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Cannabinoids. I. Behavioral Effects[1]

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ABSTRACT

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The effects of two new cannabinoids, nabilone and canbisol, have been compared to Δ^9-tetrahydrocannabinol (Δ^9-THC) and chlordiazepoxide in behavioral tests in mice, rats, dogs and rhesus monkeys. Activity of mice was measured in a photocell device. Oral doses of 5 and 10 mg/kg of Δ^9-THC and 200 mg/kg of chlordiazepoxide caused only a decrease in the initial high activity. Doses of 5 and 10 mg/kg of nabilone and 2.5, 5.0 and 10 mg/kg of canbisol decreased the initial high activity but increased the subsequent low activity. In rats Δ^9-THC, nabilone and canbisol, but not chlordiazepoxide, slowed muricide and intracranial self-stimulation. Chlordiazepoxide, nabilone and canbisol, but not Δ^9-THC, reduced reactivity of septal-lesioned rats. At the dosages studied only nabilone and canbisol reduced food consumption by rats. Ataxia in dogs was detected following as little as 0.062 mg/kg of Δ^9-THC, 0.032 mg/kg of nabilone and 0.004 mg/kg of canbisol when given intravenously; orally, doses of more than 0.25 mg/kg of Δ^9-THC, and 0.1 mg/kg of nabilone or canbisol were necessary. Rhesus monkeys working under multiple fixed-ratio fixed-interval scheules showed an increase in rate at some dose of all three cannabinoids but higher doses reduced responding, and responding was abolished following 3.0 mg/kg of Δ^9-THC or nabilone or 0.3 mg/kg of canbisol. Chlordiazepoxide increased responding at all doses studied, 3.0 to 30.0 mg/kg. Nabilone and canbisol resemble chlordiazepoxide in some tests and Δ^9-THC in other tests.

The great upsurge of use of cannabis in the 1960s and the identification of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the main pharmacologically active component of *Cannabis sativa* rekindled interest in the pharmacology of the cannabinoids and in their potential use in therapeutics. Despite the large amount of work in recent years, however, the pharmacology of the cannabinoids remains unsatisfactorily understood.

One deficiency in our knowledge has come about because Δ^9-THC was not discovered in the search for a therapeutic agent and has been less systematically compared with other drugs in standard tests than would have been the case for a new moiety. In view of the interest in two new synthetic cannabinoids, results on Δ^9-THC and chlordiazepoxide in standard tests have been compared to the results on the new agents. The new compounds were synthesized by Archer *et al.* (1977). They are 3-alkyldibenzo-b,d-pyrans (fig. 1) and have been given the names of nabilone for the 9-one and canbisol for the 9-ol. They are crystalline preparations, contrasting with the resinous nature of most cannabinoids. The present report deals with the behavioral effects of the drugs. A subsequent report will compare the cardiovascular effects of the same agents Stark and Dews (1980).

Methods

Mouse activity. Groups of five male mice, of the Belaire Swiss Strain and weighing between 16 and 18 g were placed together in doughnut-shaped cages about 30 cm in diameter. The cages had six photoelectric cells evenly spaced around and on to each a filtered infrared beam impinged after crossing the cage on a radius. Each interruption of a beam by a mouse was counted.

Mice were put into the apparatus 90 min after oral dosing and counts were recorded in each 30-min interval for 2 hr. At least two groups of mice were studied at each dose level and compared with at least 25 groups given saline.

Rat food consumption. Male Long-Evans rats weighing 250 to 300 g were individually housed. They were fasted 21 hr and then allowed 3 hr access to Taklad rat chow each day. The amount eaten was measured. Water was continuously available. Drugs were given orally 1 hr before the feeding period. The average amount eaten on the 2 days preceding the dose of drug was taken as the control level of eating. Five rats were studied at each dose level of Δ^9-THC and chlordiazepoxide and 10 at each dose level of nabilone and canbisol. Each rat served as its own control.

Rat muricide. Male Long-Evans rats killing mice within 5 sec of the introduction of the mouse into the home cage of the rats were selected. The time to kill was measured at hourly intervals and scored as follows: 0 to 59 sec = 0; 60 to 120 sec = 0.5; and more than 120 sec = 1. The scores at 3, 4, 5 and 6 hours after oral dosing were averaged.

Rat reactivity after septal lesions. Male Long-Evans rats were made hyper-reactive by destruction of an area in the septal region. Seven different tests of reactivity were scored from 0 to 2 in intensity and the scores were summed (Stark and Henderson, 1966a, b). Scores after drugs were divided by control scores of the same rats, and the quotient was subtracted from 1 to yield a metric that increased in value from 0 to 1 as reactivity was suppressed. Effects were assessed at hourly intervals and the values at 3, 4, 5 and 6 hours after oral dosage were averaged.

Rat self-stimulation. Bipolar stainless steel electrodes were aimed

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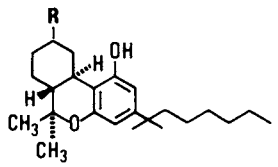
for the posterior hypothalamus of anesthetized Long-Evans rats as described by Stark *et al.* (1969). Two weeks after the surgical procedure the animals were trained to press a lever for electrical stimulation through the implanted electrodes. Every press of the lever resulted in the delivery of a 0.25-sec train of 60-Hz sine-wave current. Threshold for each animal was determined. Threshold is defined as the lowest current at which an animal will press a lever at a greater rate than when pressing has no consequence. Four current intensities, 5 μA apart, one below and three above threshold, were delivered in a random order for 5 min each, separated by a 1-min interval. The effects of drugs on rate of responding during 5 min at the intensity 5 μA above threshold and between 1 and 1½ hours after oral dosing are presented.

Dogs. Two or three dogs were grouped together in a wire mesh observation pen and left to mingle for 1 hr. Drug was then administered intravenously or orally and the animals assessed for ataxia, after the manner of Loewe (1946), every hour for 6 hr and again next day. The ataxia was graded on a scale from 0 to 1 as follows: 0—no detectable effect; 0.25—detectable ataxia; 0.50—gross ataxia; 0.75—falling down but regaining feet; 1.00—not standing. Scores were averaged at 3, 4, 5 and 6 hours after dosing. Detectable ataxia was a swaying motion qualitatively different from any motion seen in normal dogs or dogs following vehicle only.

Rhesus monkeys. Two rhesus monkeys, restrained in primate chairs, operated a small lever mounted in front of them under a multiple fixed-ratio (FR) 50 fixed-interval (FT) 1000 sec schedule (Dews, 1978). The monkeys were modestly food deprived and food of the preferred kind was delivered according to the schedule. In the presence of a yellow light and tone, 50 operations of the key resulted in delivery of a 0.2 g pellet of high protein food at each of the first five key operations. In the presence of a green light each of the first five key operations after the elapse of 1000 sec delivered a similar pellet. The sequence of components was as follows: FR, FR, FR, FI, FR, FI, FI, FR, FR, FR, FR, FR, FR, FR, FR, FR, FI, FI, FR, FI, FR, FR, FR, FI, FI, FI, FR, FI, FR, FR, FR, FR, and the sessions lasted a little over 3 hr, the exact length depending on responding. The rates of responding and the patterns of responding in time were recorded. Duplicate doses in each monkey were studied.

Drug administration. Cannabinoids were given orally to mice (10 ml/kg) and rats (12 ml/kg) as a suspension in 1% Tween 80. To dogs they were given orally either as a suspension in 1% Tween 80 (2 ml/kg) for all three cannabinoids, or in a gelatin capsule alone (for canbisol) or as a co-precipitate with polyvinylpyrrolidine in the ratio 1:9 (for nabilone). The different forms of administration did not appear to affect the behavioral effects so will not be further distinguished. For intravenous administration, the drug was dissolved in ethanol and the solution was diluted with 0.05% Tween 80 to give a final ethanol concentration of 5%. The dose was contained in 0.2 ml/kg. To the monkey they were given intramuscularly dissolved in 0.2 ml of ethanol, which given alone had no discernible effect. Doses were spaced at least a week apart and for the larger doses at least a month apart.



NABILONE R: =O

CANBISOL R: —OH

Fig. 1. Formulas of nabilone and canbisol.

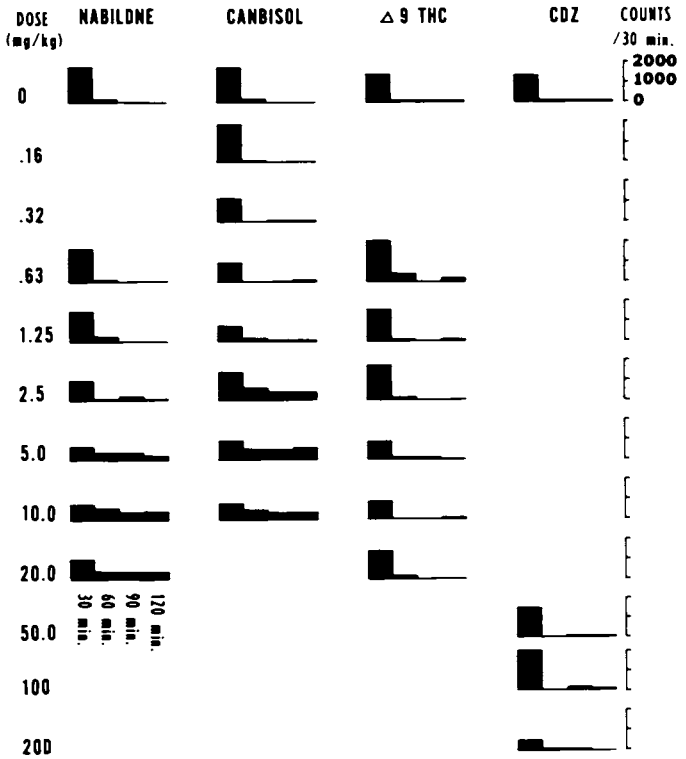


Fig. 2. Time course of effects of agents on activity of mice. Untreated mice showed a very large decrease in activity from the first half-hour period to subsequent periods. Drugs increased or decreased activity in the first period and in the subsequent periods independently. Note particularly that after the larger doses of nabilone and canbisol activity in the initial period was greatly decreased but activity in the later period was greatly increased while decreases in the first period after Δ^9-THC or chlordiazepoxide (CDZ) were not followed by increases in subsequent periods.

TABLE 1

Consumption of food by rats in the 3-hr period from 1 to 4 hr after drug

Dose	Food Eaten							
	Nabilone		Canbisol		Δ^9-THC		Chlordiazepoxide	
	Control	Drug	Control	Drug	Control	Drug	Control	Drug
mg/kg p.o.	*g*		*g*		*g*		*g*	
Vehicle	11.6	12.0	13.2	13.0	10.9	10.8	17.0	17.0
0.16			13.4	13.6				
0.31			13.6	11.4*				
0.62			12.3	8.7*				
1.25			14.2	5.3*				
2.5	13.1	12.6						
5.0	13.3	9.2*						
10.0					16.3	17.0	15.0	15.0
20.0					15.0	13.8*	15.6	15.8

* Significantly different from control ($P < .05$).

Chlordiazepoxide was given as the aqueous solution of the hydrochloride and doses are in terms of the base.

Statistics. Statistical significance was assessed by Student's t test comparisons of control values with values after individual doses of the drugs except for the muricide and dog ataxia tests where chi-squares were calculated from the numbers of animals responding at the various doses. "Significant" means $P < .05$.

Results

Mouse activity. Registered activity of normal mice declined greatly from the first to the second half-hour periods and often again from the second to a low level maintained through the third and fourth periods (fig. 2). The coefficient of variation of the counts in the first half-hour period was about 0.13, based on more than 30 determinations, so a reduction in the count to 60% of control was highly significant. In the third and fourth half-hour periods, the coefficient of variation was about 1 so a tripling was necessary to attain statistical significance; as the counts in these periods in control experiments were very low; however, any substantial count represented far more than a tripling of the control value.

Following 0.63 mg/kg of nabilone, 0.16 mg/kg of canbisol and 0.63 mg/kg of Δ^9-THC the counts were normal, showing that the lower end of the dose-effect curve had been reached and also that the vehicle itself was without detectable effect. After 5 mg/kg and higher doses of Δ^9-THC there was a significant decrease in activity in the first period and no change from the low control rate in the remaining periods. The slope of the dose-effect curve was low, with no dose-dependence apparent over the 4-fold range from 5 to 20 mg/kg.

Chlordiazepoxide significantly increased activity at 100 mg/kg. At 200 mg/kg there was a substantial and significant reduction in activity in the first half-hour period.

Nabilone and canbisol had qualitatively similar effects to one another on activity. At doses of 2.5 mg/kg and above for nabilone and 0.32 mg/kg and above for canbisol, initial activity was significantly reduced. With higher doses, the initial decrease was followed by a large and significant increase in the subsequent periods over what it would have been in the absence of the drug.

Rat food consumption. The amounts of food eaten by the individual rats were highly consistent from day to day, showing a coefficient of variation of only 0.06 (table 1).

While Δ^9-THC slightly reduced food consumption at 20 mg/kg, the highest dose studied, chlordiazepoxide did not do so. In contrast, 5.0 mg/kg of nabilone and doses of 0.31 mg/kg and above of canbisol reduced food consumption. Food intake was reduced to less than 50% of control by 1.25 mg/kg of canbisol.

Rat muricide. Untreated muricidal rats never took as long as 60 sec to kill a mouse, so control scores are uniformly zero, and so any score is probably biologically significant (table 2). Because of the variability of scores after drug, however, conventional statistical significance is attained following a dose of 20 mg/kg of Δ^9-THC but not following 10 mg/kg. Chlordiazepoxide had no effect up to 40 mg/kg. Nabilone caused a slight slowing at the lowest dose studied, 0.62 mg/kg, and statistically significantly slowed muricide at 1.25 mg/kg. Canbisol had measurable effects at 0.31 mg/kg, statistically significant effects at 0.62 mg/kg and totally suppressed muricide at 1.25 mg/kg and above.

Rat septal lesion reactivity. Rats given only vehicle showed highly consistent reactivity scores before and after intubation, so that a score after a drug greater by only 0.10 was statistically significant (table 3).

At the highest dose studied, 20 mg/kg, Δ^9-THC caused no detectable effects but 20 mg/kg of chlordiazepoxide reduced reactivity. Both nabilone and canbisol reduced reactivity at the lowest dose studied, 0.62 mg/kg. The effect was statistically significant for canbisol at 0.62 mg/kg and became so for nabilone at 1.25 mg/kg. By 5 mg/kg, canbisol suppressed reactivity essentially completely.

Rat self-stimulation. There was considerable variability in the rates of self-stimulation, even under control conditions

TABLE 2
Muricide by rats

Dose	Average of Scores at 3, 4, 5 and 6 Hr after Drug							
	Nabilone		Canbisol		Δ^9-THC		Chlordiazepoxide	
	n	Mean score	n	Mean score	n	Mean score	n	Mean score
mg/kg p.o.								
Vehicle	6	0	6	0	6	0	6	0
0.16			15	0.03				
0.31			27	0.20				
0.62	9	0.11	27	0.63*				
1.25	9	0.39*	12	1.0*				
2.50	18	0.40*	6	1.0*				
5.0	9	0.57*	6	1.0*				
10.0	6	0.79*	3	1.0*	6	0.06	6	0
20.0					6	0.60*	6	0
40.0							6	0

* Significantly different from control ($P < .05$).

TABLE 3
Reactivity of rats with lesions in septal region

Dose	Average of Scores of Reduction in Reactivity at 3, 4, 5 and 6 Hr after Drug							
	Nabilone		Canbisol		Δ^9-THC		Chlordiazepoxide	
	n	Mean score	n	Mean score	n	Mean score	n	Mean score
mg/kg p.o.								
Vehicle	3	0.01	3	0	3	0.01	3	0.01
0.62	3	0.10	12	0.18*				
1.25	9	0.15*	12	0.20*				
2.50	18	0.29*	9	0.49*				
5.0	9	0.32*	3	0.96*				
10.0	12	0.52*	3	1.00*	6	0	12	0.13*
20.0					6	0	6	0.25*
40.0								

* Significantly different from control ($P < .05$).

TABLE 4
Self-stimulating rats

Dose	Rate of Responding (responses/sec) Sampled between 1 and 1 ½ Hr after Drug							
	Nabilone		Canbisol		Δ⁹-THC		Chlordiazepoxide	
	n	Rate	*n*	Rate	*n*	Rate	*n*	Rate
mg/kg p.o.		*responses/sec*		*responses/sec*		*responses/sec*		*responses/sec*
Control	12	1.35 ± 0.27[a]	8	1.52 ± 0.18[a]	3	1.38 ± 0.69[a]	20	2.04 ± 0.19
Vehicle	12	1.37 ± 0.25[a]	8	1.40 ± 0.25[a]	3	1.44 ± 0.62[a]		
0.12	6	1.29						
0.16			6	1.47				
0.25	6	1.04	6	0.96*				
0.32								
0.50	6	1.57					7	2.12
1.0	6	0.70*						
2.0	6	1.09					6	2.08
4.0	6	0.33*						
5.0							10	1.83
10.0					3	0.75		

[a] Mean ± S.D.
* Significantly different from control ($P < .05$).

TABLE 5
Ataxia in dogs

Dose	Nabilone		Canbisol		Δ⁹-THC		Chlordiazepoxide	
	n	Mean score	*n*	Mean score	*n*	Mean score	*n*	Mean score
mg/kg p.o.								
i.v.								
0.001			4	0.06				
0.002			10	0.05				
0.004			14	0.18*				
0.008	2	0	8	0.22*				
0.016	6	0.08	3	0.42*	2	0		
0.032	17	0.21*	2	0.75	5	0.05		
0.062	6	0.54*			5	0.15*		
0.125					11	0.23*		
0.25					3	0.25*	2	0
0.50							2	0
p.o.								
0.10	2	0.75						
0.12	3	0.33*	2	0.12				
0.15			4	0.38*				
0.25			2	0.50	3	0.08		
1.0	5	0.35*	1	0.75				
1.25	1	0.25						
2.5	1	0.75						
3.0	3	0.50*						
-10.0	3	0.42*						

* Significantly different from control ($P < .05$).

(table 4). The rate of self-stimulation was reduced to almost 50% by 10 mg/kg of Δ⁹-THC, but the change did not reach statistical significance. The rate was not reduced appreciably by 5 mg/kg of chlordiazepoxide. Nabilone reduced responding at 1.0 mg/kg and canbisol at 0.32 mg/kg.

Dog ataxia. Normal dogs are not ataxic so any ataxia score is indicative of a pharmacological effect (table 5). Following a dose of drug, however, ataxia was very variable, making statistical significance hard to achieve with small numbers of subjects.

Some ataxia was detected at 0.062 mg/kg of Δ⁹-THC i.v. but 0.25 mg/kg i.v. did little more and this dose had a statistically insignificant effect when given orally. Chlordiazepoxide caused no ataxia at 0.5 mg/kg i.v. There were clear effects of nabilone at 0.032 mg/kg i.v. Orally, effects were seen at all doses from 0.10 to 10 mg/kg; the effect did not increase convincingly over this 100-fold increase in dose. Canbisol caused statistically significant effects even at 0.004 mg/kg i.v. Approximately 30 times as much was required orally, and the effect appeared to increase as the dose was increased from 0.12 to 1.0 mg/kg, but the increase is not convincing in view of the variability and irregularities with other drugs.

Monkey multi FRFI. After effective doses of the cannabinoids, sensitivity to the behavioral effects of the agents was reduced and only slowly returned to its original level. To obtain consistent effects it was found necessary to wait several weeks between doses. Combined with constraints preventing the use of many monkeys, the infrequent dosing prevented the accumulation of the desired number of observations, even over a period of years. The results presented in table 6 should therefore be regarded as semiquantitative. Following 0.1 mg/kg of Δ⁹-THC the rate of responding was increased significantly, under both FR and FI; higher doses usually decreased responding (but see fig. 3) and 3.0 mg/kg abolished responding. Chlordi-

TABLE 6
Mult FR50 FI1000 sec responding of rhesus monkeys

Dose	Ratio of Mean Rates of Responding from 20 to 2000 Min after Drug to Predrug Rates							
	Nabilone		Canbisol		Δ⁹-THC		Chlordiazepoxide	
	FR	FI	FR	FI	FR	FI	FR	FI
mg/kg								
Vehicle	1.08 ± 0.054[a]	0.97 ± 0.16[a]	1.26 ± 0.14[a]	0.61 ± 0.74[a]	1.10 ± 0.077[a]	0.70 ± 0.23[a]	1.36 ± 0.32[a]	0.76 ± 0.16[a]
0.03			0.90	1.67*				
0.1	1.20	0.89	0.91	0.15*	1.50*	1.31*		
0.3	0.99	1.05	0.20*	0.23*	1.15	0.90		
1.0	0.59*	0.35*			1.10	1.00		
3.0	0*	0*			0*	0*	1.03	1.50*
10.0							1.16	1.38*
30.0							1.59*	1.99*

[a] Mean ± S.E.
* Significantly different from control ($P < .05$).

azepoxide only increased responding up to the highest doses that could be given i.m. without unacceptable muscle irritation. Nabilone produced a statistically insignificant increase in FR responding following 0.1 mg/kg but decreased responding under both FR and FI at 1.0 mg/kg and abolished responding at 3.0 mg/kg. Canbisol caused a significant increase in rate under FI at 0.03 mg/kg but greatly reduced responding at 0.3 mg/kg. Indeed, following 0.3 mg/kg, responding occurred only in some of the experiments and then was confined to the beginning of the recording periods, to be followed by the complete suppression of responding for the rest of the session, as illustrated in figure 3.

Discussion

The effects of Δ⁹-THC on spontaneous motor activity of mice was simply to cause a decrease, in agreement with previous reports (McMillan, 1977). Chlordiazepoxide caused a slight increase, but only at a dose of 100 mg/kg, some 1000 times the human therapeutic dose. The effects of nabilone and canbisol were more complex. Control mice showed in the third and fourth half-hour observation periods only 3 to 4% of the activity in the first period. After 5 mg/kg of nabilone or canbisol the activities in the third and fourth half-hour periods were increased not only above the control rates in the corresponding periods but to as much as 20 or 30% of the activity of untreated mice in the *first* period. The increase is not a nonspecific compensation for the reduced activity in the first period, since no compensation was apparent with Δ⁹-THC or chlordiazepoxide. There is thus clear evidence of a qualitative difference between Δ⁹-THC, on the one hand, and nabilone and canbisol on the other; and chlordiazepoxide is different again.

In rats, 20 mg/kg of Δ⁹-THC failed to reduce reactivity of septal-lesioned rats, but reduced food consumption and slowed muricide in normal animals. Chlordiazepoxide reduced the reactivity of septal-lesioned rats at 20 mg/kg, a dose that did not reduce food consumption or slow muricide in normal animals. Nabilone, 1.25 mg/kg, and canbisol, 0.62 mg/kg, were active in slowing muricide, reducing reactivity of septal-lesioned rats and slowing self-stimulation. Thus, nabilone and canbisol resembled chlordiazepoxide in reducing reactivity of septal-lesioned rats but differed in reducing food consumption and slowing muricide. Nabilone and canbisol resembled Δ⁹-THC in reducing food consumption and slowing muricide but differed in that Δ⁹-THC did not reduce the reactivity of septal-lesioned rats. As nabilone and canbisol were active in all tests, no qualitative difference is the relatively low activity of nabilone in reducing food consumption and perhaps in slowing self-stimulation. Nabilone and canbisol, as well as Δ⁹-THC increased reactivity to touch as shown by vocalization, in agreement with Gough and Olley (1977).

The cannabinoids showed the familiar high activity in producing ataxia in dogs when given i.v. (Loewe, 1946). A prostrating effect of 0.5 mg/kg of Δ⁹-THC i.v. was found by Grunefeld and Edery (1969) and we confirmed their finding. We also found the dose-effect curves to have the very low slopes that have made quantitative studies in this species so imprecise. Larger doses by mouth were necessary to produce detectable effects. By mouth nabilone and canbisol were about twice as active as Δ⁹-THC in producing ataxia.

In the monkey, all four drugs tended to increase rates of responding at some doses. Proportionate increases were greater under FI than under FR, but when higher doses of the cannabinoids reduced and abolished responding there was no evidence of a substantial differential sensitivity to suppression of responding in the two components. In causing reduction in responding, nabilone was about 3 times and canbisol about 30 times as active as Δ⁹-THC, while chlordiazepoxide did not reduce responding at the highest dose studied, 30 mg/kg. An observable effect of Δ⁹-THC on the behavior of a rhesus monkey was reported by Grunefeld and Edery (1969) following 0.05 mg/kg of Δ⁹-THC i.v., while 2.0 mg/kg abolished responding under FR30 and DRL 15 sec (Harris *et al.*, 1972). In the chimpanzee, an increase in responding under DRL 10 sec but not under FR 40 followed Δ⁹-THC by mouth in doses of 1 or 2 mg/kg (Ferraro *et al.*, 1971). In view of the differences in the potency of cannabinoids by different routes our findings are quite compatible with these previous reports.

Most previous studies on mult FRFI responding in rats and pigeons have failed to find increases in rate in either component with Δ⁹-THC and other cannabinoids (Boyd *et al.*, 1963; Frankenheim *et al.*, 1971). No appreciable difference in sensitivity of FR and FI responding to Δ⁹-THC was found by Frankenheim *et al.* (1971) and to SP-1 (a pyridine analog) by Campo (1973) in pigeons. Boyd *et al.* (1963) (working before the identification of Δ⁹-THC) found FR responding to be more sensitive than FI responding to dimethylheptylpyran (dimethylheptyl THC) and methyloctylpyran (secondary nonyl THC) in rats. They also found FR responding to be more sensitive than FI responding to pentobarbital, chlorpromazine and amphetamine, which has not been the usual finding with the first two drugs by other workers (reviewed by Dews and DeWeese, 1977). In the present

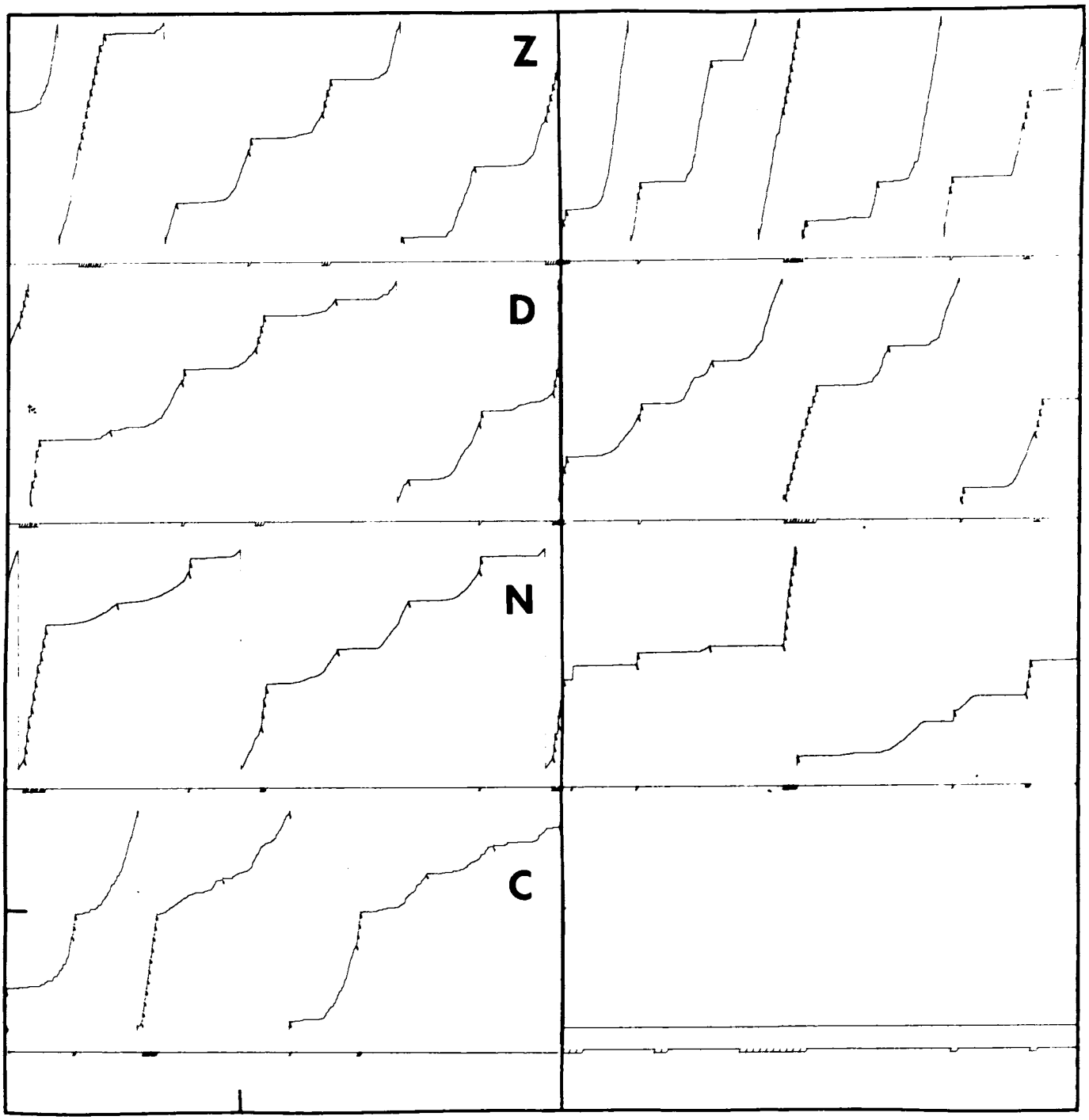


Fig. 3. Cumulative records of responding of rhesus monkeys under mult FR50 FI1000 sec. Scale shown on lower left: from origin to horizontal marker on vertical line represents 1000 responses and from origin to vertical marker on horizontal line represents 1000 sec. Each of four strips shows a control session on left and then a session after drug on the same day. The drug was given i.m. at the heavy vertical line and the subsequent session began 20 min later. *At Z* 10 mg/kg of chlordiazepoxide was given i.m. The FR rate after the drug was 1.18 times the rate before the drug (an increase not obvious on inspection) while the mean FI rate after the drug was 2.3 times the rate before the drug, an increase readily seen. The abrupt transitions from no responding to sustained responding in some of the intervals after the drug (*e.g.*, the 3rd, 4th and 6th) were not a consistent effect of chlordiazepoxide. *At D* 0.3 mg/kg of Δ^9-THC was given i.m. The rate of responding under FR was slightly increased. The mean FI rate after the drug was increased on this occasion but the finding was not consistent (table 6). The pattern of the cumulative record of FI responding was not obviously changed. *At N* 0.3 mg/kg of nabilone was given i.m. The pattern of FI responding shows serious disruptions with the fourth interval not completed and the sixth showing initial responding followed by no responding (the opposite of the normal pattern). *At C* 0.3 mg/kg of canbisol was given i.m. All responding was abolished.

studies, no convincing evidence of a difference between the sensitivity of responding under FR and FI to cannabinoids has been found, but all three cannabinoids gave an indication of increased responding at doses lower than those decreasing responding. That an increase occurred with all three drugs makes it appear likely to be a real pharmacological effect.

In conclusion, nabilone and canbisol showed similarities and differences to Δ^9-THC and to chlordiazepoxide in the different

tests. The behavioral pharmacological profile of cannabinoids is gradually emerging although it is still not possible to characterize the behavioral effects of cannabinoids in terms of a few attributes of behavior. It is now clear, however, that cannabinoids can have selective effects on different behavioral activities, and that there are qualitative differences between different cannabinoids.

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