MARIHUANA, LEARNING, AND MEMORY

By Ernest L. Abel

Research Institute on Alcoholism,
Buffalo, New York

I. Introduction

A great deal of attention has recently been focused on the effects of marihuana[1] (*Cannabis sativa* L) and its derivatives and homologs[2] on cognitive functions, particularly as regards the influence of these substances on learning and memory. Although there is general agreement among investigators that in man marihuana markedly impairs the acquisition rather than

[1] The terms cannabis, marihuana, and hashish will be used interchangeably without distinction.

[2] The active principles in cannabis are the cannabinoids of which *trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC = Δ^1-THC) and *trans*-Δ^8-tetrahydrocannabinol (Δ^8-THC = Δ^6-THC) are presently considered to be the most potent (Mechoulam, 1970). Although some of these other cannabinoids, such as cannabidiol, cannabinol, and cannabigerol, are pharmacologically inactive themselves (Edery *et al.*, 1971), evidence has recently been accumulating that these otherwise inactive cannabinoids can affect the activity of Δ^9-THC (Jones and Pertwee, 1972; Fernandes *et al.*, 1973; Karniol and Carlini, 1973) so that on a Δ^9-THC milligram per kilogram basis, crude cannabis extracts can be expected to be different from Δ^9-THC per se. In addition to these naturally occurring substances, two homologs derived from *d,l*-synthetic tetrahydrocannabinol have been widely used in psychopharmacological investigations. These homologs are the *n*-hexyl derivative pyrahexyl (also known as synhexyl), and the demethylheptyl derivative DMHP.

the retrieval of information (e.g., Abel, 1971b; Darley *et al.*, 1973a; Miller *et al.*, 1972), studies with animals have not produced the same degree of consensus as to the nature of marihuana's actions on these cognitive processes. The purpose of this paper is both to review and to examine these studies in animals and man with regard to some of the experimental problems which may have contributed to the inconsistencies in the literature.

Among the various models of memory that are currently available, one of the most elegant is that proposed by Atkinson and Shiffrin (1968) which basically posits a relatively long-term store and a relatively limited capacity short-term store. Newly acquired information first passes to a labile short-term store and is held there for a brief time. It then either decays and is replaced by new information or else it is transferred to the long-term store, where it is permanently encoded in the neural tissue for subsequent recall at a later time. In addition to this two component system, some investigators such as McGaugh (1968) have suggested that there may be other intermediate mechanisms interposed between the short-term and long-term stores. In light of such a multiphasic concept of memory, it is possible that different neurophysiological and biochemical mechanisms are operative at different phases and hence it is likely that a drug may affect some processes and not others.

With this concept or one similar to it in mind, a number of investigators have employed various methods to try to demonstrate and tease apart the effects of marihuana on short- and long-term memory function. The basic consideration in these studies has been the attempt not only to demonstrate the presence or the absence of drug-induced impairment on memory, but also to separate drug effects upon storage and retrieval processes where such differences are found.

II. Animal Studies

In general, studies of the effects of drugs on animal learning and/or memory involve the training of animals in such tasks as conditioned avoidance or maze learning and the measurement of drug-induced changes in performance. One of the main problems inherent in such studies, however, is that these cognitive processes cannot be observed directly but must be inferred from changes in the subject's behavior. Moreover, there is the additional problem of distinguishing between the concepts of learning and memory per se since each encompasses the other; for example, the acquisition of information requires registration, retention, and retrieval if there is to be a change in behavior resulting from experience.

Evidence that learning has occurred at all can only be inferred from some change in behavior that is not due to maturation or some temporal

state such as fatigue. Drugs can either have no effect or can reduce or increase the number of trials needed by an animal to reach some arbitrary criterion, e.g., 8 correct trials out of 10. Many drugs are capable of interfering with acquisition solely on the basis of their depressant effects on motor activity. An example of drug-induced facilitation of learning is the enhancement of maze and avoidance learning in various animals following injection of analeptic drugs, such as strychnine, picrotoxin, and pentylenetetrazol prior to training (McGaugh and Petrinovich, 1959; Kelemen and Bovet, 1961).

A second point of attack in studying learning/memory processes in animals is to administer drugs after the training session. The animals are then retested, and the effects of the drugs on information-consolidation processes are inferred from the animal's retest behavior. The advantages of such a paradigm are that the animals are neither trained nor tested under the influence of the drug so that variables such as attention, motivation, or locomotor activity are not relevant, and the effects of the drugs on memory storage can then be studied independent of original performance. The results of experiments of this nature have demonstrated that consolidation, i.e., the formation of a permanent memory trace following a given experience, is a rather labile process in which analeptic drugs such as strychnine enhance consolidation (McGaugh *et al.*, 1962) whereas barbiturate drugs such as pentobarbital appear to impair such processes (Garg and Holland, 1969). However, because of the time-dependent nature of the consolidation period, the implementation of this design is not feasible in the case of drugs that have a slow onset of action. Thus, marihuana cannot be used to study this process in animals unless it is administered intravenously (cf. Abel *et al.*, 1974).

The third phase of memory is retrieval of information that has already been learned and stored. Once this has happened, there is no reason to believe that information is subsequently forgotten simply because the response does not occur under a given set of circumstances. Other possibilities are that the retrieval or search process by which the memory trace is to be located becomes impaired because of a drug-induced effect on the "trace scanning" mechanism. This may occur because the drug directly interferes with the "search" process by altering neural activity, or because the cues which might normally aid in the memory search become unrecognizable due to state-dependent learning. For example, Overton (1964) has demonstrated that animals that are trained under the influence of barbiturate drugs, such as pentobarbital, will show evidence of such learning only if they are retested under the drug. This dissociation of performance between drug and nondrug conditions has been attributed to drug-induced changes in neural firing patterns associated with the storage of learned material. In order for this mate-

rial to be recalled, it is contended that the drug-induced changes in neural firing patterns must be reconstituted (John, 1967).

Having now reviewed some of the basic designs and considerations that must enter into any discussion of drug-induced changes in learning/memory, the following survey will examine the literature with respect to marihuana in this kind of framework. However, since acquisition also involves retrieval whereas retrieval can be studied independently of acquisition, we will first consider drug effects on retrieval processes. Thus, if it can be shown that retrieval is not affected by marihuana, it would not be unreasonable to assume that any effects of marihuana on learning and memory are probably due to interference with acquisitional or consolidation processes. In this regard, the following material is organized in terms of marihuana's effects on behavior that is motivated by aversive conditions, e.g., shock, followed by its effects on appetitively motivated conditions, e.g., food reward. These experiments are summarized in Table I. It is assumed that the reader is already familiar with the basic paradigms of shock avoidance, conditioned emotional response and maze learning, and hence, detailed descriptions of procedures have been omitted.

A. Drug Effects on Performance

Assessing the effects of marihuana on performance in the context of learning and memory is exceedingly problematical since, for the most part, many of the experiments discussed below were not designed to examine such processes. Criticisms in methodology vis-à-vis learning and memory are thus often not pertinent to the original intentions of many of the investigators cited below. Nevertheless, since these experiments are somewhat similar to those that have been designed for this purpose, they have been included in the present discussion.

In the conditioned shock avoidance, a stimulus such as a tone or light (the conditioned stimulus, CS) precedes the onset of shock (the unconditioned stimulus, UCS). At first the animal responds only to the shock by jumping a barrier to a safe compartment of the apparatus or by pressing a bar, which terminates shock (escape). After a number of such paired presentations, the animal eventually avoids being shocked by making the appropriate response during the warning signal.

In one of the early studies of the effects of Δ^9-THC (1–10 mg/kg, i.p.) on previously acquired shock avoidance behavior, Grunfeld and Edery (1969) reported a dose-dependent suppression of performance in rats. Although the animals were able to make an escape response to the UCS, the effect of the drug was still attributed to its cataleptic action rather than to impairment of memory retrieval.

TABLE I
EFFECTS OF MARIHUANA ON LEARNING AND MEMORY IN ANIMALS

Task[a]	Test[b]	Dose[c] (mg/kg)	Route[c]	Species	Results[d]	References
C.A.	P	(1–10) Δ^9-THC	i.p.	Rat	↓	Grunfeld and Edery (1969)
C.A.	P	(50) Δ^9-THC	i.p.	Rat	↓	Orsingher and Fulginiti (1970)
C.A.	P	(10) DMHP	i.p.	Rat	↓	Delini-Stula (1973)
C.A.	P	(30) Δ^8-THC	i.p.	Rat	↓	Delini-Stula (1973)
C.A.	P	(1–20) Δ^9-THC	i.p.	Rat	—	Pradhan *et al.* (1972)
S.A.	P	(16) Δ^9-THC	i.p.	Rat	↓	Barry and Kubena (1970)
S.A.	P	(1) Δ^9-THC	i.p.	Monkey	↓	Barry and Kubena (1970)
S.A.	P	(8) Δ^9-THC (c)	i.p.	Rat	↑	Barry and Kubena (1971)
S.A.	P	(4) Δ^9-THC	i.p.	Rat	↑ ↓	Sodetz (1972)
S.A.	P	(4–64) Δ^9-THC	i.p.	Monkey	↑ ↓	Scheckel *et al.* (1968)
S.A.	P	(0.75–9.0) Δ^9-THC	i.p.	Rat	↓	Webster *et al.* (1971)
S.A.	P	(4) Δ^9-THC	i.p.	Rat	—	Herring (1972)
C.E.R.	P	(10) Cannabis extract	i.p.	Rat	↓	Gonzalez *et al.* (1972)
C.E.R.	P	(10) Cannabis extract (c)	i.p.	Rat	↓	Gonzalez *et al.* (1972)
Maze	P	(2.5) Δ^9-THC	i.p.	Rat	↓	Carlini *et al.* (1970)
M.t.S.	P	(0.25–4) Δ^9-THC	i.p.	Monkey	– ↓	Scheckel *et al.* (1968)
M.t.S.	P	(0.5–2.0) Δ^9-THC	Oral	Monkey	↓	Zimmerman *et al.* (1971)
M.t.S.	P	(1.0) Δ^9-THC	Oral	Monkey	↓	Ferraro (1972)
M.t.S.	P	(1.0) Δ^9-THC (c)	Oral	Monkey	↓	Ferraro (1972)
M.t.S.	P	(4.0) Δ^9-THC (c)	Oral	Monkey	↓	Ferraro (1972)
C.A.	pt	(8) Δ^9-THC	i.p.	Rat	—	Barry and Kubena (1971)
C.A.	pt	(20–40) Δ^9-THC	i.p.	Mouse	—	Goldberg *et al.* (1973)
Maze	pt	(10) Cannabis extract	i.p.	Rat	—	Carlini and Kramer (1965)
C.A.	A	(3.2) Pyrahexyl	i.p.	Gerbil	—	Walters and Abel (1970)
C.A.	A	(10) Cannabis extract	i.p.	Rat	—	Orsingher and Fulginiti (1970)
C.A.	A	(10) Cannabis extract	i.p.	Rat	↓	Orsingher and Fulginiti (1970)
C.A.	A	(7.5) Δ^9-THC	i.p.	Rat	↓	Henriksson and Jarbe (1971)

(*Continued*)

TABLE I (*Continued*)

Task[a]	Test[b]	Dose[c] (mg/kg)	Route[c]	Species	Results[d]	References
C.A.	A	(15) Δ^8-THC	i.p.	Rat	—	Henriksson and Jarbe (1971)
C.A.	A	(4) Δ^9-THC	i.p.	Rat	↑ ↑	Herring (1972)
C.A.	A	(1.25-80) Δ^9-THC	i.p.	Mouse	— ↓	Goldberg *et al.* (1973)
C.E.R.	A	(10) Cannabis extract	i.p.	Rat	↓	Gonzalez *et al.* (1973)
C.E.R.	A	(10) Cannabis extract (c)	i.p.	Rat	—	Gonzalez *et al.* (1972)
P.A.	A	(5,15) Δ^9-THC	i.p.	Rat	—	Miller *et al.* (1973)
P.A.	A	(10) DMPH	i.p.	Rat	—	Delini-Stula (1973)
P.A.	A	(10) Δ^8-THC	i.p.	Rat	—	Delini-Dtula (1973)
P.A.	A	(2–8) Δ^9-THC	i.p.	Mouse		Glick and Milloy (1972)
Water escape	A	(10–20) Δ^8-THC	i.p.	Rat	↓	Jarbe and Henriksson (1973)
Water escape	A	(5) Δ^9-THC	i.p.	Rat	↓	Jarbe and Henriksson (1973)
C.E.R.	A	(15) Pyrahexyl	i.p.	Rat	↑	Abel (1969)
C.A. (extinction)	A	(62.5,125) Hashish resin	i.p.	Rat	↓	Jaffe and Baum (1971)
Maze	A	(10) Cannabis extract	i.p.	Rat	↑	Carlini and Kramer (1965)
Maze	A	(10) Cannabis extract	i.p.	Rat	↓	Orsingher and Fulginiti (1970)
Maze	A	(10) Cannabis extract	i.p.	Rat	—	Gonazlez and Carlini (1971)
Latent learn	A	(3) Δ^9-THC	i.p.	Rat	↓	Miller and Drew (1973)
Habituation	A	(1, 3.2) Δ^8-THC	i.p.	Mouse	↓	Brown (1971)

[a] C.A., conditioned avoidance: S.A., Sidman avoidance: C.E.R., conditioned emotional response: M.t.S., matching-to-sample: P.A., passive avoidance.

[b] P, performance: pt, post-trial: A, acquisition.

[c] All experiments are acute except for those followed by (c), which are chronic, Δ^8-THC and Δ^9-THC, respectively, Δ^8-*trans*- and Δ^9-*trans*-tetrahydrocannabinol: DMPH. dimethylheptyl derivative.

[d] ↑, facilitation: ↑, impairment: —, no change.

A similar suppression of conditioned avoidance behavior following administration of a cannabis extract (50 mg/kg, i.p.) in previously trained rats was reported by Orsingher and Fulginiti (1970). Interestingly, the effect was greater in animals trained with light rather than noise as the CS. However, since no information was reported concerning the effects of the drug

on intertrial activity or escape responding, it is not possible to exclude the possibility that the observed effects were due to the depressant actions of the drug on locomotor activity. Likewise, Domino (1971) observed a dose-related suppression of avoidance behavior in rats and, although he reported that escape responding was only minimally affected, no intertrial data were given so that here too an effect on locomotor activity cannot be excluded (cf. also Domino *et al.*, 1971). Impairment of performance of conditioned avoidance has also been observed in rats by Delini-Stula (1973) following administration of DMHP and Δ^8THC (10 and 30 mg/kg, i.p.). However, a depression of spontaneous motor activity, muscle coordination, and inhibition of unconditioned escape responding were also observed at these doses.

In contrast to these reports, no disruption of bar press avoidance was reported by Pradhan *et al.* (1972) although these investigators did note a significant effect of the drug on response latencies.

In the continuous Sidman avoidance procedure no exteroceptive warning signal (CS) precedes shock (UCS). Instead, shock is scheduled every 20 or 30 seconds by a timing device which is reset by each lever response. Using an avoidance procedure of this type, Barry and Kubena (1970) reported an increase in the number of shocks received by rats and monkeys following injection of Δ^9-THC (16 and 1 mg/kg, i.p., respectively) that were previously trained in the task. Since no measurements were made of the drug's effect on locomotor activity, general motor depression cannot be eliminated as the most likely explanation for these results. In a subsequent study, Barry and Kubena (1971) reported an improvement (less shocks received) in rats previously trained in this task following repeated injections of Δ^9-THC (8 mg/kg, i.p.). The effect was not evident on the first few days of drug treatment, however, and significance was determined by analyzing the trend for the 8 days of drug treatment which showed a decrease in shocks received as testing continued. The behavior of control subjects receiving the drug after 8 prior days of training was not affected, but when chronically treated drug animals were treated on days 11 and 12 without drug, there was a large increase in the number of shocks received. The authors state that the average number of lever presses per group did not appear to be different, but do not report this data nor indicate to what tests the data were subjected. Since several days of drug treatment were required for this effect to occur, it is possible that the result was due to tolerance to the depressant-effects of the drug on motor activity, which resulted in an "unmasking" of excitatory activity (cf. Carlini *et al.*, 1972) and improved avoidance on the basis of this effect.

In an experiment reported by Sodetz (1972) an improvement in the avoidance behavior in some rats but a decrement in the performance of others (number of shocks received) was observed following Δ^9-THC (4 mg/kg,

i.p.). Interestingly, three out of five of his animals died during the experiment. These results, including the mortality rate, are similar to those reported by Scheckel *et al.* (1968) for monkeys, in which it was found that i.p. doses of Δ^9-THC (4–8 mg/kg) decreased response rate whereas doses of 16, 32, and 64 mg/kg increased response rate relative to control rates (nine out of eleven subjects subsequently died). Animals receiving the low doses appeared to be depressed whereas those receiving high doses appeared to be stimulated. Rather than attributing the effects on avoidance behavior to drug-induced impairment of memory, Scheckel and co-workers imply that these results are more likely due to an effect on motor activity.

In a variant of this procedure, called discriminated Sidman avoidance, an exteroceptive signal precedes the shock stimulus, but a response at any time resets the timing device, so that it is possible to avoid receiving shock by responding either during the interval before the onset of the warning signal or during the warning signal itself. Using various doses of Δ^9-THC (0.75–9.0 mg/kg, i.p.), Webster *et al.* (1971) found that there was a significant increase in the number of shocks received in drug-treated animals previously trained to a high criterion on this task. However, it is not apparent whether performance was disrupted because of some effect of the drug on timing behavior, discrimination, or memory. Using a procedure similar to this, however, a member of this team (Herring, 1972) failed to replicate this effect on performance in rats given Δ^9-THC (4 mg/kg, i.p.).

Another type of procedure employing aversive stimuli to motivate behavior is the conditioned emotional response (CER) paradigm. Although there are a number of variations of the procedure, the basic method involves first training an animal to perform some response, such as bar pressing for food or water reinforcement, until a stable rate of responding is attained. The animal is then subjected to a number of tone-shock pairings. Next, operant behavior is reinstated and when the animal is once again responding at constant rate, the tone previously paired with shock is introduced and the number of responses emitted during presentation of this tone is compared with the number of responses emitted prior to the stimulus.

Using the CER paradigm, Gonzalez and co-workers (1972) injected animals with cannabis extract (10 mg/kg, i.p.) 24 hours after exposure to the tone-shock presentations. A second group was given 20 injections of drug or placebo prior to the shock treatment but were not given drug during exposure to the shock. Twenty-four hours later they were again injected with drug or placebo as before. The investigators found that in both the acute and the chronic conditions, the latency to approach the tube during testing was significantly shorter for drug-treated animals than for control subjects. However, since no data regarding drug effects on general activity

were presented, it is not possible to rule out some motor related effects as contributing to these results.

Several studies of marihuana and its homologs on performance of tasks motivated by positive reinforcement have also been reported. Carlini *et al.* (1970) administered Δ^9-THC (i.p.) to female rats after they had received extensive training in negotiating a Lashley III maze. Doses of 2.5 mg/kg and higher were reported as disrupting performance. However, the investigators scored any failure to complete the maze within a 5-minute period as an error, thus, confounding the time measure with error rate. To evaluate this result in terms of the drug's effect on memory would thus not be appropriate since the data were scored in terms of drug's depressant effects on motor activity.

Another appetitively motivated learning situation in which the cannabinoids have been studied is the delayed matching-to-sample task, in which monkeys are presented with a stimulus such as a colored light; then, after a delay, they are presented with a series of lights and must match the sample by touching the color previously presented to receive a reward.

Using this basic procedure, Scheckel and co-workers (1968) found that with Δ^9-THC (4 mg/kg, i.p.) one squirrel monkey would not perform in this task until a day after injection, and then even though it made more correct than incorrect responses, it failed to respond at all in the majority of trials. Similar effects were found after injections of 1 and 2 mg/kg. At 0.25 mg/kg, responding was not markedly affected, but at that dose the drug appeared to have little effect on performance.

In an analogous experiment reported by Zimmerman *et al.* (1971), rhesus monkeys that had inhaled cigarettes containing Δ^9-THC made significantly more errors than did control animals if the delay between the stimulus presentation and the test was 30 seconds. Performance was not significantly different from controls; however, at delays of zero and 5 seconds, performance was impaired. In a second study in which the animals had to select the light that was different from the sample light, all oral doses of Δ^9-THC (0.5–2.0 mg/kg) significantly impaired accuracy as before, with the longer interval between the sample and the test presentations. However, with the 2.0 mg/kg dose, accuracy was significantly impaired at the other intervals as well.

Results similar to these have also been reported by Ferraro (1972) for chimpanzees given oral doses of 1.0 mg/kg Δ^9-THC. Although accuracy decreased for both drug and control animals as the interval between sample presentation and testing lengthened, the number of correct responses by drug-treated subjects was significantly less than for control subjects. In a subsequent experiment (Ferraro, 1972) tolerance to this effect on perfor-

mance was not detected even after 21 consecutive daily administrations of the 1.0 mg/kg or 42 consecutive administrations of 4.0 mg/kg.

B. Effects on Acquisition

Surprisingly, there have not been many reports of drug effects on the acquisition of behavior. Jarvik (1972) cites time, expense, and difficulty as some of the general reasons for the lack of experimentation in this area. Nevertheless, a certain amount of work has been published regarding the effects of cannabis and its derivatives on acquisition, and this literature will comprise this section of this review.

Using the conditioned avoidance procedure to study learning, Walters and Abel (1970) failed to observe any effects on acquisition (trials to criterion) of pyrahexyl (3.2 mg/kg, i.p.) in gerbils, although the drug did significantly shorten the latency for these animals to jump a hurdle in response to the CS. Likewise, Orsingher and Fulginiti (1970) failed to observe any effect of a single dose of cannabis extract (10 mg/kg, i.p.) on acquisition of a conditioned avoidance response in rats. However, 23 daily injections up to, but not including training, markedly impaired acquisition. Although no mention of the physical condition of these animals was stated in the study, this latter result may have been due to the poor health of these animals following such chronic treatment (cf. Manning *et al.*, 1971).

A significant impairment in acquisition of conditioned avoidance behavior in rats has also been observed following administration of Δ^9-THC (15.0 mg/kg, i.p.) (Henriksson and Jarbe, 1971). Although the investigators reported that escape behavior was not suppressed by either compound, no data were given as to the effects of these drugs on intertrial responding (a measure of nonspecific responding). However, the investigators did note the presence of ataxia in some of the animals in both drug groups, suggesting that the effect on avoidance behavior may have resulted from the depressant effects on motor activity of these drugs.

In contrast to the previous experiments, Herring (1972) reported facilitated acquisition of a bar-press avoidance response in rats after administration of Δ^9-THC (4 mg/kg, i.p.). Although Herring stated that there were no significant differences in the total number of bar presses, she did not indicate whether this analysis included the number of responses during shock. If so, this might mean that while the total number of bar presses in the two groups was similar, one group was responding prior to shock (avoidance) whereas the other was responding after the onset of shock (escape).

Goldberg *et al.* (1973) administered various doses of Δ^9-THC (1.25–80.0 mg/kg, i.p.) to mice for five consecutive days but reported the effects of the drug on acquisition of shock avoidance behavior for the last training

day only. The 5 mg/kg dose depressed both avoidance and intertrial responding. Doses of 10–20 mg/kg day had no significant effect on either behavior whereas animals which received 40–80 mg/kg made significantly more avoidance and intertrial responses than did controls. However, because of the drug-induced increase in intertrial responding, the investigators declined to attribute the changes in avoidance behavior to any drug-related effect learning or memory processes.

A series of experiments by Gonzalez *et al.* (1972) examined the effect of cannabis extract on acquisition and retention using the CER paradigm. These investigators first trained rats to lick a spout in order to receive water. The animals were then injected (i.p.) with 10 mg/kg cannabis extract equivalent to approximately 2.8 mg/kg Δ^9-THC or with placebo and then subsequently subjected to five tone-shock pairings in the apparatus in which they had been trained to drink. Twenty-four hours later they were retested without shock or drug. The retesting was repeated 48, 72, 120, and 168 hours after the original shock treatment. Gonzalez and co-workers (1972) found the latency to approach the drinking tubes in the apparatus even in absence of the tone, was significantly shorter in the drug-treated animals than in placebo-treated subjects for the test periods. These findings indicate that not only the tone, but the box itself, had become associated with shock for control but not for drug-treated animals. During presentation of the tone, the previously drug-treated animals also drank more water during the 3-minute test period than did the controls. However, this latter measure was confounded with the latency measure since the tones were presented even if the animals were not drinking prior to the onset of the tone (if the animals were not drinking, the tones could not suppress drinking behavior). Consequently, only the approach data are relevant and these indicate that the cues associated with the box in which the shock was presented tended to suppress behavior to a much lesser extent in the drug-treated animals.

In a second experiment, rats were exposed to the tone-shock pairings after they had received 20 preinjections of the drug or placebo. No significant effect of the drug on either latency to approach the tube or amount consumed was observed suggesting tolerance to the effect as a consequence of the prior series of chronic injections. Gonzalez and co-workers (1972) attributed these results to an affect of the drug on the processes underlying acquisition and retention of the CER, viz, reduction of fear associated with the box and the tone during the shock treatment. This interpretation, they feel, is supported by the significant decrease in defecation scores also observed in the drug-treated subjects; a decrease in open-field defecation being accepted by many investigators as an index of fear in rats (cf. Henderson, 1970).

In passive avoidance, the subject must learn to refrain from making some response he would normally make (inhibition), typically that of entering some part of an apparatus. If inhibition does not occur, the animal receives punishment, e.g., electric shock, upon entry into the prohibited area. Using this kind of paradigm, Miller *et al.* (1973) found that Δ^9-THC (5 and 15 mg/kg, i.p.) did not affect acquisition of this inhibitory response in rats. A similar lack of effect of DMHP and Δ^8-THC (10 and 30 mg/kg, i.p.) on passive avoidance in rats has also been reported by Delini-Stula (1973). Significant impairment of passive avoidance in female mice was observed, however, by Glick and Milloy (1972) with Δ^9-THC (2–8 mg/kg, i.p.) when animals were retested as long as 4 weeks after a single learning trial.

Using water instead of shock as the aversive motivation for learning, Jarbe and Henriksson (1973) trained rats to swim to one side of a water T-maze to achieve escape from the water. Animals injected (i.p.) with either Δ^8-THC (1–20 mg/kg) or Δ^9-THC (5 mg/kg) made significantly more errors (slower rate of acquisition than did control subjects). By the sixth day of training, however, most of the animals had reached the criterion of eight correct responses out of ten. Since the dependent variable in this experiment was the number of errors made by the animals rather than swimming speed, this result cannot be accounted for on the basis of a depression of locomotor activity.

Some investigators have also studied the effects of marihuana administered during the extinction phase of an experiment (the repeated presentation of test conditions without presentation of the UCS). Since testing animals during extinction can also be thought of as another method for studying acquisition (learning that reinforcement is no longer associated with a particular response), these experiments have been dealt with as such. However, these studies themselves add little to the overall picture. For instance, in a study by Abel (1969) pyrahexyl (15 mg/kg, i.p.) decreased the latency for rats to contact a lever during extinction of a conditioned emotional response (presentation of the CS without the UCS). However, no observations were made of the drug's effect on locomotor activity and, therefore, it is possible that the result was due to some excitatory effect on locomotor activity which caused the animals to move about the Skinner box thereby causing them to come in contact with the lever.

Jaffe and Baum (1971) studied the effect of hashish resin given to female rats during the extinction period (no shock) of an active avoidance task. After reaching a criterion of 10 consecutive avoidance responses, experimental animals were injected (i.p.) with either 62.5 mg/kg or 125 mg/kg of the hashish resin or with placebo. Both drug groups made significantly more responses before reaching the criterion (no responding) than did the placebo group. Although this result could be interpreted as a demonstration of re-

tarded learning, the authors give no indication of the effects of the drug on general activity, and, hence, it is also possible that these doses of hashish resin acted to increase general activity and in so doing contributed to the less efficient performance of the animals.

The effects of marihuana have also been studied on maze-learning that is motivated by appetite reinforcement such as food and water. Again, however, no clear patterns in results are discernible. For example, although Carlini and Kramer (1965) reported that 10 mg/kg of cannabis extract (i.p.) improved learning to negotiate a Lashley III maze for food reward as indicated by fewer errors by drug-treated animals, a direct replication of this study by Orsingher and Fulginiti (1970) using the same strain of rats, a similar Lashley III maze, and the same amount of cannabis extract obtained from the same geographic area, found an opposite effect, viz, an increase in the number of errors during acquisition. In view of the similarity of experimental conditions, this discrepancy in findings is difficult to account for.

Gonzalez and Carlini (1971) studied the effects of cannabis extract (10 mg/kg, i.p.) injected during extinction in rats previously trained in T- and Lashley III mazes. In neither situation did the drug affect the overall rate of extinction (number of errors).

Following a suggestion by Abel (1971a) that the effects of marihuana on human memory might be incidental to its effects on attentional processes. Miller and Drew (1973) used a latent learning paradigm to test this hypothesis in rats. In this type of paradigm, animals are initially allowed to explore the experimental apparatus but are not rewarded therein. Animals are then food deprived and are trained in the apparatus as usual to determine whether they derived any benefit from this preexposure as indicated by the fewer number of errors they might subsequently make compared to control animals. The purpose of the Miller and Drew study was to test whether preexposure to the maze would reduce the innate curiosity of these animals during subsequent testing, and hence cause them to enter fewer culs. The results showed that animals given preexposure under the influence of Δ^9-THC (3 mg/kg, i.p.) made significantly more errors than did preexposed control animals and did not differ from animals receiving no preexposure at all, suggesting that attentional processes may have been affected as suggested. However, no separate analysis was made of the exploratory behavior of drug and control animals during the preexposure period and, therefore, it is possible that Δ^9-THC treated animals simply explored less of the maze, owing to possible depressant effects of the drug. Hence, their curiosity was not satisfied, and as a result they made more errors during testing. Alternatively, on the basis of an experiment by Brown (1971), Miller and Drew also suggested that the effect of the drug might have been to block habitua-

tion. If so, the tendency of the animals to enter previously explored but incorrect culs would still remain high, and therefore, they would tend to make more errors than control subjects upon retesting.

The experiment by Brown (1971) just referred to involved exposing mice under either drug or placebo conditions to an empty box for 15 minutes, and then returning them to their home cage. Two other groups of mice were injected with either drug or placebo but were not placed in the apparatus. Seventy-two hours later, these animals (which had been deprived of water for 24 hours) were reintroduced into the test box, which now contained a water bottle. The rationale was that previously exposed animals would have become habituated to the apparatus and, therefore, would spend less time in exploration. The data showed that animals previously exposed to the apparatus under the influence of Δ^8-THC (1 or 3.2 mg/kg, i.p.) did not manifest any effect of such prior treatment whereas their placebo counterparts exhibited significantly shorter latencies in contacting the water bottle. These data thus suggest that the drug inhibited the habituation process. Since habituation can be thought of as a simple form of learning [not to respond to stimuli which have no biological consequences (cf. Thorpe, 1956)], Brown's data can be used as evidence to support the hypothesis that Δ^8-THC suppresses acquisitional processes in learning. However, since no independent observations were made of the general activity of the treated animals, it is possible that animals receiving the drug were either depressed or overly excited during the preexposure condition, in which case they would not have attended to the culs of the apparatus to the same extent as conrol subjects. Hence, the observed effects on habituation may have been secondary to the drug's action on motor activity, or attentional processes.

C. Post-Training Drug Administration

Very little experimental work has been devoted to examining the effects of marihuana on consolidation processes using posttreatment drug administration. In an experiment by Barry and Kubena (1971) in which the effects of chronic administration of Δ^9-THC (8 mg/kg, i.p.) on shock avoidance learning in rats was investigated, animals injected 1–3 hours after training did not differ from controls on retesting. Similarly, Δ^9-THC (20–40 mg/kg, i.p.), administered 1 hour after training did not affect avoidance behavior in the mouse (Goldberg *et al.*, 1973). In a maze learning experiment reported by Carlini and Kramer (1965), rats were injected with cannabis extract (10 mg/kg, i.p.) 30 seconds after they had successfully negotiated the maze and had received food reward. In agreement with the two previous reports, no effect of this post injection procedure was apparent.

One would not expect to find any posttrial effects with Δ^9-THC in ani-

mal learning experiments, however, owing to its rather slow rate of onset when administered by routes other than intravenous (cf. Abel *et al.*, 1974).

D. State-Dependent Effects

As noted in the introductory section of this review, some centrally acting drugs act like discriminative stimuli in the control of behavior. Accordingly, behavior that is learned under the influence of a drug may not transfer, or may only partly transfer to nondrug or other drugs states and vice versa for behavior originally learned under a nondrug state.

The possibility that marihuana produces such "state dependent" learning is thus of no small importance to the present discussion. Since drugs that produce state-dependent learning are usually effective as discriminative stimuli, investigators have also examined whether the marihuana-state can be used as a discriminative internal stimulus for the learning of differential responses.

For example, Kubena and Barry (1972) trained food-deprived rats in a bar-pressing situation where either food reward or shock was delivered after every fifth response (FR 5). During training, half the animals were injected with Δ^9-THC (4 mg/kg, i.p.) while the other half were injected with placebo 30 minutes prior to testing and each of these conditions was associated with the delivery of either food or shock. The results showed that with the exception of one animal, the subjects averaged more than 90% correct responses.

A similar effect has been reported by Henriksson and Jarbe (1972). A group of rats were trained to swim to either of the two arms of a T-shaped water maze depending on whether they were treated with Δ^9-THC (5–10 mg/kg, i.p.) or with placebo. After 11–13 sessions the animals were responding at the 100% level, i.e., they differentially swam to one of the two arms of the maze depending on whether they had been given the drug or placebo.

A very interesting example of this phenomenon was reported by Bueno and Carlini (1972), in which they showed that even after the development of tolerance, a drug may still retain its internal cue properties. Rats were first trained to press one of two levers for food reinforcement until a stable baseline of behavior was achieved. The animals were next trained to climb a rope for food reward and then they were injected daily with either cannabis extract (10 mg/kg, i.p.) or placebo. After 14 such treatments, the drug-treated animals exhibited tolerance as indicated by their performance on the rope climbing task. In the final phase of the experiment, they were returned to the two lever chambers and were given an additional session without drug. Thereafter, the animals were given 30 sessions in which they were

submitted to both rope climbing and bar pressing. The marihuana-tolerant animals received the extract and control solution on alternate days. On marihuana days, only the left bar was activated whereas on placebo days the right bar delivered food reinforcement. Thus, each bar was associated with a particular drug state. The data showed that even though the animals were tolerant to the drug as indicated by their rope climbing behavior, they were still able to use the drug no-drug cue to respond correctly in the two choice situation.

To demonstrate state-dependent learning effects, four groups of animals must be studied. Two of the groups are trained under either drug or placebo conditions and are then tested under these same conditions (designated D-D and C-C, respectively). The other two groups are switched such that those originally trained under drug conditions are tested under placebo (D-C) and vice versa for those originally trained under placebo conditions (C-D).

Using this basic paradigm, Henriksson and Jarbe (1971) trained rats that had been injected daily with Δ^9-THC (7.5 mg/kg, i.p.) Δ^8-THC (15 mg/kg, i.p.) or placebo for 6 days in a shock avoidance task. On day 8, the animals were tested under either drug or placebo as described above. The data showed a complete disruption of avoidance behavior when animals were switched from the drugged to the nondrugged condition (D-C) and vice versa for the nondrugged to drugged condition (C-D), for both drugs. Animals in the D-D and C-C conditions either showed continued improvement or performance that did not differ from previous behavior.

In a second experiment of this type Jarbe and Henriksson (1973) trained rats for 6 consecutive days under either Δ^9-THC (5 mg/kg, i.p.), Δ^8-THC (10–20 mg/kg, i.p.) or placebo to swim to one of two arms of a T-shaped water maze. On the seventh day, reward training was begun. These conditions were similar to those in original training except that the correct side was reversed for all subjects. The rationale for this experiment was that if there was state-dependence associated with these drugs, animals in the D-D and C-C conditions should have more difficulty in making the switch because of the association of a particular response, e.g., right turn, with the particular drug state, and hence they should make more errors than subjects in the D-C and C-D conditions for whom the association of drug-right turn no longer holds. The data indicated that this was indeed the case for the Δ^8-THC groups, but not for the animals treated with Δ^9-THC.

Glick and Milloy (1972) used the passive avoidance shock paradigm to study state-dependent learning with Δ^9-THC (2 mg/kg) in female mice. The animals were injected (i.p.) with the drug prior to a single learning trial. They were retested on days 1 and 7 after this experience under either placebo or drug conditions. Only the animals receiving the drug prior to the initial learning experience showed impairment of retention (i.e., reentry

into the shock area). Neither the placebo or the animals receiving drug prior to training and again prior to retesting showed impairment.

Thus, these experiments demonstrate that state-dependent learning can occur under the influence of marihuana. The existence of this phenomenon thus represents another source of difficulty in trying to assess the effects of this substance on learning and retrieval processes.

III. Human Studies

In human learning/memory experiments, four basic tasks have generally been employed by investigators to assess marihuana's effects on these cognitive processes. These are digit span (DS), serial subtraction (SS), goal directed serial alternation (GDSA), and free recall. Since these tasks are also widely used, they will be described only briefly.

In the DS task, the subject hears a number of digits and is required to reproduce them accurately in the same or reverse order. The largest number of digits reproduced by the subject without an error constitutes the measure of the memory. The SS task requires the subject to repeatedly subtract some number such as 7 from some assigned number until zero is reached. In the third numerical problem, the GDSA task, the subject is given a starting number such as 110 and he is then asked to subtract 7 and then add either 1, 2, or 3 and to continue such alternate subtraction and additions until he reaches a particular numerical goal.

It is assumed that the DS task reflects short-term rote memory, the SS reflects simple arithmetic operations stored in long-term memory, and the GDSA reflects both short and long-term memory functions since the subject must simultaneoulsy hold in mind and coordinate information as well as perform cognitive operations relevant to pursuing a goal.

In general, even with simple memory tasks such as the DS, the results have been inconsistent. For example, while a number of investigators have reported that marihuana impaired performance on this task (Clark and Nakashima, 1968; Galanter *et al.*, 1973; Melges *et al.*, 1970; Tinklenberg *et al.*, 1970), other investigators have not been able to detect any differences between marihuana and control conditions (Caswell and Marks, 1973b; LaGuardia Report, 1944; Rafaelsen *et al.*, 1973; Tinklenberg *et al.*, 1972; Waskow *et al.*, 1970). As indicated by Table II this discrepancy cannot be attributed to either dose or route of administration. With respect to serial subtraction tasks, several investigators have observed poorer performance under drug compared with placebo conditions (Caswell and Marks, 1973b; Manno *et al.*, 1970; Rafaelsen *et al.*, 1973; Waskow *et al.*, 1970) although no differences have also been reported (Melges *et al.*, 1970). In evaluating

TABLE II
EFFECTS OF MARIHUANA ON SIMPLE HUMAN MEMORY TASKS

Task	Dose	Route	Effect	References
DS	1–30 mg/16	Oral	↓	Clark and Nakashima (1968)
DS	26 mg Δ^9-THC	Oral	—	Tinklenberg *et al.* (1972)
DS	10 mg Δ^9-THC	Smoke	↓	Galanter *et al.* (1973)
DS	20, 40, 60 mg Δ^9-THC	Oral	—	Tinklenberg *et al.* (1970)
DS	8, 12, 16 mg Δ^9-THC	Oral	—	Rafaelsen *et al.* (1973)
DS	3.3, 6.6 mg Δ^9-THC	Smoke	—	Caswell and Marks (1937a)
DS	20 mg/kg Δ^9-THC	Oral	—	Waskow *et al.* (1970)
DS	40, 60 mg Δ^9-THC	Oral	↓	Melges *et al.* (1970)
SS	10 mg Δ^9-THC	Smoke	↓	Manno *et al.* (1973)
SS	3.3, 6.6 mg Δ^9-THC	Smoke	↓	Caswell and Marks (1973a)
SS	40, 60 mg Δ^9-THC	Oral	—	Melges *et al.* (1970)
SS	300, 400 mg Δ^9-THC	Oral	↓	Rafaelsen *et al.* (1973)
GSDA	26 mg Δ^9-THC	Oral	—	Tinklenberg *et al.* (1972)
GSDA	3.3, 6.6 mg Δ^9-THC	Smoke	↓	Caswell and Marks (1973a)
GSDA	40, 60 mg Δ^9-THC	Oral	↓	Melges *et al.* (1970)

these data, most of these studies have given equal weight to both the time taken and the number of errors made. When errors alone have been examined, however, no differences have been observed between drug and control conditions (Rafaelsen *et al.*, 1973). This same confounding of reaction time and error rate has also characterized GDSA task. Hence, the poor performance of subjects in the task under drug condition in some experiments (Caswell and Marks, 1973b; Melges *et al.*, 1970), though not all (Tinklenberg *et al.*, 1972) must be interpreted with caution, since it is not clear whether these effects are due to drug interference with memory or with arithmetic calculation processes or both. Accordingly, other kinds of task have been used that are more complex than the simple DS and require the subject to learn and repeat passages of prose or learn lists of disconnected words or syllables. For example, in a study by Abel (1970b), subjects were required to read a story through twice under either marihuana (Δ^9-THC content not specified) or control conditions. Fifteen minutes later they were asked to write out as much of the story using as many exact words as possible. One month later the procedure was repeated with the exception that subjects previously tested under marihuana were now tested under no drug and vice versa. Analysis of the protocols indicated that in the marihuana condition subjects remembered significantly fewer ideas and fewer context words from the story than in the nondrug condition. Similar results using prose material has also been reported by Miller *et al.* (1972), who also found significantly more distortions in the marihuana (25 mg/kg) protocols (cf. also Drew *et al.*, 1972).

The data arising from these latter procedures are largely taken from the growing study of human verbal learning and memory (e.g., Cermak, 1972; Dixon and Horton, 1968; Hall, 1971) and can be interpreted within the theoretical models of short- and long-term memory processes that have been described by Atkinson and Shiffrin (1968). It is in the context of this model that the following studies will be discussed.

A. Retrieval

One plan of attack has been to read lists of words to subjects prior to giving them any drug treatments. The subjects are then asked to repeat as many words from each list as they can without regard for sequence (called free recall, in contrast to asking them to repeat the words in the order originally read to them). These subjects are matched on their predrug performance, then are given the drug or placebo. (This corresponds to the training of animals under a no-drug condition and then testing them while they are under the influence of the drug. It avoids many of the problems of such animal studies, however, because memory function is inferred from verbal rather than motor activity.) If the two groups do not differ on their predrug scores, any postdrug differences in their recall of this material can only be due to a drug-induced impairment in the retrieval of material already in long-term storage.

A failure to observe any such effect of marihuana (Δ^9-THC content not specified) on retrieval processes was initially reported by Abel (1971a,b) and has been confirmed by Darley, Tinklenberg, Roth, Hollister, and Atkinson (1973b) and Dornbush (1974) using doses of 20 mg of Δ^9-THC (oral and smoked, respectively). The absence of any significant differences between marihuana and control groups in these delayed-recall tasks has been interpreted as evidence suggesting that marihuana does not affect the retrieval of information that has already been stored in memory before drug administration.

B. Acquisition

If a subject is required to recall material to which he has been exposed while under the influence of the drug, it is reasonable to assume that an inability to do so is likely due to either (1) the information not being registered at the sensory receptor level, or (2) it enters the short-term memory store, but is not passed on to long-term memory or, (3) it is passed on to the long-term memory store but does not become permanently encoded, or, (4) it is encoded in long-term memory, but is stored in such a manner that it cannot be located except when the original drug condition is reinstated (state-dependent learning).

If the total number of words a subject recalls are plotted on the ordinate against their original serial position on the abscissa, it is then possible to use the model described by Atkinson and Shiffrin (1968) to determine which of the above-mentioned possibilities are involved in the drug-induced impairment. This analysis is based on experimental findings which indicate that the shape of the serial position curve in free recall can be altered by different procedures. Typically, the curve is U-shaped with the right side of the U slightly higher than the left, indicating that, with no delay between presentation of words and their recall, more words are recalled from the last items of the list than from the early part, whereas the fewest items are recalled from middle. This is because the subject typically repeats the words at the end of the list first while they are still "echoing" around in his head. This is called the recency effect. Items in this very end position are assumed to be those recalled from the sensory register component of memory which receives information from the sense organs (the "echo" box). This information decays very rapidly if not passed to short-term memory. Next to these items on the curve are those assumed to be recalled from the short-term store. Loss of material from this store occurs by spontaneous decay but such loss can be prevented by rehearsing items (i.e., by repeating to oneself those items) that one wishes to retain. Thus, the longer an item is rehearsed, the longer it stays in the short-term store and the longer it remains there, the greater the probability that it will be transferred to the long-term store. The left-hand side of the serial position curve is assumed to represent items that have been transferred to this long-term store. Finally, the middle of the curve reflects those items which have decayed and hence have not passed to the long-term store.

Following the assumptions of this model, Abel (1971a) reported that while marihuana did not affect the very end position (sensory register) or the middle of the serial position curve, it did affect the very beginning (long-term store) and the items near the end (short-term store). Thus, since items in the sensory register were not affected, subjects under the influence of marihuana had received the same amount of information as in the control condition. On the other hand, inspection of the curves indicated that items in the short-term store were adversely affected as were items in the long-term memory. Results similar to these have recently been reported by Darley and his associates (1973a) and Dornbush (1974) with similar procedures using 20 mg of Δ^9-THC (oral and smoking, respectively). These results, thus, suggest that marihuana has a detrimental effect on short-term storage processes in human memory.

In another experiment of this type, Dornbush *et al.* (1971) presented a consonant trigram, e.g., DKF, to the subjects and had them recall it either immediately or after a delay of 6, 12, or 18 seconds during which they were

required to perform some interpolated task. (Although not stated, subjects usually are asked to count backward out loud by 3's from some given number until the time interval is over. It is assumed that the subject cannot count backward and rehearse material at the same time. Hence, the longer the time interval from presentation to recall, the greater the opportunity for spontaneous decay of information from the short-term store.) Dornbush and her co-workers (1971) found that the longer the delay, the worse the performance by the subject in the marihuana (3.75 and 11.25 mg of Δ^9-THC, oral injestion) condition. A similar experiment was reported by Galanter and his associates (1973) in which they presented a list of numbers to subjects and then asked the subjects to recall it immediately or after a 4-second delay in which they had to recite letters of the alphabet. Subjects in the marihuana condition (10 mg of Δ^9-THC, smoking) did worse after both the zero and the 4-second delay. Since even at zero delay, marihuana impaired performance, it would appear that marihuana also affects the encoding of information in the short-term memory store.

An effect on encoding mechanisms has also been proposed by Darley *et al.* (1973a) as a possible effect of marihuana on the basis of the following study: Subjects were presented a series of items followed by a test stimulus which had or had not been in the preceding series. The subject had to press one key if the test item was part of the list and another key if it were a foreign item. Since subjects are nearly always correct in this task, the main measure of performance was reaction time, i.e., the time between presentation of the test stimulus and the response. It is assumed that three independent processes contribute to this measure. The first is the encoding time, the second is the time for comparison of the test stimulus with the memory set, and the third is the time for selection of the response (yes or no) and execution. On the basis of mathematical analysis of the data, it is possible to distinguish the first and third process from the second, but not the first from the third. With this procedure and analysis, it was found that under marihuana (20 mg of Δ^9-THC, oral) there was an increase in encoding and/or response times in short-term memory that was not due to any effect on search or comparison mechanism. However, since marihuana does affect motor activity, it is possible that the greatest effect was on response time rather than on encoding.

Abel (1971a) has suggested that information does not become stored in long-term memory in subjects under the influence of marihuana because they do not rehearse material in short-term memory and hence it does not remain in the latter long enough for it to be transferred. In order to rehearse, the subject must constantly attend to the task at hand. Such lacks of attention following marihuana have been reported anecdotally as well as experimentally. For example, in a study reported by Caswell and Marks (1973b)

subjects faced a panel containing a control light surrounded by a number of peripheral lights. The central light flashed at a rate of once per second with randomly programmed breaks interspersed, and the subject had to press a key each time a break in the sequence was detected. In addition, the peripheral lights were also programmed to flash randomly and the subject had to press a key in response to the peripheral light as well.

Caswell and Marks found that significantly more lights were missed by subjects under marihuana (3.3 and 6.6 mg of Δ^9-THC, smoking) compared to control conditions suggesting that the drug adversely affected attention (although the contribution of motor impairment per se was not examined).

It would thus appear that the effects of marihuana on human memory are due both to a loss of material in short-term memory as a result of spontaneous decay, and to an impairment of attentional mechanisms necessary for rehearsal to occur.

As noted earlier, subjects may also perform worse in memory tasks under the influence of marihuana due to a state-dependent effect. If this were so, however, one would expect differences between drug and control subjects on retrieval of information previously learned under nondrug conditions. However, there are no experimental data to support this. On the other hand, there is some evidence reported by Rickles *et al.* (1973) indicating that material originally learned under the influence of marihuana (14 mg of Δ^9-THC) is recalled better under marihuana than under placebo conditions. In this experiment, subjects were divided into four groups and were tested twice, 10 days apart. Testing was performed under either marihuana or placebo. Subjects were first required to learn paired associates consisting of a three consonant trigram and a common English word until they could anticipate each English word associated with the trigram given only the latter. This was then followed by 100% overlearning in which the subject was given as many additional practice trials as he originally required to master the list. For example, if he needed five trials to learn the list, he was given five more practice trials. Ten days later subjects were required to associate the correct English word with each trigram as before. Rickles and associates found that significantly more pairs were remembered by subjects who were both trained and tested under marihuana or placebo than did subjects trained under one condition and then switched to another. A similar effect was reported by Hill *et al.* (1973) using a task involving sequential memory (recall of ordered objects) but not in a task involving transfer of learning (subjects were taught to press one of two switches in response to a light on day 1, and then the other switch on day 2). The discrepancy between the tasks was attributed to greater difficulty in the sequential memory task, making it more sensitive to dissociative effects.

IV. Summary and Further Considerations

On the basis of the results of the various studies just reviewed, one is left with the impression that the animal and the human data are at variance with one another. For instance, while in animals marihuana appears to impair performance in previously learned tasks, it has no such effect in humans. Conversely, whereas marihuana adversely affects human performance in acquisition, it has no such clear-cut effect in animals. However, when we take into account the procedural difficulties of many of the animal studies, then one is left with the impression that most of the studies that have been conducted with regard to the effects of cannabis on learning and memory are inadequate to their intended purposes. If we subscribe to the law of parsimony, then nearly all of the animal experiments discussed with respect to acquisition are more readily explicable in terms of drug effects on motor activity, motivational levels, attentional mechanisms, etc.

As stated at the outset of this review, one of the main problems in the area of learning and memory is that these processes are not directly observable but must be inferred from a subject's behavior. Before any effect on learning and/or memory can be accepted then, all other possibilities must be eliminated. For example, if a drug is found to either depress or facilitate shock avoidance behavior it must be demonstrated that the drug has not affected general motor activity before any direct effect of the drug on learning and/or memory can be accepted. In such cases it is not merely adequate to show an effect on avoidance and no depression of escape, it is also important to determine the latency for such escape responses because of the possibility of analgesic and cataleptic effects associated with Δ^9-THC. The effects of shock level per se, which are usually totally ignored in drug studies, have also been shown to be quite important insofar as behavior is concerned. For example, the speed of running from a shock source is directly related to the intensity of the shock (Amsel, 1950; Campbell and Kraeling, 1953) as is the latency of the bar-pressing response to escape shock (Borren *et al.*, 1959). If a drug affects the sensitivity of an animal to foot shock, then any effects of that drug on learning and/or memory would be secondary to its affects on performance as a result of a change in the level of reinforcement. This has been shown to be the case for *p*-chlorophenylalanine (pCPA) by Tenen (1967), who observed that this compound had a facilitatory effect on shock avoidance learning in rats at a dose that produced no overt behavioral effects. Further experimentation, however, revealed that the drug had increased the sensitivity of the rats to the foot shock which was tantamount to increasing the shock intensity for drug-treated animals compared

to controls. Since Δ^9-THC has been observed to have analgesic effects (Bicher and Mechoulam, 1968; Bauxbaum, 1972), differences in performance may possibly be due to a perceived difference in the shock level being used to motivate behavior.

Studies of the effects of marihuana on avoidance should thus require simultaneous measurement not only of the number of conditioned (avoidance) and unconditioned responses (escape) made by the animal, but also the number of intertrial responses and the latency of response to the CS and UCS. These data are important because only with such information is it possible to draw conclusions regarding a drug's effects on conditioned versus unconditioned behavior, general motor activity, and sensitization (overall responsiveness).

A second possibility to be considered arises from the nature of the conditioned avoidance situation itself. According to the theory first proposed by Mowrer (1947) and later elaborated on the basis of further experimental evidence by Solomon and Wynne (1954), the pairing of the CS and UCS results in establishment of a conditioned emotional response ("fear") which serve as the motivation for performing the avoidance response. If this theory is accepted as a reasonable explanation of the avoidance phenomenon, then it behooves any investigator who uses this paradigm to explore the effects of a drug on the learning or retention of an avoidance response, to demonstrate that the drug has no effect on "emotionality." In some cases this can be done by independently assessing the animal's behavior in a situation such as the "open-field" (cf. Henderson, 1970).

In the case of learning/memory tasks involving food reinforcement as the motivating variable, the clearly depressant effects of marihuana and its homologs on food intake (e.g., Abel and Schiff, 1969; Manning *et al.*, 1971; Scheckel *et al.*, 1968) must be taken into account in evaluating the data from such experiments. In addition, in light of the motor effects of this compound, speed scores are clearly inappropriate in monitoring the results of maze learning performance. Finally, the evidence with respect to marihuana-induced state-dependent learning would seem to preclude any easy solution to the problems of this drug's effects on retrieval mechanisms in either maze or shock avoidance learning paradigms.

A few comments with regard to cannabis itself also seem to be in order. First and foremost, as with all drug experiments, single-dose studies are only suggestive of effects. Higher or lower doses of drug may give just the opposite effect as that observed for any single dose. This is especially likely in light of the biphasic effects connected with Δ^9-THC such as increases in motor activity following small doses and decreases in motor activity following large doses (Abel, 1970a; Carlini *et al.*, 1970; Davis *et al.*, 1972). The importance of the time variable should also not be underestimated since a period

of initial stimulation of activity followed by depression is often observed with the same dose of this drug (Garriott *et al.,* 1967; cf. Domino, 1971).

In the case of repeated training and/or testing of aimals under drug conditions, the rapid development of tolerance to cannabis in most animals (Abel *et al.,* 1974; McMillan *et al.,* 1970) must be clearly taken into account and may actually preclude assessment of the acute effects of the drug on learning and/or memory. In light of the comments regarding the role of emotionality in avoidance behavior, it should also be noted that an increase in open-field defecation, indicative of increasing fear (Henderson, 1970) has been reported following chronic treatment with cannabis (Masur *et al.,* 1971). Likewise, Carlini and co-workers (1972) have presented data which suggest that following the development of tolerance to the depressant effects of cannabis, excitatory effects of the drug are likely to become "unmasked."

In summary, the data with respect to the effects of marihuana on learning and/or memory are such that it is not possible at present to conclude that this material has or has not any effect on these cognitive processes in animals. With respect to the human data, most of the pitfalls vis-à-vis interpretation of results have been circumvented by use of tasks that do not involve measurements of the rate or speed of locomotor activity. While the problem of motivation must still be considered, the nature of the problem does not involve the difficulties inherent in the animal data such as drug effects on emotionality or hunger which must certainly enter into discussion of animal behavior studies in this area. Although previous tolerance to marihuana must also be taken into account in evaluating the human data, for the most part this possibility has not been studied. However, if tolerance were an important consideration, then we ought to expect equal impairment on both retrieval and acquisition when the same subjects are used. Since, this is not the case, it would suggest that tolerance to the adverse effects of marihuana on human learning does not occur.

ACKNOWLEDGMENTS

The comments and advice of Dr. Allen Barnett and the secretarial fortitude and assistance of Peggy Bielawicz are gratefully acknowledged.

REFERENCES

Abel, E. L. (1969). *Psychon. Sci.* **16,** 44.
Abel, E. L. (1970a). *J. Pharm. Pharmacol.* **22,** 785.
Abel, E. L. (1970b). *Nature (London)* **227,** 1151–1152.
Abel, E. L. (1971a). *Science* **173,** 1038–1040.
Abel, E. L. (1971b). *Nature (London)* **231,** 58.
Abel, E. L., and Schiff, B. B. (1969). *Psychon. Sci.* **16,** 38.
Abel, E. L., McMillan, D. E., and Harris, L. S. (1974). *Psychopharmacologia* **35,** 29–38.

Amsel, A. (1950). *J. Exp. Psychol.* **40,** 1–14.
Atkinson, R. C., and Shiffrin, R. M. (1968). *In* "The Psychology of Learning and Motivation" (K. W. Spence and J. T. Spence, eds.), Vol. 2, pp. 89–195. Academic Press, New York.
Barry, H., and Kubena, R. K. (1970). *Proc. 78th Annu. Conv. Amer. Psychol. Ass.* Vol. 5, pp. 805–806.
Barry, H., and Kubena, R. K. (1971). *Proc. 79th Annu. Conv. Amer. Psychol. Ass.* Vol. 6, pp. 747–748.
Bauxbaum, D. M. (1972). *Psychopharmacologia* **25,** 275.
Bicher, H. I., and Mechoulam, R. (1968). *Arch. Int. Pharmacodyn. Ther.* **172,** 1.
Borren, J. J., Sidman, M., and Herenstein, R. J. (1959). *J. Comp. Physiol. Psychol.* **52,** 420–425.
Brown, H. (1971). *Psychopharmacologia* **21,** 294–301.
Bueno, O. F., and Carlini, E. A. (1972). *Psychopharmacologia* **25,** 49–56.
Campbell, B. A., and Kraeling, D. (1953). *J. Exp. Psychol.* **45,** 97–101.
Carlini, E. A., and Kramer, C. (1965). *Psychopharmacologia* **7,** 175–181.
Carlini, E. A., Hamaoui, A., Bieniek, D., and Korte, F. (1970). *Pharmacology* **4,** 359–368.
Carlini, E. A., Masur, J., Karniol, I. G., and Leite, J. R. (1972). *In* "Cannabis and its Derivatives" (W. D. M. Paton and J. Crown, eds.), p. 154–173. Oxford Univ. Press, London and New York.
Caswell, S., and Marks, D. F. (1973a). *Science* **179,** 803–805.
Caswell, S., and Marks, D. (1973b). *Nature (London)* **241,** 60–61.
Cermak, L. S. (1972). "Human Memory." Ronald Press, New York.
Clark, L. D., and Nakashima, E. N. (1968). *Amer. J. Psychiat.* **125,** 379–384.
Darley, C. F., Tinklenberg, J. R., Hollister, L. E., and Atkinson, R. C. (1973a). *Psychopharmacologia* **29,** 231–238.
Darley, C. F., Tinklenberg, J. R., Roth, W. T., Hollister, L. E., and Atkinson, R. C. (1973b). *Mem. Cognit.* **1,** 196–200.
Davis, W. M., Moreton, J. E., King, W. T., and Pace, H. B. (1972). *Res. Commun. Chem. Pathol. Pharmacol* **3,** 29–35.
Delini-Stula, A. (1973). *Pharmakopsychiat./Neuro-Psychopharmakol.* **6,** 189–197.
Dixon, T. R., and Horton, D. L., eds. (1968). "Verbal Behavior and General Behavior Theory." Prentice-Hall, Englewood, New Jersey.
Domino, E. (1971). *Ann. N.Y. Acad. Sci.* **191,** 166–191.
Domino, E. F., Hardman, H. F., and Seevers, M. H. (1971). *Pharmacol. Rev.* **23,** 317–366.
Dornbush, R. L. (1974). *Trans. N.Y. Acad. Sci.* [2] **36,** 94–100.
Dornbush, R. L., Fink, M., and Freedman, A. M. (1971). *Amer. J. Psychiat.* **128,** 194–197.
Drew, W. G., Kiplinger, G. F., Miller, L. L., and Marx, M. (1972). *Clin. Pharmacol. Ther.* **13,** 526–533.
Edery, H., Grunfeld, Y., Ben-Zivi, Z., and Mechoulam, R. (1971). *Ann. N.Y. Acad. Sci.* **191,** 40–53.
Fernandes, M., Warning, N., Christ, W., and Hill, R. (1973). *Biochem. Pharmacol.* **22,** 2981–2987.
Ferraro, D. P. (1972). *In* "Current Research in Marihuana" (M. F. Lewis, ed.), pp. 49–95. Academic Press, New York.
Galanter, M., Weingarten, H., Vaughan, T. B., Roth, W. T., and Wyatt, R. J. (1973). *Arch. Gen. Psychia.* **28,** 278–281.

Garg, M., and Holland, H. C. (1969). *Psychopharmacologia* **14,** 426–431.
Garriott, J. C., King, L. J., Forney, R. G., and Hughes, F. W. (1967). *Life Sci.* **6,** 2119–2128.
Glick, S. D., and Milloy, S. (1972). *In* "Current Research in Marijuana" (M. F. Lewis, ed.), pp. 1–24. Academic Press, New York.
Goldberg, M. E., Hefner, M. A., Robichaud, R. C., and Dubinsky, B. (1973). *Psychopharmacologia* **30,** 173–184.
Gonzalez, S. C., and Carlini, E. A. (1971). *Psychon. Sci.* **24,** 203–204.
Gonzalez, S. C., Karniol, I. G., and Carlini, E. A. (1972). *Behav. Biol.* **7,** 83–94.
Grunfeld, Y., and Edery, H. (1969). *Psychopharmacologia* **14,** 200–210.
Hall, J. F. (1971). "Verbal Learning and Retention." Lippincott, Philadelphia, Pennsylvania.
Henderson, N. D. (1970). *J. Psychol.* **75,** 19–34.
Henriksson, B. G., and Jarbe, T. (1971). *Psychopharmacologia* **22,** 23–30.
Henriksson, B. G., and Jarbe, T. (1972). *Psychon. Sci.* **27,** 25–26.
Herring, B. (1972). *Psychopharmacologia* **26,** 401–406.
Hill, S. Y., Schwin, R., Powell, B., and Goodwin, D. W. (1973). *Nature (London)* **243,** 241–242.
Jaffe, P. G., and Baum, M. (1971). *Psychopharmacoolgia* **20,** 97–102.
Jarbe, T. U. C., and Henriksson, B. G. (1973). *Psychopharmacologia* **31,** 321–332.
Jarvik, M. E. (1972). *Ann. Rev. Psychol.* **23,** 457–486.
John, E. R. (1967). "Mechanisms of Memory." Academic Press, New York.
Jones, G., and Pertwee, R. G. (1972). *Brit. J. Pharmacol.* **45,** 375–377.
Karniol, I. G., and Carlini, E. A. (1973). *Psychopharmacologia* **33,** 53–70.
Keleman, K., and Bovet, D. (1961). *Acta Physiol.* **19,** 143–154.
Kubena, R. K., and Barry, H. (1972). *Nature (London)* **235,** 397–398.
La Guardia Report (1944). "The Marihuana Problem in the City of New York." Jacques Cattell Press, Lancaster, Pa.
McGaugh, J. L. (1968). *Atti. Accad. Naz. Lincei* **109,** 13–24.
McGaugh, J. L., and Petrinovich, L. F. (1959). *Amer. J. Psychol.* **72,** 99–102.
McGaugh, J. L., Thompson, C. W., Westbrook, W. H., and Hudspeth, W. (1962). *Psychopharmacologia* **3,** 352–360.
McMillan, D. E., Harris, L. S., Frankenheim, J. M., and Kennedy, J. S. (1970). *Science* **169,** 501–503.
Manning, F. J., McDonough, J. H., Elsmore, T. F., Saller, C., and Sodetz, F. J. (1971). *Science* **174,** 424–426.
Manno, J. E., Kiplinger, G. F., Haine, S. E., Bennett, I. F., and Forney, R. B. (1970). *Clin. Pharmacol. Ther.* **11,** 808–815.
Manno, J. E., Kiplinger, G. F., Haine, S. E., Roth, W. T., and Wyatt, R. J. (1973). *Arch. Gen. Psychiat.* **28,** 278–281.
Masur, J., Martz, R. M. W., and Carlini, E. A. (1971). *Psychopharmacologia* **19,** 388–392.
Mechoulam, R. (1970). *Science* **168,** 1159–1166.
Melges, F. T., Tinklenberg, J. R., Hollister, L. E., and Gillespie, H. K. (1970). *Science* **168,** 1118–1120.
Miller, L. L., and Drew, W. G. (1973). *Nature (London)* **243,** 473–474.
Miller, L. L., Drew, W. G., and Kiplinger, G. F. (1972). *Nature (London)* **237,** 172–173.
Miller, L. L., Drew, W. G., and Joyce, P. (1973). *Behav. Biol.* **8,** 421–426.
Mowrer, O. H. (1947). *Harvard Educ. Rev.* **17,** 102–148.

Orsingher, O. A., and Fulginiti, S. (1970). *Pharmacology* **3,** 337–344.
Overton, D. A. (1964). *J. Comp. Physiol. Psychol.* **57,** 3–12.
Pradhan, S. N., Bailey, P. T., and Ghosh, B. (1972). *Res. Commun. Chem. Pathol. Pharmacol.* **3,** 197–204.
Rafaelsen, L., Christrup, H., Bech, P., and Rafaelsen, O. J. (1973). *Nature (London)* **242,** 117–118.
Rickles, W. H., Cohen, M. J., Whitaker, C. A., and McIntyre, K. E. (1973). *Psychopharmacologia* **30,** 349–354.
Schneckel, C. L., Boff, E., Dahlen, P., and Smart, T. (1968). *Science* **160,** 1467–1469.
Sodetz, F. J. (1972). *In* "Current Research in Marijuana" (M. F. Lewis, ed.), pp. 25–48. Academic Press, New York.
Solomon, R. L. and Wynne, L. C. (1954). *Psychol. Rev.* **61,** 353–385.
Tenen, S. S. (1967). *Psychopharmacologia* **10,** 204–219.
Thorpe, W. H. (1956). "Learning and Instinct in Animals." Methuen, London.
Tinklenberg, J. R., Melges, F. T., Hollister, L. E., and Gillespie, H. K. (1970). *Nature (London)* **226,** 1171–1172.
Tinklenberg, J. R., Kopell, B. S., Melges, F. T., and Hollister, L. E. (1972). *Arch. Gen. Psychiat.* **27,** 812–815.
Walters, G. C., and Abel, E. L. (1970). *J. Pharm. Pharmacol.* **22,** 310–312.
Waskow, I. E., Olsson, J. E., Salzman, C., and Katz, M. M. (1970). *Arch. Gen. Psychiat.* **22,** 97–107.
Webster, C. D., Willinsky, M. D., Herring, B. S., and Walters, G. C. (1971). *Nature (London)* **232,** 498–501.
Zimmerman, B., Glick, S. D., and Jarvik, M. E. (1971). *Nature (London)* **233,** 343–345.