Pleistocene record is also provided by changes in the coiling direction of *G. truncatulinoides*.

The most important criteria which distinguish Pleistocene pelagic sediments from sediments of earlier epochs of the Cenozoic Period are the general occurrence of *Globorotalia truncatulinoides* in abundance and the absence of discoasters.

Our time scale, based on magnetic reversals, dates the beginning of the Pleistocene, as defined by the first appearance of *Globorotalia truncatulinoides* in abundance, at about 2 million years ago.

References and Notes

1. R. Selli, *Progr. Oceanogr.* **4**, 67 (1967).
2. W. A. Berggren, J. D. Phillips, A. Bertels, D. Wall, *Nature* **216**, 253 (1967).
2a. ———, *Deep-Sea Res.* **14**, No. 2 (1968).
3. J. D. Hays and W. A. Berggren, *Micropaleontology of Marine Bottom Sediments* (Cambridge Univ. Press, New York, in press).
4. W. Schott, *Wiss. Ergeb. Deut. Atlantischen Expedition Vermess. Forschungsschiff 'Meteor' 1925–27* **3**, 43 (1935).
5. D. B. Ericson, M. Ewing, G. Wollin, *Science* **146**, 723 (1964).
6. C. G. A. Harrison and B. M. Funnell, *Nature* **204**, 566 (1964).
7. M. D. Fuller, C. G. A. Harrison, Y. R. Nayudu, *Amer. Ass. Petrol. Geol. Bull.* **50**, 566 (1966).
8. N. D. Opdyke, B. Glass, J. D. Hays, J. Foster, *Science* **154**, 349 (1966).
9. B. Glass, D. B. Ericson, B. C. Heezen, N. D. Opdyke, J. A. Glass, *Nature* **216**, 437 (1967).
10. J. D. Hays and N. D. Opdyke, *Science* **158**, 1001 (1967).
10a. For our first report on this method, see D. B. Ericson and G. Wollin, *Micropaleontology* **2**, No. 3 (1956).
11. D. B. Ericson, G. Wollin, J. Wollin, *Deep-Sea Res.* **2**, 152 (1954).
12. J. A. Cushman and L. G. Henbest, *U.S. Geol. Survey Profess. Paper 196-A* (1940), p. 49.
13. F. B. Phleger, *Bull. Geol. Soc. Amer.* **53**, 1073 (1942).
14. C. D. Ovey, *Centenary Proc. Roy. Meteorol. Soc.* **1950**, 211 (1950).
15. F. L. Parker, *Rep. Swedish Deep-Sea Expedition* **8**, 219 (1958).
16. J. D. H. Wiseman, *Proc. Roy. Soc. London Ser. A* **222**, 296 (1954).
17. D. B. Ericson, M. Ewing, G. Wollin, B. C. Heezen, *Bull. Geol. Soc. Amer.* **72**, 193 (1961).
18. D. B. Ericson, *Ann. N.Y. Acad. Sci.* **95**, 537 (1961).
19. F. B. Phleger, F. L. Parker, J. F. Peirson, *Rep. Swedish Deep-Sea Expedition* **7**, No. 1, 1 (1953).
20. G. Arrhenius, *ibid.* **5**, pt. 3, 194 (1952).
21. W. R. Riedel, *ibid.* **6**, No. 3, 65 (1957).
22. ———, M. N. Bramlette, F. L. Parker, *Science* **140**, 1238 (1963).
23. D. B. Ericson, M. Ewing, G. Wollin, *ibid.* **139**, 727 (1963).
24. A. McIntyre, A. W. H. Be, R. Preikstas, *Progr. Oceanogr.* **4**, 3 (1967).
25. O. L. Bandy, *Science* **142**, 1290 (1963).
26. C. Emiliani, *Ann. N.Y. Acad. Sci.* **95**, 521 (1961); *J. Geol.* **74**, 109 (1966).
27. H. M. Bolli, J. E. Boudreaux, C. Emiliani, W. W. Hay, R. J. Hurley, J. J. Jones, *Bull. Geol. Soc. Amer.* **79**, 459 (1968).
28. J. D. Hays, *Amer. Geophys. Union Antarctic Res. Ser.* **5**, 125 (1965).
29. F. T. Banner and W. H. Blow, *Micropaleontology* **13**, 133 (1967).
30. A. Cox, R. R. Doell, G. B. Dalrymple, *Science* **144**, 1537 (1964); A. Cox and G. B. Dalrymple, *J. Geophys. Res.* **72**, 2063 (1967).
31. D. Ninkovich, N. D. Opdyke, B. C. Heezen, J. Foster, *Earth Planet. Sci. Letters* **1**, 476 (1966).
32. J. N. Rosholt, C. Emiliani, J. Geiss, F. F. Koczy, P. J. Wangersky, *J. Geol.* **69**, 162 (1961).
33. W. M. Sackett, in "Symposium on Marine Geochemistry," *Graduate School of Oceanog. Univ. Rhode Island Occasional Pub. No. 3* (1965).
34. T. L. Ku and W. S. Broecker, *Science* **151**, 48 (1966).
35. W. C. Pitman III and J. R. Heirtzler, *ibid.* **154**, 1164 (1966).

36. We are grateful to Maurice Ewing for his generous support of our research work and his active participation in it. We thank Janet Wollin, Julie McGowan, and Anne Riley for able assistance in the laboratory investigations. We also thank Arnold Finck and other members of the staff of Lamont Geological Observatory who, directly or indirectly, contributed to this study. We are grateful to N. D. Opdyke, B. Glass, and J. Foster for magnetic stratigraphy determinations and to W. S. Broecker, D. L. Thurber, and Hans Suess for radiocarbon determinations. The collection, preservation, and analysis of the cores were supported in large part by grants and contracts with the National Science Foundation (GP-4376, GA-982, and 1193) and the Office of Naval Research (TO-4). This is Lamont Geological Observatory contribution No. 1278.

CURRENT PROBLEMS IN RESEARCH

Clinical and Psychological Effects of Marihuana in Man

Andrew T. Weil, Norman E. Zinberg, Judith M. Nelsen

In the spring of 1968 we conducted a series of pilot experiments on acute marihuana intoxication in human subjects. The study was not undertaken to prove or disprove popularly held convictions about marihuana as an intoxicant, to compare it with other drugs, or to introduce our own opinions. Our concern was simply to collect some long overdue pharmacological data. In this article we describe the primitive state of knowledge of the drug, the research problems encountered in designing a replicable study, and the results of our investigations.

Marihuana is a crude preparation of flowering tops, leaves, seeds, and stems of female plants of Indian hemp *Cannabis sativa* L.; it is usually smoked. The intoxicating constituents of hemp are found in the sticky resin exuded by the tops of the plants, particularly the females. Male plants produce some resin but are grown mainly for hemp fiber, not for marihuana. The resin itself, when prepared for smoking or eating, is known as "hashish." Various *Cannabis* preparations are used as intoxicants throughout the world; their potency varies directly with the amount of resin present (*1*). Samples of American marihuana differ greatly in pharmacological activity, depending on their composition (tops contain most resin; stems, seeds, and lower leaves least) and on the conditions under which the plants were grown. In addition, different varieties of *Cannabis* probably produce resins with different proportions of constituents (*2*). Botanists feel that only one species of hemp exists, but work on the phytochemistry of the varieties of this species is incomplete (*3*). Chronic users claim that samples of marihuana differ in quality of effects as well as in potency; that some types cause a preponderance of physical symptoms, and that other types tend to cause greater distortions of perception or of thought.

Pharmacological studies of *Cannabis* indicate that the tetrahydrocannabinol fraction of the resin is the active portion. In 1965, Mechoulam and Gaoni (*4*) reported the first total synthesis of (−)-Δ^1-*trans*-tetrahydrocannabinol (THC), which they called "the psychotomimeti-

This work was conducted in the Behavioral Pharmacology Laboratory of the Boston University School of Medicine, sponsored and supported by its division of psychiatry, and at the Boston University Medical Center, Boston, Massachusetts. The present addresses of the authors are: Dr. Weil, Mt. Zion Hospital and Medical Center, San Francisco, California 94115; Dr. Zinberg, Harvard University, Cambridge, Massachusetts; and Miss Nelsen, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, Massachusetts 02118.

cally active constituent of hashish (marihuana)." Synthetic THC is now available for research in very limited supply.

In the United States, the use of *Cannabis* extracts as therapeutics goes back to the 19th century, but it was not until the 1920's that use of marihuana as an intoxicant by migrant Mexican laborers, urban Negroes, and certain Bohemian groups caused public concern (*3*). Despite increasingly severe legal penalties imposed during the 1930's, use of marihuana continued in these relatively small populations without great public uproar or apparent changes in numbers or types of users until the last few years. The fact that almost none of the studies devoted to the physiological and psychological effects of *Cannabis* in man was based on controlled laboratory experimentation escaped general notice. But with the explosion of use in the 1960's, at first on college campuses followed by a spread downward to secondary schools and upward to a portion of the established middle class, controversy over the dangers of marihuana generated a desire for more objective information about the drug.

Of the three known studies on human subjects performed by Americans, the first (see *5*) was done in the Canal Zone with 34 soldiers; the consequences reported were hunger and hyperphagia, loss of inhibitions, increased pulse rate with unchanged blood pressure, a tendency to sleep, and unchanged performance of psychological and neurological tests. Doses and type of marihuana were not specified.

The second study, known as the 1944 LaGuardia Report (*6*), noted that 72 prisoners, 48 of whom were previous *Cannabis* users, showed minimum physiological responses, but suffered impaired intellectual functioning and decreased body steadiness, especially well demonstrated by nonusers after high doses. Basic personality structures remained unchanged as subjects reported feelings of relaxation, disinhibition, and self-confidence. In that study, the drug was administered orally as an extract. No controls were described, and doses and quality of marihuana were unspecified.

Williams *et al.* in 1946 (*7*) studied a small number of prisoners who were chronic users; they were chiefly interested in effects of long-term smoking on psychological functioning. They found an initial exhilaration and euphoria which gave way after a few days of smoking to indifference and lassitude that somewhat impaired performance requiring concentration and manual dexterity. Again, no controls were provided.

Predictably, these studies, each deficient in design for obtaining reliable physiological and psychological data, contributed no dramatic or conclusive results. The 1967 President's Commission on Law Enforcement and the Administration of Justice described the present state of knowledge by concluding (*3*): ". . . no careful and detailed analysis of the American experience [with marihuana] seems to have been attempted. Basic research has been almost nonexistent. . . ." Since then, no other studies with marihuana itself have been reported, but in 1967 Isbell (*8*) administered synthetic THC to chronic users. At doses of 120 μg/kg orally or 50 μg/kg by smoking, subjects reported this drug to be similar to marihuana. At higher doses (300 to 400 μg/kg orally or 200 to 250 μg/kg by smoking), psychotomimetic effects occurred in most subjects. This synthetic has not yet been compared with marihuana in nonusers or given to any subjects along with marihuana in double-blind fashion.

Investigations outside the United States have been scientifically deficient, and for the most part have been limited to anecdotal and sociological approaches (*9–12*). So far as we know, our study is the first attempt to investigate marihuana in a formal double-blind experiment with the appropriate controls. It is also the first attempt to collect basic clinical and psychological information on the drug by observing its effects on marihuana-naive human subjects in a neutral laboratory setting.

Research Problems

That valid basic research on marihuana is almost nonexistent is not entirely accounted for by legislation which restricts even legitimate laboratory investigations or by public reaction sometimes verging on hysteria. A number of obstacles are intrinsic to the study of this drug. We now present a detailed description of our specific experimental approach, but must comment separately on six general problems confronting the investigator who contemplates marihuana research.

1) Concerning the route of administration, many pharmacologists dismiss the possibility of giving marihuana by smoking because, they say, the dose cannot be standardized (*13*). We consider it not only possible, but important to administer the drug to humans by smoking rather than by the oral route for the following reasons. (i) Smoking is the way nearly all Americans use marihuana. (ii) It is possible to have subjects smoke marihuana cigarettes in such a way that drug dosage is reasonably uniform for all subjects. (iii) Standardization of dose is not assured by giving the drug orally because little is known about gastrointestinal absorption of the highly water-insoluble cannabinols in man. (iv) There is considerable indirect evidence from users that the quality of the intoxication is different when marihuana or preparations of it are ingested rather than smoked. In particular, ingestion seems to cause more powerful effects, more "LSD-like" effects, longer-lasting effects, and more hangovers (*12, 14*). Further, marihuana smokers are accustomed to a very rapid onset of action due to efficient absorption through the lungs, whereas the latency for onset of effects may be 45 or 60 minutes after ingestion. (v) There is reported evidence from experiments with rats and mice that the pharmacological activities of natural hashish (not subjected to combustion) and hashish sublimate (the combustion products) are different (*14*).

2) Until quite recently, it was extremely difficult to estimate the relative potencies of different samples of marihuana by the techniques of analytical chemistry. For this study, we were able to have the marihuana samples assayed spectrophotometrically (*15*) for THC content. However, since THC has not been established as the sole determinant of marihuana's activity, we still feel it is important to have chronic users sample and rate marihuana used in research. Therefore, we assayed our material by this method as well.

3) One of the major deficiencies in previous studies has been the absence of negative control or placebo treatments, which we consider essential to the design of this kind of investigation. Because marihuana smoke has a distinctive odor and taste, it is difficult to find an effective placebo for use with chronic users. The problem is much less difficult with nonusers. Our solution to this dilemma was the use of portions of male hemp stalks (*16*), devoid of THC, in the placebo cigarettes.

4) In view of the primitive state of

knowledge about marihuana, it is difficult to predict which psychological tests will be sensitive to the effects of the drug. The tests we chose were selected because, in addition to being likely to demonstrate effects, they have been used to evaluate many other psychoactive drugs. Of the various physiological parameters available, we chose to measure (i) heart rate, because previous studies have consistently reported increases in heart rate after administration of marihuana (for example, *5*); (ii) respiratory rate, because it is an easily measured vital sign, and depression has been reported (*11*, *17*); (iii) pupil size, because folklore on effects of marihuana consistently includes reports of pupillary dilatation, although objective experimental evidence of an effect of the drug on pupils has not been sought; (iv) conjunctival appearance, because both marihuana smokers and eaters are said to develop red eyes (*11*); and (v) blood sugar, because hypoglycemia has been invoked as a cause of the hunger and hyperphagia commonly reported by marihuana users, but animal and human evidence of this effect is contradictory (*6*, *10*, *11*). [The LaGuardia Report, quoted by Jaffe in Goodman and Gilman (*18*) described hyperglycemia as an effect of acute intoxication.] We did not measure blood pressure because previous studies have failed to demonstrate any consistent effect on blood pressure in man, and we were unwilling to subject our volunteers to a nonessential annoyance.

5) It is necessary to control set and setting. "Set" refers to the subject's psychological expectations of what a drug will do to him in relation to his general personality structure. The total environment in which the drug is taken is the setting. All indications are that the form of marihuana intoxication is particularly dependent on the interaction of drug, set, and setting. Because of recent increases in the extent of use and in attention given this use by the mass media, it is difficult to find subjects with a neutral set toward marihuana. Our method of selecting subjects (described below), at the least, enabled us to identify the subjects' attitudes. Unfortunately, too many researchers have succumbed to the temptation to have subjects take drugs in "psychedelic" environments or have influenced the response to the drug by asking questions that disturb the setting. Even a question as simple as, "How do you feel?" contains an element of suggestion that alters the drug-set-setting interaction. We took great pains to keep our laboratory setting neutral by strict adherence to an experimental timetable and to a prearranged set of conventions governing interactions between subjects and experimenters.

6) Medical, social, ethical, and legal concerns about the welfare of subjects are a major problem in a project of this kind. Is it ethical to introduce people to marihuana? When can subjects safely be sent home from the laboratory? What kind of follow-up care, if any, should be given? These are only a few specific questions with which the investigator must wrestle. Examples of some of the precautions we took are as follows. (i) All subjects were volunteers. All were given psychiatric screening interviews and were clearly informed that they might be asked to smoke marihuana. All nonusers tested were persons who had reported that they had been planning to try marihuana. (ii) All subjects were driven home by an experimenter; they agreed not to engage in unusual activity or operate machinery until the next morning and to report any unusual, delayed effects. (iii) All subjects agreed to report for follow-up interviews 6 months after the experiment. Among other things, the check at 6 months should answer the question whether participation in the experiment encouraged further drug use. (iv) All subjects were protected from possible legal repercussions of their participation in these experiments by specific agreements with the Federal Bureau of Narcotics, the Office of the Attorney General of Massachusetts, and the Massachusetts Bureau of Drug Abuse and Drug Control (*19*).

Subjects

The central group of subjects consisted of nine healthy, male volunteers, 21 to 26 years of age, all of whom smoked tobacco cigarettes regularly but had never tried marihuana previously. Eight chronic users of marihuana also participated, both to "assay" the quality of marihuana received from the Federal Bureau of Narcotics and to enable the experimenters to standardize the protocol, using subjects familiar with their responses to the drug. The age range for users was also 21 to 26 years. They all smoked marihuana regularly, most of them every day or every other day.

The nine "naive" subjects were selected after a careful screening process. An initial pool of prospective subjects was obtained by placing advertisements in the student newspapers of a number of universities in the Boston area. These advertisements sought "male volunteers, at least 21 years old, for psychological experiments." After nonsmokers were eliminated from this pool, the remaining volunteers were interviewed individually by a psychiatrist who determined their histories of use of alcohol and other intoxicants as well as their general personality types. In addition to serving as a potential screening technique to eliminate volunteers with evidence of psychosis, or of serious mental or personality disorder, these interviews served as the basis for the psychiatrist's prediction of the type of response an individual subject might have after smoking marihuana. (It should be noted that no marihuana-naive volunteer had to be disqualified on psychiatric grounds.) Only after a prospective subject passed the interview was he informed that the "psychological experiment" for which he had volunteered was a marihuana study. If he consented to participate, he was asked to sign a release, informing him that he would be "expected to smoke cigarettes containing marihuana or an inert substance." He was also required to agree to a number of conditions, among them that he would "during the course of the experiment take no psychoactive drugs, including alcohol, other than those drugs administered in the course of the experiment."

It proved extremely difficult to find marihuana-naive persons in the student population of Boston, and nearly 2 months of interviewing were required to obtain nine men. All those interviewed who had already tried marihuana volunteered this information quite freely and were delighted to discuss their use of drugs with the psychiatrist. Nearly all persons encountered who had not tried marihuana admitted this somewhat apologetically. Several said they had been meaning to try the drug but had not got around to it. A few said they had no access to it. Only one person cited the current laws as his reason for not having experimented with marihuana. It seemed clear in the interviews that many of these persons were actually afraid of how they might react to marihuana; they therefore welcomed a chance to smoke it under medical supervision. Only one person (an Indian exchange student) who passed the screening interview refused to participate after learning the nature of the experiment.

The eight heavy users of marihuana

were obtained with much less difficulty. They were interviewed in the same manner as the other subjects and were instructed not to smoke any marihuana on the day of their appointment in the laboratory.

Subjects were questioned during screening interviews and at the conclusion of the experiments to determine their knowledge of marihuana effects. None of the nine naive subjects had ever watched anyone smoke marihuana or observed anyone high on marihuana. Most of them knew of the effects of the drug only through reports in the popular press. Two subjects had friends who used marihuana frequently; one of these (No. 4) announced his intention to "prove" in the experiments that marihuana really did not do anything; the other (No. 3) was extremely eager to get high because "everyone I know is always talking about it very positively."

Setting

Greatest effort was made to create a neutral setting. That is, subjects were made comfortable and secure in a pleasant suite of laboratories and offices, but the experimental staff carefully avoided encouraging any person to have an enjoyable experience. Subjects were never asked how they felt, and no subject was permitted to discuss the experiment with the staff until he had completed all four sessions. Verbal interactions between staff and subjects were minimum and formal. At the end of each session, subjects were asked to complete a brief form asking whether they thought they had smoked marihuana that night; if so, whether a high dose or a low dose; and how confident they were of their answers. The experimenters completed similar forms on each subject.

Marihuana

Marihuana used in these experiments was of Mexican origin, supplied by the Federal Bureau of Narcotics (*20*). It consisted of finely chopped leaves of *Cannabis,* largely free of seeds and stems. An initial batch, which was judged to be of low potency by the experimenters on the basis of the doses needed to produce symptoms of intoxication in the chronic users, was subsequently found to contain only 0.3 percent of THC by weight. A second batch, assayed at 0.9 percent THC, was rated by the chronic users to be "good, average" marihuana, neither exceptionally strong nor exceptionally weak compared to their usual supplies. Users consistently reported symptoms of intoxication after smoking about 0.5 gram of the material with a variation of only a few puffs from subject to subject. This second batch of marihuana was used in the experiments described below; the low dose was 0.5 gram, and the high dose was 2.0 grams.

Table 1. Composition of the dose. The placebo cigarette consisted of placebo material, tobacco filler, and mint leaves for masking flavor. The low dose was made up of marihuana, tobacco filler, and mint leaves. The high dose consisted of marihuana and mint leaves.

Dose	Marihuana in each cigarette (g)	Total dose marihuana (2 cigarettes) (g)	Approximate dose THC
Placebo		—	—
Low	0.25	0.5	4.5 mg
High	1.0	2.0	18 mg

All marihuana was administered in the form of cigarettes of standard size made with a hand-operated rolling machine. In any given experimental session, each person was required to smoke two cigarettes in succession (Table 1).

Placebo material consisted of the chopped outer covering of mature stalks of male hemp plants; it contained no THC. All cigarettes had a tiny plug of tobacco at one end and a plug of paper at the other end so that the contents were not visible. The length to which each cigarette was to be smoked was indicated by an ink line. Marihuana and placebos were administered to the naive subjects in double-blind fashion. Scented aerosols were sprayed in the laboratory before smoking, to mask the odor of marihuana. The protocol during an experimental session was as follows. The sessions began at approximately 5.30 p.m.

Time	Procedure
0:00	Physiological measurements; blood sample drawn
0:05	Psychological test battery No. 1 (base line)
0:35	Verbal sample No. 1
0:40	Cigarette smoking
1:00	Rest period
1:15	Physiological measurements; blood sample drawn
1:20	Psychological test battery No. 2
1:50	Verbal sample No. 2
1:55	Rest period (supper)
2:30	Physiological measurements
2:35	Psychological test battery No. 3
3:05	End of testing

Experimental Sessions

Chronic users were tested only on high doses of marihuana with no practice sessions. Each naive subject was required to come to four sessions, spaced about a week apart. The first was always a practice session, in which the subject learned the proper smoking technique and during which he became thoroughly acquainted with the tests and the protocol. In the practice session, each subject completed the entire protocol, smoking two hand-rolled tobacco cigarettes. He was instructed to take a long puff, to inhale deeply, and to maintain inspiration for 20 seconds, as timed by an experimenter with a stopwatch. Subjects were allowed 8 to 12 minutes to smoke each of the two cigarettes. One purpose of this practice smoking was to identify and eliminate individuals who were not tolerant to high doses of nicotine, thus reducing the effect of nicotine on the variables measured during subsequent drug sessions (*21*). A surprising number (five) of volunteers who had described themselves in screening interviews as heavy cigarette smokers, "inhaling" up to two packs of cigarettes a day, developed acute nicotine reactions when they smoked two tobacco cigarettes by the required method. Occurrence of such a reaction disqualified a subject from participation in the experiments.

In subsequent sessions, when cigarettes contained either drug or placebo, all smoking was similarly supervised by an experimenter with a stopwatch. Subjects were not permitted to smoke tobacco cigarettes while the experiment was in progress. They were assigned to one of the three treatment groups listed in Table 2.

Physiological and Psychological Measures

The physiological parameters measured were heart rate, respiratory rate, pupil size, blood glucose level, and conjunctival vascular state. Pupil size was measured with a millimeter rule under constant illumination with eyes focused on an object at constant distance. Conjunctival appearance was rated by an experienced experimenter for dilation of blood vessels on a 0 to 4 scale with ratings of 3 and 4 indicating "significant" vasodilatation. Blood samples were collected for immediate determinations of serum glucose and for the serum to be frozen and stored for pos-

sible future biochemical studies. Subjects were asked not to eat and not to imbibe a beverage containing sugar or caffeine during the 4 hours preceding a session. They were given supper after the second blood sample was drawn.

The psychological test battery consisted of (i) the Continuous Performance Test (CPT)—5 minutes; (ii) the Digit Symbol Substitution Test (DSST)—90 seconds; (iii), CPT with strobe light distraction—5 minutes; (iv) self-rating bipolar mood scale—3 minutes; and (v) pursuit rotor—10 minutes.

The Continuous Performance Test was designed to measure a subject's capacity for sustained attention (*22*). The subject was placed in a darkened room and directed to watch a small screen upon which six letters of the alphabet were flashed rapidly and in random order. The subject was instructed to press a button whenever a specified critical letter appeared. The number of letters presented, correct responses, and errors of commission and omission were counted over the 5-minute period. The test was also done with a strobe light flickering at 50 cycles per second. Normal subjects make no or nearly no errors on this test either with or without strobe distraction; but sleep deprivation, organic brain disease, and certain drugs like chlorpromazine adversely affect performance. Presence or absence of previous exposure to the task has no effect on performance.

The Digit Symbol Substitution Test is a simple test of cognitive function (see Fig. 1). A subject's score was the number of correct answers in a 90-second period. As in the case of the CPT, practice should have little or no effect on performance.

The self-rating bipolar mood scale used in these experiments was one developed by Smith and Beecher (*23*) to evaluate subjective effects of morphine. By allowing subjects to rate themselves within a given category of moods, on an arbitrary scale from + 3 to − 3, it minimizes suggestion and is thus more neutral than the checklists often employed in drug testing.

The pursuit rotor measures muscular coordination and attention. The subject's task was to keep a stylus in contact with a small spot on a moving turntable. In these experiments, subjects were given ten 30-second trials in each battery. The score for each trial was total time in contact with the spot. There is a marked practice effect on this test, but naive subjects were brought to high levels of performance during their practice session, so that the changes due to practice were reduced during the actual drug sessions. In addition, since there was a different order of treatments for each of the three groups of naive subjects, any session-to-session practice effects were minimized in the statistical analysis of the pooled data.

Table 2. Order of treatment.

Group	Drug session		
	1	2	3
I	High	Placebo	Low
II	Low	High	Placebo
III	Placebo	Low	High

Table 3. Subjects' appraisal of the dose.

Actual dose	Guessed dose			Fraction correct
	Placebo	Low	High	
Placebo	8	1		8/9
Low	3	6		6/9
High	2	6	1	1/9

At the end of the psychological test battery, a verbal sample was collected from each subject. The subject was left alone in a room with a tape recorder and instructions to describe "an interesting or dramatic experience" in his life until he was stopped. After exactly 5 minutes he was interrupted and asked how long he had been in the recording room. In this way, an estimate of the subject's ability to judge time was also obtained.

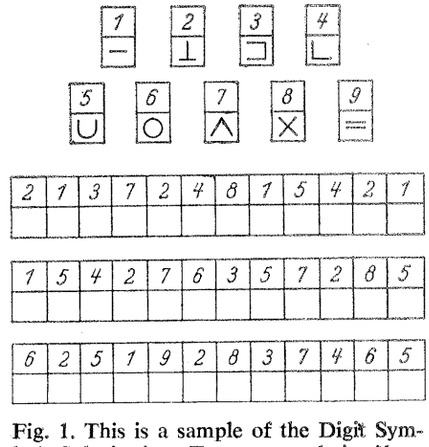

Fig. 1. This is a sample of the Digit Symbol Substitution Test as used in these studies. On a signal from the examiner the subject was required to fill as many of the empty spaces as possible with the appropriate symbols. The code was always available to the subject during the 90-second administration of the test. [This figure appeared originally in *Psychopharmacologia* **5**, 164 (1964)]

Results

1) *Safety of marihuana in human volunteers.* In view of the apprehension expressed by many persons over the safety of administering marihuana to research subjects, we wish to emphasize that no adverse marihuana reactions occurred in any of our subjects. In fact, the five acute nicotine reactions mentioned earlier were far more spectacular than any effects produced by marihuana.

In these experiments, observable effects of marihuana were maximum at 15 minutes after smoking. They were diminished between 30 minutes and 1 hour, and they were largely dissipated 3 hours after the end of smoking. No delayed or persistent effects beyond 3 hours were observed or reported.

2) *Intoxicating properties of marihuana in a neutral setting.* With the high dose of marihuana (2.0 grams), all chronic users became "high" (*24*) by their own accounts and in the judgment of experimenters who had observed many persons under the influence of marihuana. The effect was consistent even though prior to the session some of these subjects expressed anxiety about smoking marihuana and submitting to tests in a laboratory.

On the other hand, only one of the nine naive subjects (No. 3) had a definite "marihuana reaction" on the same high dose. He became markedly euphoric and laughed continuously during his first battery of tests after taking the drug. Interestingly, he was the one subject who had expressed his desire to get high.

3) *Comparison of naive and chronic user subjects.* Throughout the experiments it was apparent that the two groups of subjects reacted differently to identical doses of marihuana. We must caution, however, that our study was designed to allow rigorous statistical analysis of data from the naive group—it was not designed to permit formal comparison between chronic users and naive subjects. The conditions of the experiment were not the same for both groups: the chronic users were tested with the drug on their first visit to the laboratory with no practice and were informed that they were to receive high doses of marihuana. Therefore, differences between the chronic and naive groups reported below—although statistically valid—must be regarded as trends to be confirmed or rejected by additional experiments.

4) *Recognition of marihuana versus*

placebo. All nine naive subjects reported that they had not been able to identify the taste or smell of marihuana in the experimental cigarettes. A few subjects remarked that they noticed differences in the taste of the three sets of cigarettes but could not interpret the differences. Most subjects found the pure marihuana cigarettes (high dose) more mild than the low dose or placebo cigarettes, both of which contained tobacco.

The subjects' guesses of the contents of cigarettes for their three sessions are presented in Table 3. It is noteworthy that one of the two subjects who called the high dose a placebo was the subject (No. 4) who had told us he wanted to prove that marihuana really did nothing. There were three outstanding findings: (i) most subjects receiving marihuana in either high or low dose recognized that they were getting a drug; (ii) most subjects receiving placebos recognized that they were receiving placebos; (iii) most subjects called their high dose a low dose, but none called his low dose a high dose, emphasizing the unimpressiveness of their subjective reactions.

5) *Effect of marihuana on heart rate*. The mean changes in heart rate from base-line rates before smoking the drug to rates at 15 and 90 minutes after smoking marihuana and placebo (Table 4) were tested for significance at the .05 level by an analysis of variance; Tukey's method was applied for all possible comparisons (Table 5). In the naive subjects, marihuana in low dose or high dose was followed by increased heart rate 15 minutes after smoking, but the effect was not demonstrated to be dose-dependent. The high dose caused a statistically greater increase in the heart rates of chronic users than in those of the naive subjects 15 minutes after smoking.

Two of the chronic users had unusually low resting pulse rates (56 and 42), but deletion of these two subjects (No. 11 and No. 15) still gave a significant difference in mean pulse rise of chronic users compared to naives. Because the conditions of the sessions and experimental design were not identical for the two groups, we prefer to report this difference as a trend that must be confirmed by further studies.

6) *Effect of marihuana on respiratory rate*. In the naive group, there was no change in respiratory rate before and after smoking marihuana. Chronic users showed a small but statistically significant increase in respiratory rate

Table 4. Change in heart rate (beat/min) after smoking the best material. Results are recorded as a change from the base line 15 minutes and 90 minutes after the smoking session.

Subject	15 Minutes			90 Minutes		
	Placebo	Low	High	Placebo	Low	High
			Naive subjects			
1	+16	+20	+16	+20	− 6	− 4
2	+12	+24	+12	− 6	+ 4	− 8
3	+ 8	+ 8	+26	− 4	+ 4	+ 8
4	+20	+ 8			+20	− 4
5	+ 8	+ 4	− 8		+22	− 8
6	+10	+20	+28	−20	− 4	− 4
7	+ 4	+28	+24	+12	+ 8	+18
8	− 8	+20	+24	− 3	+ 8	−24
9		+20	+24	+ 8	+12	
Mean	+7.8	+16.9	+16.2	+0.8	+7.6	−2.9
S.E.	2.8	2.7	4.2	3.8	3.2	3.8
			Chronic subjects			
10		+32			+ 4	
11		+36			+36	
12		+20			+12	
13		+ 8			+ 4	
14		+32			+12	
15		+54			+22	
16		+24				
17		+60				
Mean		+33.2			+15.0	
S.E.		6.0			5.0	

Table 5. Significance of differences (at the .05 level) in heart rate. Results of Tukey's test for all possible comparisons.

Comparison	15 Minutes	90 Minutes
Low dose versus placebo	Significant	Significant
High dose versus placebo	Significant	Not significant
Low dose versus high dose	Not significant	Significant
Chronic users versus high dose	Significant	Significant

Table 6. Significance of differences (at the .05 level) for the Digit Symbol Substitution Test. Results of Tukey's test for all possible comparisons.

Comparison	15 Minutes	90 Minutes
Low dose versus placebo	Significant	Significant
High dose versus placebo	Significant	Significant
Low dose versus high dose	Significant	Not significant
Chronic users versus high dose	Significant	Significant

Table 7. Digit Symbol Substitution Test. Change in scores from base line (number correct) 15 and 90 minutes after the smoking session.

Subject	15 Minutes			90 Minutes		
	Placebo	Low	High	Placebo	Low	High
			Naive subjects			
1	− 3	—	+ 5	− 7	+ 4	+ 8
2	+10	− 8	−17	− 1	−15	− 5
3	− 3	+ 6	− 7	−10	+ 2	− 1
4	+ 3	− 4	− 3		− 7	
5	+ 4	+ 1	− 7	+ 6		− 8
6	− 3	− 1	− 9	+ 3	− 5	−12
7	+ 2	− 4	− 6	+ 3	− 5	− 4
8	− 1	+ 3	+ 1	+ 4	+ 4	− 3
9	− 1	− 4	− 3	+ 6	− 1	−10
Mean	+ 0.9	− 1.2	− 5.1	+ 0.4	− 2.6	− 3.9
S.E.	1.4	1.4	2.1	1.9	2.0	2.0
			Chronic users			
10			− 4			−16
11			+ 1			+ 6
12			+11			+18
13			+ 3			+ 4
14			− 2			− 3
15			− 6			+ 8
16			− 4			
17			+ 3			
Mean			+ 0.25			+ 2.8
S.E.			1.9			4.7

after smoking, but we do not regard the change as clinically significant.

7) *Effect of marihuana on pupil size.* There was no change in pupil size before and after smoking marihuana in either group.

8) *Effect of marihuana on conjunctival appearance.* Significant reddening of conjunctivae due to dilatation of blood vessels occurred in one of nine subjects receiving placebo, three of nine receiving the low dose of marihuana, and eight of nine receiving the high dose. It occurred in all eight of the chronic users receiving the high dose and was rated as more prominent in them. The effect was more pronounced 15 minutes after the smoking period than 90 minutes after it.

9) *Effect of marihuana on blood sugar.* There was no significant change in blood sugar levels after smoking marihuana in either group.

10) *Effect of marihuana on the Continuous Performance Test.* Performance on the CPT and on the CPT with strobe distraction was unaffected by marihuana for both groups of subjects.

11) *Effect of marihuana on the Digit Symbol Substitution Test.* The significance of the differences in mean changes of scores at the .05 level was determined by an analysis of variance by means of Tukey's method for all possible comparisons. Results of these tests are summarized in Tables 6 and 7.

The results indicate that: (i) Decrements in performance of naive subjects following low and high doses of marihuana were significant at 15 and 90 minutes after smoking. (ii) The decrement following marihuana was greater after high dose than after low dose at 15 minutes after taking the drug, giving preliminary evidence of a dose-response relationship. (iii) Chronic users started with good base-line performance and improved slightly on the DSST after smoking 2.0 grams of marihuana, whereas performance of the naive subjects was grossly impaired. Experience with the DSST suggests that absence of impairment in chronic users cannot be accounted for solely by a practice effect. Still, because of the different procedures employed, we prefer to report this difference as a trend.

12) *Effect of marihuana on pursuit rotor performance.* This result is presented in Table 8. Again applying Tukey's method in an analysis of variance, we tested differences in mean changes in scores (Table 9). Decrements in performance of naive subjects after both low and high doses of marihuana were significant at 15 and 90 minutes. This effect on performance followed a dose-response relation on testing batteries conducted at both 15 minutes and 90 minutes after the drug was smoked.

All chronic users started from good baselines and improved on the pursuit rotor after smoking marihuana. These data are not presented, however, because it is probable that the improvement was largely a practice effect.

13) *Effect of marihuana on time estimation.* Before smoking, all nine naive subjects estimated the 5-minute verbal sample to be 5 ± 2 minutes. After placebo, no subject changed his guess. After the low dose, three subjects raised their estimates to 10 ± 2 minutes, and after the high dose, four raised their estimates.

14) *Subjective effects of marihuana.* When questioned at the end of their participation in the experiment, persons who had never taken marihuana previously reported minimum subjective effects after smoking the drug, or, more precisely, few effects like those commonly reported by chronic users. Nonusers reported little euphoria, no distortion of visual or auditory perception, and no confusion. However, several subjects mentioned that "things seemed to take longer." Below are examples of comments by naive subjects after high doses.

Subject 1: "It was stronger than the previous time (low dose) but I really didn't think it could be marihuana. Things seemed to go slower."

Subject 2: "I think I realize why they took our watches. There was a sense of the past disappearing as happens when you're driving too long without sleeping. With a start you wake up to realize you were asleep for an instant; you discover yourself driving along the road. It was the same tonight with eating a sandwich. I'd look down to discover I'd just swallowed a bite but I hadn't noticed it at the time."

Subject 6: "I felt a combination of being almost-drunk and tired, with occasional fits of silliness—not my normal reaction to smoking tobacco."

Subject 8: "I felt faint briefly, but the dizziness went away, and I felt normal or slightly tired. I can't believe I had a high dose of marihuana."

Subject 9: "Time seemed very drawn out. I would keep forgetting what I was doing, especially on the continuous performance test, but somehow every time an "X" (the critical letter) came up, I found myself pushing the button."

After smoking their high dose, chronic users were asked to rate themselves on a scale of 1 to 10, 10 representing "the highest you've ever been." All subjects placed themselves between 7 and 10, most at 8 or 9. Many of these subjects expressed anxiety at the start of their first battery of tests after smoking the drug when they were feeling very high. Then they expressed surprise during and after the tests when they judged (correctly) that their performance was as good as or better than it had been before taking the drug.

15) The effect of marihuana on the self-rating mood scale, the effect of marihuana on a 5-minute verbal sample, and the correlation of personality type with subjective effects of marihuana will be reported separately.

Table 8. Pursuit rotor (naive subjects). Changes in scores (averages of ten trials) from base line (seconds).

Subject	15 Minutes			90 Minutes		
	Placebo	Low	High	Placebo	Low	High
1	+ 1.20	− 1.04	− 4.01	+ 1.87	− 1.54	− 6.54
2	+ 0.89	− 1.43	− 0.12	+ 0.52	+ 0.44	− 0.68
3	+ 0.50	− 0.60	− 6.56	+ 0.84	− 0.96	− 4.34
4	+ 0.18	− 0.11	+ 0.11	+ 0.06	+ 1.95	− 1.37
5	+ 3.20	+ 0.39	+ 0.13	+ 2.64	+ 3.33	+ 0.34
6	+ 3.45	− 0.32	− 3.46	+ 2.93	+ 0.22	− 2.26
7	+ 0.81	+ 0.48	− 0.79	+ 0.63	+ 0.16	− 0.52
8	+ 1.75	− 0.39	− 0.92	+ 2.13	+ 0.40	+ 1.02
9	+ 3.90	− 1.94	− 2.60	+ 3.11	− 0.97	− 3.09
Mean	+ 1.8	− 0.6	− 2.0	+ 1.6	+ 0.3	− 1.9
S.E.	0.5	0.3	0.8	0.4	0.5	0.8

Table 9. Significance of differences (at the .05 level) for the pursuit rotor. Results of Tukey's test for all possible comparisons, 15 and 90 minutes after the smoking session.

Comparison	15 Minutes	90 Minutes
Low dose versus placebo	Significant	Significant
High dose versus placebo	Significant	Significant
Low dose versus high dose	Significant	Significant

Discussion

Several results from this study raise important questions about the action of marihuana and suggest directions for future research. Our finding that subjects who were naive to marihuana did not become subjectively "high" after a high dose of marihuana in a neutral setting is interesting when contrasted with the response of regular users who consistently reported and exhibited highs. It agrees with the reports of chronic users that many, if not most, people do not become high on their first exposure to marihuana even if they smoke it correctly. This puzzling phenomenon can be discussed from either a physiological or psychosocial point of view. Neither interpretation is entirely satisfactory. The physiological hypothesis suggests that getting high on marihuana occurs only after some sort of pharmacological sensitization takes place. The psychosocial interpretation is that repeated exposure to marihuana reduces psychological inhibition, as part of, or as the result of a learning process.

Indirect evidence makes the psychological hypothesis attractive. Anxiety about drug use in this country is sufficiently great to make worthy of careful consideration the possibility of an unconscious psychological inhibition or block on the part of naive drug takers. The subjective responses of our subjects indicate that they had imagined a marihuana effect to be much more profoundly disorganizing than what they experienced. For example, subject No. 4, who started with a bias against the possibility of becoming high on marihuana, was able to control subjectively the effect of the drug and report that he had received a placebo when he had actually gotten a high dose. As anxiety about the drug is lessened with experience, the block may decrease, and the subject may permit himself to notice the drug's effects.

It is well known that marihuana users, in introducing friends to the drug, do actually "teach" them to notice subtle effects of the drug on consciousness (*25*). The apparently enormous influence of set and setting on the form of the marihuana response is consistent with this hypothesis, as is the testimony of users that, as use becomes more frequent, the amount of drug required to produce intoxication decreases—a unique example of "reverse tolerance." (Regular use of many intoxicants is accompanied by the need for increasing doses to achieve the same effects.)

On the other hand, the suggestion arising from this study that users and nonusers react differently to the drug, not only subjectively but also physiologically, increases the plausibility of the pharmacological-sensitization hypothesis. Of course, reverse tolerance could equally well be a manifestation of this sensitization.

It would be useful to confirm the suggested differences between users and nonusers and then to test in a systematic manner the hypothetical explanations of the phenomenon. One possible approach would be to continue to administer high doses of marihuana to the naive subjects according to the protocol described. If subjects begin reporting high responses to the drug only after several exposures, in the absence of psychedelic settings, suggestions, or manipulations of mood, then the likelihood that marihuana induces a true physiological sensitization or that experience reduces psychological inhibitions, permitting real drug effects to appear, would be increased. If subjects fail to become high, we could conclude that learning to respond to marihuana requires some sort of teaching or suggestion.

An investigation of the literature of countries where anxieties over drug use are less prominent would be useful. If this difference between responses of users and nonusers is a uniquely American phenomenon, a psychological explanation would be indicated, although it would not account for greater effects with smaller doses after the initial, anxiety-reducing stage.

One impetus for reporting the finding of differences between chronic and naive subjects on some of the tests, despite the fact that the experimental designs were not the same, is that this finding agrees with the statements of many users. They say that the effects of marihuana are easily suppressed—much more so than those of alcohol. Our observation, that the chronic users after smoking marihuana performed on some tests as well as or better than they did before taking the drug, reinforced the argument advanced by chronic users that maintaining effective levels of performance for many tasks—driving, for example (*26*)—is much easier under the influence of marihuana than under that of other psychoactive drugs. Certainly the surprise that the chronic users expressed when they found they were performing more effectively on the CPT, DSST, and pursuit rotor tests than they thought they would is remarkable. It is quite the opposite of the false sense of improvement subjects have under some psychoactive drugs that actually impair performance.

What might be the basis of this suppressibility? Possibly, the actions of marihuana are confined to higher cortical functions without any general stimulatory or depressive effect on lower brain centers. The relative absence of neurological—as opposed to psychiatric—symptoms in marihuana intoxication suggests this possibility (*7*).

Our failure to detect any changes in blood sugar levels of subjects after they had smoked marihuana forces us to look elsewhere for an explanation of the hunger and hyperphagia commonly reported by users. A first step would be careful interviewing of users to determine whether they really become hungry after smoking marihuana or whether they simply find eating more pleasurable. Possibly, the basis of this effect is also central rather than due to some peripheral physiological change.

Lack of any change in pupil size of subjects after they had smoked marihuana is an enlightening finding especially because so many users and law-enforcement agents firmly believe that marihuana dilates pupils. (Since users generally observe each other in dim surroundings, it is not surprising that they see large pupils.) This negative finding emphasizes the need for data from carefully controlled investigations rather than from casual observation or anecdotal reports in the evaluation of marihuana. It also agrees with the findings of others that synthetic THC does not alter pupil size (*8*, *27*).

Finally, we would like to comment on the fact that marihuana appears to be a relatively mild intoxicant in our studies. If these results seem to differ from those of earlier experiments, it must be remembered that other experimenters have given marihuana orally, have given doses much higher than those commonly smoked by users, have administered potent synthetics, and have not strictly controlled the laboratory setting. As noted in our introduction, more powerful effects are often reported by users who ingest preparations of marihuana. This may mean that some active constituents which enter the body when the drug is ingested are destroyed by combustion, a suggestion that must be investigated in man. Another priority

consideration is the extent to which synthetic THC reproduces marihuana intoxication—a problem that must be resolved before marihuana research proceeds with THC instead of the natural resin of the whole plant.

The set, both of subjects and experimenters, and the setting must be recognized as critical variables in studies of marihuana. Drug, set, and setting interact to shape the form of a marihuana reaction. The researcher who sets out with prior conviction that hemp is psychotomimetic or a "mild hallucinogen" is likely to confirm his conviction experimentally (*10*), but he would probably confirm the opposite hypothesis if his bias were in the opposite direction. Precautions to insure neutrality of set and setting, including use of a double-blind procedure as an absolute minimum, are vitally important if the object of investigation is to measure real marihuana-induced responses.

Conclusions

1) It is feasible and safe to study the effects of marihuana on human volunteers who smoke it in a laboratory.

2) In a neutral setting persons who are naive to marihuana do not have strong subjective experiences after smoking low or high doses of the drug, and the effects they do report are not the same as those described by regular users of marihuana who take the drug in the same neutral setting.

3) Marihuana-naive persons do demonstrate impaired performance on simple intellectual and psychomotor tests after smoking marihuana; the impairment is dose-related in some cases.

4) Regular users of marihuana do get high after smoking marihuana in a neutral setting but do not show the same degree of impairment of performance on the tests as do naive subjects. In some cases, their performance even appears to improve slightly after smoking marihuana.

5) Marihuana increases heart rate moderately.

6) No change in respiratory rate follows administration of marihuana by inhalation.

7) No change in pupil size occurs in short term exposure to marihuana.

8) Marihuana administration causes dilatation of conjunctival blood vessels.

9) Marihuana treatment produces no change in blood sugar levels.

10) In a neutral setting the physiological and psychological effects of a single, inhaled dose of marihuana appear to reach maximum intensity within one-half hour of inhalation, to be diminished after 1 hour, and to be completely dissipated by 3 hours.

References and Notes

1. R. J. Bouquet, *Bull. Narcotics* **2**, 14 (1950).
2. F. Korte and H. Sieper, in *Hashish: Its Chemistry and Pharmacology*, G. E. W. Wolstenholme and J. Knight, Eds. (Little, Brown, Boston, 1965), pp. 15–30.
3. Task Force on Narcotics and Drug Abuse, the President's Commission on Law Enforcement and the Administration of Justice, *Task Force Report: Narcotics and Drug Abuse* (1967), p. 14.
4. R. Mechoulam, and Y. Gaoni, *J. Amer. Chem. Soc.* **67**, 3273 (1965).
5. J. F. Siler, W. L. Sheep, L. B. Bates, G. F. Clark, G. W. Cook, W. A. Smith, *Mil. Surg.* (November 1933), pp. 269–280.
6. Mayor's Committee on Marihuana, *The Marihuana Problem in the City of New York*, 1944.
7. E. G. Williams, C. K. Himmelsbach, A. Winkler, D. C. Ruble, B. J. Lloyd, *Public Health Rep.* **61**, 1059 (1946).
8. H. Isbell, *Psychopharmacologia* **11**, 184 (1967).
9. I. C. Chopra and R. N. Chopra, *Bull. Narcotics* **9**, 4 (1957).
10. F. Ames, *J. Ment. Sci.* **104**, 972 (1958).
11. C. J. Miras, in *Hashish: Its Chemistry and Pharmacology*, G. E. W. Wolstenholme and J. Knight, Eds. (Little, Brown, Boston, 1965), pp. 37–47.
12. J. M. Watt, in *Hashish: Its Chemistry and Pharmacology*, G. E. W. Wolstenholme and J. Knight, Eds. (Little, Brown, Boston, 1965), pp. 54–66.
13. AMA Council on Mental Health, *J. Amer. Med. Ass.* **204**, 1181 (1968).
14. G. Joachimoglu, in *Hashish: Its Chemistry and Pharmacology*, G. E. W. Wolstenholme and J. Knight, Eds. (Little, Brown, Boston, 1965), pp. 2–10.

15. We thank M. Lerner and A. Bober of the U.S. Customs Laboratory, Baltimore, for performing this assay.
16. We thank R. H. Pace and E. H. Hall of the Peter J. Schweitzer Division of the Kimberly-Clark Corp. for supplying placebo material.

17. S. Garattini, in *Hashish: Its Chemistry and Pharmacology*, G. E. W. Wolstenholme and J. Knight, Eds. (Little, Brown, Boston, 1965), pp. 70–78.
18. J. H. Jaffee, in *The Pharmacological Basis of Therapeutics*, L. S. Goodman and A. Gilman, Eds. (Macmillan, New York, ed. 3, 1965), pp. 299–301.

19. We thank E. L. Richardson, Attorney General of the Commonwealth of Massachusetts for permitting these experiments to proceed and N. L. Chayet for legal assistance. We do not consider it appropriate to describe here the opposition we encountered from governmental agents and agencies and from university bureaucracies.
20. We thank D. Miller and M. Seifer of the Federal Bureau of Narcotics (now part of the Bureau of Narcotics and Dangerous Drugs, under the Department of Justice) for help in obtaining marihuana for this research.

21. The doses of tobacco in placebo and low-dose cigarettes were too small to cause physiological changes in subjects who qualified in the practice session.
22. K. E. Rosvold, A. F. Mirsky, I. Sarason, E. D. Bransome, L. H. Beck, *J. Consult. Psychol.* **20**, 343 (1956); A. F. Mirsky and P. V. Cardon, *Electroencephalogr. Clin. Neurophysiol.* **14**, 1 (1962); C. Kornetsky and G. Bain, *Psychopharmacologia* **8**, 277 (1965).
23. G. M. Smith and H. K. Beecher, *J. Pharmacol.* **126**, 50 (1959).
24. We will attempt to define the complex nature of a marihuana high in a subsequent paper discussing the speech samples and interviews.
25. H. S. Becker, *Outsiders: Studies in the Sociology of Deviance* (Macmillan, New York, 1963), chap. 3.
26. Although the motor skills measured by the pursuit rotor are represented in driving ability, they are only components of that ability. The influence of marihuana on driving skill remains an open question of high medico-legal priority.
27. L. E. Hollister, R. K. Richards, H. K. Gillespie, in preparation.

28. Sponsored and supported by Boston University's division of psychiatry, in part through PHS grants MH12568, MH06795-06, MH7753-06, and MH33319, and the Boston University Medical Center. The authors thank Dr. P. H. Knapp and Dr. C. Kornetsky of the Boston University School of Medicine, Department of Psychiatry and Pharmacology, for consistent support and excellent advice, and J. Finkelstein of 650 Madison Avenue, New York City, for his support at a crucial time.