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Effects of Δ^9-Tetrahydrocannabinol and Cannabinol in Man[1]

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Abstract. The interaction of Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabinol (CBN) was studied in man. Five male volunteers were given placebo, 50 mg CBN, 25 mg Δ^9-THC, 12.5 mg Δ^9-THC + 25 mg CBN, and 25 mg Δ^9-THC + 50 mg CBN (orally). Administrations were spaced 1 week apart. With physiological measures, Δ^9-THC produced an increase in heart rate while CBN did not. When combined, no change of the Δ^9-THC effect occurred. No changes occurred on the electrocardiogram, blood pressure, or body temperature. With psychophysical measures no changes occurred in pain thresholds or skin sensitivity as a function of drug treatment. In time estimates of the passage of 1 minute, Δ^9-THC alone produced underestimates of the passage of 1 minute and CBN alone had no effect. In combination the two drugs had a tendency to produce significant overestimates and underestimates of the passage of 1 minute. On a 66-item adjective-pair drug reaction scale, the volunteers reported feeling drugged, drunk, dizzy, and drowsy under the Δ^9-THC condition, but not under the CBN condition. With combined drug treatment, volunteers reported feeling more drugged, drunk, dizzy, and drowsy than under the Δ^9-THC condition alone. None of the drug treatments produced significant changes on other items which included items on perception, emotion, cognition and sociability. It appears that CBN increases the effect of Δ^9-THC on some aspects of physiological and psychological processes, but that these effects are small and cannot account for the greater potency which has been reported when plant material is used.

Interest is growing with respect to the pharmacological effects of several cannabis constituents, other than (–) Δ^9-trans-tetrahydrocannabinol (Δ^9-THC). Among these cannabidiol (CBD) and cannabinol (CBN) have received special attention. Both occur in considerable amounts in samples of marihuana plants

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(*Doreenbos et al.*, 1971; *De Vree et al.*, 1972; *Turner and Hadley*, 1973), are involved in the synthetic and degradation pathways of Δ^9-THC and were formerly said to be devoid of pharmacological activity (*Frankenheim et al.*, 1971; *Mechoulam et al.*, 1970). Evidence is growing rapidly which challenges the latter statement. Although inactive in man (*Hollister*, 1973; *Perez-Reyes et al.*, 1973; *Karniol et al.*, 1974a), CBD clearly possesses effects of its own in laboratory animals. It decreases ambulation of rats in an open field, induces catatonia in mice, potentiates barbiturate sleeping time in mice and has anticonvulsant activity in rats and mice (*Karniol and Carlini*, 1973a; *Paton and Pertwee*, 1972; *Izquierdo et al.*, 1973; *Karler et al.*, 1973). On the other hand, CBD potentiates Δ^9-THC effects on some liver enzymes (*Poddar et al.*, 1974), on intestinal motility (*Anderson et al.*, 1974), on induced analgesia in mice and on impairment of rope climbing of performance of rats (*Karniol and Carlini*, 1973a). CBD also blocks other effects of Δ^9-THC, such as catatonia in mice, corneal areflexia in rabbits, open-field defecation and aggressiveness in rats. *Karniol and Carlini* (1973a) suggested that CBD directly antagonizes the excitatory effects and/or potentiates the depressant effects of Δ^9-THC. In humans, *Karniol et al.* (1974a) have shown that CBD blocks Δ^9-THC effects such as increased heart rate, impairment of time production and psychotomimetic effects.

Data are also accumulating which show that CBN has activity of its own. *Mechoulam et al.* (1970) and *Frankenheim et al.* (1971) have reported no effect on monkeys and pigeons, *Fernandes et al.* (1973) have found that CBN, as CBD, binds to hepatic drug-metabolizing enzymes and inhibits the metabolism of aminopyrine and morphine. *Anderson et al.* (1974) reported that CBN produces a dose-dependent depression of intestinal motility in mice. *Takahashi and Karniol* (1975) showed that CBN provokes corneal areflexia in rabbits, induces analgesia, catatonia and prolongs barbiturate sleeping time in mice; induces aggressiveness and hyperirritability in REM sleep-deprived rats and impairs rope climbing performance of rats. In all these tests, the potency of CBN was considerably less than Δ^9-THC. CBN also has weak anticonvulsant activity (*Izquierdo et al.*, 1973; *Karler et al.*, 1973) and *Karniol et al.* (1974b) reported that it is about one eighth as active as Δ^9-THC in decreasing operant responses of rats. All these recent reports confirm the early observation of *Loewe* (1945) that 12 mg/kg of CBN produced marked ataxia and should be included among the compounds having marihuana activity. Concerning the interaction between CBN and Δ^9-THC the reports are conflicting. *Mechoulam et al.* (1970) reported that CBN did not alter Δ^9-THC effects on monkeys; *Krantz et al.* (1971) observed that CBN antagonized the prolongation of pentobarbital sleeping time produced by Δ^9-THC in mice; *Takahashi and Karniol* (1975) observed that CBN did not interfere with Δ^9-THC effects on rabbits' corneal areflexia and rats' open-field behavior, and slightly blocked Δ^9-THC effects on rats' aggressiveness and irritability. Furthermore, *Takahashi and Karniol* (1975), and *Karniol et al.*

(1974b) found that CBN effects added up to those of Δ^9-THC on analgesia, catatonia and prolongation of barbiturate sleeping time in mice and on operant responses and rope climbing performance of rats. As for man, *Perez-Reyes et al.* (1973) observed that intravenous CBN produced an effect comparable to that of Δ^9-THC although of less intensity. *Hollister* (1973), however, did not observe any effects in humans after receiving CBN orally. To the best of our knowledge there is no report published concerning an interaction between CBN and Δ^9-THC in humans.

These data led us to undertake the present experiments in which human volunteers ingested CBN, Δ^9-THC and different mixtures of both compounds.

Material and Methods

Drugs. (–) Δ^9-THC (kindly supplied by NIMH) and CBN (purchased from Makor Chemicals Ltd., Israel) were dissolved in 0.9 ml of ethanol, then placed in 200 ml of artificial orange juice.

Subjects. Five male human volunteers, from 25 to 29 years old, were used in this study. Four of the subjects were psychiatric residents at Escola Paulista de Medicina and the other was an architect.

Procedure. Each subject was given 6 drug administrations as follows: (1) placebo (0.9 ml ethanol in 200 ml of orange juice); (2) CBN 50 mg; (3) Δ^9-THC 25 mg; (4) Δ^9-THC 25 mg + CBN 12.5 mg; (5) Δ^9-THC 25 mg + CBN 25 mg; (6) Δ^9-THC 25 mg + CBN 50 mg. Drugs were given to each subject in a random order. 1 week between administrations was standard throughout, and a double-blind procedure was employed.

Prior to the initial test session, all subjects were given a physical examination (by *E.K.*) and a psychiatric interview which included drug use history (by *I.S.*). Table I presents the protocol for each test session, and the times at which various physiological and behavioral measures described below were taken.

Heart rate taken by standard pulse procedure, electrocardiogram (ECG), and systolic and diastolic blood pressure (sitting and standing). Body temperature was taken with an oral thermometer.

Time production task was measured using the method of *Karniol and Carlini* (1973b). At the times indicated on the protocol (table I), the subject was asked to estimate when he thought a 60-sec interval had passed ten times. In the first five time estimations (T1) no feedback was given to the subject concerning his accuracy. In the second five estimations (T2) the experimenter gave feedback by saying 'correct', 'too short', or 'too long' following each production. 50 min after drug ingestion (90–100 min) the subjects produced five more estimations without feedback (T3) and five with feedback (T4).

The analgesia test was the cold pressor test of *Wolff* (1971). In this test the subject immerses his hand in a lukewarm water bath (37 °C) for 2 min and then transfers it to an ice-water bath saturated with crushed ice. The subject was told to say 'now' when pain commenced (pain threshold) and removed his hand from the ice water when he could no longer tolerate the pain (pain tolerance threshold). This test was carried out with both right and left hands.

Skin sensitivity was measured using an anesthesiometer for determination of the two-point threshold on the smooth skin of the forearm. Both ascending and descending thresholds were taken. For further details on this method refer to *Lawson et al.* (1975).

Table I. Protocol for Δ^9-THC + CBN experiment

Time (min)	
Pre-drug	
0–10	explanation of the experiment
0–5	pulse rate: control measurements (5 times, 30-min interval)
5–15	blood pressure (BP): sitting and standing (2 times each), ECG
15–20	temperature (oral)
20–30	time production tasks (T1, T2)
30–45	analgesia, skin sensitivity
45–55	drug reaction scale
55–60	drug ingestion
Post-drug ingestion	
0–55	resting period
55	pulse rate
55–65	analgesia, skin sensitivity
65–75	drug reaction scale
75–90	BP, pulse rate, temperature, ECG
90–100	time production tasks (T3, T4)
100–120	psychological reaction (subjective scale) of drug action
120–130	analgesia, skin sensitivity
160–170	BP, pulse rate, temperature
170–180	drug reaction scale

Instructions to subjects prior to experiment: (1) do not drink alcohol the day before the experiment; (2) sleep normally, if possible, at your regular hours; (3) for breakfast have a slice of bread with butter and cheese, and a cup of coffee with milk, 1.5 h before the experiment; (4) after the experiment do not discuss it with anyone.

A subjective drug reaction scale (DRS) was administered at the times indicated on the protocol. It consisted of 66 subjective pairs and was modelled after the semantic differential of *Osgood et al.* (1957). The subject was given the following instructions:

'The purpose of the following questions is to verify how are you feeling at this moment. We will read 2 words together, generally with opposite meaning. If you do not think that either of the 2 words represent your feeling, that is, you are in intermediate state between the two situations, answer 'indifferent'. If one of the 2 words represent your feeling repeat the word and give a degree of intensity varying from 1 to 4. Degree 1 represents low intensity; degree 2, intermediate intensity, and 3 strong; degree 4 indicates the strongest intensity that you have ever felt. For instance: I will say the words well-ill. If you are not feeling either well or ill, you will answer indifferent. If you are feeling well, you will repeat this word (well) and you will try to quantify this state by one number. For example, if you are well, with little intensity will be degree 1. Your answer will be considered indifferent if you are not able to respond within 10 seconds.'

The DRS was broken down into seven factors as follows: perception of state, drugged-undrugged, sober-drunk (2 pairs); alertness and attention, adjective pairs concerning the sleep-waking cycle and attention, e.g., alert-drowsy (5 pairs); physical feelings, adjective

pairs concerning perception of physical reactions, e.g., dizzy-not dizzy, cold-hot (11 pairs); perception, adjective pairs concerning perception, e.g., seeing details-seeing the whole (6 pairs); emotion, adjective pairs concerning the emotions, e.g., serious-silly, euphoric-depressed (10 pairs); cognitive, adjective pairs concerning thinking and abstract mental states, e.g., coherent-incoherent, cautious-careless (18 pairs); sociability, adjective pairs concerning feelings of sociability, e.g., friendly-unfriendly, sociable-unsociable (5 pairs).

After the data were collected, the postdrug scores were subtracted from the predrug score for each item for each subject. This score represents the change from predrug baseline. Items which produced mean changes of greater than 2 scale points were subjected to analysis of variance.

Psychological reactions (subjective scale) to the drug were rated from 0–4, by the experimenter, using the previous criteria of *Karniol and Carlini* (1973b).

Table II. Pulse rates at several time intervals after drug ingestion[1]

Drug and dose(s), mg	Time after ingestion, min			
	50		75	160
Placebo	95.6 (11.5)		91.6 (10.6)	80.6 (8.9)
CBN 50	91.6 (8.6)	0.05[a]	87.1 (7.3)	82.4 (6.2)
Δ^9-THC 25	109.5 (10.4)		110.8 (18.2)	90.6 (8.8)
Δ^9-THC 25 + CBN 12.5	106.8 (7.2)	0.05[b]	110.6 (15.2)	98.0 (21.9)
Δ^9-THC 25 + CBN 25	104.2 (10.1)		104.0 (8.6)	92.4 (13.7)
Δ^9-THC 25 + CBN 50	102.8 (11.0)		100.0 (13.7)	99.2 (23.7)

[1] Percentage scores, where the mean of 5 pre-drug pulse rates is considered 100 %. SE shown in parentheses. Significance levels indicated to the right of the 50-min column (a = one-tailed test; b = two-tailed test; individual comparisons tests, *Winer,* 1962). No other comparisons were significant.

Table III. Percent of five time estimates from five subjects following various drug treatments without feedback (T3) and with feedback (T4)

Drug and dose, mg	Percent of estimates							
	T3 (sec)				T4 (sec)			
	< 45	45–55	55–65	> 65	< 45	45–55	55–65	> 65
Placebo	8	24	52	16	4	16	60	20
CBN 50	8	52	28	12	0	16	64	20
Δ^9-THC 25	28*	36	32	4	4	28	32	36
Δ^9-THC 25 + CBN 12.5	28*	32	24	16	16	40	28	16
Δ^9-THC 25 + CBN 25	16	36	12***	36	0	59***	27**	14
Δ^9-THC 25 + CBN 50	32**	24	20***	24	12	24	20***	44

* $p \leqslant 0.09$; ** $p \leqslant 0.05$; *** $p \leqslant 0.025$; (McNemar test), when compared with placebo condition (*Winer,* 1962).

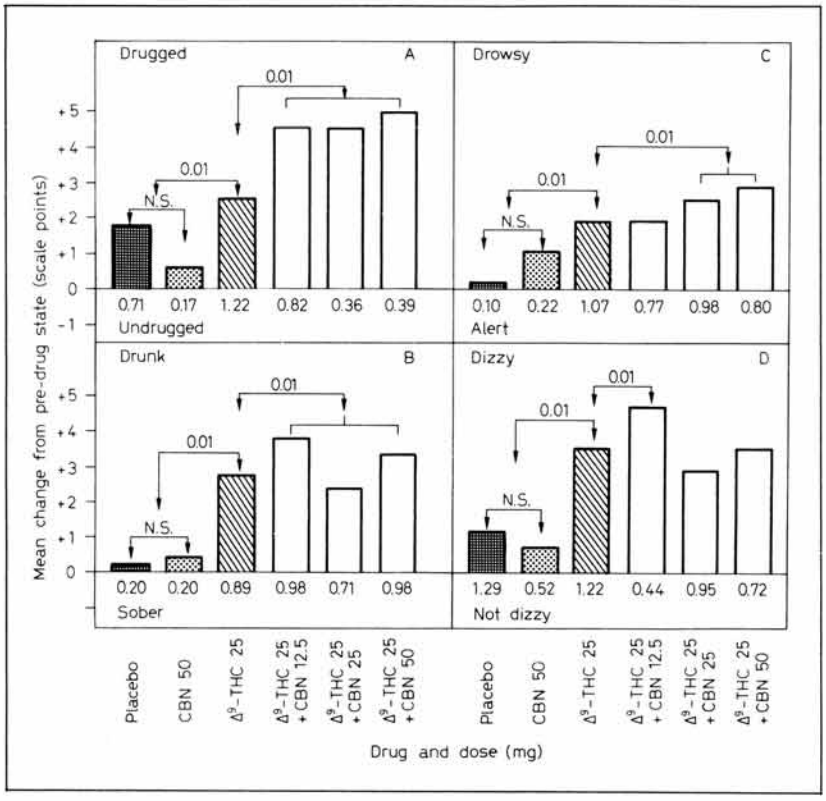

Fig. 1. Mean change from pre-drug state on 4 items of the DRS. Significant differences indicated by arrows above bars. SE are below each bar. (Individual comparisons test following analysis of variance, *Winer,* 1962.)

Results

Cardiovascular measures. Table II shows that 50 min after drug ingestion, Δ^9-THC produced a significant increase in heart rate, while CBN did not. When administered in combination, (Δ^9-THC and CBN) heart rate remained high. No clear pattern of summation or subtraction seemed to occur when the effects of the combined drugs are examined at 50, 75, and 160 min. Heart rate taken from the ECG 75 min confirmed these results in all respects. In all other ECG measures, no changes were observed that were related to drug treatment in any condition. No significant changes in blood pressure were observed under any condition.

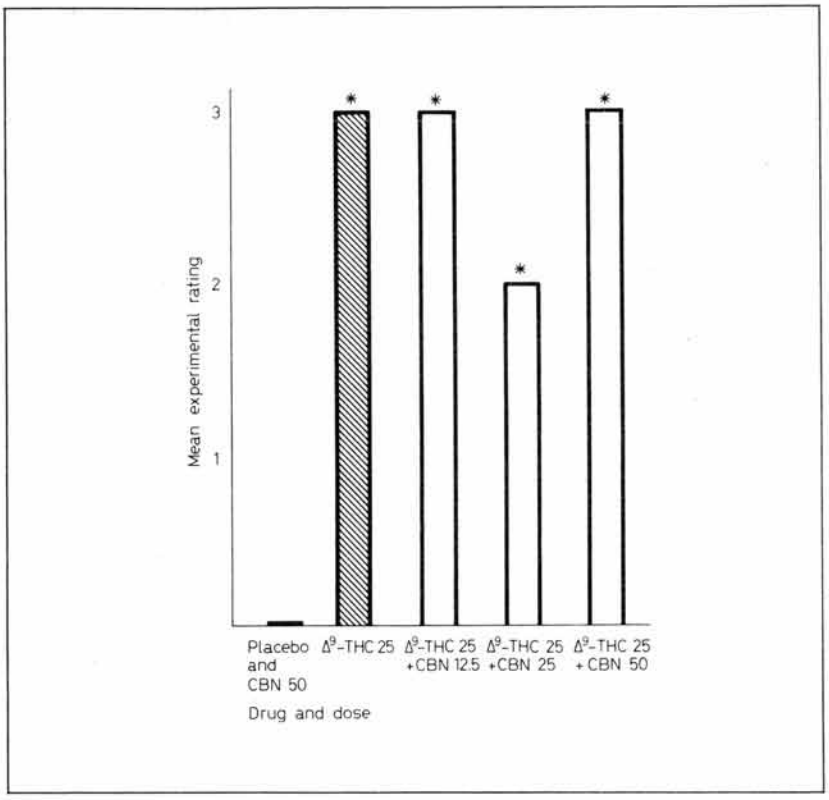

Fig. 2. Mean experimenter rating of the intensity of drug reaction experienced by the subjects in all treatment conditions. (*) Differs significantly from placebo group, $p \leqslant 0.001$, individual comparison test. SE do not exceed 0.1 scale point in any case.

Analgesia, skin sensitivity and body temperature. No significant changes in pain thresholds, pain tolerance thresholds, skin sensitivity or body temperature were observed as a function of drug treatments.

Time production task. Table III presents the effects of drug treatments. Without feedback (T3) Δ^9-THC and Δ^9-THC + CBN induced the subjects to underestimate the passage of 60 sec, while CBN alone did not. Furthermore, under the mixtures of Δ^9-THC + the larger doses of CBN the subjects made time estimations which were shorter and longer than placebo estimates, which resulted in a significant reduction of estimations made in the 55–65 sec category. With feedback (T4), combination of Δ^9-THC and CBN also produced fewer time estimates in the 55–65 sec range, while Δ^9-THC, CBN and placebo conditions do not differ from each other.

Drug reaction scale. On the first factor, perception of state (fig. 1A; the item drugged-undrugged), Δ^9-THC produced the feeling of being drugged and CBN was without effect. Combinations of both drugs increased feelings of being drugged when compared with the Δ^9-THC condition. Similar results were obtained for the item 'drunk-sober' (fig. 1B). On the second factor, alertness and attention, subjects reported that they felt drowsy under the influence of Δ^9-THC, but not under the influence of CBN. With combinations of Δ^9-THC and CBN, the subjects gave scores indicating they were more drowsy than with Δ^9-THC alone (fig. 1C). Other items on the alertness factor did not show any statistically significant differences as a function of drug treatment. On the third factor, physical feelings, Δ^9-THC causes subjects to feel dizzy (fig. 1D), CBN had no effect and Δ^9-THC + CBN, causes subjects to feel more dizzy than with Δ^9-THC alone. No other physical feelings items changed significantly. No changes of significant magnitude were found on the perceptual, emotion, cognitive or sociability factors.

Subjective scale. The experimenter judgment of the intensity of drug reaction is shown in figure 2. The experimenter was always able to tell when the subject had been given Δ^9-THC, or Δ^9-THC + CBN, while he could not distinguish placebo treatments from CBN alone. No differences were detectable on ratings of Δ^9-THC compared with Δ^9-THC + CBN.

Discussion

Δ^9-THC produced the expected effects on heart rate (table II), on time production task (table III), on the drug reaction scale (fig. 1) and on the psychological reaction observed by the experimenters (fig. 2). These effects have been reported before (*Isbell et al.*, 1967; *Tinklenberg et al.*, 1972; *Hosko et al.*, 1973; *Karniol and Carlini*, 1973b; *Carlini et al.*, 1974). On the other hand, Δ^9-THC did not change skin sensitivity, blood pressure, or body temperature and did not produce analgesia. Other authors have reported lack of effect of Δ^9-THC on some of these measures (*Hollister*, 1971; *Hill et al.*, 1973; *Tashkin et al.*, 1973).

The present data show that the 50 mg dose of CBN was inactive. It did not change the pulse rate (table II), did not impair time production (table III), and did not change the psychological reactions (fig. 1, 2) of the subjects. *Hollister* (1973) also reported that CBN, up to 400 mg orally, is inactive in man. *Hollister*'s data and ours, however, do not agree with the findings of *Perez-Reyes et al.* (1973) showing that 200 μg/kg of intravenous CBN has effects in humans. Obviously the route of administration is important in attempts to understand the contradictory reports. On the other hand, it remains to be seen whether CBN will have any effect when smoked.

In spite of being inactive *per se*, CBN discretely potentiated some effects of

Δ^9-THC. With both drugs combined, fewer subjects estimated the passage of 1 min within the normal range of 55–65 sec. The volunteers also reported to be more drugged (fig. 1A), more drunk (fig. 1B), more drowsy (fig. 1C) and more dizzy (fig. 1D) with the combination than under Δ^9-THC alone. CBN did not change Δ^9-THC effects on pulse rate (table II) and did not affect the experimenter's subjective estimation of drug effect on the subjects (fig. 2). As to the latter method, it is possible that, as Δ^9-THC alone produced such a large effect (grade 3) that a ceiling effect occurred thus masking any observable CBN potentiation.

Several authors have suggested that the activity of a marihuana sample cannot be explained on the basis of the Δ^9-THC content of one. For example, *Karniol and Carlini* (1972) and *Carlini et al.* (1974), in a comparative study of the effect of three marihuana samples and Δ^9-THC in rats, mice, rabbits and human beings, have shown that the effects of the samples were 2–4 times greater than should be expected from their Δ^9-THC content alone. Other authors have also presented similar data (*Isbell,* 1971; *Kubena and Barry,* 1972; *Galanter et al.,* 1973). *Carlini et al.* (1970) hypothesized that CBD and/or CBN could interact with the effects of Δ^9-THC. Recent work has actually demonstrated that CBD can interact with Δ^9-THC on laboratory animals (*Karniol and Carlini,* 1973a) and is able to block the Δ^9-THC effects on man (*Karniol et al.,* 1974a). The present work shows that CBN is different from CBD since it discretely potentiates Δ^9-THC effects in man. The potentiation, however, occurs with certain actions of Δ^9-THC and is of low potency. Therefore, we feel that CBN cannot account for the large increase in activity when Δ^9-THC is administered in the plant material as compared with the effects of Δ^9-THC alone (*Carlini et al.,* 1974).

References

Anderson, P.F.; Jackson, D.M., and Chesher, G.B.: Interaction of Δ^9-tetrahydrocannabinol and cannabidiol on intestinal motility in mice. J. Pharm. Pharmac. *26:* 138 (1974).

Carlini, E.A.; Santos, M.; Claussen, U.; Bieniek, D., and Korte, F.: Structure activity relationship of four tetrahydrocannabinols and the pharmacological activity of five semipurified extracts of *Cannabis sativa.* Psychopharmacologia *18:* 82–93 (1970).

Carlini, E.A.; Karniol, I.G.; Renault, P.F., and Schuster, C.R.: Effects of marihuana in laboratory animals and in man. Br. J. Pharmac. *50:* 299–309 (1974).

De Vree, T.B.; Breimer, D.D.; Van Ginneken, C.A.M., and Van Rossum, J.M.: Identification in hashish of tetrahydrocannabinol, cannabidiol and cannabinol analogs with a methyl side-chain. J. Pharm. Pharmac. *24:* 7–12 (1972).

Doreenbos, N.J.; Fetterman, P.S.; Quimby, M.W., and Turner, C.E.: Cultivation, extraction, and analysis of *Cannabis sativa* L. Ann. N.Y. Acad. Sci. *191:* 3–14 (1971).

Fernandes, M.; Warning, N.; Christ, W., and Hill, R.: Interactions of several cannabinoids with the drug hepatic metabolizing system. Biochem. Pharmac. *22:* 2981–2987 (1973).

Frankenheim, J.M.; McMillan, D.E., and Harris, L.S.: Effects of 1-Δ^9 and Δ^8-trans-tetrahydrocannabinol and cannabinol on schedule-controlled behavior of pigeons and rats. J. Pharmac. exp. Ther. *178:* 241–253 (1971).

Galanter, M.; Weingartner, H.; Vaughen, T.B.; Roth, W.T., and Wyatt, R.J.: Δ^9-transtetrahydrocannabinol and natural marihuana. Archs gen. Psychiat. *28:* 278–281 (1973).

Hill, S.Y.; Goodwin, D.W.; Schwin, R., and Powel, B.: Marijuana: CNS depressant or excitant? Am. J. Psychiat. *131:* 313–315 (1973).

Hollister, L.E.: Marihuana in man: three years later. Science *172:* 21–29 (1971).

Hollister, L.E.: Cannabidiol and cannabinol in man. Experientia *29:* 825–826 (1973).

Hosko, M.J.; Kochar, M.S., and Wang, I.H.: Effects of orally administered Δ^9-tetrahydrocannabinol in man. Clin. Pharmac. Ther. *14:* 344 (1973).

Isbell, H.; Gorodetzsky, C.W.; Jasinsky, D.; Claussen, U.; Spulak, F.V., and Korte, F.: Effects of (–) Δ^9-trans-tetrahydrocannabinol in man. Psychopharmacologia *11:* 184–188 (1967).

Isbell, H.: Clinical pharmacology of marihuana. Pharmac. Rev. *23:* 337–338 (1971).

Izquierdo, I.; Berardi, A.C., and Orsingher, O.: Effect of cannabidiol and of other *Cannabis sativa* compounds on hippocampal seizure discharges. Psychopharmacologia *28:* 95–102 (1973).

Karler, R.; Cely, W., and Turkanis, S.A.: The anticonvulsant activity of cannabidiol and cannabinol. Life Sci. *13:* 1527–1531 (1973).

Karniol, I.G. and Carlini, E.A.: The content of (–) Δ^9-trans-tetrahydrocannabinol (Δ^9-THC) does not explain all biological activity of some Brazilian marihuana samples. J. Pharm. Pharmac. *24:* 833–835 (1972).

Karniol, I.G. and Carlini, E.A.: Pharmacological interaction between cannabidiol and Δ^9-tetrahydrocannabinol. Psychopharmacologia *33:* 53–70 (1973a).

Karniol, I.G. and Carlini, E.A.: Comparative studies in man and in laboratory animals on Δ^8 and Δ^9-trans-tetrahydrocannabinol. Pharmacology *9:* 115–126 (1973b).

Karniol, I.G.; Shirakawa, I.; Kasinsky, N.; Pfeferman, A., and Carlini, E.A.: Cannabidiol interferes with the effects of Δ^9-tetrahydrocannabinol in man. Eur. J. Pharmacol. *28:* 172–177 (1974a).

Karniol, I.G.; Takahashi, R.N., and Musty, R.E.: Effects of Δ^9-tetrahydrocannabinol and cannabinol on operant performance in rats. Archs int. Pharmacodyn. Thér. *212:* 230–237 (1974b).

Krantz, J.C.; Berger, H.J., and Welch, B.L.: Blockade of (–) trans Δ^9-tetrahydrocannabinol depressant effect by cannabinol in mice. Am. J. Pharm. *143:* 149–152 (1971).

Kubena, R.K. and Barry, H., III: Stimulus characteristics of marihuana components. Nature, Lond. *235:* 397–398 (1972).

Lawson, R.B.; Goldstein, S.G., and Musty, R.E. Experiments in psychology (Oxford University Press, New York 1975).

Loewe, S.: Marihuana activity of cannabinol. Science *102:* 615–616 (1945).

Mechoulam, R.; Shani, A.; Edery, H., and Grunfeld, Y.: Chemical basis of hashish activity. Science *169:* 611–612 (1970).

Osgood, C.E.; Suci, G.J., and Tannenbaum, P.H.: The measurement of meaning (Univ. Illinois Press, Urbana 1957).

Paton, W.D.M. and Pertwee, R.G.: Effects of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. Br. J. Pharmac. *44:* 250–261 (1972).

Perez-Reyes, M.; Timmons, M.C.; Davis, K.H., and Wall, E.M.: A comparison of the pharmacological activity in man of intravenously administered Δ^9-tetrahydrocannabinol, cannabinol and cannabidiol. Experientia *29:* 1368–1369 (1973).

Poddar, M.K.; Bhattacharyya, K.C., and Ghosh, J.J.: Potentiating effect of cannabidiol on Δ^9-tetrahydrocannabinol-induced changes in hepatic enzymes. Biochem. Pharmac. *23:* 758–759 (1974).

Takahashi, R.N. and Karniol, I.G.: Pharmacological interaction between cannabinol and Δ^9-tetrahydrocannabinol. Psychopharmacologia *41:* 277–284 (1975).

Tashkin, D.P.; Shapiro, B.J., and Frank, I.M.: Acute pulmonary physiologic effects of smoked marijuana and oral Δ^9-tetrahydrocannabinol in healthy young men. New Engl. J. Med. *289:* 336–341 (1973).

Tinklenberg, J.R.; Kopeli, B.S.; Melges, F.T., and Hollister, L.E.: Marihuana and alcohol. Time production and memory functions. Archs gen. Psychiat. *27:* 812 (1972).

Turner, C.A. and Hadley, K.: Constituents of *Cannabis sativa* L.: absence of cannabidiol in an African variant. J. pharm. Sci. *62:* 251–255 (1973).

Winer, B.: Statistical principles in experimental design, pp. 105–116 (McGraw-Hill, New York 1962).

Wolff, B.B.: Factor analysis of human pain responses: pain endurance as a specific pain factor. J. abnorm. Psychol. *78:* 292–298 (1971).

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