

Operant Acquisition of Marihuana by Women¹

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ABSTRACT

Marihuana acquisition and use patterns were studied in 21 women on a clinical research ward. Women could earn one 1-g marihuana cigarette or 50 cents in 30 min of performance on a second-order Fixed-Ratio 300 (Fixed-Interval 1 sec:S) schedule of reinforcement. A 7-day drug-free base line was followed by 21 days of marihuana availability and a postmarihuana drug-free period of 7 days. Five heavy marihuana users smoked an average of 6.1 (± 1.45) marihuana cigarettes per day and increased marihuana use significantly through time ($P < .001$). Seven moderate marihuana users smoked an average of 2.72 (± 0.16) marihuana cigarettes per day and used significantly less marihuana through time ($P < .01$). Nine occasional marihuana users smoked less than one cigarette per day (0.90 ± 0.22) and maintained stable patterns of marihuana use. Women who increased marihuana use during the premenstruum reported significantly greater premenstrual dysphoria on the Premenstrual Assessment Form than women whose marihuana use decreased

or remained the same ($P < .05$ to $.01$). There were no marihuana dose-related effects on operant performance. The heavy, moderate and occasional marihuana smokers did not differ in operant purchase points earned, hours worked or money earned. Each marihuana dose-group earned an equivalent number of purchase points during the drug-free periods and the period of marihuana availability. Some subjects continued to work for money when smoking 15 to 20 marihuana cigarettes per day and periods of maximal operant work coincided with periods of maximal marihuana smoking (noon-midnight). There was an inverse relationship between reported duration of unemployment and amount of marihuana used. Marihuana smoking did not change the amount and temporal distribution of tobacco smoking in 16 women who also used tobacco cigarettes. One woman had signs and symptoms of withdrawal after smoking an average of 11.62 (± 1.47) marihuana cigarettes per day for 21 days. These findings in women are compared and contrasted with data from studies of men.

Marihuana is one of the most commonly used recreational drugs despite continued sanctions against its possession and use (Clayton, 1984). Recent surveys have shown that the number of young Americans (ages 18–25) who have used marihuana increased from 5 to 64% between 1972 and 1982 (Cisin *et al.*, 1983), and there is no evidence that this trend is declining (*cf.* Smart, 1983; Kandel, 1980; Jessor, 1979; Johnston *et al.*, 1980 for review). Marihuana use among young women appears to be increasing, although men are more likely to be daily users (Smart, 1983).

Concern about the medical and behavioral consequences of marihuana use has stimulated research to clarify the acute and chronic effects of marihuana (Fehr and Kalant, 1983; Jones, 1978; National Commission on Marihuana and Drug Abuse, 1972; Institute of Medicine Report, 1982). However, virtually all of the clinical studies of the behavioral and biological effects of marihuana have been carried out in men. Four studies examined marihuana self-administration (Cohen *et al.*, 1976;

Mendelson *et al.*, 1974, 1976a; Miles *et al.*, 1974) and, in two other studies, the daily dose of marihuana in cigarettes (Frank *et al.*, 1976) or in oral Δ^9 -tetrahydrocannabinol capsules (Jones and Benowitz, 1976) was determined by the investigators. This report describes the first clinical study of marihuana acquisition and use patterns by young women under controlled residential research ward conditions. This report is part of a series of studies designed to examine marihuana effects on female reproductive function (Mendelson *et al.*, 1985a,b,c).

This study of marihuana use patterns, tobacco smoking and the operant acquisition of marihuana and money by young women was designed to be similar to our previous clinical studies in young men (Mendelson *et al.*, 1976a; Mello *et al.*, 1978, 1980a) so that possible gender differences could be examined. Young women were allowed to work at a simple operant task to earn points for money for 35 days. They could also work for marihuana during a 21-day period of marihuana availability. This operant paradigm simulates a real world situation in which drugs are rarely freely available, and some work output must occur to acquire money to exchange for marihuana cigarettes (Mello and Mendelson, 1985). Operant work for money during drug-free conditions can be compared with performance during

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marihuana intoxication and the resulting data are relevant to a recurring unresolved question about the effects of marihuana on "motivation."

Apathy, lethargy, diminished "drive" and ambition, decreased productivity and goal directedness, indolence and a preoccupation with marihuana use are among the effects often ascribed to marihuana. Objective clinical studies have provided scant support for the notion that marihuana use produces a drug-specific "amotivational syndrome" (see Negrete, 1983; Mendelson, 1983; Halikas, 1974 for review). But the concordance between adolescent indolence and marihuana use have infused the amotivational syndrome construct with a resilient vitality. Inasmuch as motivation is a hypothetical construct which cannot be directly observed and can only be inferred from some behavior, it has been difficult to evaluate. In studies in which motivation was operationally defined in terms of some measure of performance and time spent working, there has been no evidence of a marihuana-induced impairment in work and/or motivation (Lessin and Thomas, 1976; Mendelson *et al.*, 1974, 1976a,b; Miles *et al.*, 1974). The present study addresses this issue in young women in whom the effects of occasional, moderate and heavy marihuana smoking on an objective measure of motivation (unrestricted operant work) was examined under controlled research ward conditions.

A third goal of the current study was to evaluate the extent to which marihuana acquisition and use patterns might covary with specific phases of the menstrual cycle. There is clinical evidence that women with alcohol problems drink more during the premenstruum (Podolsky, 1963; Belfer and Shader, 1976; Belfer *et al.*, 1971), but no comparable clinical data exist for female marihuana users. The hypothesis that psychoactive drug use may covary with the premenstruum is plausible in view of the abundant clinical evidence that dysphoric mood states in women often occur several days before menstruation (*cf.* Mello, 1980 for review). A syndrome often referred to as "premenstrual tension" is characterized by increased anxiety, tension, depression, irritability, sleep disturbances, lethargy, impaired concentration, headaches, constipation, bloating, backaches, breast tenderness, weight changes and changes in sexual feeling and activity (Smith, 1975; Steiner and Carroll, 1977). These symptoms most commonly occur during the premenstrual period, but the periovulatory phase and menstruation may also be associated with increased anxiety and depression. Although these symptoms do not occur in all women at every cycle and are not uniquely specific to women or to the menstrual cycle process, the periodic recurrence of this constellation of symptoms has been implicated in exacerbation of psychotic disorders, especially depression (Smith, 1975; Steiner and Carroll, 1977). The design of this study permitted us to examine the covariance between marihuana self-administration and menstrual cycle phase.

Methods

Subjects. Twenty-one adult female volunteers, with a history of regular marihuana use, gave informed consent for participation in studies to evaluate the effects of marihuana smoking on reproductive function in an inpatient clinical research study. Volunteer subjects were recruited through advertisements in local newspapers. Subjects were fully informed about the nature and duration of each phase of the study and were told that they could withdraw at any time.

Each woman was in good health as determined by clinical and laboratory examinations. Each subject was given a complete physical

examination, mental status assessment, chest X-ray, electrocardiogram and the following laboratory assessments: albumin, alkaline phosphatase, bilirubin total, blood urea nitrogen, calcium, chloride, cholesterol, creatinine, glucose, iron, lactic acid dehydrogenase, phosphorus, potassium, serum glutamic oxaloacetic transaminase, sodium, total protein, triglycerides, uric acid, routine urinalysis, hematocrit, hemoglobin, white blood count, differential and Australian antigen and serology. Urine screens for drug use other than marihuana and pregnancy tests were performed before admission to the research ward and all were negative.

These women had smoked marihuana for an average of 8.1 (± 0.89) years with a range of 1 to 15 years. Their average age was 26.7 (± 1.15) years with a range of 21 to 36 years. They had an average of 13.6 (± 0.33) years of formal education (range, 11–16 years). At the time of selection for the study, 2 subjects were employed, 1 subject was in a training program and 18 subjects were unemployed. These subjects had worked most recently as waitresses, clerical workers or salespersons.

Subjects were studied in groups of three or four and lived on a hospital research ward for 35 days. The research ward contained four private bedrooms, a nursing station, an examining room, kitchen and lavatories and a spacious, comfortably furnished day room with television, high fidelity equipment and other recreational materials. The clinical nursing staff was present 24 hr each day.

Sequence of drug conditions. After admission to the research ward, subjects were drug-free for 7 days. Marihuana cigarettes were available for 21 days. After the period of marihuana availability, subjects remained on the ward for an additional 7 days under drug-free conditions, to evaluate the time course and severity of any marihuana related abstinence syndromes (*cf.* Mendelson *et al.*, 1984).

Marihuana cigarettes. All marihuana cigarettes were obtained from NIDA in lot standard dosage form. Maximal standardization and the equivalent dosage and "draw" characteristics of these cigarettes were insured by machine rolling. Each cigarette weighed approximately 1 g and contained 1.83% of Δ^9 -tetrahydrocannabinol as assayed by NIDA. Details of the Soxhlet and modified Lerner extraction procedures and the gas chromatographic assay procedure are available from NIDA.

Marihuana and money acquisition procedures. Operant techniques were used to provide an objective and quantitative measure of performance for two alternative reinforcers, marihuana and money. Subjects could work for money at a simple operant task throughout the study. The opportunity to work for money was intended to encourage subjects to remain in the study during the 14 days when marihuana was not available. Points earned at the operant task could be accumulated for money, payable at the end of the study, or could be exchanged for marihuana cigarettes during the period of marihuana availability. Women could work at the operant task in the day room or in their bedrooms at any time for as long as they wished.

Operant manipulanda. A completely portable operant manipulandum with self-contained programming and recording circuitry was developed for this study. The manipulandum shown in figure 1 was a molded plastic rectangle (15.4 \times 9.0 \times 3.2 cm) that weighed 265 g and was color coded for each subject. A response button was located at one end of the manipulandum and each depression of the button on a Fixed Interval 1-sec schedule entered one point and increased the accumulated number of points visible through an aperture (4.7 \times 1.3 cm) on the face of the manipulandum.

The manipulandum contained a battery operated calculator (Texas Instruments TI-1750), an integrated circuit board and a magnetic safety Reed switch. The calculator and programming circuitry only operated when both sides of the magnetic switch were in contact. If a subject opened the manipulandum to try to tamper with the system, these contacts were disconnected and all the accumulated points were automatically erased.

Staff recorded the number of FI 1-sec points earned once every 4 hr. Each time a marihuana cigarette was requested, research staff subtracted the cost of the cigarette in points from the accumulated total points by placing a stylus in the "memory recall" aperture.

Human Operant Manipulandum

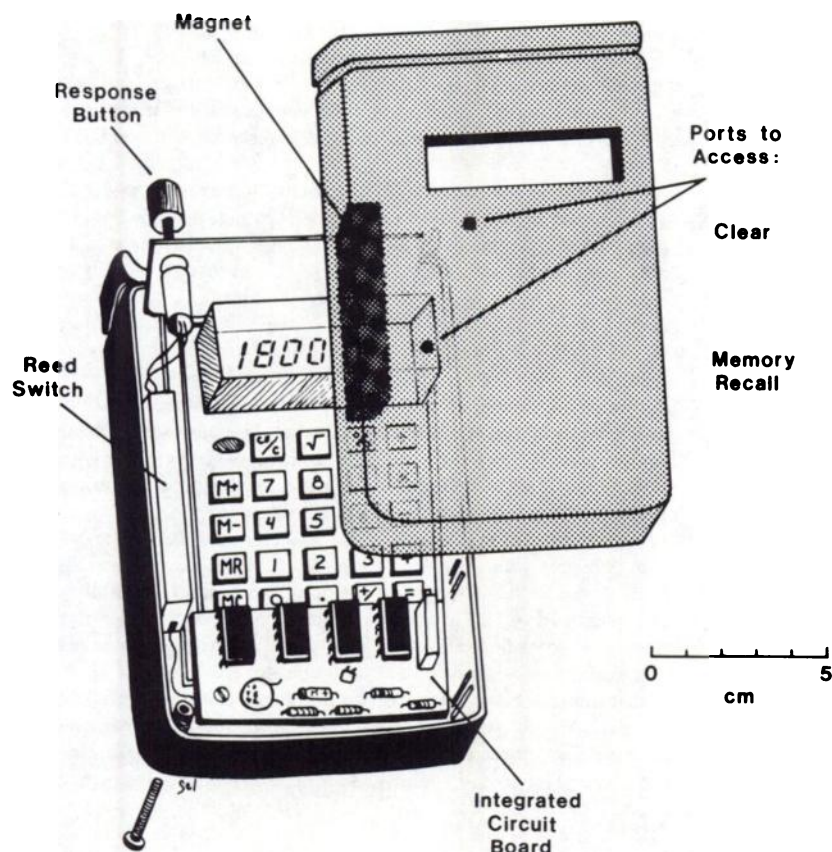


Fig. 1. Operant manipulandum used to acquire points for marihuana and money. Depression of the response button activated the circuitry and completion of each effective response on a FI 1-sec schedule increased the number of points visible through the aperture shown at the top of the cover. The magnet and the Reed switch had to be in contact for the calculator and programming circuitry to operate. Disconnection of these contacts automatically erased all the accumulated points. The calculator was programmed to subtract the number of points required for a single marihuana cigarette each time a stylus was placed in the memory recall port.

Response requirements. Subjects worked for money and for marihuana on a second-order schedule of reinforcement, an FR 300 (FI 1 sec:S). A fixed ratio (FR) of 300 responses on the fixed interval (FI) 1-sec component of the schedule was required to earn a single purchase point. The FI 1-sec schedule specified that only the first response after 1 sec had elapsed was recorded as an effective response by the programming circuitry. About 5 min of operant performance was required to earn 300 effective responses, or one purchase point on the FI 1-sec schedule. Six purchase points were required to buy one marihuana cigarette or to earn 50 cents upon completion of the study. Subjects had to work at the operant task for about 30 min to earn one marihuana cigarette or 50 cents.

Marihuana smoking conditions. Subjects were allowed to buy only one marihuana cigarette at a time and were required to return the unsmoked portion to the ward staff. The unsmoked portions were weighed at the end of the study and subjects received a cash refund for any unsmoked marihuana that was purchased. Subjects were not allowed to purchase another marihuana cigarette until the unused portion of the first cigarette was returned. Smoking was permitted only in the day room and only when there were no visitors on the ward. There was no limit on the number of marihuana cigarettes that subjects could elect to smoke each day.

Tobacco cigarettes were also available upon request. The time of each tobacco cigarette request and the number of tobacco cigarettes smoked each day were recorded.

Additional compensation. In addition to money earned by working at the operant task, subjects could also earn about \$185 for cooperation with the various ward procedures. Subjects earned \$5 for each blood sample and a bonus of \$100 was paid for completion of the entire 35-day study.

Medical status and related measures. Each subject was carefully monitored throughout the study to ensure that marihuana smoking was not associated with any adverse reactions. Pulse, temperature and blood pressure were measured every 8 hr and subjects were weighed every day. Daily medical rounds and periodic physical examinations were complemented by weekly clinical laboratory studies. Pregnancy tests were carried out every 2 weeks.

Women completed the PAF (Halbreich *et al.*, 1982) during the premenstrual period and once each week during the study. The PAF consists of 95 items which compare the severity and directionality of changes in mood, behavior and physical symptoms to the subject's usual (nonpremenstrual) state. A variety of other self-reports of subjective states, intoxication levels and staff reports of behavioral observations were made at frequent intervals throughout the study. These data will be reported separately. Blood samples for the analysis of pituitary and gonadal hormones were collected on alternate days and these data will be reported separately.

Data analysis. Measures of operant performance, marihuana cigarettes purchased and tobacco smoking were examined with *t* tests, ANOVA (Madigan and Lawrence, 1983) and Least Significant Difference follow-up tests (Ott, 1977). Within each marihuana dose group, behavioral measures were compared for drug-free and successive 7-day blocks of marihuana availability with *t* tests for related samples. Each subject's operant performance, marihuana and tobacco use over successive 7-day periods were also compared with *t* tests for related samples. Comparisons between marihuana dose groups were evaluated with *t* tests for independent samples (Madigan and Lawrence, 1982).

Unipolar summary scale scores for 18 factors on the PAF reported by subjects who were premenstrual during marihuana availability were examined with ANOVA (Madigan and Lawrence, 1983). Least Signifi-

cant Difference follow-up tests were used to compare PAF scores for women whose marihuana use during the premenstruum increased, decreased or stayed the same (Ott, 1977).

Results

Marihuana cigarettes purchased. The 21 women were classified as heavy, moderate or occasional marihuana users on the basis of the actual number of marihuana cigarettes acquired on the clinical research ward. Heavy users smoked an average of 6.1 (± 1.45) marihuana cigarettes per day. Moderate users smoked an average of 2.72 (± 0.16) marihuana cigarettes per day. Occasional users smoked less than one marihuana cigarette per day (0.90 ± 0.22) during the 21-day period of marihuana availability. The average number of marihuana cigarettes per day purchased by each group differed significantly as evaluated by independent *t* tests ($P < .05$ to $.0005$).

The average daily patterns of marihuana acquisition by the heavy, moderate and occasional marihuana users are shown in figure 2. The heavy user group showed a consistent tendency to increase marihuana acquisition as a function of time and this trend was statistically significant as evaluated by ANOVA ($P < .001$). The moderate marihuana smokers tended to use less marihuana through time and this trend was also statistically significant ($P < .01$). The occasional marihuana users maintained a consistent smoking pattern across the 21 days of marihuana availability.

Heavy marihuana smokers. Five subjects were classified as heavy users and reported using marihuana for an average of 7.4 years (± 2.79). Each woman reported daily marihuana smoking during the month before admission to the study. These subjects smoked significantly more marihuana than either the moderate ($P < .05$) or occasional ($P < .0005$) marihuana smokers.

Daily patterns of marihuana acquisition by two heavy smokers (FM 1 [1] and FM 7 [53]) are shown in the upper panel of figures 3 and 4. The subject shown in figure 3 smoked more

marihuana than any male subject previously studied on our inpatient clinical research ward (*cf.* Mendelson *et al.*, 1974, 1976a; Mello *et al.*, 1978). This woman purchased an average of 11.62 (± 1.47) cigarettes per day across the 21-day period of marihuana availability and smoked 25 marihuana cigarettes on the last day of marihuana availability. During the final 7 days of marihuana availability, this subject acquired significantly more marihuana than during the first and second 7-day periods of marihuana availability ($P < .01$). The subject shown in figure 4 smoked an average of 6.52 (± 0.26) cigarettes per day and there were no significant changes in marihuana acquisition over the first, second and third 7-day periods of marihuana availability.

Moderate marihuana smokers. Seven subjects were classified as moderate marihuana smokers and these subjects smoked significantly more marihuana than the occasional user group ($P < .0005$). These women reported using marihuana an average of 12.9 (± 2.64) times during the month immediately before admission to the study. The moderate marihuana smokers had used marihuana for an average of 7.7 (± 1.43) years.

Patterns of marihuana acquisition by two moderate marihuana users (FM 4 [32] and FM 6 [51]) are shown in the upper panels of figures 5 and 6. The subject shown in figure 5 purchased an average of 3.2 (± 0.22) marihuana cigarettes per day and smoked significantly more during the last 7 days of marihuana availability than during the first 7 days ($P < .01$). The subject shown in figure 6 smoked an average of 2.6 (± 0.37) cigarettes per day. However, she acquired significantly less marihuana during the second and third 7-day periods than during the first 7 days of marihuana availability ($P < .01$).

Occasional marihuana users. Nine subjects were classified as occasional users. These women have used marihuana for an average of 8.78 (± 1.08) years and reported using marihuana an average of 9.11 (± 1.70) times during the month before admission to the study. Only one subject showed a statistically significant increase in marihuana smoking during the last 7 days of marihuana availability in comparison to the first 7 days ($P < .001$). The other eight subjects maintained relatively stable patterns of marihuana use across the 21 days of marihuana availability as shown in figure 2.

Marihuana use as a function of menstrual cycle phase. Because subjects were studied in groups, it was not possible to schedule admissions to coincide with any specific phase of the menstrual cycle. The 1st day of marihuana availability coincided with menstruation in four subjects; with the follicular phase in seven subjects; with the midcycle periovulatory phase in five subjects; with the luteal phase in two subjects and with the premenstruum in three subjects.

The period of marihuana availability extended over most of a complete menstrual cycle in seven women. Four women showed no significant changes in marihuana use across the phases of the menstrual cycle. Two women showed a statistically significant decline in marihuana use over the menstrual cycle ($P < .01$). Only one subject showed a significant increase in marihuana use that coincided with the periovulatory and luteal phase of the menstrual cycle ($P < .01$) (fig. 3).

Marihuana availability coincided with the premenstruum, the 3 days immediately before menstruation, in 15 women: three heavy users, five moderate users and seven occasional users. Five subjects increased marihuana use on the day before menstruation; five subjects decreased marihuana use before

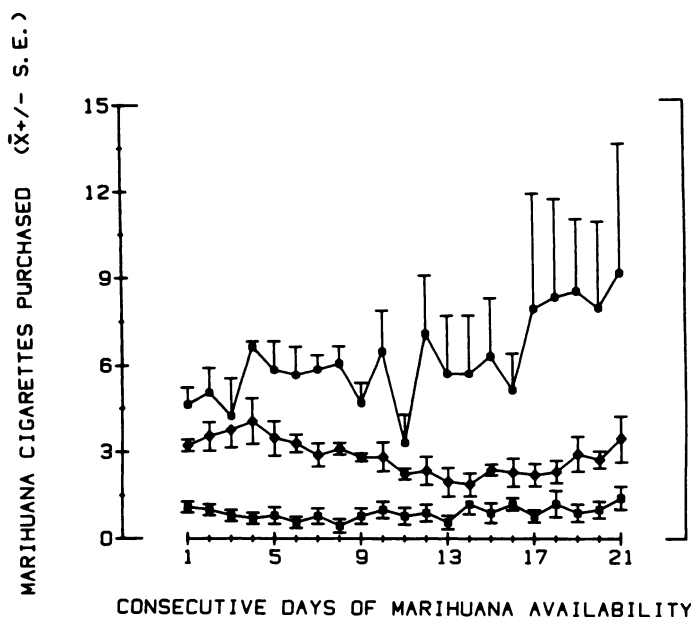


Fig. 2. Average daily marihuana acquisition by the heavy (●), moderate (◆) and occasional (■) marihuana users. The number of 1-g marihuana cigarettes purchased ($\bar{X} \pm S.E.$) is shown on the left ordinate and consecutive days of marihuana availability are shown on the abscissa.

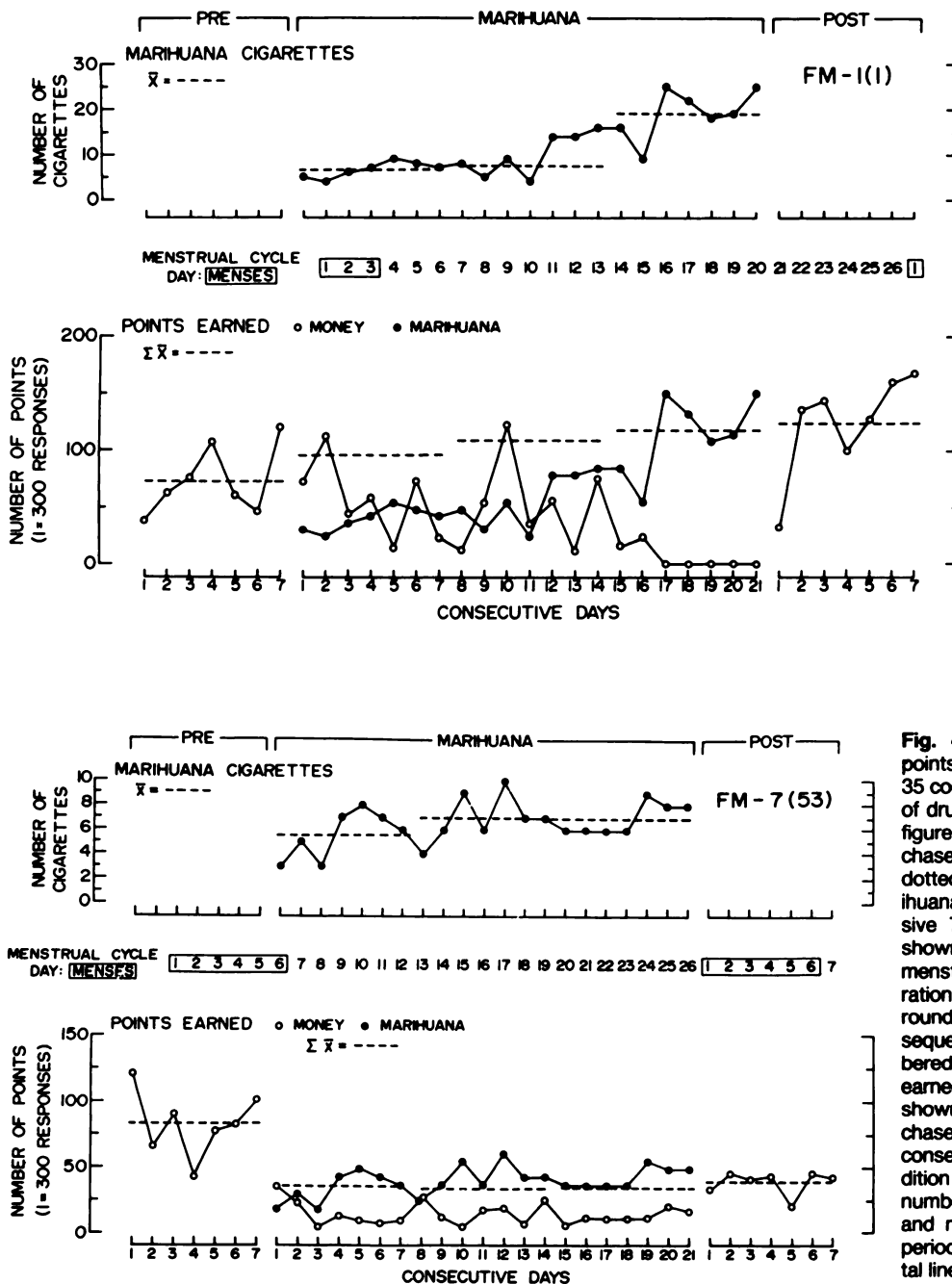


Fig. 3. Marihuana acquisition and purchase points earned for money and for marihuana over 35 consecutive days. The successive conditions of drug availability are shown at the top of the figure. The number of marihuana cigarettes purchased each day are shown in the top row. The dotted line indicates the average number of marihuana cigarettes acquired during each successive 7-day period. Menstrual cycle status is shown in the center of the figure. The onset of menstruation is indicated as day 1 and the duration of menses is shown as a rectangle surrounding the appropriate number of days. Subsequent days of that menstrual cycle are numbered consecutively. The number of points earned for money (○) and marihuana (●) are shown in the second row. The number of purchase points are shown on the left ordinate and consecutive days of each drug availability condition are shown on the abscissa. The average number of total points earned for both money and marihuana during each successive 7-day period of the study are shown as dotted horizontal lines.

Fig. 4. Marihuana acquisition and purchase points earned for money and for marihuana over 35 consecutive days. The successive conditions of drug availability are shown at the top of the figure. The number of marihuana cigarettes purchased each day are shown in the top row. The dotted line indicates the average number of marihuana cigarettes acquired during each successive 7-day period. Menstrual cycle status is shown in the center of the figure. The onset of menstruation is indicated as day 1 and the duration of menses is shown as a rectangle surrounding the appropriate number of days. Subsequent days of that menstrual cycle are numbered consecutively. The number of points earned for money (○) and marihuana (●) are shown in the second row. The number of purchase points are shown on the left ordinate and consecutive days of each drug availability condition are shown on the abscissa. The average number of total points earned for both money and marihuana during each successive 7-day period of the study are shown as dotted horizontal lines.

menstruation and five subjects showed no change in marihuana use during the premenstruum.

The women who increased marihuana smoking during the premenstruum also reported more symptoms of premenstrual distress than women whose marihuana use was unchanged or decreased. Their menstrual distress scores were higher on 17 of the 18 factors of the PAF; only scale 9, increased well-being, was not higher in this group. Women who increased premenstrual marihuana smoking had significantly higher scores than the other groups on 11 of the 18 factors including: 1, low mood/loss of pleasure; 2, endogenous depressive features; 3, mood lability; 4, atypical depressive features; 5, hysteroid features; 6, hostility/anger; 7, social withdrawal; 8, anxiety; 10, impulsivity; 12, signs of water retention; and 16, impaired social functioning ($P < .05$ to $.01$). The three groups of premenstrual women did not differ significantly on seven of the 18 factors including: 9,

increased well being; 11, "organic" mental features; 13, general physical discomfort; 14, autonomic physical discomfort; 15, fatigue; 17, miscellaneous mood/behavior changes; and 18, miscellaneous physical changes.

Marihuana effects on operant performance. All subjects worked at the operant task every day throughout the 35-day study. The average number of purchase points and money earned and the hours spent working at the operant task each day before, during and after marihuana availability by the heavy, moderate and occasional marihuana smokers is summarized in table 1.

Purchase points earned. Total purchase points earned remained relatively constant during the drug-free and marihuana availability conditions in all three groups. Total purchase points earned during marihuana smoking did not differ significantly from the drug-free period before or after marihuana in

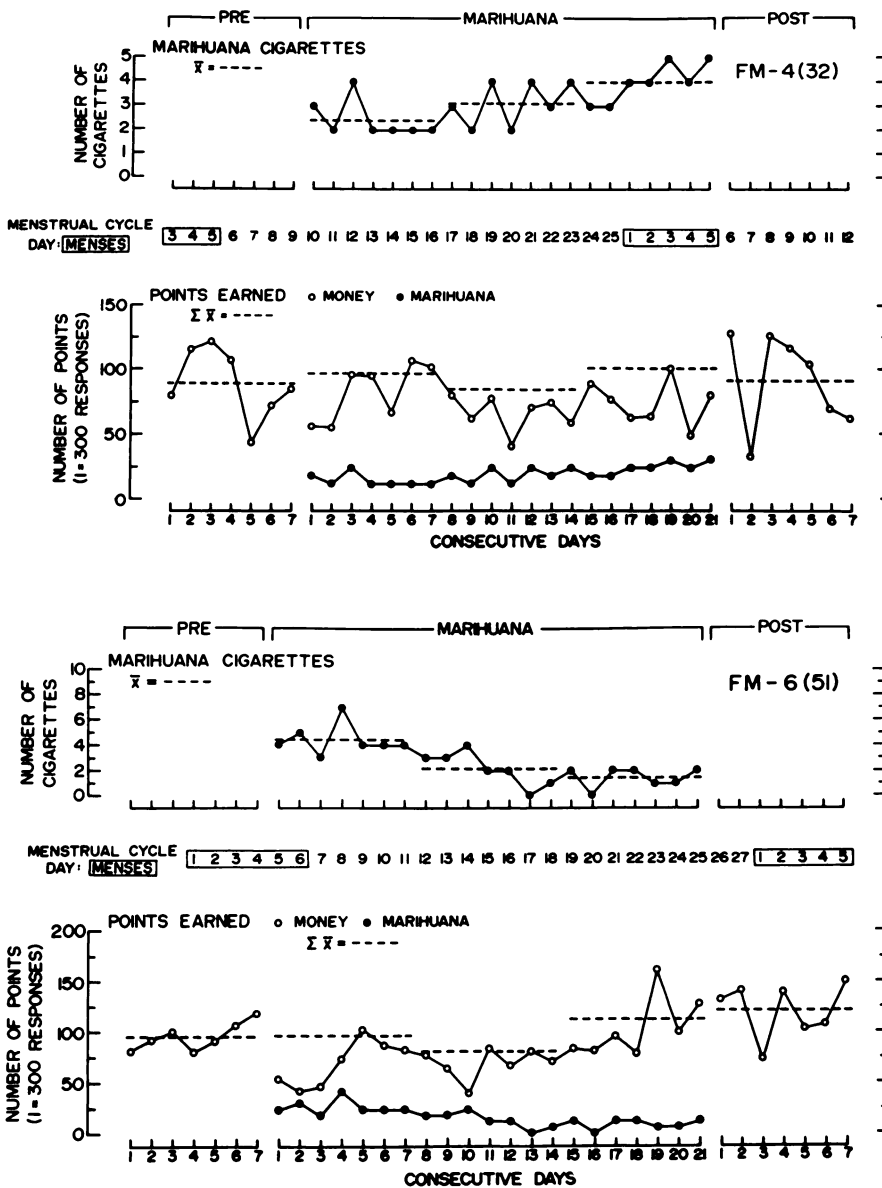


Fig. 5. Marihuana acquisition and purchase points earned for money and for marihuana over 35 consecutive days. The successive conditions of drug availability are shown at the top of the figure. The number of marihuana cigarettes purchased each day are shown in the top row. The dotted line indicates the average number of marihuana cigarettes acquired during each successive 7-day period. Menstrual cycle status is shown in the center of the figure. The onset of menstruation is indicated as day 1 and the duration of menses is shown as a rectangle surrounding the appropriate number of days. Subsequent days of that menstrual cycle are numbered consecutively. The number of points earned for money (O) and marihuana (●) are shown in the second row. The number of purchase points are shown on the left ordinate and consecutive days of each drug availability condition are shown on the abscissa. The average number of total points earned for both money and marihuana during each successive 7-day period of the study are shown as dotted horizontal lines.

Fig. 6. Marihuana acquisition and purchase points earned for money and for marihuana over 35 consecutive days. The successive conditions of drug availability are shown at the top of the figure. The number of marihuana cigarettes purchased each day are shown in the top row. The dotted line indicates the average number of marihuana cigarettes acquired during each successive 7-day period. Menstrual cycle status is shown in the center of the figure. The onset of menstruation is indicated as day 1 and the duration of menses is shown as a rectangle surrounding the appropriate number of days. Subsequent days of that menstrual cycle are numbered consecutively. The number of points earned for money (O) and marihuana (●) are shown in the second row. The number of purchase points are shown on the left ordinate and consecutive days of each drug availability condition are shown on the abscissa. The average number of total points earned for both money and marihuana during each successive 7-day period of the study are shown as dotted horizontal lines.

the heavy, moderate or occasional marihuana users. When total purchase points were averaged across the entire study, the three groups also earned an equivalent number of points (table 1, column 4). *t* Test comparisons of average points earned per day across the entire study showed no significant differences between groups. Between group analysis of operant points earned during base line, during marihuana availability and during the postdrug base line also were not significantly different.

The heaviest marihuana smoker earned progressively more purchase points during each successive 7-day period of the study (fig. 3). Another heavy smoker abruptly decreased overall operant work when marihuana became available (fig. 4). Two moderate marihuana smokers showed relatively constant purchase point acquisition despite a progressive increase (fig. 5) or decrease (fig. 6) in marihuana smoking.

Hours worked. The time spent working at the operant task was extrapolated from total purchase points which could be acquired no more rapidly than one point every 5 min. There were no significant differences in hours worked during the drug-free base line, the period of marihuana availability and the postdrug base line within the heavy, moderate or the

occasional marihuana user groups. The three groups also did not differ in hours worked during the predrug base line, the marihuana availability period and the postdrug base line. The average hours worked over the entire 35 days also was equivalent across groups.

Dollars earned. Money earned at the operant task reflected purchase points that were not spent for marihuana. All subjects earned more money than they spent for marihuana (e.g., figs. 3-6). However, both the heavy and moderate marihuana users earned significantly fewer dollars during the period of marihuana availability than during the drug-free periods before and after marihuana smoking ($P < .005$; $P < .05$). There were no significant differences in dollars earned during the drug-free period before and after marihuana availability in either group. The occasional users earned comparable amounts of money in all conditions.

Comparisons between the three groups showed that there were no significant differences in total dollars earned over the entire 35-day study between the heavy, moderate and occasional marihuana users. The three groups also did not differ in money earned during the predrug base-line period, the postdrug

TABLE 1

Total purchase points, money earned and hours worked before, during and after marihuana availability ($\bar{X}/\text{day} \pm \text{S.E.}$)

	Predrug Base Line (7 Days)	Marihuana Availability (21 Days)	Postdrug Base Line (7 Days)	35 Day $\bar{X}/\text{Day} \pm \text{S.E.}$
Heavy marihuana users (n = 5)				
Points	95.18 \pm 8.37	82.98 \pm 12.49	89.77 \pm 14.57	86.78 \pm 10.95
Hours	7.89 \pm 0.74	6.91 \pm 1.04	7.48 \pm 1.21	7.23 \pm 0.91
Dollars	7.89 \pm 0.74	4.28 \pm 1.14**	7.48 \pm 1.21	5.40 \pm 1.06
Moderate marihuana users (n = 7)				
Points	83.04 \pm 6.18	85.98 \pm 9.61	87.41 \pm 12.0	85.69 \pm 8.55
Hours	6.93 \pm 0.51	7.16 \pm 0.80	7.29 \pm 1.00	7.14 \pm 0.71
Dollars	6.93 \pm 0.51	5.82 \pm 0.74*	7.29 \pm 1.00	6.32 \pm 1.79
Occasional marihuana users (n = 9)				
Points	81.40 \pm 18.09	87.68 \pm 20.51	86.74 \pm 22.33	87.17 \pm 19.55
Hours	7.19 \pm 1.33	7.31 \pm 1.71	7.17 \pm 1.87	7.27 \pm 1.63
Dollars	7.19 \pm 1.33	6.95 \pm 1.68	7.17 \pm 1.87	6.99 \pm 4.88

* Significantly less than premarihuana base line as determined by *t* tests (1-tailed) ($P < .05$); ** Significantly less than premarihuana base line as determined by *t* tests (1-tailed) ($P < .005$).

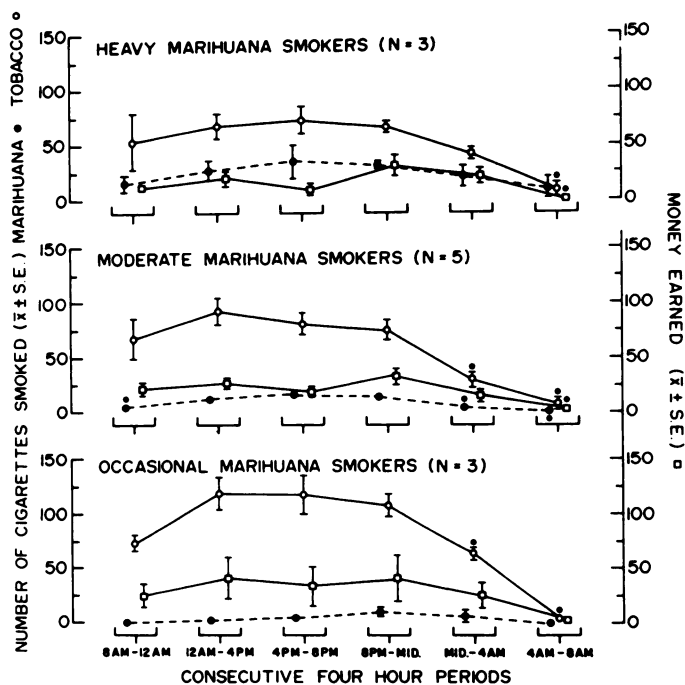


Fig. 7. Temporal patterns of marihuana and tobacco smoking and money acquisition are shown for the heavy, moderate and occasional marihuana smokers. Marihuana (●) and tobacco (○) cigarettes acquired are shown on the left ordinate ($\bar{X} \pm \text{S.E.}$) and money earned (□) is shown on the right ordinate. Each measure was averaged over consecutive 4-hr periods during the 21-day period of marihuana availability for each group.

base-line period and the first and second 7 days of marihuana availability. The only significant difference between groups as a function of the drug availability condition was during the last 7 days of marihuana availability when the heavy marihuana users earned significantly less money than the moderate marihuana users ($P < .05$).

Concurrent use of marihuana and tobacco. Sixteen of the 21 marihuana users also smoked tobacco. During the premarihuana base-line period, four of the heavy marihuana smokers used an average of 14 (± 3.5) tobacco cigarettes each day. Six of the moderate marihuana smokers used an average of 14 (± 3.7) tobacco cigarettes per day and six of the occasional marihuana smokers used an average of 13 (± 3.9) tobacco cigarettes per day.

The availability of marihuana had no significant effect on

tobacco smoking in either the heavy or moderate marihuana smokers. The heavy marihuana smokers smoked an average of 13.8 (± 3.6) tobacco cigarettes per day and the moderate marihuana users smoked an average of 14.5 (± 3.5) cigarettes per day throughout the 35-day study. However, the occasional marihuana smokers smoked significantly more tobacco during the period of marihuana availability ($P < .02$) and the post-marihuana drug-free period ($P < .01$) than during the premarihuana base line. Average cigarettes per day increased from 13 (± 3.9) to 14 (± 4.2) to 15 (± 4.3) cigarettes per day.

Temporal distribution of marihuana and tobacco smoking. The number of marihuana and tobacco cigarettes purchased and money earned by the heavy, moderate and occasional marihuana smokers as a function of time of day is shown in figure 7. Each data point represents the group average ($\pm \text{S.E.}$) during each consecutive 4-hr block for the entire 21-day period of marihuana availability. The asterisks indicate values that were significantly lower than the preceding values ($P < .05$ to $.01$). The dollars earned do not include money spent for marihuana. It is apparent that all three groups smoked more marihuana between 4:00 P.M. and 12:00 MIDNIGHT than at other times. Tobacco cigarettes were smoked primarily between 12:00 NOON and midnight by all three groups. The heavy and moderate marihuana smokers earned the most money between 8:00 P.M. and midnight, when they were also smoking considerable amounts of marihuana.

Figure 8 shows the average interval between successive tobacco and marihuana cigarette purchases by the three subjects who were very heavy marihuana users and tobacco smokers. The distribution of intervals between successive tobacco cigarette purchases during the drug-free base line and the period of marihuana availability and the average interval between marihuana purchases are shown for each subject. Subject FM 1 (1) showed a comparable distribution of tobacco smoking during base line and marihuana use. She smoked marihuana cigarettes most often at an interval of 16 to 30 min. Subjects FM 3 (30) and FM 4 (38) also showed similar distributions of tobacco smoking during base line and the period of marihuana availability but their intermarihuana smoking intervals tended to be 6 hr or more. These data suggest that the availability of marihuana cigarettes did not greatly alter the pattern of tobacco smoking among heavy smokers who were also marihuana users.

Marihuana effects on medical status. No adverse effects of marihuana were detected during the period of marihuana smoking. Vital signs, laboratory tests and information derived

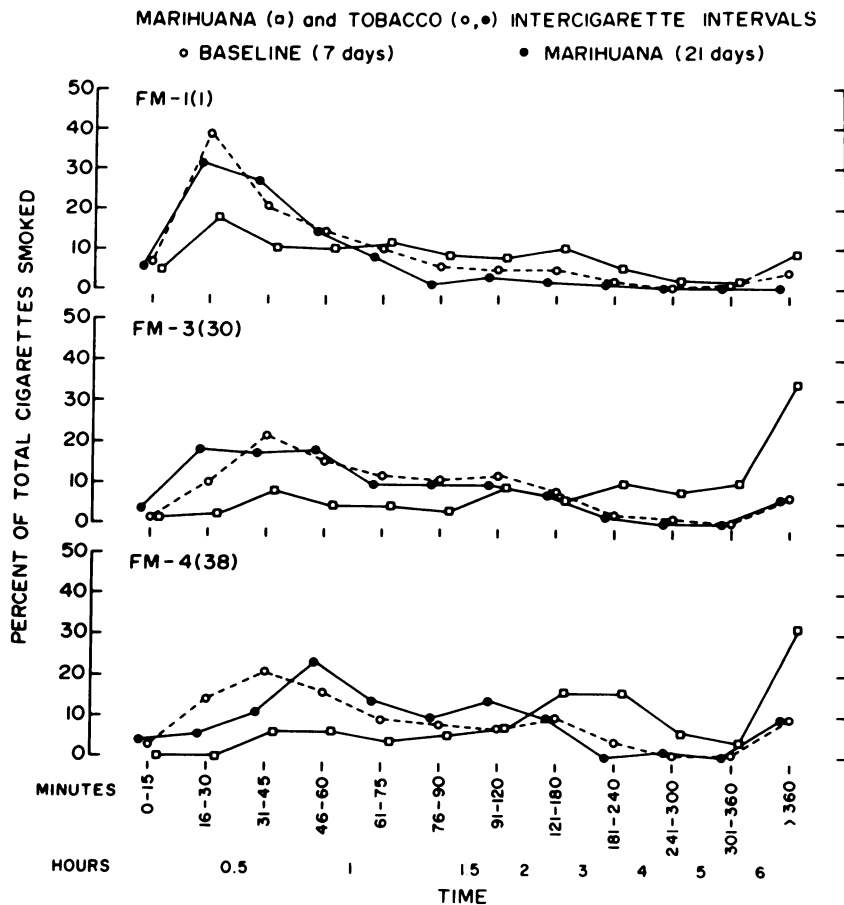


Fig. 8. Distribution of inter-cigarette intervals of tobacco acquisition during the 7-day drug-free base line (○) and 21 days of marihuana availability (●). The inter-cigarette interval of marihuana acquisition is shown as open squares connected by dotted lines. The interval between successive tobacco and marihuana cigarette requests is shown on the abscissa. The percentage of the total number of cigarettes smoked within each interval during the 7-day drug-free base-line period and the 21 days of marihuana availability is shown on the left ordinate. Intersmoking interval data are presented for three heavy marihuana smokers who were also heavy tobacco users.

from physical examination remained normal throughout the 21 days of marihuana availability. During the postmarihuana period, only the subject shown in figure 3 had signs of marihuana withdrawal characterized by tremulousness, hyperactive deep tendon reflexes, sweating, lateral gaze nystagmus, anxiety, insomnia, dysphoria, anorexia and weight loss. Withdrawal signs and symptoms began within 10 hr after cessation of marihuana smoking, were maximal at 48 hr and declined gradually. A complete case report has been published elsewhere (Mendelson *et al.*, 1984).

Discussion

Marihuana use patterns. The female heavy marihuana smokers smoked more marihuana (between 4.0 and 11.62 1-g marihuana cigarettes per day) than the male heavy marihuana smokers (between 4.3 and 6 1-g marihuana cigarettes per day) (Mendelson *et al.*, 1976a). The significant increase in marihuana smoking over time by the heavy marihuana smokers (fig. 2) is consistent with that previously observed in 15 male heavy smokers and 12 male moderate smokers (Mendelson *et al.*, 1976a,b) and 11 heavy and five moderate male marihuana smokers given concurrent access to alcohol (Mello *et al.*, 1978). However, the female moderate and occasional marihuana smokers showed a distinctly different marihuana use pattern from the male moderate smokers. These women decreased marihuana smoking or maintained a relatively stable pattern of marihuana use across the 21 days of marihuana availability (fig. 2), whereas the men who smoked comparable amounts of marihuana, *i.e.*, between two and three marihuana cigarettes

per day, showed a consistent increase in marihuana use as a function of time (Mendelson *et al.*, 1976a,b; Mello *et al.*, 1978). The marked increase in marihuana use on the final day of marihuana availability consistently observed in men was seen in only 8 of the 21 women studied (*cf.* Figs. 3 and 5).

Marihuana effects on operant performance. The number of marihuana cigarettes acquired by the heavy, moderate and occasional marihuana users was significantly different, but there were no differential effects of marihuana dose on operant performance. The three marihuana dose groups were surprisingly comparable in the number of total purchase points earned, the amount of money earned and time spent working at the operant task (table 1). All three groups worked at the operant task every day during both the drug-free and marihuana availability periods. The total number of points earned and the number of dollars earned in excess of dollars spent on marihuana did not differ as a function of marihuana dose. Operant performance for money was sustained even by the heaviest users, when marihuana smoking increased during the period of marihuana availability (figs. 3-6). However, the temporal concordance between marihuana smoking and operant work by women (fig. 7) was also seen in previous studies with men (Mendelson *et al.*, 1976a,b).

The lack of significant effects of high doses of marihuana on performance is consistent with previous studies in young men (Lessin and Thomas, 1976; Mendelson *et al.*, 1974, 1976a,b; Mello *et al.*, 1978; Miles *et al.*, 1974). These data are not compatible with the hypothesis that marihuana smoking produces an amotivational syndrome as subjects continued to work for money, a conventional reinforcer, as well as for marihuana,

even during heavy marijuana smoking. The amotivational syndrome hypothesis would predict that marijuana availability would greatly decrease operant performance and that subjects would not work for money during marijuana intoxication.

Although there was no evidence that marijuana use impaired operant performance in comparison to drug-free periods in these young women, it is noteworthy that 18 of the 21 were unemployed at the time of selection for the study. The observed and reported pattern of marijuana use was inversely related to reported duration of unemployment. The occasional users reported an average of 9.28 (± 2.20) weeks of unemployment upon admission to the study, whereas the heavy and moderate marijuana smokers were unemployed for an average of 4.7 (± 2.20) and 3.46 (± 1.68) weeks, respectively. Inasmuch as women who reported using the least marijuana were unemployed longest, it is possible that these young women may have had problems which were unrelated to marijuana use. All women reported premenstrual depression on the PAF and there is increasing evidence that an amotivational syndrome may be synonymous with clinical depression in college-age youth (*cf.* Halikas, 1974 for discussion).

Marijuana self-administration and menstrual cycle phase. There was no consistent covariation between marijuana self-administration and menstrual cycle phase in this sample of 21 women. Outpatient self-report data based on daily diaries also failed to show increased marijuana use at the premenstruum (M. Griffin, personal communication). But when the PAF scores were examined in women who were premenstrual during marijuana availability, there was a striking concordance between marijuana use and premenstrual dysphoria. Women who increased marijuana use at the premenstruum reported significantly greater depression, anxiety, mood lability, anger, irritability and impaired social functioning ($P < .05$ to $.01$) than women whose marijuana use decreased or stayed the same. Severity of premenstrual dysphoria was more important in differentiating the three groups of women than physical discomfort associated with the premenstruum. Although women who increased marijuana use reported greater physical discomfort, pain, nausea, dizziness and general malaise than the other two groups, with the exception of signs of water retention, these differences were not statistically significant. These data suggest that the dysphoric component of premenstrual tension, rather than physical discomfort, may be most closely associated with increased drug use by women.

Covariance between severity of premenstrual tension and increased marijuana use is consistent with clinical reports of increased alcohol abuse during periods of premenstrual dysphoria (Podolsky, 1963; Belfer *et al.*, 1971; Belfer and Shader, 1976). These observations of alcoholic women led us to postulate that the periodic recurrence of premenstrual dysphoria may have an important influence on patterns of alcohol use and abuse by women (Mello, 1980). The association between increased marijuana use and premenstrual dysphoria reported here lends support to the notion that, in women, depression and anxiety associated with the premenstruum may be one proximal determinant of episodic increases in drug use. The factors that contribute to the maintenance of drug use and abuse are poorly understood (*cf.* Mello, 1983 for review) and it is not possible to impute causality to premenstrual tension as numerous factors may exacerbate drug use. However, it is unlikely that premenstrual dysphoria occurred as a consequence of increased marijuana use rather than the converse.

Marijuana use is not commonly associated with increased dysphoria and the acute effects of marijuana on mood and pulse rate in women did not differ as a function of menstrual cycle phase (Lex *et al.*, 1984).

Concordance of tobacco and marijuana use. The amount and temporal pattern of tobacco cigarette smoking observed during drug-free conditions was not changed during concurrent marijuana use by the heavy and moderate marijuana smokers (Figs. 7 and 8). These data are consistent with our previous studies of the covariance between tobacco and marijuana smoking by young men (Mello *et al.*, 1980a). Marijuana availability did not change average cigarette smoking in comparison to the drug-free base line by men (Mello *et al.*, 1980a). Although it might be expected that marijuana smoking and tobacco smoking might be antithetical, in fact, both drugs usually were smoked in close temporal contiguity (fig. 7).

These data have unfortunate implications for one medical consequence of marijuana and tobacco smoking, impaired pulmonary function. Adverse effects of marijuana smoking on pulmonary function have been consistently demonstrated in numerous studies with men (Tashkin *et al.*, 1973, 1976, 1980; Vachon *et al.*, 1973; Bernstein *et al.*, 1976). Studies of pulmonary function in our female marijuana users have shown that single breath carbon monoxide carbon infusion capacity was significantly lower than both tobacco cigarette smokers and nonsmokers (Goldenheim *et al.*, 1985). These data were interpreted to suggest that marijuana smoking may cause significant impairment of pulmonary function associated with the gas exchange surface of the lung (Goldenheim *et al.*, 1985).

The lack of effect of marijuana on tobacco smoking is inconsistent with previous studies of the effects of other intoxicants on tobacco use. It has been consistently observed that alcohol, opiate and opiate mixed-agonist-antagonist intoxication, as well as acute administration of *d*-amphetamine, are associated with increased tobacco smoking (Griffiths *et al.*, 1976; Mello *et al.*, 1980a,b, 1985; Chait and Griffiths, 1983; Henningfield and Griffiths, 1981). These marijuana and tobacco smoking data are consistent with an emerging literature that the concurrent use of drugs from different pharmacological classes with divergent, or even contradictory effects, is not uncommon (*cf.* Mello, 1983 or review).

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