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MARIHUANA-INDUCED "HIGH": INFLUENCE OF EXPECTATION, SETTING AND PREVIOUS DRUG EXPERIENCE*

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The expectancies or "set" held by a subject, the characteristics of the experimental milieu or setting in which the drug is given and previous experience with the drug are important determinants of the subjective effects produced by marihuana (1, 16, 18). Although usually acknowledging the importance of such considerations the emphasis in most recent laboratory studies has been on the effects of dose, route of administration and tetrahydrocannabinol content of the plant material on performance and physiological measures (2, 3, 5, 6, 8, 10, 12). There has been relatively little formal study of psychosocial factors, particularly their relationship to subjective changes induced by marihuana in a laboratory setting (5, 16). In this report I will present some data demonstrating that an experimental subject's set, his previous experience with marihuana and the experimental setting are factors as important as the dose of tetrahydrocannabinol in determining the subjective state produced by the marihuana when given in socially relevant doses.

Marihuana is an ideal drug to study if one is interested in the more psychological aspects of psychopharmacology. In this country marihuana is generally consumed in low doses that allow psychological factors to play an important role in the resulting experience (5, 18). As a result of the culture and ritual surrounding marihuana use (1) a volunteer subject tends to arrive in the laboratory loaded with often unrealistic beliefs concerning the effects of the drug. Many studies with psychoactive drugs have demonstrated that the expectancies of the subject provide a cognitive framework in which relatively non-specific drug effects are interpreted (4, 9, 15). The experienced marihuana user with a well developed set of expectations concerning the drug makes a fine subject in which to study placebo effects and the relationship between the physiological and cognitive determinants of subjective states.

The experiments were all done in a scientific-looking laboratory. The subjects were 100 paid volunteers who came from contacts in the San Francisco Bay area student community or who called the laboratory after news releases about the study. They were all young adults age 21 through 30 years. All were experienced marihuana smokers. The total experience of 12 subjects was with as few as five cigarettes. At the other extreme were six subjects who smoked up to five cigarettes daily at times. Although this group of San Francisco residents considered

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themselves enthusiastic and regular users the modal pattern of use was only about four cigarettes per month. The group had been smoking marihuana for an average of 2.9 years.

The marihuana was obtained from the California Bureau of Narcotic Enforcement. It was probably grown in Western Mexico and had been stored at room temperature for some months before it was given to us. We prepared both cigarettes and an ethanol extract. Stems and seed were removed and the remaining material meshed through a size 10–20 mesh. We then assayed it for cannabinoids with gas chromatography. To prepare the placebo for smoked experiments all cannabinoids were removed from a portion of the well mixed plant material. This was done by thoroughly extracting that portion with 95% ethanol with the technique for preparing cannabis tincture described in the U.S. Pharmacopoeia, 11th edition. The placebo material was rehydrated with water and dried at room temperature. Both the active marihuana and placebo were maintained at approximately 12% humidity. The placebo is similar to that used by Manno *et al.* (10, 11).

The unextracted plant material contained 0.9% Δ^9-tetrahydrocannabinol (Δ^9-THC). The plant residue after the ethanol extraction contained no measurable cannabinoids as measured by gas chromatography. There was approximately 1.3% cannabinol by weight and a trace of Δ^8-THC in the unextracted plant material. Repeated assays with a gas chromatograph were done throughout the experimental period which spanned almost 2 years. There was no significant change in THC content.

Since we were interested in the effects of "socially relevant" doses of marihuana it was necessary to establish what dose our subjects smoked in a typical social situation. Unfortunately the best we can make are crude estimates based on scattered information. The THC content of plant material varies widely. Our experience is that marihuana smoked in San Francisco rarely contains more than 1% THC. Although a few specimens of "good grass" given to us by our subjects for analysis contained 1.5 to 2% THC a more typical assay was under 0.5%. A generous assumption is that marihuana generally available in the United States averages about 1.0% THC. Experienced smokers given material in this potency range judged it to be average quality (7, 17).

The quantity of marihuana smoked by a typical American user is even more difficult to determine. Most of our subjects smoked only one or two cigarettes during an evening of smoking. Frequently a cigarette was shared among five or six people. A 1-g cigarette containing 1% THC can deliver a maximum of 5 mg of THC to an individual smoker (10). This amount is often divided among five smokers all of whom reach an acceptable "social high." This suggests many users do not seek large doses of THC in a social setting. We believe the doses used in these experiments are realistic in terms of what our subjects claim to use socially. Patterns of drug use vary in different geographic areas and in different subject groups. The doses used by our experimental subjects may be quite different from those used in the Far East or in other areas of this country. In this respect generalizing about "average" doses of marihuana is like talking about average doses of alcohol or tobacco.

We made cigarettes containing 1 g of plant material on a hand-rolling machine. This was considered to be an average size cigarette by most of the subjects. The cigarette contained 9 mg of THC. Identical cigarettes were made from the placebo material. Each subject was allowed approximately 10 min to smoke the cigarette. They were asked to use 2- to 4-sec inhalations and to retain the smoke 30 to 40 sec before expiration. Subjects were instructed to smoke the entire cigarette holding the butt ("roach") with forceps. At the finish of smoking the residue consisted of only a fragment of charred paper and a few particles of partially burned marihuana.

Two techniques were used to assess subjective state. The subject made a global rating of his degree of intoxication with a 0 to 100 scale 30 min after smoking and at the end of the experimental session. Zero was defined as sober and 100 as the most intoxicated or most "stoned" they had ever been. At the end of the experimental session (usually about 3 hr) subjects also filled in a 272-item symptom checklist developed by Waskow *et al.* (16). The subject is asked to report any effects experienced during the 3-hr test session. The Subjective Drug Effects Questionnaire (SDEQ) is comprehensive, covering all aspects of subjective response and minimizes the effects of suggestion. We also recorded an array of physiological and behavioral measures, but we have no space to report in detail on the physiological changes at this time.

We were interested in the level of intoxication produced by a measured amount of marihuana when smoked by an experienced user. A number of investigators have used the subject's subjective evaluation of his "high" to partially validate their findings in studies with smoked marihuana so determination of the validity and reliability of such a rating is important (2, 3, 14, 17). Global estimations of intoxication made 30 min after smoking a cigarette containing 9 mg of THC or placebo are listed in table 1. The estimations made at 3 hr after smoking were not significantly different. The cigarettes were administered in a counterbalanced order in a double-blind test situation at least 2 days apart. The subjective potency, 61, as rated on the 0–100 scale is consistent with the chemical assay of the plant material. Marihuana with a THC content of 0.9 % is representative of

TABLE 1

Level of intoxication—distribution of global subjective ratings after smoking marihuana and placebo

Subjective rating of intoxication 0–100 scale*	No. of subjects reporting†	
	Marihuana	Placebo
0–19	15	35
20–39	11	28
40–59	20	21
60–79	32	12
80–100	22	4
Mean subjective rating of intoxication level	61	34

* 0 = Sober; 100 = maximally intoxicated.

† N = 100.

average marihuana in the San Francisco area. We have assayed many samples that contained far less THC (0.1 % or less). Samples that contain over 1.2 % are unusual. The important and troublesome finding is the distribution of the ratings. The mean rating of the placebo, 34, is significantly lower than that assigned to marihuana ($P < .05$). However the placebo ratings ranged from 0 to 90 and the ratings of unextracted plant material ranged from 0 to 95. Many subjects rated their level of intoxication after smoking placebo to be identical to that after smoking marihuana.

There are a number of alternate explanations for this pattern of response. The possibility that the placebo still contained psychoactive substances even though the THC had been completely removed is I think an unlikely one. If this was so, such a substance would seem to be almost devoid of measurable objective effects. This is demonstrated in table 2 in which differences are shown on selected physiological and performance measures obtained before and at the time of peak subjective effects after smoking. Space does not allow for a detailed description of these measures but in our previous studies (7) and in studies done in other laboratories (10, 11, 17) such measures showed dose related changes after smoked marihuana. Products of combustion non-specific to cannabis such as carbon monoxide should have been produced in approximately equal quantities by both the placebo and marihuana cigarettes and are unlikely to account for the observed differences. Note that there are no significant changes after smoking THC-free placebo. Pulse rate and salivary flow changes after marihuana were opposite in sign to those measured after placebo. The variations in the latter two measures after placebo are no different than those occurring in a "no treatment" group who were simply retested after the passage of an appropriate time period.

We also examined the possibility that there was some conversion of a component of the placebo to THC in the smoking process. No measurable amounts of

TABLE 2

Effects of smoking marihuana (1 g) or placebo (means and standard deviations—pre- and post-drug)

Test and No. of Subjects	Marihuana		Placebo	
	Before	After*	Before	After†
Pulse rate (N = 100) resting rate, beats/min	74.2 ± 9.2	98.2 ± 16.5	74.4 ± 8.9	70.0 ± 9.1
Salivary flow, total ml for 5 min (N = 40)	4.6 ± 1.8	3.0 ± 1.3	3.9 ± 0.16	4.7 ± 1.9
Conjunctival injection 0 to 4 scale (N = 40)	0.18 ± 0.37	2.1 ± 1.5	0.16 ± 0.30	0.20 ± 0.42
Digit symbol substitution total number correct in 90 sec (N = 80)	68 ± 7	60 ± 10	66 ± 9	67 ± 11

* All significant $P < .05$, Wilcoxon signed ranks test.

† Pre-post changes not significant.

cannabinoids remained in the placebo material. We examined the smoke produced by the placebo cigarette in a smoking machine similar to that used by Manno *et al.* (10). The smoke was collected in ethanol and the ethanol analyzed for cannabinols with gas chromatography. No cannabinoids were seen in the smoke with this technique.

This pattern of subjective response after smoking a substance without any relevant pharmacological activity reflects the important role of expectations and past experience of the subjects tested in what was for them a novel situation. Most of the subjects anticipated they would get high even though they were told that an inactive substance might be given. The typical marihuana user in San Francisco is exposed to a wide range of potencies and tends to set broad limits for what he is willing to call marihuana. The criteria he must use to set those limits are confounded by a host of psychological and social variables in addition to the THC content of the plant. The experienced user comes to the laboratory with an over-learned set of expectations. The overt and covert advertising in the media and in the marihuana with culture is a potent force. Prior experience with a drug is an important determinant of the placebo effect (4, 9). It may be that smoking of a material that smells and tastes like marihuana may serve as a signal that produces an internal state that is interpreted by the subject as being high. The frequent misjudgments of psychoactive drug effects by both users and professionals is described in some detail by Lennard *et al.* (9).

If "learning to get high" is an important factor there should be differences between more and less well practiced subjects. We looked for such differences by selecting from the original group of 100 subjects 25 infrequent users and 25 frequent users representing extremes in the pattern of use in the group. We selected only those subjects where two judges, after reviewing the drug histories, agreed on the ranking as to pattern of use. The 50 subjects not assigned to either extreme group could not be ranked reliably by independent judges because of variable patterns of use or inconsistent or absent historical data. The infrequent users admitted to smoking less than two cigarettes per month on an average. The frequent users smoked at least seven cigarettes per week regularly and in six cases claimed to use two or three daily. The division represented stable patterns of use for at least 2 months before the tests. In most respects the groups were similar to the casual and heavy users described by Mirin *et al.* (13) particularly in their use of drugs other than marihuana.

The global intoxication ratings when subjects are grouped by frequency of use are described in table 3. The infrequent users made a significant distinction between the placebo and marihuana. The higher potency rating for the placebo made by the frequent users is consistent with the hypothesis that one "learns to get high." The familiar smell and taste seems to be an adequate cue to induce an identifiable subjective state. These data do not support the concept of "reverse tolerance" that has been somewhat uncritically entertained in the recent marihuana literature (8, 17) unless the increased "sensitivity" to a pharmacologically inactive placebo is so interpreted. In fact there is a suggestion that the frequent users show true tolerance to subjective effects if one examines the ratings for the

active material. Increased sensitivity to placebo and tolerance to active marihuana may at first seem paradoxical. However, this illustrates the complex interplay of psychological and pharmacological factors. The response to placebo represents *mainly* the effect of psychological factors and the response to active marihuana at this dose reflects *mainly* pharmacological factors but includes psychological factors as well. In the group of frequent users the two sets of factors tend to have opposite effects on the subjective ratings made for the marihuana.

Performance and physiological measures demonstrate differences between frequent and infrequent users and are consistent with the development of tolerance to some of the effects of marihuana in frequent users. The scores in table 4 reflect the changes associated with smoking 1 g of marihuana (9 mg of THC). There is a diminished drug effect in the frequent users both on physiological and behavioral measures.

In an experiment comparing subjective effects of an oral dose and smoked marihuana and placebos, the interaction between psychological and pharmaco-

TABLE 3

Level of intoxication—global subjective rating differences between frequent and infrequent users after smoking 1 g of marihuana or placebo

Degree of Use	Mean Subjective Rating and Standard Deviation		
	Marihuana	Placebo	P value
Infrequent (N = 25) < 2 cigarettes/month	67 ± 23	22 ± 18	< .01
Frequent (N = 25) < 7 cigarettes/week	52 ± 26	48 ± 21	n.s.
Significance level	n.s.	P < .05	

* 0 = sober; 100 = maximally intoxicated.

TABLE 4

Mean changes in physiological and performance measures after smoking marihuana—frequent and infrequent users compared

Test Procedure and Score	Mean Changes in Scores after Smoking 1 g Marihuana	
	Frequent users (N = 25) >7 cigarettes/week	Infrequent users (N = 25) <2 cigarettes/month
Pulse rate increase (beats/min)	17.3*	31.2*, †
Salivary flow decrease (ml/5 min)	0.9	1.8*, †
Conjunctival injection (0–4 scale)	1.5*	2.1*
Digit symbol substitution (decrease in number completed)	2	8*
Complex Reaction Time; increase (msec)	21	52*

* P < .05 between change scores after placebo and after marihuana.

† P < .05 between frequent and infrequent users.

logical factors may be more apparent. The same subjective ratings but with important differences in the experimental situation are described in table 5. We administered the marihuana and placebo with familiar cues (smell and taste) in the smoked condition and also we gave a roughly equivalent dose of THC (5) without any of the familiar taste and smell cues by means of an ethanol extract of marihuana. The ethanol extract was similar to that used by Hollister and other investigators (12). The extract contained 10 mg of THC in 1 ml of 95% ethanol. The treatments were given in a double-blind counterbalanced order. The oral placebo was an ethanol extract of cannabinoid free marihuana and had the same disagreeable taste as the active extract when given diluted in water. The ratings of maximum level of intoxication were made at the conclusion of the experimental session when the subjects were no longer intoxicated. The time of peak intoxication was later with the orally administered cannabis (128 *versus* 25 min). In the smoked situation these subjects responded in the same fashion as those already described; however, note there is no difference between frequent and infrequent users in the oral placebo condition. Without the familiar smell and taste cues both groups responded similarly to a placebo. With the active orally administered extract there is again evidence for tolerance to the subjective effects of marihuana rather than "reverse tolerance." The difference between frequent and infrequent users in the ratings of level of intoxication after the oral extract is not quite statistically significant but the trends are consistent.

This evidence for true pharmacological tolerance in frequent marihuana users can be considered to be only strongly suggestive at this point. The two groups differed in a number of other respects besides their marihuana smoking patterns—for example the frequency of use of other drugs (LSD, alcohol, tobacco); social adjustment, value systems, *etc.* These factors could account for some of the differences on both the physiological and subjective measures. However, when we divided subjects on some of these psychosocial criteria and held level of marihuana use constant we did not see evidence of tolerance on the measures in tables 3, 4 and 5. Additional evidence that suggests marihuana can produce a pattern of mild tolerance and withdrawal symptoms similar to those seen with a variety of central nervous system depressants are reports from five of the most

TABLE 5

Level of intoxication—global subjective ratings after oral and smoked marihuana

Degree of Use	Mean Subjective Rating and Standard Deviation			
	Marihuana		Placebo	
	Oral extract containing 25 mg THC	Cigarette containing 1 g 9 mg THC	Oral extract	Smoked cigarette
Infrequent users N = 8 < 2 cigarettes/month	72 ± 21	62 ± 16	2 ± 8	26 ± 20
Frequent users N = 8 > 7 cigarettes/week	32 ± 22	56 ± 25	5 ± 12	51 ± 23

frequent users that sound like mild withdrawal symptoms. These consist of feelings of irritability, restlessness, insomnia, perspiration and salivation occurring 24 to 48 hr after the cessation of regular use and relieved by barbiturates, alcohol or resumption of marihuana use.

An analysis of the patterns of responses on the SDEQ describing specific symptoms supports the notion that a rather non-specific internal state was interpreted as a marihuana-induced high by many subjects smoking placebo. Even subjects who rated themselves as significantly intoxicated after the placebo (a rating of 40 or more on the global intoxication scale) responded affirmatively to relatively few items on the symptom checklist. In table 6, the items from the SDEQ that were responded to by more than 50 % of the subjects after smoking placebo are contrasted to the items that were responded to by at least 50 % of the subjects who smoked marihuana and rated themselves similarly intoxicated. The subjects were instructed to respond affirmatively to any of the items describing phenomena experienced during the 3 hr of testing. As measured by the detailed symptom check list, the marihuana produced a different and more drug specific internal state than did the placebo. However, it is the labeling of this internal state in the total context of the experimental situation and his past experience that determines much of subject's subjective report on a global rating of intoxication or concerning the drug ingested. A similar situation has been demonstrated over and over again in psychopharmacological studies where low doses of a psychoactive drug are administered (4, 9, 15, 18).

TABLE 6

A comparison of subjective symptoms in subjects given placebo and marihuana—most common responses

Marihuana (74 Subjects)	Placebo (37 Subjects)
Noticing passing of time more	Body relaxed
Time going slower	Unsteady
Speech sounds slower	Sluggish
Thoughts moving faster	Felt high
Imagination more lively	Sleepy
Heart beating faster	More relaxed
Throat drier	Felt more at peace with the world
Hungrier than usual	Losing sense of time
Thinking clearer	Thoughts moved slower
Easier to concentrate	Noticing passing of time less
Felt more free	
Felt more serious	
Noticing things more	
Colors brighter	
Arms and legs more sensitive	
Disliked answering these questions	

The folklore concerning the effects of marihuana on mood, emphasizes setting as an important determinant. Our subjects frequently commented on the effects of this factor when making judgments of level of intoxication. We investigated the effects of setting on the marihuana high with 16 subjects of the sort already described. Subjects smoked marihuana on two occasions, 1 week apart. On one occasion they were tested individually. In another session with the treatment order assigned in a balanced fashion, the subject smoked with a four-man group. During each session they smoked a 1-g marihuana cigarette containing 9 mg of THC. In the group situation, subjects engaged in 45 min of unstructured conversation. In the individual test situation, the subjects were free to read, listen to the radio or do nothing for 45 min. A friendly research assistant was in the area. After 45 min they filled out the subjective drug effects questionnaire.

Subjects tested individually demonstrated the relaxed, slightly drowsy, undramatic state usually seen in our laboratory. In the group situation there was a consistent and impressive difference in behavior with elation, euphoria, uncontrolled laughter, and a marked *lack* of sedation. The differences in the SDEQ response are illustrated in table 7. This table lists scores on some of the empirical clusters of items derived from the questionnaire. The names of the scales describes their general content. A more detailed description of the items has been published (16). Examples of items making up the 34-item *Euphoria* scale commonly responded to include: body feeling more relaxed; mood more relaxed; happier; feeling like laughing; seeing the comical side of things more; liking people around more; colors seem brighter; feeling it is easier to talk. Common responses on the 47-item *Dysphoria* Scale include: head feeling heavier and stuffier; throat drier; hungrier; body sluggish and heavier; sleepier. Items on the 20-item *Thinking* cluster include: easier to concentrate; thinking clearer; thoughts moving faster; thoughts moving slower; imagination more lively; feel less like paying close attention to something. Items responded to on the 43-item *Perception* scale include: colors seem brighter; speech sounds slower; time going slower.

TABLE 7

Comparing subjective drug effects questionnaire (SDEQ) scores after smoking marihuana in group and solitary setting

SDEQ Clusters (No. of Items)	Mean Cluster Scores	
	Group setting	Solitary setting
1. Euphoria (N = 20)	21.2*	13.8
2. Dysphoria (N = 47)	11.6	17.6
3. Perceptual change (N = 43)	21.3†	7.8
4. Thinking change (N = 20)	12.7†	6.5
Mean total SDEQ symptoms	102.2	79.9

* $P < .01$.
† $P < .05$.

Subjects in the group setting experienced more symptoms on all but the Dysphoria scale. Symptoms in the individual test situation were predominantly sedative effects. A greater variety of symptoms were reported after the group condition. Although not instructed to, each group spent much time exploring for the presence of symptoms and tended to reinforce and encourage the appearance of minimal symptomatology. The global ratings of intoxication were 71 (range 55 to 90) in the group condition and 62 (range 25 to 80) in the individual testing situation. This suggests that the interpersonal situation is more a significant consideration than the physical setting, since both sessions were run in the same laboratory.

In summary, these data suggest that marihuana when smoked at what was, for our subject population, a socially relevant dose, a level of intoxication is produced that allows the attitude of the subject, his set and expectations, the setting and his past experience to interact in a complex way to determine how the subjective state will be labeled and reported. Such findings should not be surprising and certainly suggest nothing pharmacologically unique about marihuana. Evaluations of the effects of low or modest doses of any psychoactive drug have to deal with these issues (4, 9). The situation with marihuana is a bit different in that so many people have uncritically accepted the belief that the drug has specific effects on behavior and experience and that these can be readily identified. Such an erroneous model has been accepted by both users and professionals and is continually reinforced by the media. Although at high doses such a model may be valid, at the doses most youthful drug users are discussing there is ample evidence that the effects of psychoactive drugs on behavior and experience are often to a great extent independent of the drugs' pharmacological effects (1, 9).

The investigator who depends on a subject reaching a certain "social high" does so at the risk of studying behavior in a non-specific psychological state rather than the pharmacological effects of a given dose of marihuana. Moreover, in addition to the important and complex problems associated with specifying the delivered doses of THC the researcher must also in a sense quantify the dose of "interpersonal stimulation" and the dose of "subject expectation" if he is going to relate in any meaningful way marihuana induced physiological changes to a given subjective state.

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