PHARMACOLOGICAL REVIEWS
Vol. 23, No. 4

Printed in U.S.A.

GENERAL PHARMACOLOGICAL ACTIONS OF SOME SYNTHETIC TETRAHYDROCANNABINOL DERIVATIVES[1]

HAROLD F. HARDMAN,[2] EDWARD F. DOMINO AND MAURICE H. SEEVERS

Department of Pharmacology, University of Michigan, Ann Arbor, Michigan

In the 1940's Dr. Roger Adams synthesized a number of tetrahydrocannabinol derivatives. Subsequent studies by Loewe (26) indicated that these compounds have a wide spectrum of pharmacological activity. Adams *et al.* (1) designated 1-hydroxy-3(1,2-dimethylheptyl)-6,6,9-trimethyl7,8,9,10-tetrahydro-6-dibenzopyran (DMHP) as the most potent of his series of synthetic tetrahydrocannabinols. The parent compound of this series is 1-hydroxy-3-(n-amyl)-6,6,9-trimethyl 7,8,9,10-tetrahydro-6-dibenzopyran (NAP). The structures of these compounds are shown in figures 1 and 2, respectively. NAP has the same empirical formula as Δ^9-tetrahydrocannabinol (Δ^9-THC) (fig. 3). These compounds differ in that the double bond in the A ring is located in the 6A-10A position in NAP and in the 9–10 position in Δ^9-THC. According to the monoterpene numbering system NAP can be designated as Δ^3-THC. Another compound in this series with high potency is 1-hydroxy-3-(secondary nonyl)-6,6,9-trimethyl 7,8,9,10-tetrahydro-6-dibenzopyran (MOP). The structure of this compound is shown in figure 4.

From 1955 to 1959, under contract with the Army Chemical Center, Edgewood Arsenal, Maryland, the authors investigated the pharmacological activity of a series of eight synthetic tetrahydrocannabinols. The results of these studies were considered to be classified security information; permission to publish the data obtained was not granted until August 1970. The structural formulas and general cardiovascular activities of the series of eight compounds studied have been discussed by Hardman *et al.* (17, 18). The present paper will review in greater depth the pharmacological properties of a few of the compounds investigated by the authors, and will relate our observations to other publications on marihuana and its analogues. The accompanying paper by Domino *et al.* (10) presents discussion of the central nervous system (CNS) actions of marihuana and its surrogates.

Introduction of a double bond in the A ring at the 6A–10A position of the synthetic tetrahydrocannabinols eliminates *cis-trans* isomerism at these carbon atoms. Consequently the synthetic compounds are more rigid and planar than is Δ^9-THC, in which the double bond of the A ring is not located at the interface of

[1] Reference 15 represents the second summary progress report made to the Army Chemical Center, Edgewood Arsenal, Maryland, under contract number DA-18-108-CML-5663, order number CP5-4763, which was concluded in 1959. The data obtained in our studies were declassified and released for publication in August 1970. Three of our seven progress reports are now available for public distribution. They may be obtained from the Clearinghouse for Federation Scientific and Technical Information, Springfield, Va., 22151. The reports are identified by Accession Numbers AD 707 667, AD 707 668 and AD 707 669.

[2] Present address: Department of Pharmacology, The Medical College of Wisconsin, Milwaukee, Wisconsin 53233.

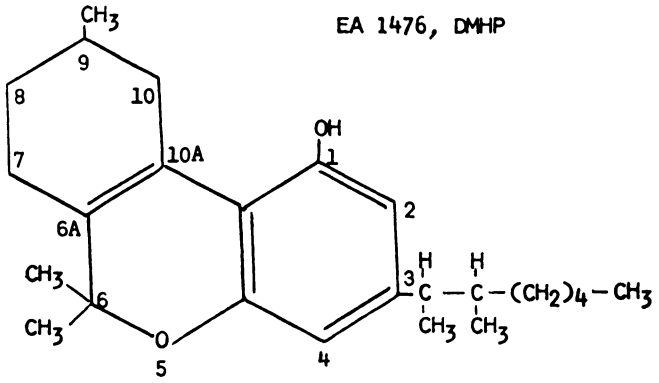


FIG. 1

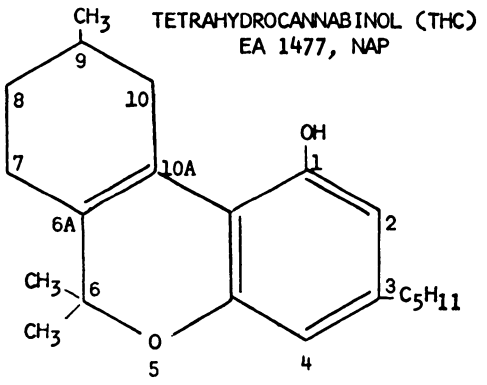
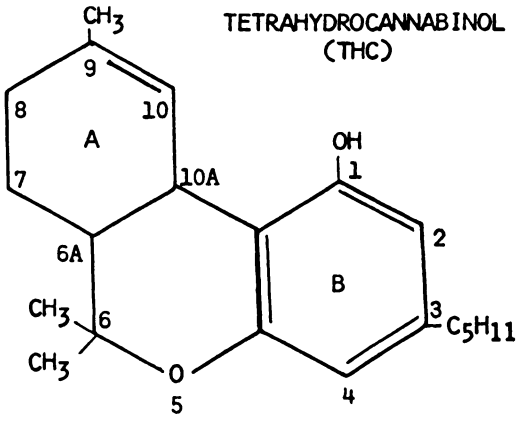


FIG. 2

two rings. DMHP contains three asymmetrical carbon atoms, and exists as eight optical isomers. Differences in pharmacological potency and efficacy which have been reported may be explainable on the basis of differing content of these isomers in the DMHP samples employed. For example, Davis and Ramsey (8) found DMHP to be 150 times as potent as diphenylhydantoin in the clinical suppression of grand mal epilepsy and also found DMHP to be effective in patients refractory to diphenylhydantoin. These studies were terminated when subsequent syntheses failed to yield samples of DMHP having similar activity (Davis, personal communication).

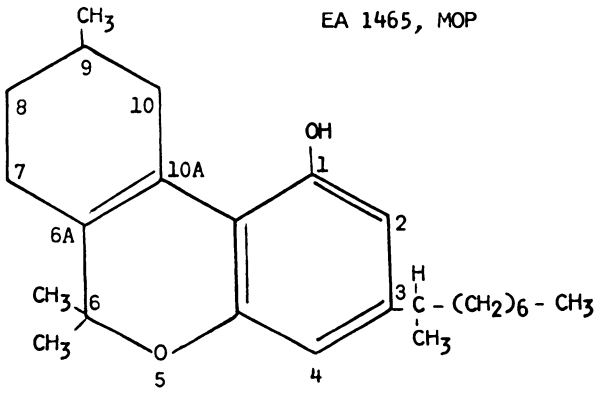
DMHP, NAP and MOP are water soluble, amber colored oils which can be dissolved in 95% ethanol, organic solvents, propylene glycol, or polyethylene glycol 400. A suspension of these oils may be prepared in saline solution containing 4% Tween-80, or an emulsion may be prepared by use of corn oil as the solvent and lecithin as the emulsifying agent. Since each of these solvents or suspending agents has some degree of pharmacological activity, control experiments are mandatory to evaluate the activity of the vehicle.

DMHP, NAP and MOP were furnished to the authors by Edgewood Arsenal under the code numbers EA 1476, EA 1477 and EA 1465, respectively. Samples of DMHP from two syntheses were provided, and were compared for pharmacolog-



Δ^9 THC

FIG. 3



MOP = METHYL OCTYL PYRAN

1-HYDROXY-3(SECONDARY NONYL)-6,6,9-TRIMETHYL
7,8,9,10-TETRAHYDRO-6-DIBENZOPYRAN

FIG. 4

TABLE 1

Pharmacological comparison of old versus new samples of DMHP (1.0 mg/kg, i.v.) in unanesthetized dogs in which the range of values observed is presented for controls and response*

	DMHP	Control	24-Hr Response	N
A. Heart rate/min	Old	80–120	36–60	5
	New	72–112	24–64	5
B. Respiratory rate/min	Old	20–40	2–10	5
	New	16–40	2–10	5
C. Hypothermia, °C	Old	39.5–41.2	25.5–34.3	5
	New	38.5–41.2	25.5–36.0	5

* Old: Non-refrigerated sample stored in closed container for 2 years.

ical activity. The pharmacological activities of these two samples (designated Old and New) were found to be indistinguishable (table 1). Storage of the original sample of DMHP for 2 years in a non-refrigerated, closed container in a desiccator did not alter potency. Loewe (personal communication) stated that DMHP is very stable and may be stored in an open container at room temperature for several years without showing marked alteration of pharmacological activity.

I. GROSS BEHAVIORAL RESPONSES

In animals, DMHP, MOP and NAP elicit CNS depression qualitatively similar to that produced by the naturally occurring Δ^9-THC. The duration of effect is dose dependent, and may last from several hours to several days. During the interval of drug effect animals do not respond in a normal manner to painful stimuli; a marked degree of analgesia is apparent. Very small doses of these agents (0.1 to 0.2 mg/kg of DMHP or MOP, administered intravenously) produce selective CNS depression in the dog. The animals show no signs of central excitation or analgesia and lie quietly; they passively resent being disturbed. Larger doses are required to produce a similar response in the monkey. As the dose is increased, a period of initial CNS stimulation followed by prolonged depression can be observed in both species. The recovery period is heralded by signs characteristic of emergence from general anesthesia. The animals, however, are not anesthetized at any time, and can be aroused from the depressed state through adequate sensory stimulation. The procedure of righting a dog or monkey and placing him in the normal position for locomotion usually produces arousal of short duration. This procedure may, in fact, induce a period of hyperexcitation and a very brief return of almost normal behavior. When the dose administered is sufficient to produce marked initial excitation (characterized by tremors or convulsions), these symptoms may return when the animal is subjected to forced arousal.

The three synthetic THC derivatives tested have nearly identical spectra of

pharmacological activity. They differ in potency; DMHP is the most potent, MOP is slightly less potent, and NAP, the parent compound of this class, is considerably less potent than DMHP. These drugs possess several additional interesting properties. DMHP in a single large dose (10 mg/kg, i.v.) can render a dog unconscious for 5 to 6 days, after which recovery is uneventful. In addition, a marked reduction in body temperature occurs during the phase of CNS depression. Elevation of body temperature to normal by placing the dog in warm water during the phase of CNS depression can initiate behavioral arousal.

II. CARDIOVASCULAR PHARMACOLOGY

Hypotension

The cardiovascular actions of a synthetic tetrahydrocannabinol (Parahexyl) and THC acetate obtained from cannabis resin were systematically studied by Loewe (26). He observed that these compounds have no effect upon the blood pressure of anesthetized dogs when administered over a wide dosage range. The only consistent cardiovascular effect he observed in dogs was a moderate decrease in pulse rate. Hardman *et al.* (15) reported that DMHP possesses marked hypotensive activity in the anesthetized dog. This hypotensive action is characterized by a prolonged latent period after intravenous administration. A profile of the cardiovascular activity of DMHP is presented in table 2. It can be seen that a concentration of 1.0 mg/kg DMHP produced an average decrease in mean arterial pressure of 72 mm Hg in a series of eight anesthetized dogs.

Additional studies were undertaken by the authors to determine a threshold dose of DMHP which can produce a significant reduction in mean arterial pressure. Comparative data are presented in table 3 to demonstrate the relative hypotensive potency of DMHP, NAP and reserpine. At the time of this investigation reserpine was not available in a water soluble form. N,N-dimethylacetamide was employed as a solvent for reserpine; the effect of this solvent on mean arterial pressure also is shown in table 3. It can be seen that 2 hr after administration of DMHP (0.05 mg/kg) to dogs a hypotensive response occurred which was statistically significant in comparison to the control group (dogs which received only the ethanol solvent). The reserpine treated group of dogs demonstrated a sig-

TABLE 2

Cardiovascular responses of the anesthetized dog 4 hr after DMHP (1.0 mg/kg, i.v.)*

	Control $\bar{x} \pm$ S.E.	4-Hr Response $\bar{x} \pm$ S.E.	Mean Diff.	N	P Value
Mean arterial pressure mm Hg	177 ± 8.6	105 ± 8.5	−72	8	<0.01
Heart rate/min	177 ± 7.1	130 ± 2.3	−47	8	<0.01
Respiratory rate/min	18 ± 3.6	11 ± 1.4	−7	8	<0.05
Rectal temp. °C	38.3 ± 0.3	37.3 ± 0.6	−1.0	8	<0.02

* Sodium pentobarbital (30 mg/kg, i.v.).
Room temperature = 23°C.

TABLE 3

Percentage of change in mean arterial blood pressure to DMHP, NAP and reserpine, i.v., in the dog anesthetized with sodium pentobarbital (30 mg/kg, i.v.)

Controls				Experimental			
Time	% Change	±S.E.	N	% Change	±S.E.	N.	P Value
	EtOH* 0.1 ml/kg			DMHP 0.05 mg/kg			
10 min	+0.04	1.2	5	−2.1	1.4	6	>0.20
30 min	−1.40	2.8	5	−7.4	3.0	6	>0.20
1 hr	−0.60	3.3	5	−15.1	5.6	6	>0.05
2 hr	+0.40	5.7	5	−18.4	4.8	5	<0.05
3 hr	+1.20	4.6	5	−23.3	3.1	5	<0.01
4 hr	+1.90	1.8	3	−22.4	3.2	5	<0.01
	EtOH* 0.1 ml/kg			NAP 10.0 mg/kg			
10 min	+1.0	0.1	6	−6.7	3.7	6	>0.05
30 min	−0.1	1.5	6	−11.2	5.8	6	>0.10
1 hr	−6.4	4.7	6	−21.3	5.7	6	>0.05
	NNDMA† 0.1 ml/kg			Reserpine 1.0 mg/kg			
10 min	−2.5	1.7	6	+6.5	2.3	5	<0.02
30 min	−5.7	2.5	6	+3.7	4.4	5	>0.05
1 hr	−17.7	5.9	6	−12.1	3.2	5	>0.05
1.5 hr	−11.2	3.4	6	−29.5	7.6	5	<0.05
2 hr	−15.8	2.6	6	−25.4	2.3	5	<0.05

* 95% ethyl alcohol.

† 100% N,N-dimethylacetamide.

nificant pressor response 10 min after drug administration and a significant hypotensive response 1.5 hr after drug administration.

Trapold *et al.* (34) and Bein (2) postulated that reserpine produces a fall in blood pressure by depressing sympathetic outflow at the level of the hypothalamus. Experiments were conducted in our laboratory to evaluate the role of the sympathetic nervous system in the depressor response initiated by DMHP.

The common carotid occlusion (CCO) pressor reflex was studied in dogs anesthetized with sodium pentobarbital. DMHP, NAP and reserpine were evaluated in this preparation by the method of Prochnik *et al.* (31). In this procedure percentage of change in the pressor response to carotid occlusion is corrected for changes in the control mean arterial pressure. The data obtained are presented in table 4. DMHP (0.05 mg/kg, i.v.) significantly reduces the CCO pressor response within 30 min; NAP (10.0 mg/kg, i.v.) produces a significant reduction in the CCO pressor response within 10 min. In contrast, it was not possible to demonstrate a significant effect with reserpine (1.0 mg/kg, i.v.), although Trapold *et al.* (34) had shown that this dose can cause a significant reduction in the CCO pressor response 1 hr after intravenous administration. This discrepancy may be related to the solvent employed in the reserpine solution, since N,N-dimethyl-

acetamide has an effect upon the CCO pressor response and also has hypotensive activity (see table 3).

The CCO pressor reflex has been utilized by Lape and Hoppe (24) as an index of functional sympathetic activity and by Trapold *et al.* (34) as a screening procedure to identify drugs which have reserpine-like activity. It is a sensitive and reproducible method for evaluating drugs which inhibit central sympathetic outflow. Hardman *et al.* (16) have described a quantitative method whereby the inhibition of sympathetic outflow which reduces the CCO pressor response can be evaluated independently from a reduction in blood pressure. It is of interest to note that the reduction in CCO pressor response by DMHP (table 4) is statistically significant long before mean arterial blood pressure (table 3) is reduced significantly. This suggests that peripheral compensatory mechanisms may operate to maintain mean arterial blood pressure despite a significant reduction in sympathetic tone to peripheral blood vessels.

Administration of NAP in doses 200 times those employed for DMHP also

TABLE 4

Percentage of change in common carotid occlusion (CCO) (30 sec) pressor response in the dog anesthetized with sodium pentobarbital, 30 mg/kg, i.v.*

	Control			Experimental			
Time	% Change	±S.E.	N	% Change	±S.E.	N	P Value
	EtOH† 0.1 ml/kg			DMHP 0.05 mg/kg			
10 min	−1.8	2.9	5	−4.7	3.0	6	>0.50
30 min	+5.3	4.0	5	−15.0	3.4	6	<0.01
1 hr	−0.6	5.5	5	−29.8	2.6	6	<0.01
2 hr	−1.9	8.5	5	−35.8	8.4	6	<0.05
3 hr	−5.2	4.8	5	−30.5	6.0	5	<0.02
4 hr	−9.8	8.5	3	−24.5	11.7	5	>0.30
	NNDMA‡ 0.1 ml/kg			Reserpine 1.0 mg/kg			
10 min	−0.3	6.3	6	−13.0	2.1	5	>0.30
30 min	−7.3	6.7	6	−18.0	6.5	5	>0.40
1 hr	−16.0	9.1	6	−15.0	9.6	5	>0.50
1.5 hr	−11.0	6.0	6	−10.3	6.0	5	>0.50
2 hr	−12.0	5.0	6	−25.0	8.1	5	>0.20
	EtOH† 0.1 ml/kg			NAP 10.0 mg/kg			
10 min	+2.5	2.4	6	−22.8	6.7	6	<0.01
30 min	−5.3	1.4	6	−32.8	8.9	6	<0.02
1 hr	−6.3	2.5	6	−32.2	10.5	6	<0.05

* The percentage of change in the CCO pressor response represents the difference, expressed as percent, between the mean value of 3 control pressor responses taken at 10-min intervals at the beginning of the experiment and a single pressor response obtained after drug administration at the time indicated.

† 95% ethyl alcohol.

‡ N,N-dimethylacetamide 100%.

significantly reduces the CCO pressor response (table 4). Although the onset of action is more rapid than that of DMHP, there is no significant difference between the magnitude of response to these two compounds 1 hr after administration. Thus, DMHP is approximately 200 times as potent as is NAP in regard to ability to reduce the CCO pressor response.

Bose *et al.* (4) reported that cannabis resin (8 mg/kg, i.v.) reduces the CCO pressor response by approximately 75% 30 min after administration to anesthetized dogs. Dewey *et al.* (9) observed that Δ^9-THC (3.0 mg/kg, i.v.) does not inhibit the contraction of the cat nictitating membrane after electrical stimulation of the preganglionic fiber to the superior cervical ganglion. They concluded that the inhibitory effect of 1 mg/kg of Δ^9-THC on the CCO pressor response is not due to ganglionic blockade. The authors also report that Δ^9-THC (1 mg/kg) produces a hypotensive effect in anesthetized dogs, and therefore they eliminate peripheral ganglionic blockade as a possible explanation for the reduction in blood pressure produced by this compound.

Hardman *et al.* (15) reported that DMHP (0.1 mg/kg, i.v.) does not significantly lower blood pressure of cats in which the spinal cord has been transected at the first cervical vertebra. These spinal cats show a normal pressor response after administration of graded doses of epinephrine. In anesthetized dogs, the pressor response to graded doses of epinephrine is retained after administration of DMHP (0.05 mg/kg, i.v.). The relative rise in blood pressure produced by graded doses of epinephrine is enhanced when mean arterial pressure has been reduced significantly by DMHP. However, the absolute pressure attained is not significantly different from that observed during the control pressor responses to epinephrine. These observations are consistent with the hypothesis that DMHP reduces blood pressure in dogs and in cats by decreasing sympathetic tone to peripheral blood vessels. The possibility that DMHP may possess *alpha*-adrenergic blocking activity also is excluded.

Subsequent studies by Dagirmanjian and Boyd (7) confirmed the observation that high spinal section (C-1) in the cat effectively blocks the hypotensive response to DMHP (0.1 mg/kg, i.v.). They also reported that in the atropinized cat pretreated with hexamethonium (2.5 mg/kg) administration of DMHP as described above produces a further reduction in blood pressure. This observation eliminates ganglionic blockade as a possible mechanism of hypotensive action of DMHP, and is compatible with the hypothesis proposed by Hardman *et al.* (15) that DMHP reduces peripheral vascular sympathetic tone *via* a central action. However, the statement by Dagirmanjian and Boyd (7) that dibenamine hydrochloride (10 mg/kg) and piperoxan hydrochloride (10 mg/kg) do not alter the blood pressure response of the anesthetized cat to DMHP does not support the hypothesis that DMHP acts centrally to reduce peripheral sympathetic tone. From their data it is not possible to determine the effectiveness of the *alpha*-adrenergic blockade produced before administration of DMHP. If that blockade was complete, further blood pressure reduction resulting from reduced sympathetic activity would not be expected. Additional data are needed to substantiate the statement of Dagirmanjian and Boyd that the hypotensive response to

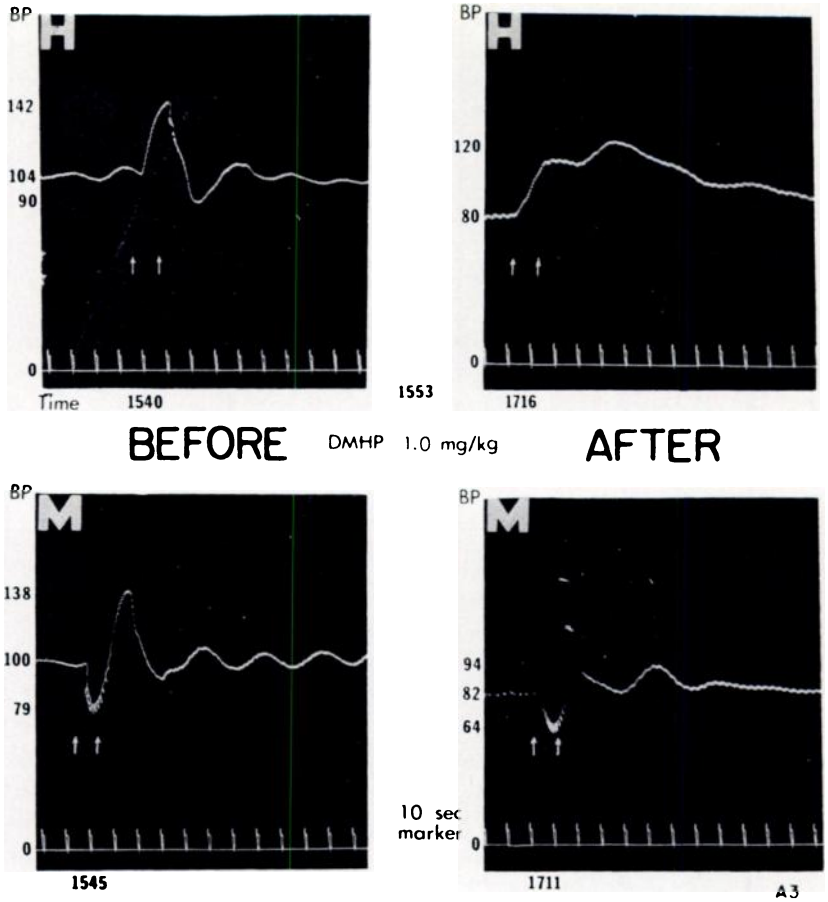


FIG. 5

DMHP is not inhibited by prior administration of *alpha*-adrenergic blocking agents.

Hardman *et al.* (15) studied the effect of DMHP (1.0 mg/kg, i.v.) upon electrical stimulation of the hypothalamic and medullary vasomotor areas of the cat anesthetized with sodium pentobarbital. By means of the stereotaxic technique stimulating electrodes were placed in the posterolateral area of the hypothalamus and in the medullary vasomotor center. The blood pressure response to 10-sec stimulation of these areas before and after administration of DMHP is illustrated in figure 5. Note the biphasic response of arterial pressure to stimulation of the medullary vasomotor area. The mean blood pressure is reduced by about 20% 1 hr and 23 min after administration of DMHP (1.0 mg/kg, i.v.). The pressor response to hypothalamic stimulation is of the same magnitude as the control response, but the form and duration is modified. Hypothalamic stimulation is accompanied by pilomotor erection and pupillary dilatation. Stimulation of the medullary vasomotor area produces a fall in blood pressure of about the same

magnitude as that of the control response, while the anticipated pressor response is greatly reduced. Experiments of this type suggest that DMHP has some direct depressant effect on medullary vasomotor sites. Recent experiments by Hosko and Hardman (20) indicate that Δ^9-THC can raise the stimulation threshold for pressor responses obtained by stimulation of the medullary or hypothalamic areas of the cat.

Dagirmanjian and Boyd (7) suggested that DMHP may act on central sympathetic centers concerned with vasomotor control. They implicated the region between the mesencephalon and the first cervical vertebra, because sectioning of the neuraxis at the midbrain level did not alter the anticipated hypotensive response to DMHP (0.1 mg/kg, i.v.) in cats. In contrast, the hypotensive response to DMHP was prevented when the neuraxis was sectioned at C-1.

Other sites have been explored in an attempt to explain the mechanism of the hypotensive action of DMHP. Hardman *et al.* (15) examined the effect of DMHP (1.0 mg/kg) in the denervated dog heart-lung preparation. The drug was added to 1 liter of circulating blood when the heart was in a state of semifailure [Competence Index value of 0.5 according to Wollenberger (35)]. Under this condition both negative and positive inotropic drug effects can be detected. No effect upon cardiac output or heart rate was seen with DMHP in this preparation. Manno *et al.* (27), however, have reported that Δ^9-THC has a negative inotropic effect in the isolated, perfused rat heart. Dewey *et al.* (9) reported that Δ^9-THC reduces cardiac output and heart rate in anesthetized dogs without producing a significant effect on stroke volume. The possibility that Δ^9-THC may reduce cardiac output by effecting a decrease in heart rate has not been ruled out. Bradycardia has been observed by Loewe (26) after administration of both THC and Parahexyl to dogs. He noted that this effect could be abolished by atropinization or by sectioning the vagus nerves. Hardman *et al.* (15) observed that atropinization of the anesthetized dog reduces but does not eliminate the bradycardia induced by DMHP. DMHP consistently produces bradycardia in doses greater than 0.1 mg/kg, intravenously, when administered to dogs anesthetized with sodium pentobarbital (35 mg/kg). They also reported that bradycardia is a prominent feature after DMHP administration to unanesthetized dogs or monkeys. An initial tachycardia, followed by the characteristic bradycardia usually is seen when DMHP is administered to unanesthetized dogs or monkeys. Dagirmanjian and Boyd (7) did not observe a significant bradycardia in anesthetized cats after DMHP administration in doses ranging from 0.05 to 0.4 mg/kg, intravenously. They did record a consistent but not significant decrease in heart rate in a large series of cats.

Boyd *et al.* (5) recently reported that Δ^9-THC and Δ^8-THC administration in cumulative doses of 0.25 to 1.5 mg/kg, intravenously, to the squirrel monkey produces a consistent and marked fall in mean arterial blood pressure. This observation was unexpected in view of reports by Isbell *et al.* (21) and Isbell and Jasinski (22) that Δ^9-THC does not affect blood pressure in man. In contrast, however, DMHP has been shown by Sim and Tucker (33) to be an effective hypotensive agent in man when administered orally in microgram quantities.

The data cited support the concept that synthetic THC derivatives which contain a double bond in the 6A—10A position have marked hypotensive properties in dogs, cats, monkeys and man. The most active compound in this series to date, DMHP, appears deserving of clinical trial in treatment of essential hypertension. Hypotensive action of Δ^9-THC and Δ^8-THC has not been clearly demonstrated, although preliminary reports suggest that they reduce blood pressure in cats, dogs and monkeys when administered in doses of approximately 1.0 mg/kg, intravenously. The difference between the hypotensive action of Δ^9-THC and of the synthetic THC derivatives such as DMHP appears to be quantitative rather than qualitative. The synthetic THC derivative, DMHP, is clearly more potent and has a much longer duration of action as a hypotensive agent than does Δ^9-THC.

III. DRUG INTERACTIONS

A. Potentiation of barbiturate sleeping time

Shore *et al.* (32) reported potentiation of barbiturate sleeping time in white mice by reserpine pretreatment. In our laboratory these experiments were repeated with the difference that DMHP was substituted for reserpine. The data (table 5) indicate that DMHP, in doses which range from 1.0 to 3.0 mg/kg, produces a progressive increase in hexobarbital-induced hypnosis of Webster strain Swiss mice. The maximal increase in sleeping time occurs at a dose of approxi-

TABLE 5

Mouse sleeping time potentiation by DMHP

Date	Hexobarbital 100 mg/kg, i.p.					Hexobarbital 100 mg/kg + DMHP,* i.p.						P Value
	Group no.	Avg. wt.	Average sleeping time	Range	N	Group no.	Dose DMHP	Avg. wt.	Average sleeping time	Range	N	
		g	*min*				*mg/kg*	*g*	*min*			
9–30	3	35	41	30–54	10	4	1.0†	34	74	50–89	10	<0.01
10–3	5	36	49	33–69	10	6	1.0	36	88	72–105	10	<0.01
10–5	7	35	49	36–65	10	8	3.0	36	123	80–180	10	<0.01
10–7	9	35	51	33–74	9	10	3.0	38	167	137–192	10	<0.01
10–10	13	18	50	40–59	10	12	5.0	18	114	82–136	8	<0.01
10–12	15	19	54	37–77	10	14	3.0	19	103	72–137	10	<0.01
10–14	20	19	47	39–54	5	17	3.0†	20	68	56–78	10	<0.01
10–26	21	25	61	56–67	10	22	1.0†	25	68	61–76	9	<0.01
10–26	21	25	61	56–67	10	23	3.0†	25	79	67–87	9	<0.01
10–28	24	20	57	42–66	9	26	Hexobarbital in 10% EtOH	19	56	34–91	10	>0.50
10–28	25	36	56	46–76	8	27	Hexobarbital in 10% EtOH	36	57	48–63	8	>0.50

* DMPH was administered 1 hr before hexobarbital.

† Fresh solutions of DMHP were made up on these days.

Groups 24–27 represent a comparison of hexobarbital (100 mg/kg) when saline or a 10% solution of ethanol is used as the drug solvent.

mately 3 mg/kg, intraperitoneally of DMHP. Comparison of groups 24 and 25 with groups 26 and 27 shows that ethanol in the amounts administered to solubilize DMHP does not prolong the hexobarbital-induced sleeping time.

Many similarities exist between the pharmacological actions of DMHP and reserpine. Since both drugs exert a tranquilizing action it is difficult to distinguish between them on the basis of gross behavioral effects alone. In addition, these two drugs have important similarities in regard to their effects on the cardiovascular system. The data in table 5 indicate further similarity in that both compounds can potentiate hexobarbital-induced sleeping time in mice. Dagirmanjian and Boyd (7) also have reported that DMHP and MOP significantly prolong hexobarbital-induced sleeping time in mice. They employed DMHP in doses of 0.2 mg/kg and obtained shorter sleeping time periods than those noted by the authors after administration of doses ranging from 1.0 to 5.0 mg/kg (table 5). The data of Dagirmanjian and Boyd show MOP to be approximately half as potent as DMHP. Garriot *et al.* (13) reported that several substituted 3-hydroxy-6-dibenzopyrans significantly prolong hexobarbital-induced sleeping time in mice. The compounds tested were effective in doses of 50 to 100 mg/kg and therefore are considerably less potent than DMHP. Gill *et al.* (14) demonstrated that a tincture of cannabis, in a dose range of 50 to 200 mg/kg, intraperitoneally, also can prolong barbiturate-induced sleeping time in mice. They noted a latent period of approximately 3 hr between administration of the cannabis extract and demonstration of sleeping time potentiation. The potentiation could not be demonstrated 24 or 48 hr after administration of cannabis.

Cannabis can cause a significant reduction in body temperature; information regarding the effect of such a drug-induced hypothermia on the duration of barbiturate-induced sleeping time was considered by Gill *et al.* (14) to be necessary to the interpretation of their sleeping time data. When mice were tested at 30°C environmental temperature (the thermal neutral zone for mice), cannabis still was capable of prolonging barbiturate-induced sleeping time. The authors also demonstrated no effect of cannabis on sleeping time induced by ether, a non-metabolized anesthetic. On the basis of these data, they suggest that cannabis interferes with the microsomal degradation of barbiturates and prolongs barbiturate sleeping time by this mechanism.

B. Gross behavioral interactions in the dog

Hardman *et al.* (15) have described the interaction in unanesthetized dogs of DMHP with other drugs which alter CNS activity. A summary of these experiments is presented in table 6.

The results obtained with DMHP plus either cocaine, *d*-amphetamine, caffeine or nalorphine indicate that each of these agents can antagonize the CNS depressant action of DMHP. Despite this apparent antagonism there were a marked number of fatalities in the double-treated groups. All drug doses employed were sufficiently low so that no animal died from treatment with a single drug. In this series of experiments administration of the second drug resulted in a transient period of stimulation which was followed by prolonged depression; the fatalities occurred during the phase of prolonged depression. Those animals which received

TABLE 6

Drug interactions with DMHP in the dog

Group No.	Drug No. 1 mg/kg, i.v. + Drug No. 2* mg/kg, i.v.	Behavioral Responses	Mortality†/No. Tested
1	DMHP, 1.0	Marked CNS depression for 24 hr. Complete recovery in 3 days.	0/3
2	Cocaine, 4.0	Immediate excitation, hyperpnea, then mild excitation for several hours.	0/4
3	DMHP, 1.0 + Cocaine, 2.0	DMHP sedation antagonized by cocaine, disorientation persists.	1/4
4	DMHP, 1.0 + Cocaine, 4.0	Cocaine induced convulsions in all dogs, sedation prominent 1 hr later.	2/4
5	*d*-Amphetamine, 1.0	Hyperactivity, piloerection, mydriasis. Complete recovery in <24 hr.	0/3
6	DMHP, 1.0 + *d*-Amphetamine, 1.0	Amphetamine induced arousal which persisted for several hours.	0/2
7	DMPH, 1.0 + *d*-Amphetamine, 2.0	Marked amphetamine arousal persisted for 3 hr.	3/3
8	Caffeine, 10.0	Hyperactivity and muscle tremors which disappeared in 3–4 hr.	0/2
9	DMHP, 1.0 + Caffeine, 10.0	Caffeine induced arousal and tonic extensor convulsions.	2/3
10	DMHP, 1.0 + Nalorphine, 6.0	Nalorphine induced arousal, convulsions and reversal of analgesia.	1/4
11	Morphine SO_4, 2.0‡	Emesis followed by CNS depression with recovery in 6 hr.	0/2
12	DMHP, 0.1 + Morphine SO_4, 2.0‡	After morphine sulfate, emesis, ataxia, hyperreflexia and respiratory stimulation. CNS depression and analgesia appeared to be enhanced after morphine sulfate.	0/4

* Drug no. 2 was administered 3 hr after drug no. 1 when the full effects of DMHP were evident.

† Mortality was counted for 3 days after drug administration.

‡ Subcutaneously.

DMHP (1.0 mg/kg, i.v.) plus *d*-amphetamine (2.0 mg/kg, i.v.) were examined postmortem for signs of duodenal bleeding, but the mucosa appeared normal.

Although quantitative measurements were not performed, it is the impression of the authors that morphine enhances both the CNS depressant effects and the analgesic properties of DMHP. In addition, it was noted that this combined drug regimen resulted in a normal or above normal respiratory rate; this observation was unexpected since either drug alone has definite respiratory depressant properties.

IV. TEMPERATURE REGULATION

One of the unique pharmacological actions of the tetrahydrocannabinol derivatives is the effect on body temperature. This action was described first by Hardman *et al.* (15) who observed that hypothermia could be induced in unanes-

TABLE 7

Effect of DMHP (1.0 mg/kg, i.v.) on deep rectal temperature in the unanesthetized dog

N	Mean °C ± S.E.					P Value
	Control	12 hr	Δ°C	24 hr	Δ°C	
5	39.1 ± 0.33	36.2 ± 0.55	−2.9 ± 0.6	29.6 ± 1.8	−9.5 ± 1.6	<0.01

Room temperature = 23°C.

thetized dogs after the intravenous administration of 1 mg/kg DMHP. These data are presented in table 7; it can be seen that the rectal temperature 12 and 24 hr after administration of DMHP is significantly reduced from control values. In these animals the hypothermic response became significant within 2 hr after drug administration; body temperature gradually returned to normal over a period of several days. The hypothermic response also can be demonstrated in anesthetized dogs (table 2).

Miras (30) reported that low doses of a cannabis resin extract (100–500 mg/kg in olive oil) injected intraperitoneally produce a definite hypothermic effect in rats. He estimated that the cannabis resin extract contained about 0.5 mg of THC per 200 mg of extract. After administration of doses above 500 mg/kg the hypothermic response persists for more than 12 hr. In experiments utilizing synthetic tetrahydrocannabinols administered at doses of 1.5 mg/kg, body temperature of the experimental animals fell progressively over a 24 hr period to values below 30°C. The experiments are quite similar to those reported by Hardman *et al.* (15) in table 7 of this paper regarding the hypothermic effect of DMHP. Miras did not identify the specific synthetic tetrahydrocannabinol used. Garattini (12) demonstrated that hashish extract can reduce body temperature of rats by 2°C. This was the maximum obtainable effect, and was not proportional to the dose of drug employed. Intracerebral injection of his extract consistently produces a hypothermic response which reaches a maximum value within 2 hr after injection. Holtzman *et al.* (19) demonstrated that Δ^9-THC in doses greater than 1 mg/kg, intraperitoneally consistently produces hypothermia in mice. After administration of a dose of 10 mg/kg they noted a body temperature decrease of 2 to 3°C within 30 min; normal body temperature was regained within 2 to 3 hr. Administration of 50 mg/kg resulted in a body temperature decrease of 3 to 5°C. When the dose was increased further to 200 mg/kg the hypothermic response became significant within 5 to 10 min after drug administration and persisted for at least 24 hr. Full recovery occurred within 48 hr. Holtzman *et al.* (19) also reported that doses of 500 mg/kg of Δ^9-THC decrease body temperature of mice by 5 to 6°C. Under these conditions onset of hypothermia is rapid and its duration roughly parallels the duration of increased norepinephrine and 5-hydroxytryptamine concentration in the whole brain. This observation is of particular interest in view of the work of Feldberg (11) and associates, who have proposed that temperature control at the level of the hypothalamus is regulated by release of catecholamines and of 5-hydroxytryptamine.

Gill *et al.* (14) have demonstrated that tincture of cannabis BPC produces hypothermia in mice. This dose-dependent response was observed in an environmental temperature of 20°C. They report that the hypothermic effect in mice increases with increasing intravenous dosage in both magnitude (>8°C) and duration (>8 hr). They suggest that peripheral factors may contribute to the observed hypothermia, but believe the principal hypothermic action of cannabis to be mediated centrally. This conclusion was based upon the observation that the drug is more effective after intraventricular injection than after intravenous injection. A dose of 25 mg/kg injected into the cerebral ventricles produces a hypothermia of more than 8 hr duration, and a maximum depression of body temperature of 6°C. They also suggest that the hypothermic effect of cannabis may influence behavioral responses to the drug and may influence specific physiological and pharmacological responses to the drug. The interpretation of pharmacological responses to the tetrahydrocannabinols should consider the effects of hypothermia *per se* upon the parameter being evaluated.

The maximum hypothermic response to DMHP has not been established, although studies in dogs in which doses as low as 1 mg/kg, intravenously were employed have produced marked hypothermia. We have verified ventricular fibrillation as a cause of death after DMHP administration (1 mg/kg, i.v.) to unanesthetized dogs. In the two cases observed, deep rectal temperature of the dog was below 29°C at the onset of ventricular fibrillation. Environmental temperature is an important factor in determining both the magnitude of the hypothermic response and the lethality of a given dose of DMHP. DMHP is more toxic when administered in a cold environment (4°C) or in a hot environment (36.5°C) than when administered in an environmental temperature of 23 to 34°C. When experiments were performed in a room maintained at 36.5°C, administration of 1 mg/kg, intravenously of DMHP produced a hyperthermic response in eight dogs. The rectal temperatures of these animals stabilized at 40 to 41°C; four of the eight animals died within 48 hr. When the environmental temperature was reduced to 34°C or 33°C the same dose of drug did not produce a change in body temperature significantly different from control values; 48 hr after drug administration the 11 dogs tested appeared completely recovered from effects of the drug. None of these animals expired during the subsequent 48 hr interval. The observation that DMHP can produce hyperthermia when the environmental temperature is maintained above 34°C suggests that this drug, like chlorpromazine [as reported by Kollias and Bullard (23)] is capable of inducing poikilothermia. Sim and Tucker (33) have established that DMHP is effective in producing hypothermia in man.

The observation by Holtzman *et al.* (19) that duration of the hypothermic response to Δ^9-THC in mice can be correlated with elevation of brain norepinephrine and 5-hydroxytryptamine levels suggests a mechanism by which the tetrahydrocannabinols may influence body temperature. Their observations should be confirmed, since Garattini (12) could not demonstrate altered norepinephrine or 5-hydroxytryptamine levels in rat brain after intraperitoneal or intracerebral injection of graded concentrations of hashish extract. In parallel experiments

Garattini did demonstrate that graded doses of reserpine (1.25–2.5 mg/kg, i.p.) produce a dose-dependent reduction in norepinephrine and 5-hydroxytryptamine levels in rat brain.

V. TOLERANCE DEVELOPMENT

The authors have demonstrated the development of tolerance to the behavioral effects of DMHP following daily administration of this agent to dogs and monkeys. Four dogs received DMHP (0.5 mg/kg, i.v.) once daily for 4 days. Two of the dogs died by the end of the 4th day; the remaining dogs received DMHP (1.0 mg/kg, i.v.) for 3 additional days. After 7 days of daily injection the two surviving animals appeared healthy. They showed slight ataxia and minor reduction of motor activity in response to the last DMHP injection. On the 8th day the experimental dogs and two control dogs were given 3.0 mg/kg of morphine sulfate, subcutaneously. Both the experimental and control animals showed characteristic responses to the morphine administration, including emesis, retching, defecation and reduced motor activity. The DMHP treated dogs had lost 20% of their body weight during the prior 7-day experimental period and were slightly more sedated than the control animals which received the same dose of morphine. The results of this experiment suggest that there is no cross tolerance between DMHP and morphine.

Tolerance development to DMHP was studied in an additional series of 8 dogs. The drug was injected once daily (1.0 mg/kg, i.v.) for 1 week, and development of tolerance to the behavioral effects of this drug was noted. When drug administration was discontinued no withdrawal syndrome was observed. The animals then were divided into four groups; each group of dogs was challenged with DMHP (1.0 mg/kg, i.v.) 1, 2, 3 or 4 weeks later. After 4 weeks of abstinence the response to DMHP (1.0 mg/kg, i.v.) was less profound than the initial response of the dogs to the drug.

A series of *Macaca mulatta* monkeys was given an initial dose of DMHP (0.5 mg/kg, i.v.); when no further drug effects were observable a subsequent dose was administered. The animals required 3 days to recover from the first dose of DMHP, but only 12 hr to recover from the third dose. Within 1 week 1.0 mg/kg, intravenously, daily produced only slight depressant effects. Withdrawal of the drug for 1 week did not result in a withdrawal syndrome. DMHP treatment was resumed at the same dosage level and relative tolerance to the depressant effect was retained by the monkeys. Drug treatment was continued (by stomach tube) on alternate days and with progressively increasing doses. When the dosage level of 50 mg/kg had been attained the animals appeared healthy and somewhat lethargic. Electroencephalographic (EEG) analysis was performed on 2 of the monkeys before and after administration of an intravenous dose of DMHP (1.0 mg/kg). Neither monkey exhibited the typical high voltage, slow wave pattern characteristically seen after initial DMHP administration. These results were interpreted as providing objective evidence of drug tolerance and supported the subjective impression of the authors that repeated doses of DMHP result in a

diminished CNS depressant effect. Both animals were sacrificed; gross and microscopic examination of their tissues by a pathologist showed no abnormal findings.

It seems clear that tolerance to the effects of DMHP can develop in both dogs and monkeys. Such tolerance is incomplete, but may last for many weeks. Abrupt withdrawal of the drug after the development of tolerance does not result in any grossly observable signs of withdrawal.

Additional experiments were conducted by the authors to investigate the possible existence of cross tolerance between DMHP and morphine. Morphine was abruptly withdrawn from a series of addicted monkeys. When the withdrawal syndrome was fully developed, administration of DMHP (1.0–2.0 mg/kg, i.v.) failed to produce a remission of the withdrawal symptoms. These data indicate that there is neither cross dependence nor cross tolerance between DMHP and morphine.

In 1968 Carlini (6) demonstrated that repeated intraperitoneal injection of cannabis extract to rats results in tolerance to drug action. He employed behavioral methods of analysis, including measurement of rope climbing and of operant behavior. Lipparini *et al.* (25) could not demonstrate the development of tolerance to Δ^9-THC in the rabbit. He administered 3 mg/kg, intravenously daily for 6 days and noted no appreciable attenuation of the EEG or behavioral response to the drug. McMillan *et al.* (28, 29) reported that daily injection of Δ^9-THC produces tolerance in pigeons trained to peck a key under a multiple fixed-ratio, fixed-interval schedule of food presentation. Under the conditions employed the pigeons did not key peck for at least 4 hr after injection of Δ^9-THC (1.8 mg/kg, i.m.); the rate gradually returned to control levels after 5 to 8 daily injections. When the dose subsequently was increased to 180 mg/kg, intramuscularly 3 times per week the pigeons continued to key peck at rates not significantly different from control rates. However, this dose of Δ^9-THC was lethal when administered to 2 non-tolerant pigeons. In a series of birds made tolerant to Δ^9-THC, the administration of 36 mg/kg, intramuscularly of Δ^8-THC did not affect the rate of key pecking. This dose of Δ^8-THC, when administered to non-tolerant pigeons inhibited key pecking for more than 24 hr; the response rate did not return to normal until 72 hr after injection. Black *et al.* (3) observed the effects of Δ^9-THC, DMHP and n-hexyl-tetrahydrocannabinol (Synhexyl) on key pecking rates in the pigeon. Each drug was administered once a week for 7 consecutive weeks. Initially the drugs produced a marked reduction in response rate but tolerance was observed with successive administration. In the 8th week experiments were performed to test for cross tolerance among these three drugs. Cross tolerance was found to exist between Synhexyl and Δ^9-THC, and between DMHP and Δ^9-THC.

VI. CONCLUSIONS

Five major areas of the pharmacology of marihuana and its surrogates have been reviewed. Emphasis has been placed upon the activity of the synthetic tetrahydrocannabinols, as exemplified by DMHP. Most of the data of the authors

which were obtained during the period of 1955 to 1959 has not been available to the general scientific community because it was categorized by the Army Chemical Center as classified security information. However, reports of the data have been available for a number of years to scientists who held contracts with the Army Chemical Center on related projects.

A selective, chronological review of the literature has been presented. Investigations in which marihuana extracts of unknown THC concentration were employed have been reviewed when the data are indicative of the biological actions of marihuana and its surrogates.

The availability of pure samples of the tetrahydrocannabinols from NIMH in recent years has provided the pharmacologist with an opportunity to obtain reproducible and quantitative experimental data. As a result, emphasis has been placed upon improvements in technique and experimental design. These developments permit the investigator to obtain conclusive data regarding the spectrum of pharmacological activity of the tetrahydrocannabinols.

We are only beginning to understand the pharmacological properties of marihuana and its surrogates. There are many clues to the mechanisms of action of the tetrahydrocannabinols, but detailed understanding of these mechanisms lies ahead.

There are points of remarkable similarity between the actions of the tetrahydrocannabinols and both the phenothiazines and the rauwolfia alkaloids. Dissimilarities exist which suggest that different mechanisms may be involved in the action of these drugs. The availability of reserpine and the publication of Trapold *et al.* (34) and Bein (2) provided clues which permitted Hardman *et al.* (15) to discover the hypotensive and hypothermic actions of DMHP, a synthetic tetrahydrocannabinol. Subsequent studies by Dagirmanjian and Boyd (7) also showed that DMHP produces a hypotensive response. Recent studies with purified Δ^9-THC and Δ^8-THC indicate that these compounds also have hypotensive activity [Dewey *et al.* (9), Hosko and Hardman (20), Boyd *et al.* (5)]. The hypothermic activity of Δ^9-THC has been demonstrated by Holtzman *et al.* (19). This hypothermic action has been correlated with elevated brain 5-hydroxytryptamine and norepinephrine levels [Holtzman *et al.* (19)]. By contrast, Garattini (12) has not observed a correlation between the hypothermic effect of an extract of hashish and brain levels of 5-hydroxytryptamine or norepinephrine. Thus the relationship between brain 5-hydroxytryptamine and norepinephrine and the pharmacological actions of the tetrahydrocannabinols needs clarification. Further studies also are needed to determine whether the hypotensive or behavioral changes induced by the tetrahydrocannabinols can be related to alterations in the level of biogenic amines in the brain or in peripheral structures. The slow onset of hypotensive and hypothermic action after administration of low doses of the tetrahydrocannabinols suggests that these drugs may act by depletion or blockade of endogenous substances which regulate central autonomic nervous system function. Additional studies regarding possible sites and mechanisms of action of the tetrahydrocannabinols should include the limbic system and related structures; these areas are considered by many investigators to be the primary autonomic area of the forebrain.

The data presented suggest that many drugs may influence the behavioral effects and the toxicity of the tetrahydrocannabinols. The use of CNS stimulants such as *d*-amphetamine, cocaine, caffeine or nalorphine as potential antagonists of the depressant effect of the tetrahydrocannabinols greatly increases the toxicity of these drugs. Extrapolation of these findings to the clinical situation suggests that general supportive therapy rather than drug therapy may be the prudent treatment of tetrahydrocannabinol-induced CNS depression. In addition, maintenance of the patient in a moderate environmental temperature should serve to minimize tetrahydrocannabinol toxicity. The compound DMHP has outstanding ability to lower the body temperature of dogs when the environmental temperature is maintained in the range of 23 to 33°C. This effect may have important therapeutic application in the treatment of hyperpyrexia or in surgical and medical procedures in which it is desirable to reduce the rate of metabolism of the subject through lowering body temperature.

The development of tolerance to the effects of the tetrahydrocannabinols on the behavior of dogs and monkeys is suggested by the data presented. It appears that cross tolerance and cross dependence between these compounds and morphine does not occur in dogs or monkeys. Carlini (6) suggests that rats also may become tolerant to the depressant effects of cannabis. McMillan *et al.* (28, 29) have observed a similar response in pigeons after administration of Δ^9-THC, and reported cross tolerance between Δ^9-THC and Δ^8-THC. Black *et al.* (3) observed tolerance to Δ^9-THC in pigeons and cross tolerance between Δ^9-THC and synthetic tetrahydrocannabinols such as DMHP. Further studies are needed to determine the selectivity and mechanism of tolerance development.

It is difficult to assess the relative potency of purified Δ^9-THC and Δ^8-THC with respect to the synthetic tetrahydrocannabinols. In most cases, threshold doses and ED50 values have not been reported for the pharmacological responses to these drugs. The difficulty in obtaining graded responses in a single animal suggests either that tolerance develops rapidly or that tachyphylaxis is a complicating factor. A preliminary comparison indicates that the synthetic tetrahydrocannabinols, as exemplified by DMHP, are more potent and have a longer duration of action than does Δ^9-THC or Δ^8-THC. It appears that Δ^9-THC and DMHP have a similar spectrum of pharmacological activity, but additional work is needed to define the quantitative relationships. Some preliminary comparisons suggest that DMHP is more potent than Δ^9-THC. The authors hope that standardized samples of DMHP will be made available by the NIMH so that investigations regarding the potential therapeutic usefulness of this agent can be pursued. The data reported here suggest that the tetrahydrocannabinols warrant evaluation in the treatment of essential hypertension, epilepsy and hyperpyrexia.

Acknowledgments. The authors wish to acknowledge the assistance of Drs. Henry J. Wills and Van M. Sim who served as our contract officers with the Medical Research Laboratories, Edgewood Arsenal, Maryland. We are also indebted to many members of the Pharmacology Department, University of Michigan who assisted us in our work during the period of 1955 to 1959 without knowledge of the identity of the compounds we were evaluating.

The authors also wish to acknowledge the assistance of Dr. Coryce O. Haavik in the preparation of this manuscript.

REFERENCES

1. Adams, R., Harfenst, M. and Loewe, S.: New analogs of tetrahydrocannabinol. XIX. J. Amer. Chem. Soc. 71: 1624–1628, 1949.
2. Bein, H. J.: Significance of selected central mechanisms for the analysis of the action of reserpine. Ann. N. Y. Acad. Sci. 61: 4–16, 1955.
3. Black, M. B., Woods, J. H. and Domino, E. F.: Some effects of (−)-Δ^9-*trans*-tetrahydrocannabinol and other cannabis derivatives on schedule-controlled behavior. Pharmacologist 12: 258, 1970.
4. Bose, B. C., Saifi, A. Q. and Bhagwat, A. W.: Studies on pharmacological actions of cannabis indica(linn). Part III. Arch. Int. Pharmacodyn. Thér. 147: 291–297, 1964.
5. Boyd, E. S., Boyd, E. H., Muchmore, J. S. and Brown, L. E.: Effects of two tetrahydrocannabinols and of pentobarbital on cortico-cortical evoked responses in the squirrel monkey. J. Pharmacol. Exp. Ther. 176: 480–488, 1971.
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.: Some pharmacological effects of two tetrahydrocannabinols. J. Pharmacol. Exp. Ther. 135: 25–33, 1962.
8. Davis, J. P. and Ramsey, H. H.: Antiepileptic action of marihuana-active substances. Fed. Proc. 8: 284–285, 1949.
9. Dewey, W. M., Yonce, L. R., Harris, L. S., Revis, W. M., Griffin, E. D. and Newby, V. E.: Some cardiovascular effects of *trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC). Pharmacologist 12: 259, 1970.
10. Domino, E. F., Hardman, H. F. and Seevers, M. H.: Central nervous system actions of some synthetic tetra hydrocannabinol derivatives. Pharmacol. Rev. 23: 317–336, 1971.
11. Feldberg, W.: Adrenergic mechanisms in the nervous system. Pharmacol. Rev. 18: 713–716, 1966.
12. Garattini, S.: Effects of a cannabis extract on gross behavior. *In* Hashish: Its Chemistry and Pharmacology, pp. 70–82, Ciba Foundation Study Group, No. 21, Little, Brown & Co., Boston, 1965.
13. Garriott, J. C., Forney, R. B., Hughes, F. W. and Richard, A. B.: Pharmacological properties of some cannabis related compounds. Arch. Int. Pharmacodyn. Thér. 171: 425–434, 1968.
14. Gill, E. W., Paton, W. D. M. and Pertwee, R. G.: Preliminary experiments on the chemistry and pharmacology of cannabis. Nature (London) 228: 134–136, 1970.
15. Hardman, H. F., Domino, E. F. and Seevers, M. H.: The chemistry and pharmacology of certain compounds affecting the central nervous system of animals and man. Clearinghouse for Federal Scientific and Technical Information, AD 707 699, pp. 1–53, 1957.
16. Hardman, H. F., Baird, W. M., Suits, D. B. and Lum, B. K. B.: Analysis of the common carotid occlusion pressor reflex in the anesthetized dog. Amer. J. Physiol. 196: 445–448, 1959.
17. Hardman, H. F., Domino, E. F., Woods, L. A. and Seevers, M. H.: Pharmacological actions of Δ^1-tetrahydrocannabinol derivatives. Pharmacologist 12: 258, 1970.
18. Hardman, H. F., Domino, E. F. and Seevers, M. H.: Structure-activity relationships of Δ^1-tetrahydrocannabinols. Proc. West. Pharmacol. Soc. 14: 14–20, 1971.
19. Holtzman, D., Lovel, 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.
20. Hosko, M. J. and Hardman, H. F.: Effect of Δ^9-THC on cardiovascular responses to stimulation of vasopressor loci in the neuraxis of anesthetized cats. Pharmacologist 13: 296, 1971.
21. Isbell, H., Gorodentzky, C. W., Jasinski, D., Claussen, U., Spulak, F. v. and Korte, F.: Effects of (−)Δ^9-trans-tetrahydrocannabinol in man. Psychopharmacologia 11: 184–188, 1967.
22. Isbell, H. and Jasinski, D. R.: A comparison of LSD-25 with (−)Δ^9-trans-tetrahydrocannabinol (THC) and attempted cross tolerance between LSD and THC. Psychopharmacologia 14: 115–123, 1969.
23. Kollias, J. and Bullard, R. W.: The influence of chlorpromazine on physical and chemical mechanisms of temperature regulation in the rat. J. Pharmacol. Exp. Ther. 145: 373–381, 1964.
24. Lape, H. E. and Hoppe, J. O.: The use of serial carotid occlusion, nicititating membrane and cross-circulation technics in the investigation of the central hypotensive activity of ganglionic blocking agents. J. Pharmacol. Exp. Ther. 116: 453–461, 1956.
25. Lipparini, F., de Carolis, A. S. and Longo, V. G.: A neuropharmacological investigation of some trans-tetrahydrocannabinol derivatives. Physiol. Behav. 4: 527–532, 1969.
26. Loewe, S.: Studies on the pharmacology and acute toxicity of compounds with marihuana activity. J. Pharmacol. Exp. Ther. 88: 154–161, 1946.
27. Manno, B. R., Manno, J. E., Kilsheimer, G. S. and Forney, R. B.: Response of the isolated, perfused heart to Δ^9-tetrahydrocannabinol (THC). Toxicol. Appl. Pharmacol. 17: 311, 1970.
28. 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.
29. 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.
30. Miras, C. J.: Some aspects of cannabis action. *In* Hashish: Its Chemistry and Pharmacology, pp. 37–53, Ciba Foundation Study Group, No. 21, Little, Brown & Co., Boston, 1965.
31. Prochnik, G., Maison, G. L. and Stutzman, J. W.: Carotid-occlusion-pressor reflex: influence of existing mean

arterial pressure, of anesthetics and of ganglionic- and adrenergic-blocking drugs. Amer. J. Physiol. **162**: 553–559, 1950.

32. SHORE, P. A., SILVER, S. W. AND BRODIE, B. B.: Interaction of reserpine, serotonin and lysergic acid diethylamide in brain. Science **122**: 284–285, 1955.
33. SIM, V. M. AND TUCKER, LAM. A.: Summary report on EA 1476 and EA 2233 (U). Clearinghouse for Federal Scientific and Technical Information, AD 342332, pp. 1–65, 1963.
34. TRAPOLD, J. H., PLUMMER, A. J. AND YONKMAN, F. F.: Cardiovascular and respiratory effects of serpasil, a new crystalline alkaloid from Rauwolfia serpentina benth, in the dog. J. Pharmacol. Exp. Ther. **110**: 205–214, 1954.
35. WOLLENBERGER, A.: On the energy-rich phosphate supply of the failing heart. Amer. J. Physiol. **150**: 733–745, 1947.