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Cannabis: Effects on Hunger and Thirst[1]

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The effects of cannabis and its derivatives on food and water intake in humans and animals are reviewed. Possible mechanisms underlying these effects are discussed. No unequivocal explanations for the phenomenon in humans or animals are readily acceptable and a general consideration of the problem raises more questions than answers.

One of the many subjective effects of cannabis and its derivatives about which there tends to be a general consensus is the propensity of this drug to stimulate hunger, particularly for foods that are sweet tasting. This would tend to suggest its potential usage as a pharmacological agent in the treatment of conditions where there is a loss of appetite. However, attempts to corroborate this experience in the laboratory have produced equivocal results. For instance, while the human literature tends to support the assertion of increased hunger following use of cannabis, the subhuman data leaves no doubt that cannabis has anorexiclike effects in animals. The purpose of the following review is to summarize these data and to examine some of the possible reasons for the disparate effects of cannabis on food intake in humans and laboratory animals. In addition, this review will consider the effects of cannabis and its derivatives on thirst and fluid intake where such considerations appear relevant to the discussion.

Throughout this review, the terms cannabis and marihuana will not be differentiated. The active principles in cannabis are *trans*-Δ^9-tetrahydrocannabinol (Δ^9THC) and *trans*-Δ^8-tetrahydrocannabinol (Δ^8THC) (Mechoulam, 1970). Although some of the other cannabinoids present in cannabis such as cannabidiol, cannabinol, and cannabigerol are relatively inactive themselves, evidence recently has been accumulating that these cannabinoids can affect the activity of Δ^9THC present in mixtures (Jones and Pertwee, 1972; Fernandes, Warning, Christ, and Hill, 1973; Karniol and Carlini, 1973) so that on a Δ^9THC mg/kg basis, the potency of crude cannabis

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extracts can be expected to be different from that of Δ^9THC per se. In addition to these naturally occurring substances, two homologs derived from d, l-synthetic tetrahydrocannabinol have been widely used in psychopharmacological investigations. These homologs are the *n*-hexyl derivative, pyrahexyl (also known as synhexyl) and the dimethyl heptyl derivative, DMHP. Although the actual compounds used in each study under review will be identified, no attempt will be made to distinguish between differences in effect produced by a particular cannabinoid unless such remarks will aid in clarifying a particular aspect of that compound's action.

HUMAN STUDIES

As far back as 300 A.D., cannabis has been recommended in India as a treatment for loss of appetite (cf. Chopra and Chopra, 1939). However, cannabis has also been used by ascetics and Indian mendicants to overcome the sensations of hunger and thirst (Chopra and Chopra, 1939) so that among the ancients, cannabis was also reported to have a quieting effect on hunger. In one of the first modern medical reports dealing with cannabis, O'Shaughnessy (1838), an English physician stationed in India, stated that moderate doses of cannabis extract did indeed stimulate appetite. Since the appearance of this report, a number of other physicians and writers of the last century have commented upon the increased stimulation of appetite following ingestion of cannabis (cf. Walton, 1938). In 1933, Siler *et al.*, reported that soldiers whom they had had a chance to study, all stated that they felt hungry after smoking marihuana and this sensation was corroborated by the amount of food these subjects subsequently ate. Unfortunately, no data were presented in their report. In 1941, Adams stated that an increase in hunger was an "invariable characteristic" associated with the use of marihuana, and he suggested that as such, cannabis "might be applicable in psychoneuroses in which a lack of desire for food exists." The capacity of cannabis and its homologs to stimulate appetite has been frequently described in subsequent reports as well (e.g., Allentuck and Bowman, 1942; Mayor's Committee on Marihuana, 1944; Williams, Himmelsbach, Wikler, Ruble, and Lloyd, 1946; Stockings, 1947). Ames (1958) reported that although subjects in her experiment stated that they did not feel hungry during the first 3 hr after receiving marihuana, they did eat "with great relish" when food was offered to them. The Mayor's Committee (1944) reported that in heroin and cocaine addicts undergoing withdrawal, those given cannabis "maintained their appetite and in some cases actually gained weight," although the general attitude of such individuals was a lack of interest in food.

The potentially therapeutic use of marihuana and its homologs as appetite stimulants was also noted by Parker and Wrigley (1950) who

administered pyrahexyl to a group of psychotic patients. Although the drug produced no change in the psychiatric condition of their patients, these clinicians observed that "some of the patients who had previously refused food began to demand it" following pyrahexyl treatment. A similar amelioration of anorexia was also reported by Thompson and Proctor (1953) in their treatment of alcoholics and by Pond (1948) in his treatment of depressives using pyrahexyl.

In summary, the general impression from the early clinical and anecdotal literature is that cannabis and its homologs stimulate the desire for food in humans. However, it should also be noted that in nearly all of the instances in which cannabis was studied clinically in this manner, the observations were conducted under conditions which would not be acceptable by present-day scientific standards of observation.

Nevertheless, the general sensation of an increase in hunger is buoyed by the survey literature which tends to corroborate this impression (cf. Tart, 1970; Haines and Green, 1970; Halikas, Goodwin, and Guze, 1972; Jasinski, Haertzen, and Isbell, 1972).

Apart from the above-mentioned clinical studies and surveys, little experimentation has been directed at the effects of cannabis on consummatory behavior in humans, although there are a number of such investigations involving animals. Interestingly, however, the animal data not only do not corroborate the human studies, but actually suggest that cannabis has an opposite effect on consummatory behavior.

Apart from the previously mentioned clinical studies and subjective reports obtained during interviews and surveys, there is a paucity of research devoted to systematic studies of cannabis' effects on consummatory behavior in humans. The only two studies in this area that could be located were reported by Hollister (1971) and by Abel (1971).

Hollister (1971) administered either a cannabis extract (containing 27-39 mg Δ^9THC), a placebo, dextroamphetamine (0.2 mg/kg), or alcohol (95%, 1 ml/kg) to fasted subjects in a noncaloric soft drink so as to mask taste differences. Prior to receiving the drug, the subjects were given a hunger questionnaire and this questionnaire was readministered 3 hr postdrug, following which the subjects were offered food (milkshakes). Food offerings were again made 0.5, 1, and 2 hr later. The entire experiment was then repeated (excluding amphetamine) with a different group of subjects that were not fasted prior to testing.

Although there was a trend of greater food intake in both experiments following ingestion of marihuana compared to placebos, this trend was only significant in subjects that were not previously fasted. By contrast, amphetamine reduced and alcohol had little effect on food intake. Although all subjects reported being more hungry as testing continued, the differences in

subjective ratings between the marihuana and other drug conditions were not significant.

The experiment reported by Abel (1971) was divided into two parts. During the predrug session, the subjects were told that they were to participate in a study of memory function and that they were to restrict their movements. Plates of marshmallows were placed before them "in case someone might get hungry during the experiment." At the end of the session, the marshmallows were removed and unbeknownst to the subjects, the number eaten by each was determined by a confederate of the experimenter. In part B, the plates of marshmallows were returned to the subjects and those in the drug group were then given two marihuana cigarettes to smoke (Δ^9THC content not specified). Control subjects did not smoke anything. After the second test session, the marshmallows eaten by each subject were again determined. Although less controlled than the Hollister (1971) experiment, the results of this study demonstrated a significant increase in food intake on the part of experimental compared to control subjects. However, because of the lack of placebos, this latter result could not be unequivocally attributed to the effects of the drug.

For the most part, these clinical and experimental studies support the anecdotal reports of an increase in hunger on the part of the subjects that have taken marihuana. However, it should be pointed out that those studies that have just been cited, both clinical and experimental, along with the anecdotal reports, are based on acute administration of cannabis or its derivatives. The effect of chronic administration on hunger in humans has not been examined as yet. Nor should one lose sight of the fact that most of the preparations given to humans experimentally or clinically contain very little Δ^9THC. This fact should be kept in mind in light of the observations reported by Chopra and Chopra (1939) and Bouquet (1951). The former report that while *bhang* (a weak cannabis preparation) is said to stimulate appetite, *ganja* and *charas* (more potent cannabis preparations) usually have an opposite effect such that chronic users of these preparations are often underweight. Bouquet (1951) notes that with chronic use of cannabis, a progressive anorexia develops such that the chronic user "eats only one very frugal meal per day, even if he does go without it altogether, and instead just eats a few sweet pastries or chews dry seeds."

Thus, no final statement regarding the effects of cannabis on hunger in humans can be made until there is more information regarding dose-response relationships and the possible effects of long-term use of this substance.

ANIMAL STUDIES

In an early study of the effects of cannabis on maze learning in rats, Carlini and Kramer (1965) reported that animals treated with cannabis extract

(10 mg/kg, ip) ate more than control animals during the first hour postinjection. This observation seemed to corroborate the anecdotal human literature regarding the effects of cannabis on hunger and suggested the possibility of using animals to explore the phenomenon in greater detail. However, no systematic measurements of food intake were conducted by Carlini and Kramer (1965) to substantiate this original observation and subsequent studies have generally shown that rather than stimulating food intake, animals treated with cannabis exhibit reduced food intake (see summary in Table 1).

A number of different possibilities have been considered in attempting to account for the opposite effects of cannabis on food intake in humans and animals. Some of the important variables in addition to species differences that have been suggested in this regard are differences in drug dosage, route of drug administration, secondary effects of decreases in fluid consumption, general malaise, inhibition of alimentary tract activity, etc. Some of these possibilities will now be considered in detail.

Drug dosage. One of the major difficulties in comparing the effects of drugs on different animals is that of equating drug dosage across species (see review by Abel, 1974). Because of inherent differences in rates and routes of metabolism and excretion, rates of absorption, etc., comparisons of drug effects on the basis of administered dosage may be misleading. One alternative that has been suggested is that of using the plasma levels of free drug in each species as a standard referent with which to compare the effects of a particular drug (Brodie and Reed, 1971). However, the levels of unchanged Δ^9THC in human blood are generally too low to detect at the doses that are generally administered in human experiments so that unless radioactively labeled compounds are used, such comparisons between humans and animals are not presently practical.

Although animals typically receive much more Δ^9THC than do humans, Paton (1973) has pointed out that the effects of any given dose of drug varies more closely with surface area and metabolic rate than with body weight so that just as animals eat proportionally more food than humans relative to body weight, they also may require much more of a drug such as Δ^9THC to produce a given effect. Thus, he argues that doses of Δ^9THC of the order of 50 mg/kg in some animals are therefore not irrelevant to human experience. This is a moot point, however, since doses of 16-64 mg/kg are lethal to monkeys (cf. Hockman, Perrin, and Kalant, 1971; Scheckel, Boff, Dahlen, and Smart, 1968), and cats and dogs receiving only small amounts of cannabis (e.g., 0.5-4.0 mg/kg) often vomit following oral administration of the drug (e.g., Hare 1887; Chopra and Chopra, 1939; Loewe, 1950) as do some humans (cf. Walton, 1938; Baker and Lucas, 1969). The problem of comparing drug dosage across species, therefore, should not be minimized. Moreover, since Δ^9THC generally has a sedating effect in animals at doses above 10 mg/kg body wt, studies employing doses higher than this should be viewed with caution in terms of the drug's effects on behavior.

TABLE 1

Effect of Cannabinoids on Food and Fluid Consumption

Species	Drug and dosage	Route of administration	Effect on intake: Food	Effect on intake: Water	Comment	Reference
Cat	Cannabis extract (dose not stated)	po	↓			Marshall (1896)
	Cannabis extract (1-2 mg/kg)	po	↓			Chopra and Chopra (1939)
Chick	Δ^9THC (1-10 mg/kg)	im	↓			Abel *et al.* (1972)
Dog	Δ^9THC (0.5-32 mg/kg)	iv	↓		Decreased body weight; food intake not measured	Dewey *et al.* (1972)
	Cannabis extract	Smoke	↑		No vehicle control	Huy *et al.* (1974)
	Δ^9THC (225-3600 mg/kg)	po	↓			Thompson *et al.* (1974)
	Δ^8THC (225-3600 mg/kg)	po	↓			Thompson *et al.* (1974)
	Cannabis extract (225-3600 mg/kg)	po	↓			Thompson *et al.* (1974)
Hamster	Cannabis extract (200, 300 mg/kg)	sc	↓	–		Geber and Schramm (1969)
Monkey	Cannabis extract	Smoke	↓			Indian Hemp Drug Commission (1893)
	Δ^9THC (4, 8 mg/kg)	ip	↓			Scheckel *et al.* (1968)
	Δ^9THC (100 μg)	iv	↓			Grunfeld and Edery (1969)
	Δ^8THC (500 μg)	iv				
	Δ^9THC (225-3600 mg/kg)	po	↓			Thompson *et al.* (1974)
	Δ^8THC (225-3600 mg/kg)	po	–			Thompson *et al.* (1974)
	Cannabis extract (225-3600 mg/kg)	po	–			Thompson *et al.* (1974)

TABLE 1–Cont'd

Species	Drug and dosage	Route of administration	Effect on intake: Food	Effect on intake: Water	Comment	Reference
Pigeon	Δ^9THC (36 mg/kg)	im	↓		No systematic observations of food intake	McMillan *et al.* (1970)
Rabbit	Cannabis extract	po	↓			Marshall (1898)
	Cannabis extract (25, 50 mg/kg)	sc	↓	–		Geber and Schramm (1969)
Rat	Cannabis extract (10 mg/kg)	ip	↑		No systematic observations	Carlini and Kramer (1965)
	Pyrahexyl (15 mg/kg)	ip	↓	–	No tolerance	Abel and Schiff (1969)
	Δ^9THC (0.01-200 mg/kg)	sc	↓			Borgen *et al.* (1971)
	Cannabis extract	ip	↓			Fernandes *et al.* (1971)
	Δ^9THC (8 mg/kg)	po	↓	–		Manning *et al.* (1971)
	Δ^9THC (0.5-32 mg/kg)	*ip*	↓	–		Manning *et al.* (1971)
	Cannabis extract (0.15-15 mg/kg)	po	↓			Wetle and Sangstake (1971)
	Δ^9THC (1.0 mg/kg)	ip	↑	–	Small sample size	Glick and Milloy (1972)
	Δ^9THC (2.0 mg/kg)	ip	↓	↓		
	Cannabis extract (10 mg/kg)	*ip*	↓			Gonzalez *et al.* (1972)
	Δ^8THC (10 mg/kg)	ip	↓			Rating *et al.* (1972)
	Cannabis extract (10 mg/kg)	ip	–	–		Graham and Li (1973)
	Cannabis extract (50 mg/kg)	ip	↓	–	Tolerance development	Graham and Li (1973)
	Δ^9THC (1.2-5.0 mg/kg)	*ip*	–	↓		Järbe and Henriksson (1973)
	Δ^8THC (2.5-10.0 mg/kg)	ip	↓	↓		
	Δ^9THC (0.25-2.5 mg/kg)	iv		↓		Kilbey *et al.* (1973)

TABLE 1–Cont'd

Species	Drug and dosage	Route of administration	Effect on intake: Food	Effect on intake: Water	Comment	Reference
	Δ^9THC (5-25 mg/kg)	po	↓		Decrease in body weight	Nahas *et al.* (1973)
	Cannabis extract (5-25 mg/kg)	po	↓		Tolerance development to hypotensive effect but not to decrease in body weight	Nahas *et al.* (1973)
	Cannabis extract	po	↓		No systematic observations	Siemens (1973)
	Δ^9THC (2.5 mg/kg)	ip	–	↓	Body weight not changed	Sjöden *et al.* (1973)
	Δ^8THC (5 mg/kg)	ip	–	↓		Sjöden *et al.* (1973)
	±^{9}THC (225-3600 mg/kg)	po	↑	↑	Animals group housed. Data analysis unclear	Thompson *et al.* (1973)
	Δ^8THC (225-3600 mg/kg)	po	↑	↑	Despite increase in food and water intake, body weight decreased	Thompson *et al.* (1973)
	Cannabis extract (225-3600 mg/kg)	po	↑	↑		Thompson *et al.* (1973)
	Δ^9THC (0.25-0.75 mg/kg)	ip	↓	↓	No decrease in body weight	Wagner *et al.* (1973)
	Δ^9THC (5-80 mg/kg)	ip	↓	↓		Fernandes *et al.* (1974)
	Δ^9THC (110 mg/kg)	po	↑	↑		Gluck and Ferraro (1974)
	Δ^9THC	Smoke	↑	–	Animals group housed. Data analysis unclear	Rosenkrantz and Braude (1974)
	Δ^9THC (2.5, 5.0 mg/kg)	ip	↓	↓	No tolerance to anorexia	Sofia and Barry (1974)

Route of administration. The route by which a drug is administered could also conceivably account for the overall depression in food intake in animals given cannabis. Peritonitis has been reported in animals given Δ^9THC intraperitoneally (Manning, McDonough, Elsmore, Saller, and Sodetz, 1971), and several investigators have called attention to the apparent abdominal discomfort experienced by animals treated with cannabis (e.g., Carlini, Hamaoui, Bieniek, and Korte, 1970; Silva, Carlini, Claussen, and Korte, 1968). Thus, the anorexia associated with cannabinoid treatment in animals could conceivably be a result of abdominal distress rather than a specific central inhibitory effect on feeding mechanisms.

To test the possibility that the intraperitoneal route of administration was in some way contributing to Δ^9THC-induced anorexia, Manning and his colleagues (1971) administered Δ^9THC either by gavage (8 mg/kg) or intraperitoneally (4 mg/kg) while control animals received the vehicle by one of these two routes of drug administration. The treatment continued for 30 consecutive days during which the food and water intake, body weight, and feces weight were recorded.

The two drug groups did not differ from one another in food intake but both experienced a significant weight loss compared to controls during the first 4 days of drug treatment. Thereafter, body weight began to increase, albeit at an apparently slower rate (not analyzed) than for control subjects. Thirty days after drug treatment was discontinued, the body weights of the experimental animals were still significantly less than that of control animals, although weight gain per se was not apparently different (not analyzed). Analysis of food and water intake and feces weight indicated that the drug groups differed from controls only in food intake suggesting that the weight loss was previously due to the effects of the drug on food intake. Although all subjects receiving the drug by the intraperitoneal route developed peritonitis, the fact that animals receiving the drug orally also consumed less food indicates that the peritonitis associated with drug administration is not the main causative factor in the decrease in food intake in animals. In a subsequent study, these investigators repeated this experiment using doses of 0.5, 2.0, and 32 mg/kg and observed a similar effect on food intake even at the lowest dose of drug.

Other studies using the oral route of administration have also reported decreases in food intake (Marshall, 1898; Chopra and Chopra, 1939; Nahas *et al.*, 1973; Siemens, 1973; cf., however, Gluck and Ferraro, 1974). In addition, experimenters have reported decreases in food intake or body weight following administration of cannabis extract or its derivatives to animals intravenously (Grunfeld and Edery, 1969; Kilbey *et al.*, 1973), subcutaneously (Gerber and Schramm, 1969; Borgen *et al.*, 1971), or intramuscularly (Abel *et al.*, 1972; McMillan *et al.*, 1970). Interestingly, however, two recent studies have reported an increase in food intake in animals given cannabis via smoke

inhalation (Huy *et al.*, 1974; Rosenkrantz and Braude, 1974). However, because of methodological problems, these results are equivocal (see below). Nevertheless, the fact that smoke inhalation is the major route of administration in man, coupled with these reports of increased food intake in animals given cannabis by smoke inhalation, suggests that route of administration may indeed be a major factor accounting for the anorexic effects of cannabis in animals.

Vehicle considerations. Closely related to the problem of route of adiministration is that of drug vehicles. Since the cannabinoids are insoluble in water, various organic solvents or suitable suspending agents must be used. Some of the vehicles that have commonly been used in this regard are dimethyl sulfoxide, ethyl alcohol, propylene glycol, polyethylene glycol, Triton x-100, Tween-80, sesame oil, and sodium glycocholate. Although the cannabinoids readily go into solution or suspension in these solvents, the solvents themselves have various effects of their own which may act additively or synergistically with the cannabinoids. In humans to whom cannabis was administered orally, Perez-Reyes and his colleagues (Perez-Reyes, Lipton, Timmons, Wall, Brine, and Davis, 1973) found marked differences in the pleasantness attributed to a given amount of drug depending on the vehicle in which it was administered. Since smoking does not require the use of such vehicles, the differences in the effects of cannabis administered to humans or animals may be due to the fact that no vehicle is generally used in cannabis consumption by the former, whereas this is typically the case for the latter.

Fluid intake. Sjöden and his colleagues (Sjöden, Järbe, and Henriksson, 1973) have argued that the weight loss exhibited by animals treated with the cannabinoids is due primarily to a reduction in fluid intake and only secondarily to the consequent decrease in food consumption. The basis of this conclusion was a study in which rats were given (i.p.) either Δ^9THC (2.5 mg/kg), Δ^8THC (5 mg/kg), or vehicle alone for 19 consecutive days following which all animals received vehicle injections for 4 days more. The drug groups did not differ from controls in food intake, but did consume significantly less water than controls during drug and postdrug treatment. However, only the body weights of the animals receiving Δ^8THC were significantly lower than controls. The authors suggest that the results of their study indicate that the weight loss shown by animals receiving Δ^8THC was due to the reduction of fluid intake during testing. However, this argument was weakened by the fact that while the water intake of animals receiving Δ^9THC was also significantly reduced compared with controls, their body weights were not significantly depressed. Moreover, the use of different solvents for each treatment (polyethylene glycol-300 for Δ^8THC, propylene glycol for Δ^9THC, and 1:1 mixture of both for placebo animals, no volume data given) is rather questionable.

Järbe and Henriksson (1973) reported a similar decrease in fluid intake in rats that had previously been water-deprived for 22 hr. During the first 30

min postinjection a clear dose-dependent decrease in fluid intake for both Δ^9THC (1.25-5.0 mg/kg, ip) and Δ^8THC (2.5-10 mg/kg, ip) subjects relative to control animals was observed. This difference disappeared when animals were observed at 2.5, 4.5, 24, and 48 hr later. During the 2.5- and 4.5-hr postinjection periods, experimental animals began to drink more than controls, suggesting a disappearance of drug effect in these animals. Although there was no significant effect of Δ^9THC on food intake at any time period, Δ^8THC did produce a significant dose-dependent decrease in food intake and body weight by 24 hr postdrug treatment.

In discussing these results, Järbe and Henriksson again attribute the loss of body weight exhibited by Δ^8THC-treated animals to the drug's apparent effect on fluid intake. Although this may be true, it is possible that the results, obtained at 0.5 hr postdrug were primarily due to an effect of the drug on motor activity such that the animals did not approach the water bottles.

This same criticism can be leveled at the experiments reported by Kilbey, Forbes, and Olivetti (1973). These investigators examined the effects of Δ^9THC (0.25-2.5 mg/kg, iv) on 23-hr water-deprived rats. The injections were given 30 min before presentation of water. Analysis of the data indicated that water consumption was depressed at all drug doses compared with the control group.

In a second experiment, carbachol was administered to the area of the lateral hypothalamus via a cannula 1 hr prior to a 1-hr test period. Animals exhibiting a "substantial increase" in water consumption were then retested with combinations of Δ^9THC (1.25 mg/kg, iv) and centrally administered carbachol. Animals receiving Δ^9THC were found to drink less than animals receiving carbachol plus placebo. This result was interpreted as suggesting that peripheral administration of Δ^9THC blocked centrally induced drinking.

In a final experiment in this series, Δ^9THC (30 μg in 5% propylene glycol) was injected directly into the lateral hypothalamus and its effects on deprivation-induced drinking were compared with that of placebo and atropine (80 μg). Water consumption was measured at 15 min and again at 60 min following drug treatment. Both atropine and Δ^9THC were found to depress water consumption significantly at 15 min compared to baseline levels of water intake collected during the 6 days prior to testing. However, at the 60-min period, only the atropine differences were still significant.

The authors concluded from these studies that acute administration of Δ^9THC depresses deprivation- and carbacol-induced drinking. However, because of the depressant characteristics of the drug and the short time period in which behavior was assessed, these data and conclusions are not convincing in light of the lack of information regarding the activity of the animals during the test periods. In short, it is possible that the observed effects were due to motor inhibition or general malaise rather than to any anti-cholinergic properties of the drug.

Wayner, Greenberg, Fraley, and Fisher (1973) examined the effects of Δ^9THC (0.25-0.75 mg/kg, ip) on water consumption of rats under different circumstances. Using the schedule-induced polydipsia phenomenon as their experimental model, these investigators found a rather variable effect of Δ^9THC such that one type of adjunctive behavior, licking the water tube in conjunction with bar pressing for food reward, was either increased or not affected by drug treatment. In the home cage, however, both food and water intake were reported as being depressed on the day Δ^9THC (0.375 mg/kg, ip) was administered and for the next 2 days thereafter. The depression of food and water intake appeared relatively minor and interestingly, mean body weights continued to increase over predrug levels. However, no statistical evaluation of these data was presented so that the significance of these observations is difficult to assess.

There are data, however, suggesting that Δ^9THC does affect salivary flow in animals, but these data suggest an effect opposite to that reported in the previous studies. Cavero, Buckley, and Jandhyala (1972) electrically stimulated the chorda tympani of dogs for 30 sec and weighed the amount of saliva secreted from the submaxillary duct before and after administration of Δ^9THC (2.5 mg/kg, iv). The effects of Δ^9THC on carbacol-induced salivation were also examined in the same preparation. Although Δ^9THC markedly inhibited salivary output following electrical stimulation, carbacol-induced salivation was not affected (cf. however, Gill, Paton, and Pertwee, 1970). A similar inability of Δ^9THC (1.3 and 13.0 mg/kg, iv) to affect pilocarpine-induced secretions has also been reported in the rat by Nagle, DiGregoria, and Chernick (1974).

In terms of hunger, a decrease in salivation ought to reduce desire for food since most organisms eat less when deprived of water (Adolph, 1947; cf. Grossman, 1967). The sensation of dry mouth following cannabis has been frequently reported in humans (cf. Ludlow, 1857; Baudelaire, 1859; Marshall, 1898; Walton, 1938; Allentuck and Bowman, 1942; Hollister, 1970; Halikas *et al.*, 1971). However, animals treated with this compound or its homologs either do not increase their fluid consumption (Abel and Schiff, 1969; Manning *et al.*, 1971) or drink less water (see above) than do vehicle treated animals. In any case, one would expect the desire for food to be reduced if a subject experiences dryness of the mouth.

Another observation suggesting that cannabis ought to increase rather than decrease fluid intake is that there is a marked increase in urine output following use of cannabis (Ames, 1958; Beaconsfield, Ginsburg, and Rainsburg, 1972). Thus, decrease in fluid balance might be expected to result in an increase in fluid intake.

In summary, the various studies dealing with the effects of Δ^9THC and Δ^8THC on water consumption warrant attention as a possible explanation of

the anorexic effect of these drugs. However, methodological problems inherent in the design of the various studies in this area render the point concerning the drug's effects on water consumption less than conclusive.

Before leaving this problem, a recent study by Leite and Carlini (1974) should also be mentioned. These experimenters found that rats that have marihuana (1.0 mg/ml) placed in their drinking water and are thus forced to ingest this substance orally, drink less of this fluid and as a result, they gain less weight than do control animals. No evidence of tolerance to this effect was observable despite 18 weeks of treatment. At the end of the experiment, when subjects were allowed to drink control solutions ad lib., they began to gain weight.

General malaise and conditioned taste aversions. Because of the general malaise that the cannabinoids typically produce in animals, depression of behavior tends to be the predominant effect of these drugs on animals. As a result of behavioral depression, food intake in the animal is diminished, although the same physiological changes that are responsible for the increased sense of hunger in the human may still be present.

In addition to sedation, the possibility also exists that at the doses given to animals the decrease in the consummatory behavior of rats following treatment with Δ^9THC may be due to aversive internal states produced by the drug which are associated with gustatory cues. Numerous studies have previously shown that rats will avoid novel-tasting food or fluids that are followed by illness, even if the illness occurs as long as 8 hr postingestion. Such an aversion has been shown for apomorphine, metamphetamine, X-radiation, and various anesthetics (Garcia and Ervin, 1968; Revusky, 1968). The association between Δ^9THC and food, it has been suggested, likewise results in a "conditioned taste aversion" such that the animal refuses to accept previously palatable food or fluids.

In a reported study by Elsmore and Fletcher (1972) designed to test this hypothesis, previously water-deprived rats were given brief access to a 0.1% solution of saccharin in tap water instead of plain water during a 1-hr watering period. Immediately following this exposure, the animals were injected either orally or intraperitoneally with various doses of Δ^9THC (0.25, 1.0, 2, 4, 8, or 32 mg/kg) or vehicle. The next day, water was again the only fluid available for the 1-hr watering period. On the second day postinjection, the rats were presented with two drinking tubes, one containing water and the other containing saccharin solution, and the amount ingested during the test period was determined.

Examination of the data indicated that there was a significant decrease in the amount of saccharin consumed by animals that had previously received Δ^9THC although rats normally prefer this substance over water. The aversion for saccharin was not related to route of administration since there were no

significant differences between animals given the drug orally or ip. However, the aversion was clearly related to dose; the higher the amount of drug received, the less saccharin solution consumed.

One difficulty with this explanation, however, is that the data upon which this hypothesis rests involves pairing cannabis with novel testing substances such as saccharin, whereas most of the experimental results in animals have looked at the effects of this drug on consumption of familiar lab food and water. Whether this explanation extends to familiar gustatory cues is thus a moot point and has not been dealt with unequivocally thus far.

Inhibition of alimentary motility. The effects of cannabis on alimentary tract activity should also be mentioned. Although there are some reports both of diarrhea occurring in rats, mice, and dogs (Loewe, 1944, 1946; Miras, 1965) and relaxation of the ileum occurring in anesthetized cats given cannabis extract or DMHP (Dagirmanjian and Boyd, 1962), Dewey and co-workers (Dewey, Harris, and Kennedy, 1972) and Chesher and his group (Chesher, Everingham, Jackson, Marchant-Williams, and Starmer, 1973) have reported a depression of intestinal motility (passage of charcoal meal) in mice given Δ^9THC, Δ^8THC, or cannabis extract. However, in this regard, the potency of these substances was observed to be much less than that of morphine. Anderson, Jackson, and Chesher (1974) corroborated these findings and also demonstrated that while cannabinol (10 mg/kg) itself had no effect on intestinal motility in mice, the combination of Δ^9THC (10 mg/kg) plus cannabinol (10 mg/kg) had a greater depressant effect than Δ^9THC alone, exceeding that of 20 mg/kg Δ^9THC. These findings suggest that the effects of crude cannabis on intestinal motility are influenced not only by its Δ^9THC content but by the ratio of the cannabinoids it contains. Clinical reports of diarrhea, abdominal cramps, and weight loss have been reported in individuals chronically smoking large amounts of cannabis for long periods of time (Tennant, Preble, Pendergast, and Ventry, 1971; cf. also King and Cowen, 1969). Nausea and vomitting following the use of cannabis which was severe enough to warrant hospitalization has also been reported (Baker and Lukas, 1969).

With respect to *in vitro* studies using the guinea pig ileum preparation, Layman and Milton (1971) found the Δ^9THC blocked the response of the ileum to acetycholine whereas Gill, Paton, and Pertwee (1970) found no such inhibition. In fact, in some cases, they observed potentiation. Dewey *et al.* (1972) reported that Δ^9THC and Δ^8THC were both very weak inhibitors in this respect. More recently, Gascon and Péres (1973) observed a biphasic effect of Δ^8THC on the contraction of the guinea- pig ileum which was characterized by a brief potentiation followed by inhibition. It would thus appear that the effect of cannabis and its derivatives on alimentary activity is still unsettled.

Changes in blood glucose. In addition to these possibilities, there are also a number of peripheral somatic changes associated with cannabis that must also be considered in the present context.

A number of investigators have examined blood sugar levels before and after cannabis administration to humans and animals to determine if cannabis lowers blood sugar concentration. The rationale for these studies is a body of clinical and experimental literature showing that decreases in blood sugar levels which occur spontaneously or after treatment with insulin are often accompanied by sensations of hunger, improvement in appetite, and weight gain (Short, 1929; MacKay, Calloway, and Barnes, 1940) whereas increases in blood glucose levels as a consequence of intravenous injections of glucose or epinephrine (which causes the release of glucose into the blood from the liver) result in diminution of feelings of hunger and a reduction in food intake (Mayer and Bates, 1952; Stunkard and Wolf, 1954). These results have led to the formulation of Mayer's (1953, 1955) glucostatic theory of hunger which states that receptors in the central nervous system monitor the rate of glucose utilization rates by the cells of the body and that low utilization rates (i.e., a decrease in uptake of glucose by the cells) initiate neural impulses which result in sensation of hunger, whereas high utilization rates inhibit the activity of the glucose receptors and this translates into a feeling of satiety. The actual rate in utilization of glucose by the cells of the body, Mayer, suggests, can be determined on the basis of A-V glucose utilization, i.e., the difference between blood glucose concentration in the arteries that supply the brain and the veins which carry blood away from that organ.

Working with this theoretical framework, most investigators have reported that regardless of route of administration (smoking or oral) or whether subjects were fasted or not, cannabis does not significantly lower blood sugar levels (Ames, 1958; Beaconsfield, Rainsburg, and Ginsburg, 1972; Dornbush, Fink, and Freedman, 1971; Hollister, 1971; Hollister, Richards, and Gillespie, 1968; Lukas and Temple, 1974; Miras, 1965; Papadakis, Michael, Kephalas, and Miras, 1974; Weil, Zinberg, and Nelson, 1968; cf., however, Marx and Eckhardt, 1933). On the contrary, a number of investigators have actually observed an increase in blood sugar content following marihuana or pyrahexyl (Mayor's Committee, 1944; Dahi, 1951; El-Sourogy, Malek, Ibrahim, Farag, and El-Shitry, 1966; Paton and Temple, 1971; cf. also Hughes, Steahly, and Bier, 1970; King and Cowen, 1969; King, Pechet, and Pechet, 1970; Lockhart and Desser, 1970). Alteration of the glucose tolerance curve has been observed by several investigators (Padolsky, Pattovina, and Amaral, 1972; Hollister and Reaven, 1974), but exceptions have also been noted (Lukas and Temple, 1974). These observations would seemingly invalidate blood glucose changes as a factor underlying the mechanism of cannabis' effect on hunger in humans. However, the increased levels of blood glucose could account for the decreases in food intake observed in animals. If cannabis alters the cellular utilization of glucose such that there is increased activity in the "satiety center" (e.g., ventromedial hypothalamus) of the brain, impulses from this area might then inhibit activity in the "hunger centers" (e.g., ventrolateral hypothalamus) resulting in diminished food intake. In light of the possibility that specific

areas of the hypothalamus may be involved in the mediation of cannabis' effect on food consumption, studies of the effects of this drug in combination with animals bearing ventromedial hypothalamic lesions ought to prove of interest.

Changes in body temperature. Yet another possible factor underlying the increased desire for food following the use of marihuana is the decrease in deep body temperature produced by this drug. This effect has been observed in various species of animals given cannabis or its derivatives (Miras, 1965; Garattini, 1965; Holtman, Lovell, Jaffee, and Freedman, 1969; Gill, Paton, and Pertwee, 1970; Haavik and Hardman, 1973a, 1973b; Lomax, 1971, Kalmakçalan and Deneau, 1972; Abel, 1972; Abel *et al.*, 1972) and in humans (Isbell, Gorodetzsky, Jasinski, Claussen, von Spulak, and Korte, 1967; Waskow, Olsson, Salzman, and Katz, 1970; Dittrich and Woggen, 1973; Hosko, Kochar, and Wang, 1973; cf., however, Hollister *et al.*, 1968). The basis of this admittedly speculative possibility is Brobeck's (1947-48, 1957) thermoregulatory hunger hypothesis which holds that animals eat to keep warm. In light of the decrease in body temperature produced by marihuana, the desire for food may stem in part from neural impulses signaling a need to increase body temperature. In man, peripheral vasodilation occurs following the use of marihuana, an effect which is accompanied by an increase in cutaneous toe temperature (Beaconsfield *et al.*, 1972). In this regard, it is interesting to note that changes in cutaneous vasodilation and peripheral skin temperature have been associated with satiety rather than hunger (Booth and Strong, 1936). The effects of cannabis on body temperature thus cannot account for the changes in feeding behavior that have been reported.

Neurochemical changes. Still another possibility is that marihuana produces changes in the biochemistry of putative neurotransmitters that mediate eating behavior. Grossman (1960, 1962) has shown that placement of norepinephrine directly into the lateral hypothalamus of rats results in voracious and prolonged eating in these animals. Changes in the levels and turnover of norepinephrine in the brains of animals have often been reported following administration of cannabis, although this effect appears highly variable. For example, a lowering in brain norepinephrine or increased turnover has been reported by some investigators (Holtzman *et al.*, 1969; Schildkraut and Efron, 1971; Ho, Taylor, Englert, and McIssac, 1971; Abel, 1972), whereas an increase in levels or decrease in turnover has been reported by others (Holtzman *et al.*, 1969; Constantinidis and Miras, 1971; Truitt and Anderson, 1971), and no changes have been reported by still others (Maitre, Staehelin, and Bein, 1970; Welch, Welch, Messiha, and Berger, 1971) so that the relationship among cannabis, brain norepinephrine, and eating is far from clear.

Tolerance development. A number of investigators have also examined the effects of chronic administration of the cannabinoids to determine whether tolerance develops to its anorexic effects.

In an early study, Abel and Schiff (1969) administered the marihuana homolog, pyrahexyl, (15 mg/kg, ip) to rats for 6 days. Food and water intake, as well as body weights, were recorded on every second day. A decrease in both food intake and body weight occurred following treatment although water consumption was not affected by the treatment. No evidence of tolerance to these effects was observable. On the contrary, both food intake and body weight continued to decrease with testing. Similar results using Δ^9THC (2.5, 5.0 mg/kg, ip) have recently been reported in the rat by Sofia and Barry (1974).

Nahas and his colleagues (Nahas, Schwartz, Adamec, and Manger, 1973) administered Δ^9THC (5-25 mg/kg) orally to rats, and the animals were weighed daily. Measurements were also made of blood pressure and heart rate response following drug administration. Although there was evidence of tolerance to the effects on blood pressure by the second day of treatment, body weight continued to fall during the 7 days of drug treatment. In a second experiment, rats were given a marihuana extract containing 5-25 mg of Δ^9THC (oral) for 3 days and were then weighed daily after the drug was discontinued. Weight gain under these conditions was still depressed for several days despite termination of drug treatment. The data thus indicate that although tolerance developed to some of the effects of the drug, weight loss still persisted, indicating an absence of tolerance. However, no records were kept of food or water intake, nor was there any information given as to housing conditions so that the reason for the changes in body weight cannot be determined.

There are a number of reports, however, in which food intake did resume following a period of drug administration (e.g., Manning *et al.*, 1971; Gerber and Schramm, 1969; Fernandes, Rating, and Klune, 1971; Graham and Li, 1973; Abel, McMillan, and Harris, 1972; Abel, Cooper, and Harris, 1974; Rating, Broermann, Honecker, Klune, and Coper, 1972; Thompson, Rosenkrantz, Shaeppi, and Braude, 1973), although animals receiving drug did not exhibit any signs of "catch-up" growth, i.e., they did not attain the same body weight as control subjects.

In a study conducted by Siemens (1973), rats were chronically administered with a cannabis extract (5 mg/kg, oral) and were observed to lose weight for the first 6 days after which they began to gain weight at a rate that was not significantly different from that of control animals as determined by linear regression analysis (Siemens, personal communication). Increasing the dose at days 11 (7.5 mg/kg) and 21 (10 mg/kg) had no subsequent effect on weight gain. Unfortunately, no records were kept of food or water intake so that the basis for the initial weight loss could not be identified.

Increases in food intake and/or body weight. A number of reports have now begun to appear in the literature describing increases in food intake on the part of animals given Δ^9THC. However, methodological problems inherent in these studies render the interpretation of these data equivocal.

Glick and Milloy (1972) reported that female rats given 1.0 mg/kg Δ^9THC consumed significantly more food in a 2-hr period than control subjects when the drug was administered (ip) after a previous period of food deprivation (24 hr). Water intake was not affected at this dose. Since the number of animals per group was rather small ($N = 4$) and pretreatment body weights or food intake were not determined, it is possible that the drug itself may not have had any effect on food consumption at the low dose but that inherent differences between the control and 1.0 mg/kg groups were responsible for the test differences. At a dose of 2.0 mg/kg, food and water intake were both reduced. The effects of the higher dose of drug can readily be attributed to depression of motor activity.

Hypothesizing that Δ^9THC may have an anorexic effect only in animals that have not been food deprived, Gluck and Ferraro (1974) first adapted male rats to 23-hr food or water deprivation for 150 days prior to drug administration. Following this period, rats were given Δ^9THC (1.0 mg/kg, po) or vehicle immediately after the 1-hr access to either food or water for 12 days. On the 13th day, animals were given Δ^9THC (1.0 mg/kg, po) 2 hr before the 1-hr access to food or water for 12 days more. The changes in food and water intake during the second phase were then compared with the first phase of drug treatment for the 1-hr food and watering period. Although there was a marked increase in both food and water intake in the second phase compared to the first on the part of drug-treated subjects, this was also true for subjects receiving the vehicle only. Apparently, no analysis was made of the intragroup differences in food and water intake, but inspection of the data suggest that the drug *per se* had no effect on either measure. These results thus do not suggest that the anorexia seen in animals given cannabis is related in some way to their previous histories of food deprivation.

An interesting study of the effects of cannabis on food intake and body weight of dogs was recently reported by Huy, Gailes, and Roy (1974). One group of dogs was exposed to the smoke from marihuana cigarettes over a 3-month period. One group of control animals inhaled smoke containing nicotine. Another control group received no drug treatment. At the conclusion of the test period, the growth of the dogs smoking marihuana was decreased by 57% despite the fact that their food consumption was increased by 28% relative to dogs not receiving any treatment. The dogs in the nicotine group ate much less than the latter but did not manifest any significant depression in growth. Because of the absence of a group inhaling the smoke of cigarettes from which the cannabinoids had been removed, the effects of Δ^9THC on food intake and body weight can only be regarded as suggestive.

An increase in food intake on the part of male and female rats chronically exposed to smoke containing Δ^9THC (for 5 days) has also been observed by Rosenkrantz and Braude (1974). This increase in food consumption declined after drug treatment. No consistent changes in water consumption were observed during the period. In a second study lasting 23 days, food

intake was initially decreased in both male and female rats. However, by day 29, the decrease in food intake were no longer present. Water consumption was also reported to be depressed, but by day 19, this effect was no longer present.

It should be noted, however, that animals were housed in groups in these studies, and no information was given as to whether these effects were calculated on the basis of each cage of animals or on individual changes in food and water which would not be possible under group housing conditions.

In a study reported by Thompson, Mason, Rosenkrantz, and Braude (1973), rats were chronically treated with Δ^9THC or Δ^8THC (50-500 mg/kg per day, po) or cannabis extract (15-1500 mg/kg per day, po) for 119 days. Growth rate was depressed with all three compounds for the first 28 days but remained relatively similar thereafter to vehicle-treated subjects. Despite the depression of growth rate, however, food and water consumption were reported to be greater in drug-treated animals compared to controls. However, animals were housed "2 or 3 per galvinized steel cage" so that the means of calculating food and water intake are questionable.

SUMMARY, CONCLUSIONS, AND IMPLICATIONS

In summary, it appears that the stimulating effect of cannabis on hunger may be peculiarly human in nature since, with few exceptions, it does not occur in animals. Of the various explanations that have been proposed to account for this difference between lower animals and humans, none is completely able to account for this difference. Before any final conclusions can be stated regarding the effects of cannabis in humans, however, much more work must be devoted to the study of dose-response effects and to the effects of chronic treatment with this substance.

The role of suggestions would seem to be particularly relevant in this area since it is possible that many of the reported effects in humans may be due to social factors associated with drug use rather than to physiological effects produced by the drug. While sensations produced by a drug such as marihuana may alert the user to changes occurring within his body, the meaning that is attached to these sensations is often a function of prior beliefs concerning what that particular drug is supposed to do. This may then set in motion a kind of self-fulfilling prophesy. Believing that marihuana makes one hungry, and feeling certain vague changes within one's body, these sensations may be labeled as hunger. Hollister (1971) suggests that one of the reasons human subjects report being hungry following marihuana usage is that the drug is usually taken in social settings. As a result, some members of the group who experience vague internal changes label these sensations as hunger owing to the suggestion of other members of the group. Until there is definite evidence that marihuana does stimulate hunger for food in humans, the

relationship between marihuana and the desire for food in the human cannot be freed from what has aptly been called "drug mystification" (cf. Lennard, Epstein, Bernstein, and Random, 1971). However, prior to attributing the difference in the effects of cannabis on food intake between humans and animals to environmental factors, the basic question of unique species differences in physiological response to the drug must be eliminated as a possibility. For instance, although the cannabinoids produce bradycardia in all animals that have been studied (see review by Cavero, Solomon, Buckley, and Jandhyala, 1973), they produce tachycardia in man (e.g., Isbell *et al.*, 1967; Johnson and Domino, 1971).

The conclusion that cannabis reduces food intake in animals raises the important question of using food as a reinforcer. As pointed out by Järbe and Henriksson (1973) and Manning and co-workers (1971), a decrease in the reward properties of the reinforcement being offered an animal would result in an associated decrease in its motivation. This could then be expected to affect its performance adversely in various situations in which the inducement for a correct response is food, e.g., the resumption of bar pressing or key pecking in operant situations using food as the reinforcer. The fact that animals resume bar pressing or key pecking but do not resume eating suggests that the tolerance observed in the operant situation is behavioral rather than pharmacological in nature (Manning *et al.*, 1971). However, the development of tolerance to the anorexic effect of cannabis in animals is not seen consistently.

Although food intake is initially depressed resulting in a consequent decrease in body weight, it appears from some of the animal data that after the initial period of weight loss, animals given cannabis begin to increase in body weight at a rate that is similar to that of control subjects. The proper test for tolerance in this situation would thus seem to involve a comparison of the rates of growth or food intake of drug-and-placebo-treated animals after the initial period of anorexia.

At present, there would thus appear to be more questions than answers surrounding the problem of cannabis' effect on hunger in both animals and humans. Whatever the ultimate explanation, it would seem that present animal models have not elucidated the problem of cannabis-induced hunger in humans.

REFERENCES

Abel, E. L. (1971). Effects of marihuana on the solution of anagrams, memory and appetite. *Nature (London)* **231**, 260.

Abel, E. L. (1972). Comparative effects of Δ^9THC on thermoregulation. *In* W. D. M. Paton and J. Crown (Eds.), "Cannabis and Its Derivatives," pp. 120-141, London, Oxford Press.

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

Abel, E. L., McMillan, D. E., and Harris, L. S. (1972). Tolerance to the behavioral and hypothermic effects of 1-Δ^9tetrahydrocannabinol in neonatal chicks. *Experientia* **28**, 1188.

Abel, E. L., Cooper, C. W., and Harris, L. S. (1974). Effects of Δ^9-tetrahydrocannabinol on body weight and brain electrolytes in the chicken. *Psychopharmacology* **35**, 335-339.

Abel, E. L. (1974). "Drugs and Behavior." New York, J. Wiley.

Adams, R. (1941-1942). Marihuana. *Harv. Lect.* **37**, 169-195.

Adolph, E. F. (1947). Water metabolism. *Ann. Rev. Physiol.* **9**, 381-408.

Allentuck, S., and Bowman, K. (1942). Psychiatric aspects of marihuana intoxication. *Amer. J. Psychiat.* **99**, 248-251.

Ames, F. (1958). A clinical and metabolic study of acute intoxication with cannabis sativa and its role in the model psychosis. *J. Ment. Sci.* **104**, 972-999.

Anderson, P. F., Jackson, D. M., and Chesher, G. B. (1974). Interaction of Δ^9-tetrahydrocannabinol and cannabidiol on intestinal motility in mice. *J. Pharm. Pharmacol.* **26**, 136-137.

Baker, A. A., and Lucas, E. G. (1969). Some hospital admissions associated with cannabis. *Lancet* **1**, 148.

Baudelaire, C. (1859). Les Paradis Artificiels. Translation and reprint *In* P. Quennell (Ed.) (1956), "The Essence of Laughter." New York: World Publishing Company.

Beaconsfield, P., Ginsburg, J., and Rainsburg, R. (1972). Marihuana smoking: Cardiovascular effects in man and possible mechanisms. *N. Engl. J. Med.* **287**, 209-212.

Booth, G., and Strong, J. M. (1936). Changes in temperature of the skin following the ingestion of food. *Arch. Int. Med.* **57**, 533-543.

Borgen, L. A., Davis, W. M., and Pace, H. B. (1971). Effects of synthetic Δ^9-tetrahydrocannabinol on pregnancy and offspring in the rat. *Toxicol. Appl. Pharmacol.* **20**, 480-486.

Bose, B. C., Saifi, A. Q., and Bhagwat, A. W. (1964). Observations on the pharmacological actions of cannabis indica. Part II. *Arch. Intern. Pharmacodyn. Ther.*, **147**, 285-290.

Bouquet, J. (1951). Cannabis. *Bull. Narc.* **3**, 22-45.

Brobeck, J. R. (1947-1948). Food intake as a mechanism of temperature regulation. *Yale J. Biol. Med.* **20**, 545-552.

Brobeck, J. R. (1957). Neural control of hunger, appetite, and satiety. *Yale J. Biol. Med.* **29**, 565-574.

Brodie, B. B. and Reed, W. D. (1971). The value of determining the plasma concentration of drugs in animals and men. *In* B. N. LaDu, H. G. Mandel, and E. L. Way (Eds.), "Fundamentals of Drug Metabolism and Drug Disposition." Baltimore: Williams and Williams.

Carlini, E. A., Hamaoui, A., Bieniek, D., and Korte, F. (1970a). Effects of (-)-Δ^9-trans-tetrahydrocannabinol and synthetic derivative on maze performance of rats. *Pharmacology* **4**, 359-368.

Carlini, E. A., and Kramer, C. (1965). Effect of *Cannabis sativa* (marihuana) on maze performance of the rat. *Psychopharmacology* **7**, 175-181.

Carlini, E. A., Masur, J., Karniol, I. G., and Leite, J. R. (1972). *Cannabis sativa:* Is it possible to consider behavioral animal data as experimental models for some effects on humans? *In* W. D. M. Paton and J. Crown (Eds.), "Cannabis and its Derivatives," pp. 154-175, London: Oxford Univ. Press.

Cavero, I., Buckley, J., and Jandhyala, B. (1972). Parasympatholytic activity of (-)-Δ^9-trans-tetrahydrocannabinol in mongrel dogs. *Eur. J. Pharmacol.* **19**, 301-304.

Cavero, I., Solomon, T., Buckley, J. P., and Jandhyala, B. S. (1973). Studies on the bradycardia induced by (-)-Δ^9-trans-tetrahydrocannabinol in anesthetized dogs. *Eur. J. Pharmacol.* **22**, 263-269.

Chesher, G. B., Everingham, M., Jackson, D. M., Marchant-Williams, H., and Starmer, G. A. (1973). The effect of cannabinoids on intestinal motility and their antinociceptive effect in mice. *Brit. J. Pharmacol.* **49**, 588-594.

Chopra, R. N., and Chopra, G. S. (1939). The present position of hemp-drug addiction in India. *Ind. Med. Res. Mem.* **31**, 1-119.

Constantinidis, J., and Miras, C. J. (1971). Effect of hashish smoke sublimate on hypothalamic nor-adrenaline studied by the fluorescence method. *Psychopharmacology* **22**, 80-90.

Corcoran, M. E. (1973). Role of drug novelty and metabolism in the aversive effects of hashish injections in rats. *Life Sci.* **12**, 63-72.

Corcoran, M. E., Bolotow, I., Amit, Z., and McLaughlan, J. A. (1974). Conditioned taste aversions produced by active and inactive cannabinoids. *Pharmacol. Biochem. Behav.* **2**, 725-728.

Dagirmanjian, R., and Boyd, F. S. (1962). Some pharmacological effects of two tetrahydrocannabinols. *J. Pharmacol. Exper. Ther.* **135**, 25-33.

Dahi, M. A. Y. (1951). Mechanism of action of synthetic tetrahydrocannabinol (parahexyl). *Fed. Proc.* **10**, 290-329.

Desser, K. B. (1970). Effects of "Speed and Pot" on the juvenile diabetic. *JAMA* **214**, (no. 11), 2065.

Dewey, W. L., Harris, L. S., and Kennedy, J. S. (1972). Some pharmacological and toxicological effects of 1-trans-Δ^8- and 1-trans-Δ^9 tetrahydrocannabinol in laboratory rodents. *Arch. Intern. Pharmacodyn. Ther.* **196**, 133-145.

Dewey, W. L., Jenkins, J., O'Rourke, T., and Harris, L. S. (1972). The effects of chronic administration of trans-Δ^9-tetrahydrocannabinol on behavior and the cardiovascular system of dogs. *Arch. Int. Pharmacodyn. Ther.* **198**, 118-131.

Dittrich, A., and Woggon, B. (1973). Experimental studies with Δ^9-tetrahydrocannabinol in volunteers-subjective syndromes, physiological changes and after-effects. *In* T. A. Ban (Ed.), "Psychopharmacology, Sexual Disorders and Drug Abuse," pp. 701-702. London: North-Holland Pub. Co.

Dornbush, R. L., Fink, M., and Freedman, A. M. (1971). Marihuana, memory and perception. *Amer. J. Psych.* **128**, 194-197.

Elsmore, T. F., and Fletcher, G. U. (1972). Δ^9-Tetrahydrocannabinol: Aversive effects in rats at high doses. *Science* **175**, 911-912.

El-Sourogy, M., Malek, A. Y., Ibrahim, H. H., Farag, A., and El-Shitry, A. (1966). The effects of *Cannabis indica* on carbohydrate metabolism in rabbits. *J. Egypt. Med. Ass.* **49**, 626-628.

Fernandes, M., Rating, D., and Klume, S. (1971). The influence of subchronic tetrahydrocannabinol and cannabis treatment on Food- and water-intake, body weight and body temperature of rats. *Acta. Pharmacol. Toxicol.* **29**, 89.

Fernandes, M., Warning, N., Christ, W., and Hill, R. (1973). Interactions of several cannabinoids with the hepatic drug metabolizing system. *Biochem. Pharmacol.* **22**, 2981-2987.

Fernandes, M., Schabarek, A., Caper, H., and Hill, R. (1974). Modification of Δ^9-THC actions by cannabinol and cannabidiol in the rat. *Psychopharmacology* **38**, 329-332.

Forney, R. B., and Kiplinger, G. F. (1971). Toxicology and pharmacology of marihuana. *Ann. N.Y. Acad. Sci.* **191**, 74-82.

Garcia, J., and Ervin, F. R. (1968). Appetites, aversions, and addictions: A model for visceral memory. *Rec. Advan. Biol. Psychiat.* **10**, 284-293.

Garattini, S. (1965). Effects of a cannabis extract on gross behavior. *In* "Hashish: Its Chemistry and Pharmacology," pp. 71-79. London: Ciba Foundation Study Group.

Gascon, A. L., and Pérès, M. T. (1973). Effect of Δ^9- and Δ^8-tetrahydrocannabiol on the peripheral autonomic nervous system *in Vitro*. *Can. J. Physiol.* **51**, 12-21.

Gerber, W. F., and Schramm, L. C. (1969). Effect of marihuana extract on fetal hamsters and rabbits. *Toxicol. Appl. Pharmacol.* **14**, 276-282.

Gill, E. W., Paton, W. D. M., and Pertwee, R. G. (1970). Preliminary experiments on the chemistry and pharmacology of cannabis. *Nature (London)* **228**, 134-136.

Glick, S. D., and Milloy, S. (1972). Increased and decreased eating following THC administration. *Psychon. Sci.* **29**, 6.

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

Gonzalez, S. C., Karniol, I. G., and Carlini, E. A. (1972). Effects of *Cannabis sativa* on conditioned fear. *Behav. Biol.* 7, 83-94.

Graham, J. D. P., and Li, D. M. F. (1973). Cardiovascular and respiratory effects of cannabis in cat and rat. *Brit. J. Pharmacol.* 49, 1-10.

Grossman, S. P. (1960). Eating or drinking elicited by direct adrenergic of cholinergic stimulation of hypothalamus. *Science* **132**, 301-302.

Grossman, S. P. (1962). Direct adrenergic and cholinergic stimulation of hypothalamus mechanisms. *Amer. J. Physiol.* **202**, 872-882.

Grossman, S. P. (1967). "A Textbook of Physiological Psychology," pp. 436-437. NY: J. Wiley.

Grunfeld, Y., and Edery, H. (1969). Psychopharmacological activity of the active constituents of hashish and some related cannabinols. *Psychopharmacology* **14**, 200-210.

Haavik, C. O., and Hardman, H. G. (1973). Hypothermic action of Δ^9-tetrahydrocannabinol, 11-hydroxy-Δ^9-tetrahydrocannabinol and 11-hydroxy-Δ^8-tetrahydrocannabinol in Mice. *Life Sci.* **13**, 1771-1778.

Haines, L., and Green, W. (1970). Marihuana use patterns. *Brit. J. Addict.* **65**, 347-362.

Halikas, J. A., Goodwin, D. W., and Guze, S. B. (1971). Marihuana effects. A survey of regular users. *JAMA* **217**, 692-694.

Hare, H. A. (1887). Clinical and physiological notes on the action of *Cannabis indica*. *Ther. Gaz.* 2, 225-228.

Ho, B. T., Taylor, D., Englert, L. F., and McIssac, W. M. (1971). Neurochemical effects of 1-Δ^9-tetrahydrocannabinol in rats following repeated inhalation. *Brain Res.* **31**, 233-236.

Hockman, C. H., Perrin, R. G., and Kalant, H. (1971). Electroencephalographic and behavioral alterations produced by Δ^1-tetrahydrocannabinol. *Science* **172**, 968-970.

Hollister, L. E. (1970). Tetrahydrocannabinol isomers and homologues: Contrasted effects of smoking. *Nature (London)* **227**, 968-969.

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

Hollister, L. E., and Reaven, G. M. (1974). Delta-9-tetrahydrocannabinol and glucose tolerance. *Clin. Pharmacol. Ther.* **16**, 297-302.

Hollister, L. E., Richards, R. K., and Gillespie, H. K. (1968). Comparison of tetrahydrocannabinol and synhexyl in man. *Clin. Pharmacol. Ther.* 9, 783-791.

Holtzman, D., Lovell, R. A., Jaffe, J. H., and Freedman, D. X. (1969). 1-Δ^9-Tetrahydrocannabinol: Neurochemical and behavioral effects in the mouse. *Science* **163**, 1464-1467.

Hosko, M. H., Kochar, M. S., and Wang, R. I. H. (1973). Effects of orally administered delta-9-tetrahydrocannabinol in man. *Clin. Pharmacol. Ther.* **14**, 344-352.

Hughes, J. E., Steahly, L. P., and Bier, M. M. (1970). Marihuana and the diabetic coma. *JAMA* **214**, 1113-1114.

Huy, N. D., Gailes, L., and Roy, P. E. (1974). Effets après trois mois de l'inhalation de marihuana et de tabac chez le chien. *L'Un. Med. Canad.* **103**, 65-71.

Indian Hemp Drugs Commission (1893-1894). "Marihuana," (1972). Maryland: Silver Springs, Thomas Jefferson Publishing Company.

Isbell, H., Gorodetzsky, C. E., Jasinski, D., Claussen, V., Von Spulak, F., and Korte, F. (1967). Effects of (-) delta-9-transtetrahydrocannabiol in man. *Psychopharmacology* **11**, 184-188.

Järbe, T. U. C., and Henriksson, B. G. (1973). Influence of tetrahydrocannabinols (Δ^8-THC and Δ^9-THC) on body weight, food, and water intake in rats. *Pharmacol. Biochem. Behav.* **1**, 395-399.

Järbe, T. U. C., and Henriksson, B. G. (1973). Acute effects of two tetrahydrocannabinols (Δ^9-THC and Δ^8-THC) on water intake in water deprived rats: Implications for behavioral studies on marijuana compounds. *Psychopharmacology* **30**, 315-322.

Jasinski, D. R., Haertzen, C. A., and Isbell, H. (1971). Review of the effects in man of marihuana and tetrahydrocannabinols on subjective state and physiologic functioning. *Ann. N. Y. Acad. Sci.* **191**, 196-205.

Johnson, S., and Domino, E. F. (1971). Some cardiovascular effects of marihuana smoking in normal volunteers. *Clin. Pharmacol. Ther.* **12**, 762-768.

Jones, G., and Pertwee, R. G. (1972). A metabolic interaction *in vivo* between cannabidiol and Δ^9-tetrahydrocannabinol. *Brit. J. Pharmacol.* **45**, 375-377.

Kalmakçalan, S., and Deneau, G. A. (1972). Some pharmacologic properties of Synthetic Δ^9-tetrahydrocannabinol (THC). *Acta Med. Turc. Suppl.* **1**, 5-27.

Karniol, I. G., and Carlini, E. A. (1973). Pharmacological interaction between cannabidiol and Δ^9-tetrahydrocannabinol. *Psychopharmacology* 33, 53-70.

Kilbey, M. M., Forbes, W. B., and Olivetti, C. C. (1973). Δ^9-Tetrahydrocannabinol: Inhibition of deprivation- and carbacol-induced water consumption in the rat after central and perpheral administration. *Behav. Biol.* **8**, 679-685.

King, A. B., and Cowen, O. L. (1969). Effect of intravenous injection of marihuana. *JAMA* **210**, 724-725.

King, A. B., Pechet, G. S., and Pechet, L. (1970). Intravenous injection of crude marihuana. *JAMA* **214**, 1711.

Layman, J. M., and Milton, A. S. (1971). Some actions of Δ^9-tetrahydrocannabinol and cannabidiol at cholinergic junctions. *Brit. J. Pharmacol.* **41**, 379P-380P.

Le Dain, G. (1972). "A Report of the Commission of Inquiry into the Non-medical Use of Drugs." Ottawa.

Leite, J. R., and Carlini, E. A. (1974). Failure to obtain "Cannabis-Directed Behavior" and abstinence syndrome in rats chronically treated with *Cannabis sativa* extracts. *Psychopharmacology* **36**, 133-145.

Lennard, H. L., Epstein, L. J., Bernstein, A., and Ranson, D. C. (1971). "Mystification and Drug Misuse." San Francisco: Jossey-Bass Inc.

Lockhart, J. G., and Desser, K. B. (1970). Effect of "Speed" and "Pot" on the juvenile diabetic. *JAMA* **214**, 2065.

Loewe, A. (1946). Studies on pharmacology and acute toxicity of compounds with marihuana activity. *J. Pharmacol. Exp. Ther.* 88, 154-161.

Loewe, S. (1950). The active principles of cannabis and the pharmacology of the cannabinoids. *Arch. Exper. Pathol. Pharmakol.* **211**, 175-193.

Lomax, P. (1971). Acute tolerance to the hypothermic effect of marihuana in the rat. *Res. Commun. Clin. Pathol.* **2**, 159-167.

Ludlow, F. H. (1857). "The Hasheesh Eater." New York: Harper and Bros.

Lukas, M. C., and Temple, D. M. (1974). Some effects of chronic cannabis treatment. *Aust. J. Pharm. Sci.* NS3, 20-22.

MacKay, E. M., Calloway, J. W., and Barnes, R. H. (1940). Hyperalimentation in normal animals produced by protamine-insulin. *J. Nutr.* **20**, 59-63.

Maitre, L., Staehelin, M., and Bein, H. J. (1970). Effect on an extract of cannabis and of some cannabinols on catecholamine metabolism in rat brain and heart. *Agent. Act.* **1**, 136-143.

Manning, F. J., McDonough, J. H., Elsmore, T. F., Saller, C., and Sodetz, F. J. (1971). Inhibition of normal growth by chronic administration of Δ^9-tetrahydrocannabinol. *Science* **174**, 424-427.

Marshall, C. R. (1898). A contribution to the pharmacology of *Cannabis indica*. *Amer. Med. J.* **31**, 882-891.

Marx, H., and Eckhardt, G. (1933). Tierexperimentalle Unter Suchungen über die Wirkungr des Haschisch. *Arch. Exper. Pathol. Pharmakol.* **170**, 395-406.

Mayer, J. (1953). Glucostatic mechanisms of regulation of food intake. *N. Engl. J. Med.* **249**, 13-16.

Mayer, J. (1955). Regulation of energy intake and the body weight. The glucostatic theory and the lipostatic hypotheses. *Ann. N. Y. Acad. Sci.* **63**, 15-43.

Mayer, J., and Bates, M. W. (1952). Blood glucose and food intake in normal and hypophysectomized alloxan in treated rats. *Amer. J. Physiol.* **168**, 812-819.

Mayor's Committee on Marihuana (1944). "The Marihuana Problem in the City of New York." Pennsylvania: Lancaster, Jaques Cattell.

McMillan, D. E., Harris, L. S., Frankenheim, J. M., and Kennedy, J. S. (1970). 1-Δ^9-Trans-tetrahydrocannabinol in pigeons: Tolerance to the behavioral effects. *Science* **169**, 501-503.

Mechoulam, R. (1970). Marihuana chemistry. *Science* **168**, 1159-1166.

Merari, A., Barak, A., and Plaves, M. (1973). Effects of $\Delta^9(^2)$-tetrahydrocannabinol on copulation in the male rat. *Psychopharmacology* **28**, 243-246.

Miras, C. J. (1965). Some aspects of cannabis action. *In* "Hashish: Its Chemistry and Pharmacology," Vol. 21, pp. 37-47. Ciba Foundation Study Group.

Nagle, B. T., DiGregoria, G. J., and Chernick, W. S. (1974). The influence of Δ^9-tetrahydrocannabinol (THC) on pilocarpine induced parotid secretions of the rat. *Pharmacology* **16**, 259.

Nahas, G. G., Schwartz, I. W., Adamec, J., and Manger, W. M. (1973). Tolerance to delta-9-tetrahydrocannabinol in the spontaneously hypertensive rat. *Proc. Soc. Exp. Biol. Med.* 14L, 58-60.

O'Shaughnessy, W. B. (1838). On the preparations of the Indian hemp or gunjah. *Trans. Med. Physiol. Soc. Beng.*, 421-461.

Padolsky, S., Pattavina, C. G., and Amaral, M. A. (1971). Effect of marihuana on the glucose-tolerance test. *Ann. N. Y. Acad. Sci.* **191**, 54-60.

Papadakis, D. P., Michael, C. M., Kephalas, T. H., and Miras, C. J. (1974). Effects of cannabis smoking on blood lactic acid and glucose in humans. *Experientia* **30**, 1183-1184.

Parker, C. S., and Wrigley, F. (1950). Synthetic cannabis preparations in psychiatry: Synhexyl. *J. Ment. Sci.* **99**, 276-279.

Paton, W. D. M. (1973). Cannabis and its problems. *Proc. Roy. Soc. Med.* **66**, 714-722.

Paton, W. D. M., and Temple, D. (1971). Quoted *In* Paton, W. D. M. and Pertwee, R. G. (1973).

Paton, W. D. M., and Pertwee, R. G. (1973). The pharmacology of cannabis in animals. *In* R. Mechoulam (Ed.), "Marihuana," pp. 191-285. New York: Academic Press.

Perez-Reyes, M., Lipton, M. A., Timmons, M. C., Wall, M. E., Brine, D. R., and Davis, K. N. (1973). Pharmacology of orally administered Δ^9-tetrahydrocannabinol. *Clin. Pharmacol. Ther.* **14**, 48-55.

Podolsky, S., Pattavina, C. G., and Amaral, M. A. (1971). Effect of marihuana on the glucose-tolerance test. *Ann. N. Y. Acad. Sci.* **191**, 54-60.

Pond, D. A. (1948). Psychological effects in depressive patients of the marihuana homologue synhexyl. *J. Neurol. Neurosurg.* **11**, 271-279.

Rating, D., Broermann, I., Honecker, H., Klume, S., and Coper, H. (1972). Effect of subchronic treatment with (-)Δ^8-trans-tetrahydrocannabinol (Δ^8THC) on food intake, body temperature, hexobarbital sleeping time and hexobarbital elimination rate. *Psychopharmacology* **27**, 349-357.

Revusky, S. H. (1968). Aversion to sucrose produced by contingent X-radiation. *J. Comp. Physiol. Psychol.* **65**, 17-22.

Rosenkrantz, H., and Braude, M. C. (1974). Acute, subacute and 23-day chronic marihuana inhalation toxicities in the rat. *Toxicol. Appl. Pharmacol.* **28**, 428-441.

Scheckel, C. L., Boff, E., Dahlen, P., and Smart, T. (1968). Behavioral effects in monkeys of racemates of two biologically active marihuana constituents. *Science* **160**, 1467-1469.

Schildkraut, J. J., and Efron, D. H. (1971). The effects of Δ^9-tetrahydrocannabinol on the metabolism of norepinephrine in rat brain. *Psychopharmacology* **20**, 191-196.

Short, J. J. (1929). Increasing weight with insulin. *J. Lab. Clin. Med.* **14**, 330-335.

Siemens, A. J. (1973). "Acute and Chronic Metabolic Interactions of Δ^1-Tetrahydrocannabinol and Other Drugs." Unpub. Ph.D. Thesis, Toronto.

Siler, J. F., Sheep, W. L., Bates, L. B., Clark, G. F., Cook, G. W., and Smith, W. H. (1933). Marihuana smoking in Panama. *Mil. Surg.* **73**, 269-280.

Silva, M. T. A., Carlini, E. A., Claussen, U., and Korte, F. (1968). Lack of cross tolerance in rats among Δ^9THC, cannabis extract, mescaline and LSD-25. *Psychopharmacology* **13**, 332-340.

Sjöden, P. O., Järbe, T. U. C., and Henriksson, B. G. (1973). Influence of tetrahydrocannabinols (Δ^8THC and Δ^9THC) on body weight, food, and water intake in rats. *Pharmacol. Biochem. Behav.* **1**, 395-399.

Sofia, R. D., and Barry, H. (1974). Acute and chronic effects of Δ^9-tetrahydrocannabinol on food intake by rats. *Psychopharmacology* **39**, 213-222.

Stockings, G. T. (1947). A new euphoriant for depressive mental states. *Brit. Med. J.* **1**, 918-922.

Stunkard, A. J., and Wolf, H. G. (1954). Correlation of arteriovenous glucose differences, gastric hunger extractions and the experience of hunger in man. *Fed. Proc.*, **13**, 147-155.

Tart, C. (1971). Marihuana intoxication: Common experiences. *Nature (London)*, **226**, 701-704.

Tennant, F. S., Preble, M., Prendergast, T. J., and Ventry, P. (1971). Medical manifestations associated with hashish. *JAMA* **216**, 1965-1969.

Thompson, G. R., Mason, M. M., Rosenkrantz, H., and Braude, M. C. (1973). Chronic oral toxicity of cannabinoids in rats. *Toxicol. Appl. Pharmacol.* **25**, 373-390(b).

Thompson, G. R., Rosenkrantz, H., Schaeppi, U. H., and Braude, M. C. (1973). Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicol. Appl. Pharmacol.* **25**, 363-372(a).

Thompson, L. J., and Proctor, R. C. (1953). Pyrahexyl in the treatment of alcoholic and drug withdrawal conditions. *N. Carol. Med. J.* **14**, 520-523.

Truitt, E. B., and Anderson, S. M. (1971). Biogenic amine alterations produced in the brain by tetrahydrocannabinols and their metabolities. *Ann. N.Y. Acad. Sci.* **191**, 68-73.

Walton, R. P. (1938). "Marihuana." New York: J. B. Lippincott.

Waskow, I. E., Olsson, J. E., Salzman, C., Katz, M. M., and Chase, C. (1970). Psychological effects of tetrahydrocannabinol. *Arch. Gen. Psychiat.* **22**, 97-107.

Wayner, M. J., Greenberg, I., Fraley, S., and Fisher, S. (1973). Effects of Δ^9-tetrahydrocannabinol and ethyl alcohol on adjunctive behavior and the lateral hypothalamus. *Physiol. Behav.* **10**, 109-132.

Weil, A. T., Zinberg, N. W., and Nelsen, J. M. (1968). Clinical and psychological effects of marihuana in man. *Science* **162**, 1234-1242.

Welch, B. L., Welch, A. S., Messiha, F. S., and Berger, H. J. (1971). Rapid depletion of adrenal epinephrine and elevation of telencephalic serotonin by (-)-trans-Δ^9-tetrahydrocannabinol in mice. *Res. Commun. Clin. Pathol. Pharmacol.* **2**, 382-391.

Wetle, T., and Singstake, C. B. (1971). "The Effects of Tetrahydrocannabinol on Eating Behavior of Rats." Paper presented at Western Psychological Association, San Francisco.

Williams, E. G., Himmelsbach, C. K., Wikler, A., Ruble, D. C., and Lloyd, B. J. (1946). Studies on marihuana and pyrahexyl compound. *Pub. Health Rep.* **61**, 1059-1070.