EXHIBIT J

Psychopharmacology 49, 79 – 84 (1976)

Psycho pharmacology

Effects of Marihuana Use on Body Weight and Caloric Intake in Humans

ISAAC GREENBERG*, JOHN KUEHNLE, JACK H. MENDELSON, and JERROLD G. BERNSTEIN

Alcohol and Drug Abuse Research Center Harvard Medical School, McLean Hospital, Belmont, Massachusetts, U.S.A.

Abstract. Body weight and caloric intake were measured in a group of heavy and casual marihuana users prior to, during and following 21 days of marihuana smoking under research ward conditions. A group of control subjects were studied under identical conditions, but they did not smoke marihuana. Both heavy and casual marihuana users had a significant increase in caloric intake and gained weight during the marihuana smoking period. Heavy and casual users gained an average of 3.7 and 2.8 lbs respectively during the first 5 days of marihuana smoking. In contrast, control subjects gained only a small amount of weight (0.2 lbs) during the same time interval. Water retention did not appear to be a major factor in weight gain by the marihuana users. These findings are in agreement with both anecdotal reports and previous experimental data that marihuana use is associated with increased caloric intake and weight gain.

Key words: Marihuana smoking – Weight gain – Experimental setting – Caloric intake.

Marihuana is commonly believed to enhance food intake in man. Anecdotal accounts of increased food ingestion associated with marihuana smoking (Siler et al., 1933; Haines and Green, 1970; Snyder, 1971) have only recently been assessed in clinical studies (Hollister, 1971; Williams et al., 1946). Hollister (1971) found that subjects ingested more of a chocolate milkshake preparation after 0.5 mg/kg oral delta-9 THC than after placebo. When offered the milkshake 3 h post-drug, marihuana subjects consumed 731 ml vs. 503 ml ingested by the placebo group. Chronic exposure to marihuana (39 days) or pyrahexyl, a THC analogue, (28 days) was also associated with weight gain (Williams et al., 1946).

In a recent study, Regelson et al. (1974) administered delta-9 THC to patients with cancer to determine if the drug would retard chronic weight loss. In a preliminary communication, these investigators report the delta-9 THC appeared to stimulate appetite and the patients gained weight. However, no data concerning amount of weight gained or calories ingested was reported.

The present study was part of a larger group of experiments designed to assess the effects of chronic marihuana use on various biological and behavioral functions (Mendelson et al., 1974). This report focuses upon the influence of marihuana smoking on food intake and body weight.

METHODS

Subjects. Male volunteers were recruited through advertisements placed in local newspapers. Psychiatric and medical examinations were carried out, and only those subjects in good physical and mental health were selected for participation in the study. Twelve 'casual' and fifteen 'heavy' marihuana users were studied compared with ten subjects who served as controls.

Casual users reported a mean duration of 5.3 years marihuana use with a monthly smoking frequency of 11.5 times. Heavy users reported a mean duration of marihuana use of 5.6 years and a monthly smoking frequency of 42 times. Both groups were matched as closely as possible with regard to socioeconomic background, intelligence and level of education. Further background information about the subjects is presented in Table 1.

Ten control subjects were exposed to identical ward conditions. These subjects had a past history of casual alcohol use and could work for money or alcohol on the research ward. Control subjects did not have access to marihuana or other drugs. As Table 1 indicates, the backgrounds of the control subjects were comparable to the casual marihuana users in all relevant respects. During the study they drank virtually no alcohol (average 1.5 oz. per day) and therefore qualify as drug-free controls.

Marihuana. All marihuana smoking had to be done at time of cigarette purchase, under the observation of a staff member

* *Send offprint requests to:* Isaac Greenberg, Ph.D., Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill Street, Belmont, Mass. 02178, U.S.A.

Table 1. Background characteristics and previous drug-taking experience: casual and heavy marihuana smokers

	Casual users ($N = 12$)		Heavy users ($N = 15$)		Controls ($N = 10$)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age	23.3	(1.1)	23	(1.6)	23	(1.5)
Years formal education	14.5	(1.4)	13.6	(1.5)	15.1	(1.6)
Years used marihuana	5.3	(1.1)	5.6	(1.9)	6.4	(2.3)
Marihuana use (times/mo)	13.0	(6.2)	41.0	(26.4)	3.4	(1.3)
Alcohol use (times/mo)	9.3	(8.0)	19.9	(10.0)	6.9	(4.1)

A detailed report of the experimental analysis of marihuana acquisition and use has been presented elsewhere (Mendelson et al., 1972). Unused portions of smoked marihuana cigarettes were returned to the staff to insure that 'roaches' were not accumulated and smoked without staff knowledge. Since studies were carried out on an inpatient hospital research ward, staff were able to insure that subjects did not use drugs other than marihuana.

Cigarettes containing approximately 1 g of marihuana were obtained from the National Institute of Mental Health (NIMH) in lot standard dosage form. Each cigarette contained approximately 1.8–2.3% THC as assayed by the NIMH. Actual content analysis of the marihuana using ethanol-Soxhlet and Modified Lerner extraction procedures was as follows: cannabidiol, 0.18% ± 0.04%, Δ^8THC, 0.002, Δ^9THC, 2.06% ± 0.08%, cannabinol, 0.08% ± 0.012%.

General Design. The investigation was carried out on a four-bed clinical research ward of the Alcohol and Drug Abuse Research Center at the McLean Hospital. Each study consisted of three consecutive phases: (1) a pre-drug 5-day baseline, (2) a 21-day period during which marihuana (or alcohol for control subjects) was available, and (3) a post-drug period of 5 days duration. All other conditions were identical for the marihuana and for the alcohol control subjects.

Food was prepared in the cafeteria of McLean Hospital and was brought to the research ward and served by nurses or mental health workers. The type and amount of food eaten was recorded and caloric intake calculated. Subjects were also permitted to choose their favorite snack foods and both the cafeteria and snack foods were supplied free to the subjects. Body weight was recorded each morning at 8.00 a.m. Urine samples were collected on a 24-h basis for all the casual and 11 of the 15 heavy marihuana users.

RESULTS

Daily body weight and caloric intake are reported for the heavy and casual users and the control group. Changes in body weight and caloric intake during successive 5-day periods of the study were analyzed with paired t-tests. Comparisons were made between the pre-drug control period and the first 5 drug days (study days 6 – 10) and also between the last five drug days (study days 22 – 26) and the post-drug phase. Body weights were obtained at 8:00 a.m. and represent food consumption during the previous day. Thus, post-drug body weights are plotted for a 4-day (days 28 – 31) rather than a 5-day (days 27 – 31) period in Figure 1.

Heavy marihuana users showed a significant ($P < 0.01$) increase in caloric intake and body weight following initiation of drug use (Fig. 1). Although body weight continued to increase during the drug phase, caloric intake decreased, but remained above baseline pre-drug levels. Upon termination of the smoking phase of day 26, both body weight and caloric intake decreased significantly ($P < 0.01$). The number of marihuana cigarettes smoked per day, displayed across the top of Figure 1, progressively increased during the 21-day drug phase; there was no clear relationship, however, between the number of marihuana cigarettes smoked by any single subject and the amount of food consumed. In fact, as Figure 1 indicates, the highest weight gains during the first five drug days corresponded to the least amount of marihuana use (4.29 cigarettes per day).

The casual user group (Fig. 2) also demonstrated increases in both body weight and caloric intake. Both measures increased significantly during drug availability and use ($P < 0.05$) and caloric intake decreased significantly following cessation of marihuana use ($P < 0.01$). However, body weight loss following cessation of marihuana use did not reach a statistically significant level. As with the heavy user group, no clear dose-weight relationship emerged for any subject. Once more, the high initial increases in body weight corresponded with relatively low levels of drug use (2.02 cigarettes per day).

Control subjects (Fig. 3) sustained monotonic increases in both body weight and caloric intake during the 30-day study. This pattern is in sharp contrast to the curvilinear changes seen in both marihuana groups. Further, the magnitude of weight and caloric intake changes in the control subjects was well below that seen in the marihuana groups. Weight gain comparisons between either marihuana group and the control group were statistically significant. (Casual users vs. control: $t = 4.13$, $P < 0.005$; heavy users vs. control: $t = 4.09$, $P < 0.005$.) The control sub-

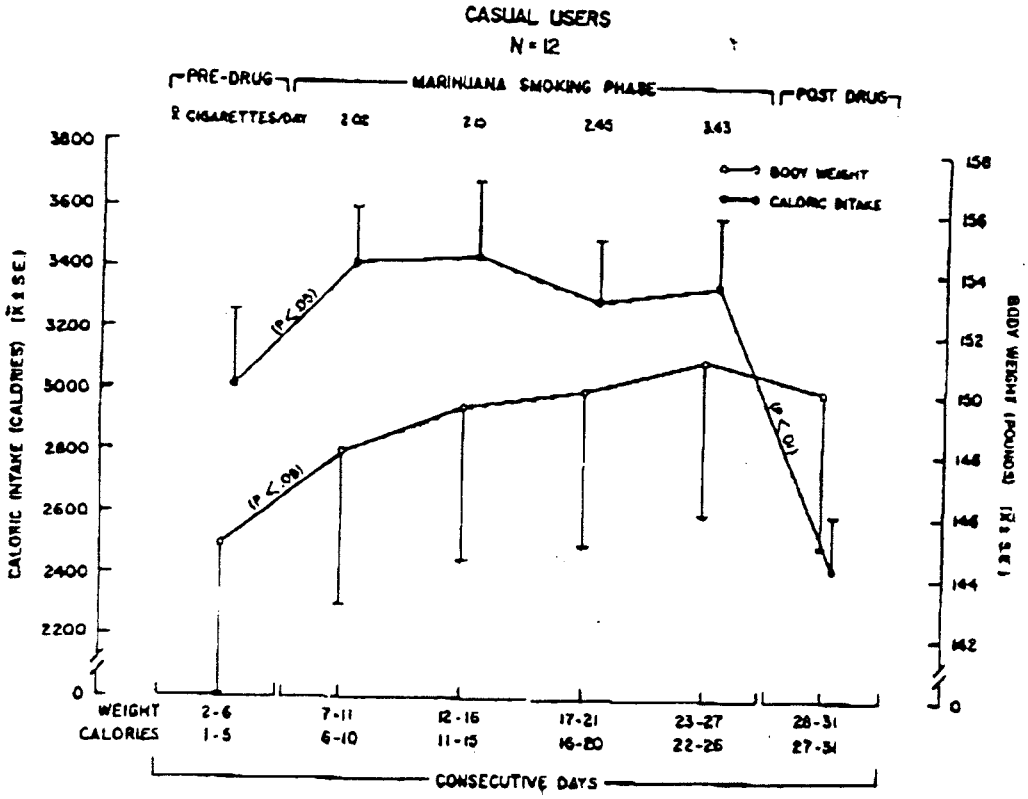

Fig. 1. Casual users ($N = 12$) patterns of body weight (O---O) and caloric intake (● ●) are shown for consecutive 5-day blocks (see text). All points are group means ± standard error of the mean. At top of figure, the mean daily number of marihuana cigarettes smoked is listed for each 5-day period

jects continued to ingest food in increasingly greater amounts during the last five days of the study, while both marihuana groups had significantly depressed food ingestion levels during this period of time.

To determine if fluctuations in body-weight might be due to water retention, urine volume output was plotted as a function of time and drug phase (Fig. 4). If water retention were a function of drug use, urine volume output should have decreased upon initiation of marihuana use and should have increased with cessation of marihuana use. However, the opposite phenomena was found in the twelve casual and eleven heavy users, indicating that increased fluid intake paralleled increased food intake.

DISCUSSION

Results obtained in this study are in agreement with the findings of others on acute (Hollister, 1971) and chronic (Williams et al., 1946) effects of marihuana use on food ingestion. Hollister (1971) found that increased caloric consumption associated with acute delta-9 THC administration could be measured 3 h following drug administration. Williams et al. (1946) found that an increase in body weight occurred during a 39 day period of marihuana use. Caloric intake, however, only increased in a transient manner and then fell steadily to below pre-drug baseline levels. Evaluation of these data is difficult since the type, content and potency of the marihuana preparation smoked is not specified. Moreover, control groups were not studied to determine if non-drug related variables such as experimental setting, prison routine, type of food available, eating schedules, etc., had any influence on patterns of food ingestion. In the present study, high caloric intake was recorded throughout the smoking period for casual users, but showed a trend toward a sustained decrease below initial values for the heavy users. Since marihuana was available in our study for 21 days (vs. 39 days as described by Williams et al., 1946), it is possible that a longer period of marihuana availability would produce an initial increase followed by a depression of caloric intake.

A possible reason for a relative decrease in caloric intake after a significant initial increase at the onset of marihuana smoking may be related to gradual

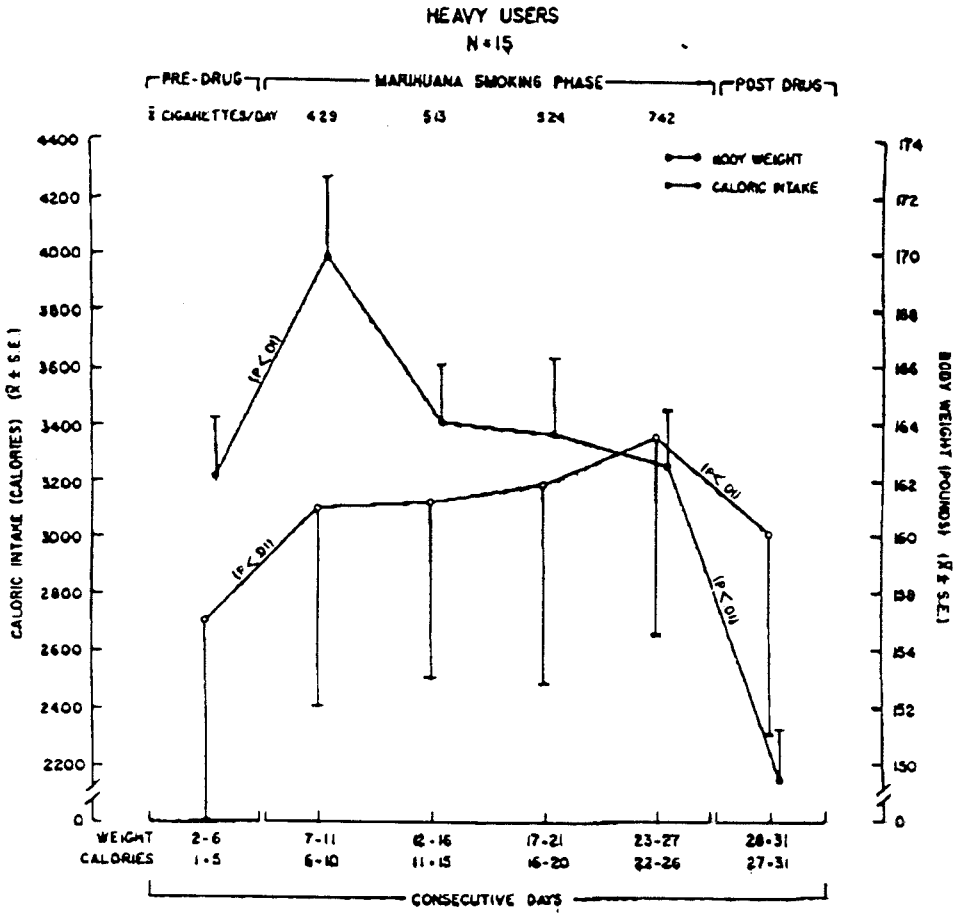

Fig. 2. Heavy users ($N = 15$) patterns of body weight (O —O) and caloric intake (● —●) are shown for consecutive 5-day blocks (see text). All points are group means ± standard error of the mean. At top of the figure, the mean daily number of marihuana cigarettes smoked is listed for each 5-day period

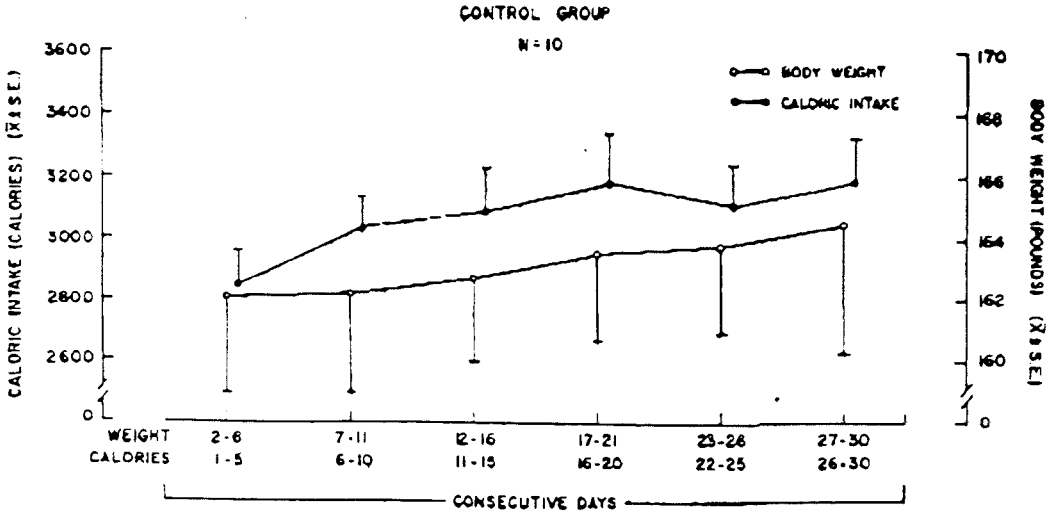

Fig. 3. Non-smoking controls ($N = 10$) patterns of body weight (O —O) and caloric intake (● —●) are shown for consecutive 5-day blocks (see text). All points are group means ± standard error of the mean

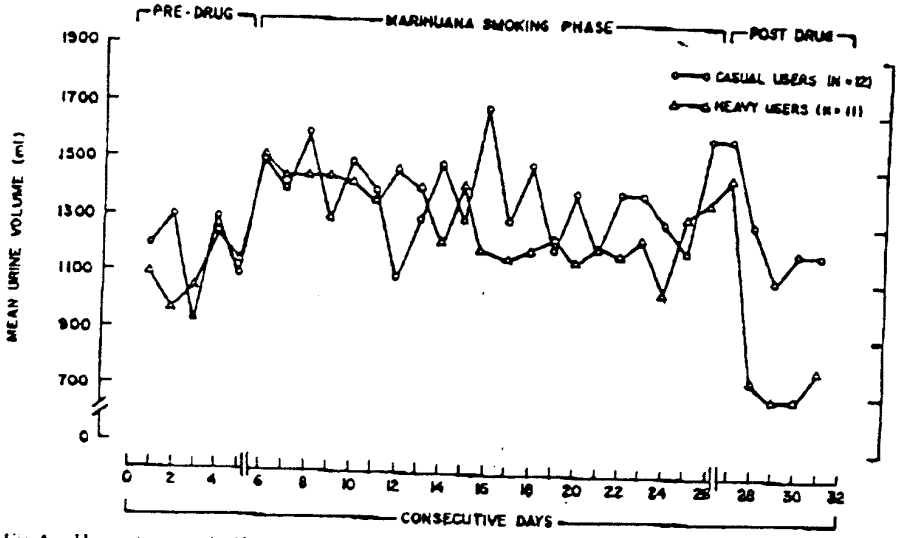

Fig 4 Heavy (Δ——Δ) (N = 10) and casual (O——O) (N = 12) user urine volume output as a function of experimental phase

development of marihuana tolerance. It is also possible that the initial increase in food intake at the beginning of the marihuana smoking phase may have generated aversive consequences (e.g., fear of being overweight) and induced subjects to reduce food intake during subsequent marihuana smoking. In fact, subjects often verbalized their concern about gaining too much weight, but when overt dieting was reported, it began during the 5-day post-smoking period.

Control subjects gained very little weight as the study progressed. Increases averaged just over two pounds during 30 days and showed a linear trend. This phenomena might be expected considering restricted ward environment and the availability of free food.

Although there was no clear evidence that marihuana use resulted in marked fluid retention, this possiblity cannot be entirely ruled out. Benowitz and Jones (1975) have recently reported that weight gain in subjects administered daily Δ^9 THC may have been due to fluid retention and plasma volume expansion. Caloric intake was not presented in their report. The subjects in the present study showed clear changes in caloric consumption accounting for at least part of the significant weight changes. More detailed studies of total body water content are now being conducted to determine how caloric intake and changes in body water influence the weight of marihuana users.

Following administration of either pyrahexyl or delta-9 THC, rats show a decrease in food intake and in body weight (Abel and Schiff, 1969; Manning et al., 1971; Sjoden et al., 1973; Sofia and Barry, 1974). Why marihuana administration depresses food intake in laboratory animals but elevates caloric intake in humans remains unknown. Dosage factors may be as important as species differences. Human subjects control the amount of marihuana they smoke, while animals are usually given dosages proportionately many times greater than those used by humans (Elsmore and Fletcher, 1972). In the single report of THC- or marihuana-related weight gain in animals, rats were first adapted to a deprivation schedula for 150 days and then given delta-9 THC (Gluck and Ferraro, 1974). Under these conditions, rats consumed food during their daily 1 h access period in contrast to non-drug conditions. Thus, long-term adaptation to limited food access may be a necessary prerequisite for marihuana-related enhanced food intake in animals. Humans are under no such deprivation schedule, and the seemingly contradictory results between humans and laboratory animals may due be to species differences or to variables which, to date, have not been identified.

Acknowledgements. This study was supported, in part, by Contract No. DADA17-73-C-3082 from the Department of the Army and Grant No. DA4RG010 from the National Institute on Drug Abuse, ADAMHA.

We wish to thank Miss Lorraine DeRubeis for her assistance in data analysis.

REFERENCES

Abel, E. L., Schiff, B. B.: Effects of the marihuana homologue, pyrahexyl, on food and water intake, and curiosity in the rat. Psychon. Sci. 16, 38 (1969)

Benowitz, N. L., Jones, R. T.: Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. Clin. Pharmacol. Ther. 18, 287–297 (1975)

Elsmore, T. F., Fletcher, G. V.: Aversive effects in rat at high doses, Δ^9-tetrahydrocannabinol. Science 175, 911–912 (1972)

Giluck, J. P., Ferraro, D. P.: Effects of Δ^9 THC on food and water intake of deprivation experienced rats. Behav. Biol. 11, 395–401 (1974)

Haines, L., Green, W.: Marijuana use patterns. Brit. J. Addict. 65, 347–362 (1970)

Hollister, L. E.: Hunger and appetite after single doses of marihuana, alcohol, dextroamphetamine. Clin. Pharmacol. Ther. 12, 44–49 (1971)

Manning, F. J., McDonough, J. H., Jr., Elsmore, T. F., Suller, C., Sodetz, F. J.: Inhibition of normal growth by chronic administration of delta-9 tetrahydrocannabinol. Science 174, 424–426 (1971)

Mendelson, J. H., Meyer, R. E., Rossi, A. M., Bernstein, J. G., Patch, V. D., Babor, T. F., Reed, H., Salzman, C., Becker, D.: In: Marihuana: A signal of misunderstanding, Technical Papers 1, 68, U.S. Government Printing Office (1972)

Mendelson, J. H., Kuehnle, J. C., Ellingboe, J., Babor, T. F.: Plasma testosterone levels before, during and after chronic marihuana smoking. New Engl. J. Med. 291, 1051–1055 (1974)

Regelson, W., Butler, J. R., Schultz, J., Kirk, T., Peck, L., Green, M. L.: Delta-9 tetrahydrocannabinol (Delta 9-THC) as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. Paper read at International Conference on the Pharmacology of Cannabis, Savannah, Ga. (1974)

Siler, J. F., Sheep, W. L., Bates, L. B., Clark, G. F., Cook, G. W., Smith, W. A.: Marijuana smoking in Panama. Milit. Surg. 269–280 (1933)

Sjoden, P., Järbe, T., Henriksson, B.: Influence of tetrahydrocannabinol (Δ^8-THC and Δ^9-THC) on body weight, food, and water intake in rats. Pharmacol., Biochem. Behav. 1, 395–399 (1973)

Snyder, S. H.: Uses of marijuana. New York: Oxford University Press 1971

Sofia, R. D., Barry, H.: Acute and chronic effects of Δ^9-Tetrahydrocannabinol on food intake by rats. Psychopharmacologia (Berl.) 39, 213–222 (1974)

Williams, E. G., Himmelsbach, C. K., Wikler, A., Ruble, D. C.: Studies on marijuana and pyrahexyl compound. Publ. Hlth. Rep. (Wash.) 61, 1059–1083 (1946)

Received February 2, 1976; Final Version April 15, 1976