WEDNESDAY, AUGUST 26 — 9:00 A.M.
Physical Science, Room 370
Chairman: Dr. M. B. Chenoweth

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PHARMACOLOGICAL ACTIONS OF Δ^3-TETRAHYDROCANNABINOL DERIVATIVES. Harold F. Hardman, Edward F. Domino, Lauren A. Woods and Maurice H. Seevers. Univ. Michigan, Ann Arbor, Mich. 48104.

A series of eight Δ^3-tetrahydrocannabinol derivatives were evaluated for pharmacological activity. EA 1476 (Δ^3THC with a 1,2-dimethyl heptyl side chain in the 4' position) and EA 1465 (Δ^3-THC with a 1-methyl octyl side chain in the 4' position) were found to be the most active derivatives in the series. The outstanding pharmacological response observed in dogs and monkeys was a profound CNS depression. Some animals remained unconscious for periods up to 8 days and recovered uneventfully. It was possible to arouse animals from their depressed state by proprioceptive stimuli such as placing them on their feet in the upright position. Intravenous d-amphetamine 0.25-2.0 mg/kg also produced arousal. EA 1476 (50 µg/kg, i.v.) produces analgesia, hypothermia and hypotension in dogs. The hypotensive response appears to result from a decrease in central sympathetic outflow and can be blocked by sectioning the spinal cord at C-1. The cardiovascular responses to direct stimulation of the hypothalamus and medullary vasomotor areas are not blocked by EA 1476. (Supported by a contract from the Army Chemical Center, Edgewood Arsenal, 1955-59, declassified in 1969.) Present address: H. F. Hardman, Marquette Sch. Med., Milwaukee, Wis. 53233; L. A. Woods, Univ. Iowa, Iowa City, Iowa 52240.

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DEVELOPMENT OF MARKED BEHAVIORAL TOLERANCE TO 1-Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC) AND CROSS TOLERANCE TO 1-Δ^8-TETRAHYDROCANNABINOL (Δ^8-THC) IN THE PIGEON. D.E. McMillan*, L.S. Harris, R.F. Turk* and J.S. Kennedy*. Dept. of Pharmacology, Sch. of Medicine, Univ. of North Carolina, Chapel Hill, N.C. 27514.

Pigeons, trained to peck a key under a multiple fixed-ratio, fixed-interval schedule of food presentation, did not key peck for at least 4 hours after an injection of 1.8 mg/kg Δ^9-THC (IM). The rate of key pecking gradually returned to control levels after 5-8 daily injections (1.8 mg/kg). Subsequently, the dose was increased to 180 mg/kg, as the frequency of administration was decreased to 3/week; yet the pigeons continued to key peck at or near the control rates. The 180 mg/kg dose of Δ^9-THC proved lethal to 2 non-tolerant birds. When the birds made tolerant to Δ^9-THC were given 36 mg/kg Δ^8-THC they key pecked at their normal rates; however, non-tolerant birds did not key peck for more than 24 hours after this dose of Δ^8-THC, and the rate of responding did not reach normal levels until 72 hours after the injection. During the 3-1/2 months of study, the tolerant birds received 50 injections of Δ^9-THC (and one of Δ^8-THC), often at high dose levels. Prior to sacrifice the health of these birds was excellent. Gross observation of liver, heart and brain tissue after sacrifice revealed no obvious abnormality. Thin layer chromatography showed the Δ^9-THC injected was about 90% pure. (Supported in part by USPHS, NIH grant MH 17001.)

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A STUDY OF TWO WATER SOLUBLE DERIVATIVES OF Δ^9-TETRAHYDROCANNABINOL. J. F. Howes* (SPON: C. J. Kensler). Arthur D. Little, Inc., Life Sciences Division, Cambridge, Massachusetts 02140.

Δ^9-Tetrahydrocannabinol (Δ^9-THC) is insoluble in aqueous media and is therefore difficult to study pharmacologically. We have prepared two water soluble derivatives; ADL 1137, a basic ester, and ADL 1131, a basic ether. These compounds have been compared to Δ^9-THC in a variety of pharmacological test procedures. Using rodents, ADL 1137 was found to be qualitatively similar to Δ^9-THC although there were quantitative differences. In dogs, the onset time of the typical cannabinoid induced ataxia was increased, and at equivalent doses was much less marked than with Δ^9-THC. Analgesia was observed in dogs at doses where little or no ataxia was present, indicating that this type of derivative may have fewer undesirable cannabinoid effects at analgesic doses. In the cardiovascular system of the anesthetized dog Δ^9-THC and ADL 1137 were qualitatively identical. The basic ether derivative ADL 1131 was much more toxic and appeared to be devoid of all cannabinoid activity. Using rat liver microsomal preparations, ADL 1137 is converted to Δ^9-THC *in vitro*. ADL 1131 was not converted to Δ^9-THC in these preparations.

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EFFECTS OF Δ-9-TETRAHYDROCANNABINOL ON LOCOMOTOR ACTIVITY AND ON PHASES OF SLEEP. J. E. Moreton* and W. Marvin Davis, Dept. of Pharmacol., Sch. of Pharm., Univ. of Mississippi, University, Miss. 38677.

Rats injected daily s.c. with 25 mg/Kg of synthetic Δ-9-tetrahydrocannabinol (THC) in olive oil and placed for 4 hrs in photocell actometers showed initially a biphasic response of stimulation during the 1st hour and depression during the 2nd. The excitant effect was no longer seen by the 4th day. With continued doses through 20 days, tolerance developed to the depressant effect by the 11th day, and lasted through at least the 9th day after withdrawal. Mice injected I.P. for 23-26 days with 50 mg/Kg of THC in a 2% Tween-65, 2% Arlacel-20, 1% olive oil, and saline suspension showed a twofold reduction in locomotor inhibitory response to THC. Rats chronically implanted with electrodes over the frontal cortex, and in the dorsal hippocampus and neck muscles were given one 10 mg/Kg dose of THC I.P. following control recordings. THC caused a pronounced reduction in the level of paradoxical sleep (PS) which required 2 days for complete recovery. In rats selectively deprived of PS for 72 hrs, 10 mg/Kg of THC caused a blockade of PS rebound. (Supported in part by NIMH Grant MH-16990).

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SOME EFFECTS OF (-)-Δ^9-TRANS-TETRAHYDROCANNABINOL AND OTHER CANNABIS DERIVATIVES ON SCHEDULE-CONTROLLED BEHAVIOR. M.B. Black*, J.H. Woods* and E.F. Domino. Univ. of Mich. Med. Sch., Ann Arbor, Michigan 48104.

The effects of (-)-Δ^9-trans-tetrahydrocannabinol (Δ^9 THC), 1',2'-dimethylhepyl-tetrahydrocannabinol (DMHP) and n-hexyl tetrahydrocannabinol (synhexyl) were studied on the key-pecking rates in the pigeon under a multiple fixed-ratio 30 response, fixed-interval 5 min schedule of food presentation. The drugs were administered i.m. 30 min prior to the 2 hr test session as a suspension in 4% Tween-saline. Δ^9 THC (10 mg/kg), DMHP (0.3 mg/kg) and synhexyl (10 mg/kg) were administered once per week for 7 consecutive weeks. All the drugs produced a marked decrease in rate of responding under both schedule components. Tolerance was observed with successive administration of each of the drugs regardless of whether the birds performed in the presence of the drug effects. Tolerance appeared to be asymptotic by the 7th weekly administration. Cross-tolerance patterns were tested for each of the drugs on the 8th week. Synhexyl exhibited cross-tolerance with Δ^9 THC and symmetrical cross-tolerance was exhibited between DMHP and Δ^9 THC at the above doses. These results indicate that tolerance and cross-tolerance can occur among these cannabis derivatives and that the tolerance is of a pharmacological origin. (Supported in part by grants MH 11846 and MH 12084, USPHS.)

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Δ^1-TETRAHYDROCANNABINOL ACTIVATION OF PITUITARY-ADRENAL FUNCTION. Herbert Barry, III, James L. Perhach, Jr.*, and Robert K. Kubena*. Dept. of Pharmacol. Sch. of Pharmacy, Univ. of Pittsburgh, Pittsburgh, Pa. 15213.

Peripheral plasma corticosterone was assayed in a total of 184 male, albino rats in a series of experiments on effects of intraperitoneally injected Δ^1-tetrahydrocannabinol (Δ^1-THC), reported to be the principal psychoactive component of marihuana. Corticosterone was elevated approximately two to three times the control levels at 45 min. after 4, 8 and 16 mg/kg. A central nervous system mechanism for hypersecretion of corticotropin was indicated by a finding that 8 mg/kg of Δ^1-THC failed to elevate corticosterone in hypophysectomized rats and also in intact animals pretreated with pentobarbital sodium (50 mg/kg) and morphine sulfate (20 mg/kg). After 8 mg/kg of Δ^1-THC, corticosterone remained elevated at 90 min. but had returned to control levels at 480 min., when all behavioral effects were absent. Inhibition of antidiuretic hormone was indicated by the further finding that during the 8-hour interval, Δ^1-THC doubled urine output over the control levels. Hypersecretion of corticotropin and diuresis have both likewise been reported after intoxicating doses of ethyl alcohol. (Supported by PHS training grant GM-1217 from NIGMS, research scientist development award K2-MH-5921 and research grant MH-13595 from NIMH.)