Pharmacology Biochemistry & Behavior, Vol. 4, pp. 17–21.

Chronic Delta-9-Tetrahydrocannabinol. Transient and Lasting Effects on Avoidance Behavior[1]

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(Received 2 May 1975)

MANNING, F. J. *Chronic delta-9-tetrahydrocannabinol: transient and lasting effects on avoidance behavior.* PHARMAC. BIOCHEM. BEHAV. 4(1) 17–21, 1976. – Delta-9-Tetrahydrocannabinol (THC) was administered to albino rats with extensive experience in free-operant (Sidman) lever-press shock avoidance. Dosing (30 mg/kg intragastrically) continued once daily, 3 hr before testing, for 1 to 6 weeks. Significant changes were noted in the response rates of several animals, but both the magnitude and direction of these were highly variable. However, shock rates were reliably elevated by THC, but complete tolerance was observed within 6 sessions. In several rats this was followed by sessions with significantly lower shock rates than the predrug baseline. These rats continued to perform at this level of proficiency until THC was discontinued, at which point the baseline was reacquired. These data emphasize that an important determinant of tolerance to a drug effect is the consequence of the effect for the organism.

Tetrahydrocannabinol Avoidance Tolerance Rats

EXPERIMENTS with a variety of non-human subjects have typically reported pronounced tolerance to the effects of THC (e.g., [2, 5, 9]). This is in striking contrast to reports by human marihuana users that they need smaller rather than larger doses to achieve the effects they desire [6,18]. It is, of course, quite possible that this apparent discrepancy is paralleled by a genuine species difference in absorption or metabolism of the drug. However, there are suggestions in the literature that this may be too glib a dismissal of an important distinction. For example, repeated use of marihuana or THC apparently does result in tolerance to some effects in humans. In formal laboratory tests of perceptual-motor or cognitive function, marihuana or THC quite often impairs the performance of inexperienced marihuana users more severely than that of heavy users [6,11]. Conversely, not all of the effects of THC in non-human animals diminish with successive doses. For example, Pirch and his colleagues [13] found that marihuana extract distillate enhanced the shuttlebox shock avoidance of rats with a previously established baseline of poor performance. No tolerance was observed. Kubena and Barry [7] have reported that when a rat is trained to make one response after THC injections and a different response after an injection of inactive vehicle, he maintains a high accuracy even after as many as 100 injections. Notably absent from these studies, and several others reporting no tolerance to an effect of THC [16,17], is any adverse consequence for the subject under the influence of the drug. Prominent examples of tolerance, on the other hand, most often have involved drug effects which cost the subject something, be it food [10], water [2], pain [12] or merely exertion (unpublished observations). The observations of human subjects may be viewed in a similar manner: it costs nothing to report to a researcher that one is high, but flunking what appears to be an IQ test might be painful indeed.

An hypothesis which seems to unify a great deal of this disparate evidence is one suggested by Schuster and his colleagues with reference to amphetamine tolerance: that tolerance to a behavioral effect of a drug will be most prominent when this effect is clearly detrimental to the subject, and less easily observed when the effect is neutral or beneficial to the subject [14]. Ferraro [4] and Sodetz [15] have previously remarked on the applicability of this view to THC work, and the following experiment tested this hypothesis, using the free-operant (Sidman) shock avoidance task. This behavior was chosen because in the Walter Reed laboratories it is improved by THC almost as often as it is impaired, with no apparent relation between established performance level and type or extent of effect.

METHOD

Animals were 7 adult male albino rats of the Wistar-derived Walter Reed strain. Each was confined, for one hr each day, in a standard operant conditioning

[1] In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Science – National Research Council.

chamber, complete with grid floor and a single lever protruding from one wall. A 250 msec pulse of 100 VAC (2.0 mA) was delivered to the rat, through the floor of the apparatus, every 5 sec, unless he pressed the lever, which postponed shock delivery for 20 sec. After 3 months of daily sessions the performance of all rats showed only very small and unsystematic changes from day-to-day. Although no rat ever avoided all shocks, and there was a very wide range, across rats, in the number of shocks received each day, it appeared that the individual baselines were fairly stable. The range of response rates over the last 5 sessions was less than 15 percent of the mean, for every rat. The following 15 sessions were preceded, by 3 hr, by intragastric intubation of one-half a milliliter of the THC vehicle, a suspension consisting of 15 percent dehydrated ethanol and 85 percent propylene glycol. After this control for the effects of vehicle and intubation, sessions were preceded, still by 3 hr, by intragastric delta-9-THC. Volume was 1 cc/kg; dose, 30 mg/kg. One rat, AV2, also received doses of 20 mg/kg and 10 mg/kg, each for 6 consecutive days, following 30 sessions at 30 mg/kg. Finally, after 10–45 sessions under the influence of THC, depending on the behavior of the rat, THC was discontinued and vehicle pretreatment was reinstituted. The original design called for administering THC until shock levels returned to baseline for those rats whose shock rate was increased. Rats whose shock rate was lowered by THC were to be treated similarly if tolerance developed, or given 3 times the number of sessions taken by the animal showing the slowest development of tolerance to a THC-induced increase in shock rate. As the experiment developed it became obvious that this plan was impractical, and the actual criteria used are discussed below.

RESULTS

Figure 1 displays the lever-press rates of each rat throughout the experiment. The three segments of each graph divide the final 5 sessions with vehicle pretreatment, all the sessions with THC pretreatment, and finally, a series of sessions preceded by vehicle pretreatment again. Although there are several instances of rather large changes for individual rats, between-animal variability is pronounced, and there is no general or typical (i.e., statistically significant) effect of Δ^9-THC on overall lever-press frequency in this situation. For example, Rats AV1, AV4 and AV8 showed marked and immediate decreases in responding upon introduction of THC pretreatment. In both the latter cases this effect disappeared quickly, while it remained essentially unchanged for the duration of AV1's treatment. Rat AV3 on the other showed an elevation in response rate rather than a decrease, and response rates of AV5, AV7, and AV2 showed little if any effect of the drug. Predrug response rate was predictive of neither the immediate effects of THC on response rate or response rate over the final 5 THC sessions: Pearson r's were 0.06 and 0.17 respectively, and parabolic, power, and exponential regression analysis also yielded non-significant coefficients.

Figure 2 displays the number of shocks received by each animal throughout the experiment. As is obvious from inspection of the data from vehicle only sessions, shock rate is not highly correlated with overall response rate in the free-operant procedure. Shock frequency depends far more on the spacing of responses than on overall number, and the effects of THC on shock rate were much more reliable than those on response rate. Six of 7 animals showed an increase in shock rate on the first day of THC treatment (pretreatment average = 116; THC session, 164; $t = 2.08$, $p<0.05$). By the last 5 THC sessions, however, mean shock rate had fallen to 96, significantly below both the vehicle ($t = 3.02$; $p<0.025$) and initial THC session ($t = 3.58$; $p<0.01$) rates. Cessation of drug treatment was followed by a gradual return to baseline (vehicle) shock rates (first 5 recovery days vs last 5 predrug days: $t = 1.495$; N.S.).

The shock data of rats AV1, AV5, and AV7 are of particular interest, for these subjects showed both impaired and facilitated avoidance during the course of THC treatment. Since the hypothesis underlying the experiment was that tolerance would appear far more rapidly for impaired avoidance than for facilitated avoidance, these three animals provide a unique and powerful test. They also forced a change from the planned treatment schedule: original plans called for cessation of THC when full tolerance to an elevated shock rate was seen. Since these animals showed not a simple return to baseline shock levels, but an actual reversal in the direction of the drug's effect, it was arbitrarily decided to continue THC treatment for 3 times the number of sessions it had taken for full tolerance to develop to THC-elevated shock rates. This was not possible in the case of AV7 (who died of pneumonia while still in the THC treatment stage of the experiment), but it is clear that although tolerance to shock elevation was complete in all cases within 6 sessions, no tolerance to the shock reduction was seen in any of the animals. The rise in shock totals, back to baseline levels, when THC was finally discontinued, argues against interpreting the lower shock levels as a result of continued training rather than as a specific drug effect, and consideration of the data of Rat AV2 rules out two other possible explanations for the lack of tolerance to THC-lowered shock rates. This animal was the sole rat in this experiment whose shock rate was reduced in the initial THC session. For this reason, and the rapidity of tolerance to elevated shock rate in the other rats, treatment of AV2 with THC was continued until the supply of drug prepared for this experiment was exhausted. The maintenance of decreased shock levels over 45 THC pretreatments (despite 2 decreases in dosage) suggests that the lack of tolerance in the other rats was not due entirely to impatience on the part of the experimenter, and also that lack of tolerance to improved avoidance is not dependent upon initial impairment and subsequent recovery.

DISCUSSION

To summarize these results, a rather large dose of delta-9-THC, 30 mg/kg PO, produced significant changes in overall lever-press rates of several subjects, but the direction, magnitude and duration of these effects were highly variable, and unrelated to baseline response or shock rates. However, shock rates were elevated by THC in 6 of the 7 rats. Tolerance to this effect was complete within 6 sessions. In 3 animals this was followed by sessions with significantly lower shock rates than the predrug baseline. The one rat not showing an initial elevation in shock rate after THC also avoided shocks better than during predrug sessions. All of these animals continued to perform at this level of proficiency until THC was discontinued, at which point baseline shock levels were reattained.

These data offer no further insight into the nature of THC's actions (i.e., why shock rates are elevated and/or reduced), but they do appear to be rather strong support for the hypothesis advanced above regarding the nature of

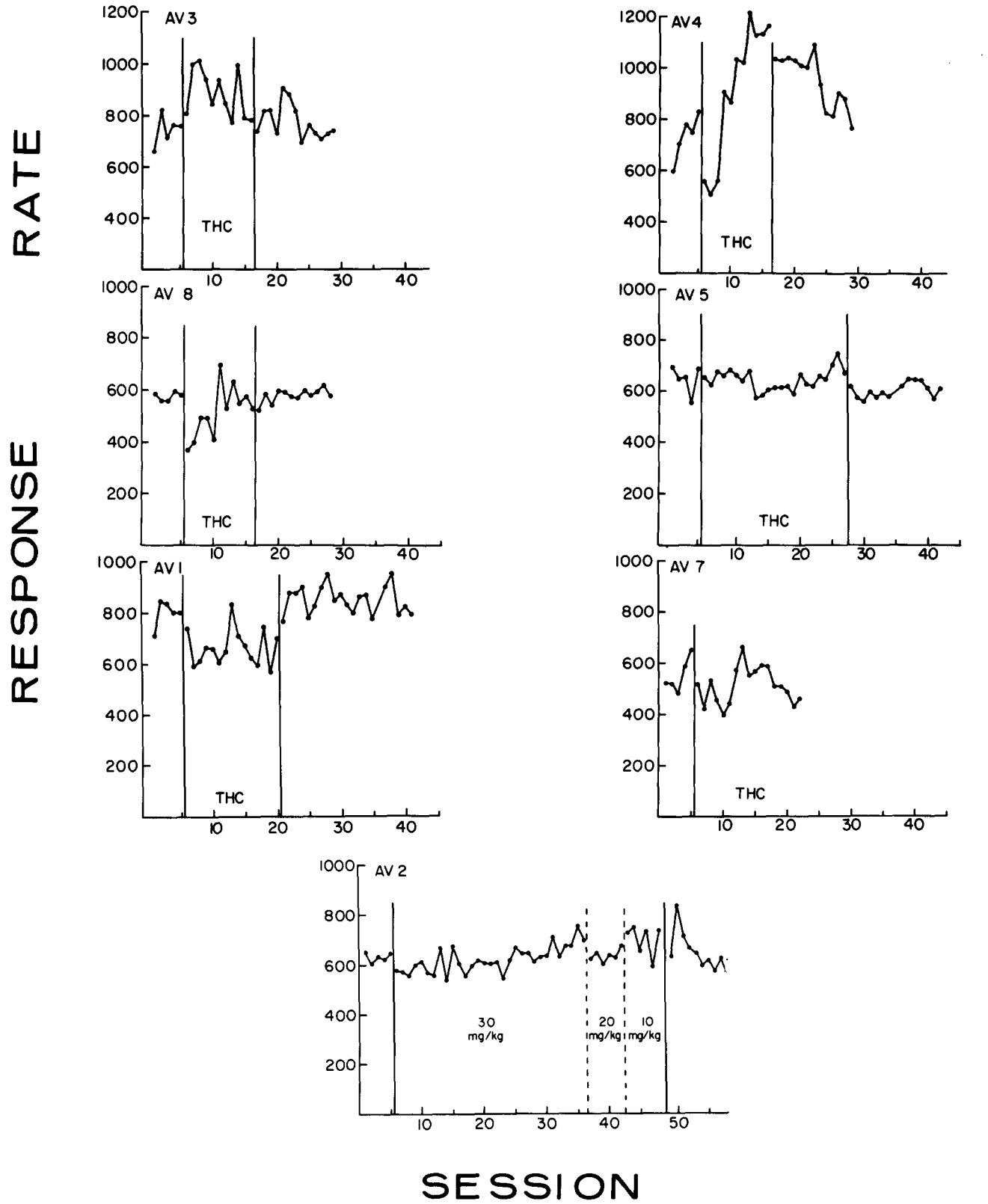

FIG. 1. Total lever-presses emitted by each animal in each session of the experiment. The sessions between the two vertical lines in each graph indicate those sessions preceded by delta-9-tetrahydrocannabinol (30 mg/kg except where noted). Other sessions were preceded by an equal volume of vehicle.

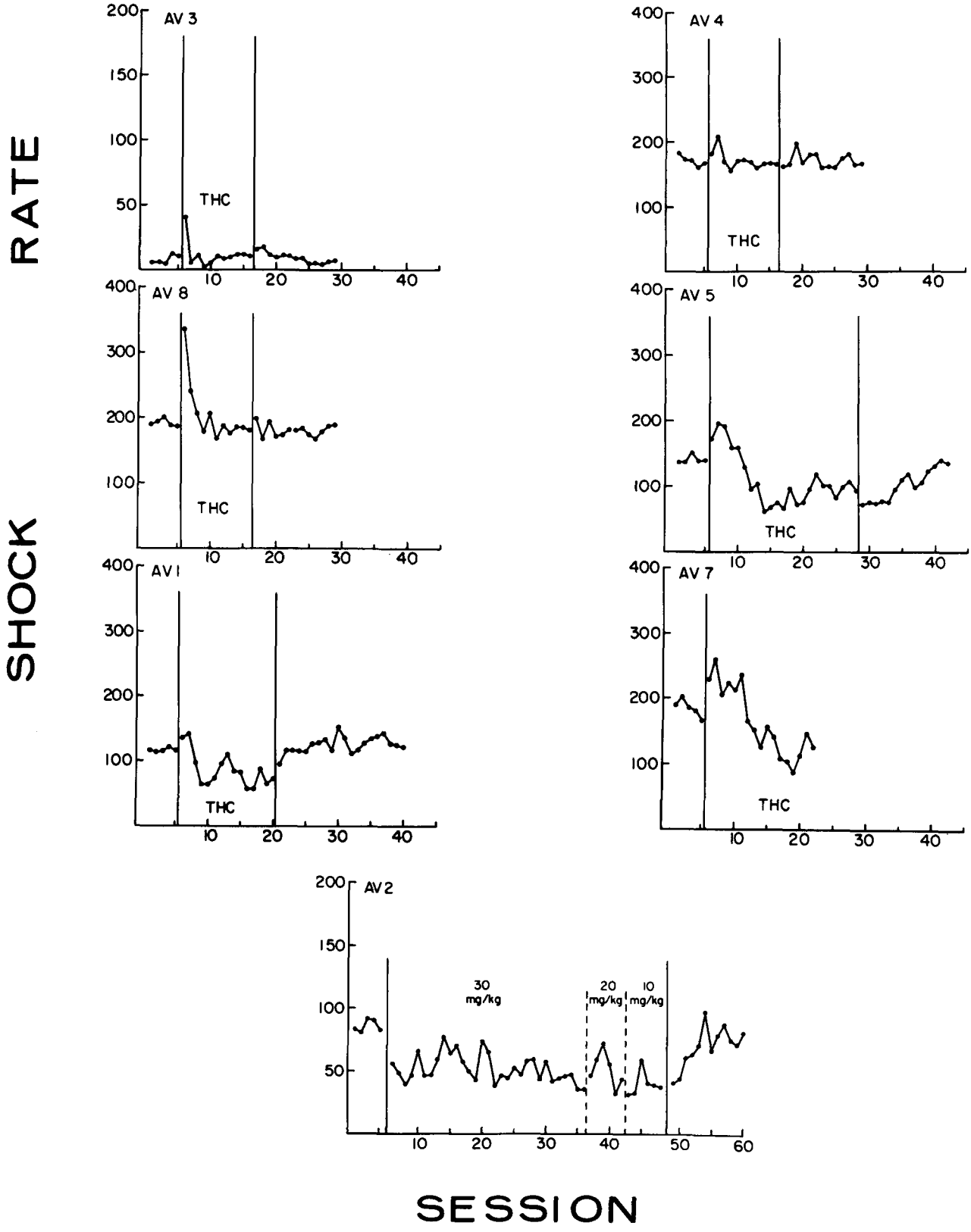

FIG. 2. Total shocks received by each animal in each session of the experiment. See Fig. 1 for further description.

tolerance: that tolerance to a behavioral effect of THC will be most prominent when this effect is clearly detrimental to the animal, for example, an increase in electrical shocks, and less easily observed when the effect is neutral or beneficial to the animal e.g., a decrease in electric shock rate. The striking similarity of this generalization to the Law of Effect should not go unnoticed. It suggests that the prominent tolerance to many behavioral effects of THC may well be function of learning as well as the result of any of the pharmacologic mechanisms traditionally associated with the word tolerance. That is, the transience of many of the THC-induced performance decrements may be viewed as a natural and adaptive response to a sudden decrease in reinforcement, a view which emphasizes the interaction of the organism and his external rather than internal environment.

Similar suggestions have been offered before, on very different kinds of evidence. Manning [9], for example, reported a prominent within-session tolerance to the disruptive effect of delta-9-THC on spaced responding by monkeys under a DRL schedule of food reinforcement. This acute tolerance was not the result of mere exposure to the drug; it was dependent upon responding under the influence of the drug. Ferraro [4] used THC to produce large decreases in the operant response rates of monkeys working for food on a variable-interval schedule. A characteristic of this sshedule is that variations in response rate, within very wide limits, have little if any effect on frequency of reinforcement. Ferraro's animals showed tolerance only when frequency was decreased, and such recovery as did occur ceased at the point at which reinforcement frequency reattained baseline levels. Loewe [8] long ago pointed out that tolerance to marihuana-induced ataxia occurred only if his dogs learned compensatory responses. Finally, Carder and Olson demonstrated that rats repeatedly tested in a lever-press operant procedure while under the influence of THC developed tolerance to the drug's rate-decreasing effect more rapidly than rats given the drug after the daily operant session [1].

Although attempts to specify a mechanism of physical or pharmacological tolerance (i.e., a change in absorption, distribution, metabolism, target sensitivity, or excretion) have met with little success thus far [10], it seems very likely that some such change occurs, in view of, for example, the increased LD_{50} observed after repeated administration of THC [10]. However, the data reported, and cited, above challenge the parsimonious assumption that behavioral changes seen over a course of repeated THC administrations are best explained by reference to such a mechanism. The addition of some version of the Law of Effect, which states that behavior is controlled by its consequences, seems unavoidable. Despite the fact that learning and reinforcement are ultimately physical and chemical events themselves, the choice of language to describe the recovery from behavioral effects of THC is not entirely a matter of taste or background, for the future experiments we design are frequently determined by the language we use to explain our present observations.

ACKNOWLEDGEMENTS

The author is indebted to Mason Jackson, Jr. for technical aid in conducting this work, Frank J. Sodetz for lengthy discussion of its interpretation and implications, and to Wilhelmina Taylor for preparation of the manuscript.

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