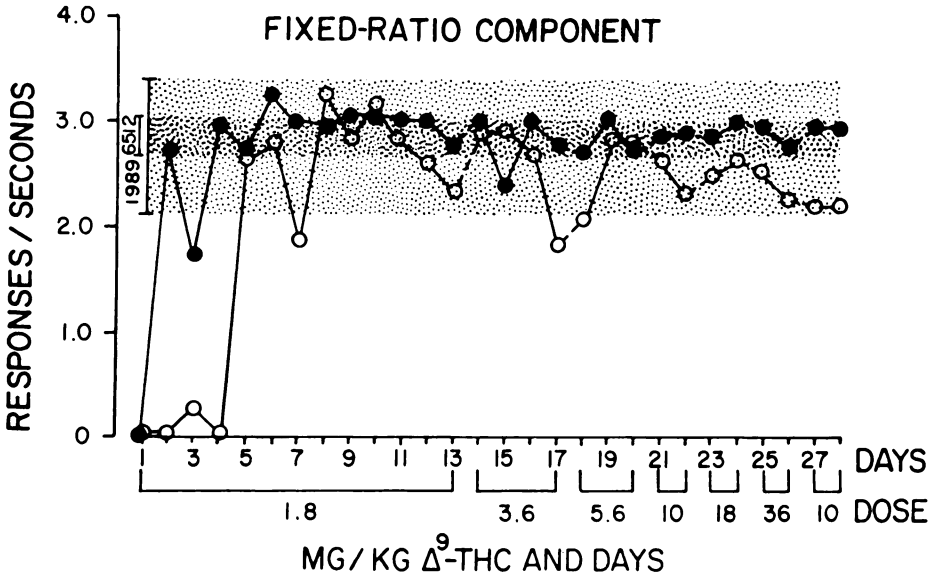

FIG. 7. Effects of long-term administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) on performance under the fixed-ratio component of the multiple schedule. The ordinates show the rate of response during a session. The abscissae show the data for consecutive daily sessions and the dose (mg/kg) of Δ^9-THC. Open circles, bird 1989; closed circles, bird 6512. The shaded areas represent the range of values after nine injections of Triton X. The darker center shading is the range for bird 6512 and the wider, lighter shading is the range for bird 1989. (From D. E. McMillan, L. S. Harris, J. M. Frankenheim and J. S. Kennedy, Science **169:** 501–503, 1971. Copyright 1970 by the American Association for the Advancement of Science.)

tion different from that of other known classes of centrally acting drugs. The discovery of a remarkable degree of tolerance to these compounds is noteworthy. That this is a real phenomenon is evidenced by the fact that it crosses species, that there is cross tolerance among cannabinoids, and that it has been observed in a number of laboratories. Also of importance is the fact that abstinence or withdrawal symptoms have not been seen. Much remains to be learned about this fascinating series of drugs.

Acknowledgments: The author gratefully acknowledges the generous supply of drugs provided by the NIMH-FDA Psychotomimetic Agents Committee. The author is also deeply indebted to Dr. William L. Dewey, Dr. Donald E. McMillan, his technical staff and graduate students whose unflagging efforts produced the results reported from our laboratory.

REFERENCES

1. ABEL, E. L.: Effects of the marihuana homologue, pyrahexyl, on a conditioned emotional response. Psychonom. Sci. 16: 44, 1969.
2. BICHER, H. I. AND MECHOULAM, R.: Pharmacological effects of two active constituents of marihuana. Arch. Int. Pharmacodyn. Thér. 172: 24–31, 1968.
3. BLACK, M. D., WOODS, J. H. AND DOMINO, E. F.: Some effects of (—)-Δ9-transtetrahydrocannabinol and other cannabinol derivatives on schedule-controlled behavior. Pharmacologist 12: 258, 1970.
4. BOYD, E. S., HUTCHINSON, E. D., GARDNER, L. C. AND MERITT, D. A.: Effects of tetrahydrocannabinols and other drugs on operant behavior in rats. Arch. Int. Pharmacodyn. Thér. 144: 533–554, 1963.

5. Buxbaum, D., Sanders-Bush, E. and Efron, D. H.: Analgesic activity of tetrahydrocannabinol (THC) in the rat and mouse. Fed. Proc. 28: 735, 1969.
6. Carlini, E. A.: Tolerance to chronic administration of *Cannabis sativa* (marihuana) in rats. Pharmacology 1: 135–142, 1968.
7. Dagirmanjian, R. and Boyd, E. S.: Peripheral effects of a tetrahydrocannabinol. Fed. Proc. 19: 267, 1969.
8. Dagirmanjian, R. and Boyd, E. S.: Some pharmacological effects of two tetrahydrocannabinols. J. Pharmacol. Exp. Ther. 135: 25–33, 1962.
9. Dewey, W. L., Harris, L. S., Howes, J. F., Granchelli, F. E., Pars, H. G. and Razdan, R. K.: Pharmacology of some marijuana constituents and two heterocyclic analogues. Nature (London) 226: 1265–1267, 1970.
10. Dewey, W. L., Harris, L. S., Howes, J. F. and Kennedy, J. S.: Pharmacological effects of some active constituents of marihuana. Pharmacologist 11: 278, 1969.
11. Dewey, W. L., Kennedy, J. S. and Howes, J. F.: Some autonomic gastrointestinal and metabolic effects of two constituents of marihuana. Fed. Proc. 29: 650, 1970.
12. Dewey, W. L., Peng, T. C. and Harris, L. S.: The effect of *l*-trans-Δ^9-tetrahydrocannabinol on the hypothalamo-hypophyseal-adrenal axis of rats. Eur. J. Pharmacol. 12: 382–384, 1970.
13. Dewey, W. L., Yonce, L. R., Harris, L. S., Reavis, W. M., Griffin, E. D., Jr. and Newby, V. E.: Some cardiovascular effects of *trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC). Pharmacologist 12: 259, 1970.
14. Domino, E.: Neuropsychopharmacological studies of marihuana. Some natural and synthetic THC derivatives in animals and man. Ann. N.Y. Acad. Sci., in press.
15. Ford, R. D. and McMillan, D. E.: Behavioral tolerance and cross tolerance to *l*-Δ^8-tetrahydrocannabinol (Δ^8-THC) and *l*-Δ^9-tetrahydrocannabinol (Δ^9-THC) in pigeons and rats. Fed. Proc. 30: 279, 1971.
16. Frankenheim, J. M., McMillan, D. E. and Harris, L. S.: Effects of *l*-Δ^9- and *l*-Δ^8-transtetrahydrocannabinol on schedule-controlled behavior of the pigeon. Fed. Proc. 29: 619, 1970.
17. Frankenheim, J. M., McMillan, D. E. and Harris, L. S.: Effects of *l*-Δ^9- and *l*-Δ^8-trans-tetrahydrocannabinol and cannabinol on schedule controlled behavior of pigeons and rats. J. Pharmacol. Exp. Ther. 178: 241–252, 1971.
18. Garriott, J. C., King, L. J., Forney, R. B. and Hughes, F. W.: Effects of some tetrahycrocannabinols on hexobarbital sleeping time and amphetamine induced hyperactivity in mice. Life Sci. 6: 2119–2128, 1967.
19. Grunfeld, Y. and Edery, H.: Psychopharmacological activity of the active constituents of hashish and some related cannabinoids. Psychopharmacologia 14: 200–210, 1969.
20. Hardman, H. F., Domino, E. F., Woods, L. A. and Seevers, M. H.: Pharmacological actions of Δ^3-tetrahydrocannabinol derivatives. Pharmacologist 12: 258, 1970.
21. Harris, L. S., Razdan, R. K., Dewey, W. L. and Pars, H. G.: The pharmacology of some new tetrahydrocannabinol analogs. Chim. Ther. 2: 167, 1967.
22. Holtzman, D., Lovell, R. A., Jaffe, J. H. and Freedman, D. X.: *l*-Δ^9-tetrahydrocannabinol: neurochemical and behavioral effects in the mouse. Science 163: 1464–1467, 1969.
23. Isbell, H., Gorodetsky, G. W., Jasinski, D., Claussen, U., Spulak, F. and Korte, F.: Effects of (—)Δ^9-transtetrahydrocannabinol in man. Psychopharmacologia 11: 184–188, 1967.
24. Jones, R. T. and Stone, G. C.: Psychological studies of marijuana and alcohol in man. Psychopharmacologia 108: 108–117, 1970.
25. Kennedy, J. S. and Waddell, W. J.: Whole body autoradiography of the pregnant mouse after administration of C^{14}-Δ^9-tetrahydrocannabinol (Δ^9-THC). Fed. Proc. 30: 279– 1971.
26. Litchfield, J. T. and Wilcoxin, F.J.: A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96: 99–113, 1949.
27. McMillan, D. E., Harris, L. S., Frankenheim, J. M. and Kennedy, J. S.: *l*-Δ^9-trans-tetrahydrocannabinol in pigeons: tolerance to the behavioral effects. Science 169: 501–503, 1970.
28. McMillan, D. E., Harris, L. S., Turk, R. F. and Kennedy, J. S.: Development of marked behavioral tolerance to *l*-Δ^9-tetrahydrocannabinol (Δ^9-THC) and cross tolerance to *l*-Δ^8-tetrahydrocannabinol (Δ^8-THC) in the pigeon. Pharmacologist 12: 258, 1970.
29. Mechoulam, R.: Marihuana chemistry. Science 168: 1159–1166, 1970.
30. Mechoulam, R., Shani, A., Edery, H. and Grunfeld, Y.: Chemical basis of hashish activity. Science 169: 611–612, 1970.
31. Phillips, R. N., Turk, R. F. and Forney, R. B.: Acute toxicity of Δ^9-tetrahydrocannabinol in rats and mice. Proc. Soc. Exp. Biol. Med. 136: 260–263, 1971.
32. Scheckel, C. L., Boff, E., Dahlen, P. and Smart, T.: Behavioral effects in monkeys of racemates of two biologically active marijuana constituents. Science 160: 1467–1469, 1968.
33. Silva, M. T. A., Carlini, E. A., Claussen, U. and Korte, F.: Lack of cross-tolerance in rats among (—)Δ^9-trans-tetrahydrocannabinol (Δ^9-THC), cannabis extract, mescaline and lysergic acid diethylamide (LSD-25). Psychopharmacologia 13: 322–340, 1968.
34. Thompson, G. R., Schaeppi, U. H. and Mason, M. M.: NIMH Contract HSM-42-70-95 Report, December 18, 1970; see also Pharmacologist, 13: 296, 1971.
35. Thompson, G. R. and Schaeppi, U. H.: NIMH Contract HSM-42-70-95 Report, November 20, 1970.
36. Weil, A. T., Zinberg, N. E. and Nelson, J. M.: Clinical and psychological effects of marihuana in man. Science 162: 1234–1242, 1968.