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Tolerance, appears to develop rapidly to high doses even when injections are spaced up to about a week apart. Tolerance to high doses appears to be long-lasting with little loss of tolerance even after a month. But at low doses in the behavioral range, tolerance appears to completely dissipate in a few days after a single dose. The magnitude of tolerance development can be large. After repeated exposure, a dose of over one hundred times the original produces little effect (McMillan et al., 1971).

The development of tolerance to THC in animals occurs for some effects but not for others (McMillan et al., 1971; Pirch et al., 1972; Thompson et al., 1971). This differential development of tolerance may explain why tolerance to certain effects studied has not been demonstrated (Masur and Khazan, 1970; McMillan et al., 1971; Barry and Kubena, 1971; Kubena et al., 1971).

Lomax (1971) and Thompson et al. (1971) have noted that the development of tolerance to one effect of the drug (hypothermia or sedation) may allow the expression of the opposite effect (hyperthermia or stimulation) to which tolerance does not develop.

Cross tolerance has been demonstrated between delta-9-THC, delta-8-THC and its synthetic analogues. Cross tolerance, has not been demonstrated between THC and lysergic acid diethylamide (LSD), mescaline or morphine (McMillan et al., 1970).

Preliminary work performed by McIsaac (1971) and Harris et al., (1972) demonstrated a reduction in the duration and quality of response on a conditioned learning task by monkeys on the second intravenously administered dose of THC. Tolerance developed extremely rapidly so that no effect on behavior was seen after five days. After a. two-week period without THC, the animals were retested and the same degree of tolerance had persisted. The researchers believe these observations might indicate a rapid behavioral adaption or "learned" functional tolerance.

However, evidence indicates that dispositional tolerance and/or physiological type of functional tolerance also plays a role at least at higher doses. Tolerance develops to the central nervous system depressant effects, hypotherma hypopnea (Thompson et al., 1971) and the EEG effects (Pirch et al., 1971) of the drug. McMillan et al., (1971) have demonstrated that tolerance to the effects of THC on behavior can be blocked by the hepatic microsomal enzyme inhibitor, SKF-525-A which has been shown to be a potent inhibitor of THC metabolism (Dingell et al., 1971). Methodological techniques must be, developed which will allow microdistribution studies to be performed in tolerant animals with low doses of THC before the mechanism of tolerance development can be clarified.

Evidence for the development of marked tolerance by man has been suggested by studies of heavy daily very long term users of hashish, charas or ganja in foreign countries. Reports from the, Eastern literature (Chopra and Chopra, 1939; Dhunjibhoy, 1930; Ewans, 1904) and more recently from Greece (Miras, 1965; Fink et al., 1971) and Afghanistan (Weiss, 1971) relate daily consumption of enormous quantities of potent cannabis preparation estimated to contain up to about one gram of THC per day.

Weiss (1971) has noted that daily charas smokers start with small doses and then in order to achieve the same effect gradually increase their daily dose about 5-6 times over a 20 to 30 year period. Generally, most reach their maximum dose by age 40 and then gradually decrease their daily dose by 50% usually ceasing use by their 60's. Some smokers have been noted to raise their original daily dose up to a maximum of 10 times within the first two years.

Others have noted that moderate use for many years does not necessitate increased doses (Sigg, 1963).

At least part of the increase in daily amount of drug used is accounted for by the finding that the duration -of the intoxicat n becomes shorter over the years so that the very heavy smoker must consume the drug more frequently to remain intoxicated. Additionally, smokers report that they have on oc sion discontinued use for days or months after which they experienced similar effects at smaller doses (Weiss, 1971).

Fink et al. (1971) noted that as hashish users total daily dose was decreased by more than half over the years, the frequency of use per day declined correspondingly.

Rubin and Comitas (1972) noted that very long term Jamaican ganja smokers generally consumed an average of seven spliffs daily (a ganja cigarette several times the size of an American marihuana cigarette) with a maximum of 24.

Further evidence for the development of tolerance, at least to certain of the depressant effects, is that these very long term smokers apparently tolerate the extremely high doses well without dysphoria or decreased ability to perform their usual activities (Weiss, 1971; Fink et al., 1971; Rubin and Comitas, 1972).

Smith and Mehl (1970) noted the, accumulating American anecdotal evidence of mild tolerance development after heavy daily use for a number of years. Jones (1971) and Meyer et al. (1971) have suggested diminished effect on physiologic and psyochomotor performance, that is, little or no impairment of function in daily users compared with infrequent, intermittent users of marihuana. Additionally, several investigators have noted that frequent users had little or no impairment on psychomotor performance tasks while marihuananaive individuals given the same dose had impaired function. (Clark et al., 1968, 1970; Jones and Stone, 1970; Mayor's Committee, 1944; Weil et al., 1968).

Subsequently (Mendelson et al., 1972) repetitive daily (free access) use over a 21-day period by groups of long-term intermittent (average 7.7 sessions per month) and moderate, marihuana users (daily average, 33 smoking sessions per month) was studied. The development, of tolerance was strongly suggested to the physiological pulse rate and general depressant effect on activity as well as psychological effects which impair recent memory, time estimation and psychomotor coordination.

No tolerance development occurred to the subjective effects of marihuana for experienced users over the 21-day period (global "highness", somatic, perceptual, awareness, feeling, control, friendliness, ambivalence and altered thinking). Furthermore, with the exception of a higher ambivalence rating for the daily riser group, there were no differences in the subjective reports of the daily users or intermittent users. (Mendelson et al., 1972). The ambivalence score is believed (Katz et al., 1968) to be the best measure of "psychedelic effects" of hallucinogenic drugs.

In a prior study (Meyer et al., 1971) found that while the heavy smokers experienced more profound subjective effects soon after smoking, they were less intoxicated than the intermittent users one hour later.

These findings suggest to the investigators that the quality of the "high" may be different for heavy and intermittent users and may change with heavy use. Tolerance, to the subjective effects of marihuana may occur predominantly to the depressant effects so that the stimulatory effects (or hallucinatory-like) would be predominant in the heavy users. The intermittent users who smoked marihuana several times daily in the, current study showed

no increase in the ambivalence, rating.

The increased daily frequency of marihuana use by both groups over time by shortening the interval between smoking sessions appears consistent with earlier observations (Meyer et al., 1971) that the duration of the desired "high" is shorter in heavy users than in intermittent users.

Fink et al. (1971) confirmed several of these findings in a study in which intermittent users smoked a fixed dose (14 mg. of THC) of marihuana. They noted a suggestion of development of tolerance to pulse rate, short-term memory, digit symbol substitution but not to the subjective high or EEG changes. However, the subjects did feel that the duration of the intoxication shortened progressively during the second half of the experiment.

Schuster and Renault (1971) administered twice daily fixed doses of marihuana (smoke from 430 mg. of marihuana with 1.5% THC content) to intermittent users over a 10-day period. A peak tachycardia, of 20 to 30 beats per minute and a usual social high were produced. Preliminary observations revealed the development of tolerance to time estimation in a few days, but no evidence for tolerance to the tachycardia, orthostatic blood pressure, or rating of the high.

Hollister (1971), in preliminary studies found no significant evidence of tolerance after five daily oral doses of 20 mg. of THC. Clinical responses measured were subjective judgment of the high, mood, pulse rate, reading comprehension or excretion of urinary metabolites.

REVERSE TOLERANCE

Smith and Mehl's (1970) clinical observations of many marihuana smokers suggest a J-shaped time curve of tolerance to marihuana. A novice marihuana smoker often reports feeling no high or requiring considerably more drug to get high on his first few trials with the drug than after he obtains more experience with the drug. This phenomenon has been called "reverse tolerance." These clinicians believed this represented "learning to get high" or acquiring the ability to appreciate or become sensitive to the subtle aspects of the intoxication.

Goode (1971) found that more frequent and term marihuana smokers tend to require fewer "joints" to get high but differences were not statistically significant.

Weil et al. (1968) reported that experienced users of marihuana achieved a "high" after being given the same dose as naive (non-users) persons who did not experience a high but did demonstrate objective physiologic and psychomotor drug effects.

Meyer et al. (1971) found that heavy marihuana, users (daily for three years) were most sensitive to the "high" and required less marihuana to achieve a social high than infrequent intermittent users (use one to four times per month for less than two years).

Phillips et al. (1971) reported an increase in severity of symptoms after repeated administration of THC to rats. This "sensitization" may be a correlate of reverse tolerance.

Lemberger et al. (1971) supplied additional evidence for reverse tolerance based on the intravenous administration of 0.5 mg of THC to experimental subjects. Naive subjects experienced no effect from this small dose. However, daily marihuana users, who were told

they were receiving a non-pharmacologically active dose of THC, reported a "marihuana high," which lasted up to 90 minutes.

Lemberger et al. (1971, 1972) and Mechoulam (1970) suggested the possibility that enzymes necessary to convert THC to a more active compound require prior use of marihuana.

Reverse tolerance appears to be a complex phenomenon. Jones (1971) presented evidence which stressed the importance of expectation, setting and prior drug experience on learning to get "high." As the user gains more experience with marihuana the more the individual's mind is able to respond to the expectation of the "high" by actually becoming high when given an inert material which smells and looks like marihuana.

Weil (1971) believes that the capacity to get "high" is an inherent characteristic of each individual's mind. He believes that marihuana facilitates the user's ability to achieve this altered state of consciousness, that is, learn how to get high.

Mendelson et al. (1972) did not find evidence for reverse tolerance. In fact, the daily users were more likely than the intermittent users to smoke two cigarettes per occasion. Both groups had had an average of five years of marihuana use. Several other investigators did not obtain any evidence of reverse tolerance after repetitive daily use in experienced subjects (Hollister, 1971; Schuster and Renault, 1971; Fink et al., 1971).

METABOLISM

Metabolism of the drug by the body exerts an important influence on the psychopharmacologic effect of marihuana. Many laboratories in many countries have been examining the metabolism, of the cannabinoids using in vitro liver microsomal enzyme preparations.

With the recent availability of radiolabeled Delta 9 and Delta 1 THC, cannabinol and cannabidiol much activity has occurred in vivo in animals. A comprehensive review of these areas including studies of absorption, disposition, excretion, metabolism and stimulation-inhibition of metabolism is beyond the scope of this report. Readers interested in further details in this area are referred to an excellent comprehensive review by Lemberger (1972).

From animal and in vitro studies it appears that the liver rapidly changes Delta 9 and Delta 11 THC in a similar manner by hydroxylation to 11-OH THC. This compound appears to be as potent or possibly more potent pharmacologically than the parent compounds This metabolite appears to be, rapidly hydroxylated to 8-11 dihydroxy Delta 9 THC (7-11 dihydroxy All THC) which is inactive. The 8-OH Delta THC appears to be a minor active metabolite (Christensen et al., 1971; Burstein et 1970; Ben-Zvi et al., 1970; Foltz et al., 1970; Wall et al., 1970,71; Nilsson et al., 1970).

These metabolites are excreted primarily into the bile and then to the feces. Some evidence exists for an enterohepatic circulation returning the drug to the blood. (Miras and Coutselinis, 1970; Klausner and Dingell, 1971)

Another metabolic pathway appears to be present resulting in a series of acidic metabolites excreted primarily in the urine (Agurell et al, I., 1970). Recently, Burstein and Rosenfeld

(1971) isolated and identified a major rabbit urinary metabolite, 11-carboxy-2'-hydroxy-Delta 9 THC. They postulate that other acidic metabolites might be esters or amides of this compound (Figure 7).

Recently, Nakazawa and Costa (1971) demonstrated that A' THC was metabolized by lung microsomes forming two unidentified products not found in liver homogenates.

Lemberger et al. (1970, 1971, 1972) and Galanter et al. (1972) have performed metabolic studies in man using intravenous, oral and smoked Delta 9 THC. These studies indicate that the THC disappears from the plasma in two phases.

The initial rapid phase has two components and represents metabolism by the liver and redistribution from the blood to the tissues. The slower second phase represents tissue retention and slow release and subsequent metabolism.

The plasma 1/2 life of THC was significantly shorter in daily users than nonusers at both the first component of phase one (10 minutes versus 13 minutes) and phase two (27 hours versus 56 hours). Tissue distribution was similar in daily and nonuser (1/2 life 2 hours).

Therefore, immediate metabolism of THC and subsequent metabolism is more rapid for daily user than the non-user implying specific enzyme induction. THC persists in the plasma for a considerable period of time, at least three days, with a half life of 57 hours for nonusers and 28 hours for daily users.

The presence of 11-hydroxy THC and more polar metabolites in the plasma of both users and nonusers within 10 minutes indicates that the metabolite probably accounts for the pharmacological activity of marihuana, not THC.

Further metabolism of the 11-hydroxy THC to more polar inactive 8-11 dihydroxy A' THC metabolite occurs more rapidly in users than nonusers. During the first few hours after injection, unchanged THC, its polar metabolites and nonpolar metabolites in the plasma, decline rapidly and then level off as they are distributed to the tissues. THC persists in the plasma, for at least three days, and both users and non-users excrete metabolites in the urine and feces for more than a week.

Delta-9-THC is extensively metabolized to more polar compounds which were excreted in the urine and feces. Urinary excretion and biliary excretion (reflected a day later in the feces) was greatest during the initial 24 hours, then gradually tapered off. All THC is metabolized since no unchanged THC was excreted in the feces or urine. No difference in total cumulative excretion was observed but a significantly larger percentage of the metabolites were excreted in the urine of users than nonusers. About 40-45% of the metabolites were collected in the feces in both groups in one week. Urinary excretion in this period accounted for 30% in daily users and 22% in nonusers. (Lemberger et al., 1970, 1971, 1972)

Perez-Reyes et al. (1971) found a similar pattern of excretion of metabolites after oral administration.

Urine contained no Delta 9 THC, only a small quantity (3%) of 11-hydroxy THC and 90% more polar acidic compounds as yet unidentified. (Lemberger, 1971). Preliminary studies by Burstein and Rosenfeld ('1971) suggest that these human acidic urinary metabolites are identical to the 11-carboxy-2' hydroxy THC found in rabbits.

In man, Lemberger et al. (1971, 1972) found that 11-OH THC and 8-11-OH THC were primarily excreted in the feces. Twenty-two percent of the metabolites in the feces were unchanged 11-hydroxy THC and slightly less were 8-11-dihyd-roxy THC. The remainder were unidentified more polar compounds, perhaps conjugates of these metabolites.

All user subjects (Lemberger et al., 1970, 1971, 1972) but no non-user noted a high after intravenous injection of the 0.5 mg dose of Delta 9 THC. This would be a dose range of 5 to 7 micrograms/kg. Highs have been noted by Kiplinger et al. (1971) with smoking THC to deliver a dose of 6.25 micrograms/kg. The high for some lasted up to 90 minutes. Thus, the plasma levels of Delta 9 THC and its metabolites seen after intravenous injection suggest that psychopharmacologic effects are seen in the first component of the rapid phase and terminated by redistribution and metabolism after the initial phase. The 11-hydroxy Delta 9 THC would be present at this early phase and is probably responsible for the activity of Delta 9 THC in marihuana.

Further evidence that the 11-OH Delta 9 THC is responsible for marihuana's effect was seen in oral and inhalation studies. By the oral route, blood levels of unchanged THC were relatively low compared to the radioactivity levels of the metabolic products at the time of peak subjective effect. While the blood level of unchanged THC at the peak oral effect was identical to that after intravenous injection of the 0.5 mg. dose, the psychologic effect was much more pronounced after oral administration of the larger 20 mg. dose of THC. Again after inhalation, the plasma levels of the metabolites correlate temporally with the subjective effects but the plasma levels of unchanged Delta 9 THC do not. (Lemberger, 1970, 1971, 1972; Galanter, 1972)

PATTERN OF USE

The drug effect of marihuana can only be realistically discussed within the context of who the user is, how long he has used, how much and how frequently he uses and what is the social context of the use. In general, for virtually any drug the heavier the use pattern, that is the longer the duration, the more frequently the use and the larger the quantity used on each occasion, the greater the risk for either direct or indirect damage.

Tolerance development is only one of a variety of occurrences which are related to the repetitive use of marihuana. Any discussion of drug effect must take into account the time period over which the drug is used (duration of use). This is necessary in order to detect cumulative effects or more subtle gradually-occurring changes. Of course, the issue of causality is quite complex because of the multitude of factors other than marihuana use that have a direct or indirect effect on the individual over a period of years.

For the purposes of this report, immediate or acute effects will refer to those drug effects which occur during the drug intoxication or shortly following it. Short-term or sub-acute will arbitrarily refer to periods of less than two years; long-term, from two to 10 years; and very long term (or chronic), greater than 10 years.

Frequency of use, will arbitrarily be designated in the following manner: experimental use refers to use of marihuana at least one time but not more than once a month; intermittent use refers to use more than once a month but not more than 10 times a month (several times a week) ; moderate use refers to use of the drug more than 10 times a month but not more than once a day; heavy use designates use more than once, daily and very heart use refers to use many times a day, usually with potent preparations (high THC content), producing almost continual intoxication so that the smoker's brain is rarely drug free.

AMOUNT OF DRUG CONSUMED

Relatively little actual data are available on the amount of marihuana, smoked per occasion or per day by current users in the United States. (McGlothlin, 1971, 1972). Estimates of the quantity of THC consumed are difficult because of the variability of potency as well as weight and size of the marihuana cigarette ("joint") and the degree of cleaning of stems and seeds from the dried leaves manicuring").

The analytic data available indicates most of the marihuana used in the United States is of Mexican origin and averages about 1 % THC per dry cleaned weight of marihuana (Lerner and Zeffert, 1968; Jones, 1971). Subjective ratings by experienced marihuana users appear to substantiate the data that marihuana containing 1% THC is of average quality (Jones and Stone, 1970; Weil et al., 1968).

Marihuana cigarettes are estimated (McGlothlin, 1971, 1972) to average about 0.5 g in weight and, therefore, contain about 5 mg of THC. Cigarettes used in the eastern states are generally smaller than those, rolled in the west (McGlothlin, 1971; New York Police Department, 1969, 1970)

Most data indicate that for the large majority of users one-half to one cigarette (2.5 to 5 mg THC) is sufficient to "get high" in intermittent moderate users, although often two or more cigarettes were smoked to achieve additional effect (Nisbet and Vakil, 1972; Shean and Fechtmann, 1971; McGlothlin et al., 1970- McGlothlin, 1972; Jones, 1971; Goode, 1970).

Current American daily users appear to consume one to two cigarettes per occasion (Jones, 1971) although some users estimate they smoke three to five cigarettes per occasion (McGlothlin et al., 1970). Goode (1971), however, found practically no relationship between amount required to get high and frequency of use (daily to less than monthly) or duration of use (less than two years to six or more years). In fact the heavy and longer term users were less likely to require more "joints."

Thus, the estimated 15 mg THC for current daily users is about one-half that estimated for confirmed regular users 30 years ago in the United States (Mayor's Committee, 1944; Charen and Perelman, 1946) and one-third to one-fourth the median daily consumption of daily users in North Africa and India.

The maximum daily consumption of 10 cigarettes (50 mg THC) for current heavy U.S. marihuana smokers (Jones, 1971; McGlothlin, 1972) is about the same as the average amount consumed by daily chronic users in other countries, and about one-fourth or less of the maximum in these countries (Soueif, 1967; Sigg, 1963; Indian Hemp Drug Commission's Report, 1893-1894; Chopra, 1940; Chopra and Chopra, 1939).

Studies of American military in Vietnam (U.S. Congress, 1971; Colbach and Crowe, 1970; Forrest, 1970), and Germany (Tennant et al., 1971) described the daily use of quantities of hashish or potent marihuana comparable to amounts consumed by regular chronic users in other countries.

Experimental data appear to confirm these estimates of quantity of THC consumed. Isbell et al. (1967) and Jones (1971) found that most subjects reported a normal "high" after smoking 5-10 mg of THC. Meyer et al. (1971) found that a "very high" state was attained

by ad libitum smoking of 3.12 mg THC by daily users and 3.78 mg THC by intermittent users.

In experiments by Johnson and Domino (1971), subjects were urged to smoke until they were as high as they had ever been on marihuana and felt they could not smoke any more. These subjects smoked from one to four cigarettes containing 8.7 mg of THC to reach this level of intoxication. The range was from 8.7 to 30 mg of THC with a mean of about 20 mg THC.

Intermittent and daily users were allowed to smoke marihuana on a free choice basis over a 21day period in studies by Mendelson et al. (1972). Each cigarette contained one gram of marihuana of approximately 2% THC content, or about 20 mg of THC.

Subjects were asked to rate their high on a 10 point scale with 10 corresponding to highest ever; five as moderately high and zero, no effect. Ratings for the daily user group ranged from zero to nine with an average of about six for all cigarettes rated. Individual means ranged f rom three to about seven. On almost all occasions, subjects in both groups smoked the entire cigarette.

Kiplinger et al. (1971) and Lemberger, et al. (1971) noted that daily long-term users were able to detect effects of the "high" at doses calculated to deliver as low as 5-7 micrograms/kg THC (equivalent to smoking about 100 mgs. of marihuana containing 1 % THC). Perhaps this explains the finding that many users are able to "get high" smoking US wild-growing marihuana containing front near zero to 0.5% THC (Lerner, 1969; Phillips et al., 1970; Fetterman et al., 1971).

Several ad libitum experiments were performed with marihuana of unknown composition (Williams et al., 1946; Siler et al., 1933) using "confirmed regular marihuana users" confined over a 39 and six-day period. The users, who generally consumed three cigarettes per day, under these rather artificial conditions of the, experiment consumed means of 17 (range nine to 26) and five (range one to 20) cigarettes per day respectively.

Miras and Coutsilinis (1970) reported recent experimental data on chronic Greek hashish users who routinely use, single smoked doses of hashish containing 100 mg of THC. Under ad libitum conditions, these users averaged 150-350 mg of THC per day over a 30-day period.

The subjects studied during a 21-day period of free choice Marihuana consumption by Mendelson et al. (1972) generally consumed all of one cigarette containing 20 mg of THC per smoking session. The subjects who were previously daily users were more likely during the experiment to consumer more, than one, cigarette per session than the, previously intermittent users.

Individual consumption by the intermittent users ranged from an average of about one-half to
six cigarettes per day (group mean three) while the daily users consumed an average of three-anda-half to nine cigarettes per day (group mean six-and-a-half). Reasons given by the subjects for the dramatic shift in the frequency of marihuana use included boredom, testing the limits of their endurance, demonstrating its harmlessness to the research staff, and subtle social pressure.

DURATION OF USE

Very little American data exists on the duration of marihuana use. Practically no data exists which demonstrates the extent that persons who initiated marihuana use some 20-40 years ago have continued its use. Robins and Murphy (1967) in a follow-up study of St. Louis black males noted that 20% of those who had tried marihuana by age 24 were still using it to some degree 15 years later. McGlothlin et al. (1970, 1971) reported on a sample of predominantly white adults who began using, marihuana in adolescence and had continued infrequent use for more than 20 years.

In the case of Western and particularly middle class American use of marihuana, the rapid climb to prominence of the phenomenon since the midsixties raises the question of whether the entire drug movement is transient or permanent. Certainly, the majority of the youthful users and many of the adults have used the drug less than 10 years and probably less than five years.

One 1970 survey (Lipp, 1970) revealed that 77% of those students who initiated marihuana use four to five years earlier were still using it to some degree. A recent study (Walters et al., 1972) indicates that students who first used marihuana before entering college in September 1965 and had continued use of marihuana in February 1969 ("old user") differed from the, vast majority of users who began their drug use in college ("new user").

The old user is more likely to experiment with a wide variety of drugs, to be extremely active in radical political organizations, to be alienated from American society, to be less definite about career plans, and to have more heterosexual activities.

The Commission-sponsored National Survey indicated that marihuana use by both youth (12-17 years of age) and adults (18 and over) is experimental in approximately 75% of those who have ever used marihuana. These individuals have, either stopped using it (66% of adults and 57% of youth) or are, using, it once, a month or less. In contrast, 13% of the ever used subsample (12% adults, 16% youth) use marihuana once a week or more.

In other non-Western countries, cannabis use frequently persists for long periods. Especially in the East, persons using it for 20-40 years or more are not uncommon. In other cultures, initiation is most common in adolescence. Once the habit is established it is likely to continue on a daily basis for many years and frequently continues as a lifetime practice (Weiss, 1971; Sigg, 1963; Soueif, 1967; Watt, 1936; Chopra and Chopra, 1939; Bouquet, 1951; VN, 1957).

Probably the duration of use will vary considerably depending on cultural acceptance or rejection (McGlothlin, 1972).

INTERACTION WITH OTHER DRUGS

Little experimental work has been done on the interaction between marihuana and other drugs used socially or medically although this will become an important area as usage increases.

Marihuana is often used with sweet wines to enhance its effect. Some evidence for an additive effect of marihuana and alcohol on motor and mental performance and subjective effect has been seen experimentally (Manno et al., 1971; Jones and Stone, 1970). Some degree of additive effects would be expected with barbiturates based on their similarity to alcohol. A more complex, mixed pattern of effect might be expected with amphetamines and hallucinogens. These latter combinations are rarely used socially (Hollister, 1971).

Acute Effects of Marihuana

(Delta 9 THC)

SUBJECTIVE EFFECTS

Descriptive accounts of marihuana intoxication have been written by noted authors, Beaudelaire (1961), scientists, Moreau (1945), and common users Tart, 1970, 1971; Isbell et al., 1967; Report by Advisory Committee, 1968). Adequate description of the state of mind produced by low doses is difficult because it is not approximated in the usual states of consciousness or by other commonly used drugs. The closest non-drug approximation may be the altered state of consciousness experienced in the hypnotic trance or transcendental meditation or the, transition zone between waking and sleep (Weil, 1971). Due to the highly subjective nature of the experience, there is much individual variation in the effects described.

Tart (1970, 1971) studied the range of potential common effects in an extensive survey of 150 users. Changes noted by these studies at low doses (usually smoked dose about five mg. THC) include euphoria, with restlessness and mild mental confusion. Sensory perception of the external environment. is altered. Users often perceive an overestimation or slowing of elapsed time and expansion of space, enhanced sense of tactile, olfactory, gustatory perceptions and often a feeling of hunger. Visual alterations reported are more vivid imagery and seeing forms and patterns in objects that are usually amorphous. Increased awareness of subtle qualities of sound such as purity, distinctness or rhythm are characteristically perceived by users. A dreamy, relaxed state and disinhibition, with uncontrollable laughter is reported and users often believe that interpersonal relations altered, and act to potentiate social interaction.

At moderate doses intensifications of changes experienced are reported. Users' reports include disturbed associations, dulling of attention, vivid visual imagery, fixed ideas, rapidly changing positive and negative emotions, fragmentation of thought, flight of ideas, impaired immediate memory, altered sense of identity, increased suggestibility and a feeling of enhanced insight. At higher doses, interpersonal relations are dulled and the user feels less social and more withdrawn.

At larger doses psychotomimetic (hallucinogenic-like) phenomena are experienced in a wavelike fashion. These include distortion of body image, depersonalization, visual illusions and distortions, synesthesia, dream-like fantasies and vivid hallucinations.

Data from Isbell et al. (1967) and Perez-Reyes et al. (1971) have indicated that the hallucinogenic oral dose is in the range of 0.4 to 0.5 mg./kg Delta 9 THC. Thus, the hallucinogenic dose is 80 times larger than the delivered dose of smoked marihuana producing minimal subjective effects (five micrograms/kg.) or about 11 to 14 times larger than the usual smoked dose.

LETHALITY

There is no conclusive evidence that short-term marihuana use alone directly results in any physical damage to man. A few scattered fatalities associated with marihuana use are occasionally reported. Most are from 19th century Indian experiences with large oral doses of charas (Deakin, 1880; Bouquet, 1951; Ewens, 1904, Walton, 1938; Indian Hemp Drugs, 1893). Brill et al. (1970) and Smith (1968) have noted that there have not been any reliable reports of human fatalities attributable purely to marihuana, although very high doses have been administered by users.

A frequently cited recent report from Belgium by Heyndrickx et al. (1970) describes an essentially negative pathological and toxicological study of a 23-year-old man found dead in the presence of marihuana, and hashish. A cannabinoid was detected in his urine. However, this finding in no way inculpates marihuana as the responsible agent. There are many possible causes of sudden death which are not toxins and do not produce observable pathology; e.g. anaphylactic reactions, insulin shock, cardiac arhythmias, etc.

A case report (Nahas, 1971) of an attempted suicide by smoking hashish, recently in France is even more anecdotal. An individual was reported to have smoked consecutively ten pipes of hashish containing approximately 200 mg of Delta 9 THC each before losing consciousness. But recovery occurred after supportive treatment.

Another case report (Hughes et al., 1970) relates severe diabetic coma with ketoacidosis after the ingestion of huge amounts of marihuana by a mental patient. However, it appears that the pronounced vomiting secondary to the marihuana ingestion caused a severe electrolyte imbalance and alkalosis. Possibly a vulnerable glucose-regulating system responded to the severe stress inappropriately. Retrospectively, there was no history of diabetes noted previously but this was not confirmed or ruled out by lab tests prior to the episode.

Several case reports (Henderson and Pugsley, 1968 King and Cowen, 1970; King et al., 1970; Lundberg et al., 1971; Gary and Keylon, 1970) noted acute severe, physiological disturbances and acute collapse (shock, chills and fever) subsequent to intravenous injection of suspensions of marihuana. These symptoms may have been due to an allergic reaction to injected foreign plant material, to a bacteremia and/or to the injection of insoluble particles which are filtered by the organs. The symptoms may be considered a complication of the mode of use, rather than results of the drug.

Although a median lethal dose has not been established in man (Brill et al., 1970), one has been found in laboratory animals. Earlier reports (Lowe, 1946; Joachimoglu, 1965) used materials of uncertain potency and composition. Recent studies utilized carefully quantified materials. One group, Phillips et al. (1971), utilizing THC extracted from marihuana, demonstrated the following LD50 (the dose that causes death in 50% of the animals) in units of mg/kg of Delta 9 THC from mice,/rats: oral 481.9/666, intraperitoneal 454-9/ 372.9, intravenous 28.6/42.47.

Thompson et al. (1971) under contract to the National Institute of Mental Health have recently carried out extensive studies in rats, dogs and monkeys in order to define the range of toxicity of the drug. The group used synthetic Delta 9 and A' THC and a crude marihuana extract (CME) of carefully define composition. Delta 9 THC was more potent than Al THC. CME was less potent than a similar quantity of A' THC.

Acute toxicity was studied using intravenous, intraperitoneal and oral routes of

administration in rats. An LD50 similar to that reported by Phillips et al. (1971) was found by the intravenous route (20 mg/kg of THC) and intraperitoneal route (400 mg/kg) but higher values were noted with oral administration (1140 mg/kg). Interestingly, the LD50 for males was 1400 mg/kg while for females it was 700 mg/kg by the oral route. The minimal lethal dose orally was between 225 and 450 mg/kg.

An LD50 was not attainable in monkeys and dogs by the oral route. Enormous dose levels (over 3000 mg/kg of Delta 9 THC) were administered without lethality to most animals. A dose of about 1000 mg/kg THC was the lowest dose which caused death in any animals The completeness of intestinal absorption of THC at these high doses is unknown. Behavioral changes in the survivors included sedation, huddled posture, muscle tremors, hypersensitivity to sound and hypermobility.

The cause of death in the rats and mice subsequent to oral THC was profound central nervous system depression leading to dyspnea, prostration, weight loss, loss of Fighting reflex, ataxia, and severe fall in body temperature which led to cessation of respiration from 10 to 46 hours after single dose oral administration. No consistent pathological changes were observed in any organs. The cause of death when it rarely occurred in the higher species did not appear to be related to the same mechanism as in the rats.

Using intravenous administration, the acute one dose LD50 for Delta 9 THC was 100 mg/kg in dogs and 15.6 to 62.5 mg/kg in monkeys depending on concentration of the solution. The minimal lethal intravenous dose for dogs, also depending upon concentration, was 25 to 99 mg/kg and for monkeys 3.9 to 15.5 mg/kg.

In contrast to the delayed death observed in rats after oral administration, lethality in rats, dogs and monkeys after intravenous injection occurred within minutes after injection. When sublethal amounts were injected, central nervous system depression with concomitant behavioral changes similar to those observed after oral doses were observed. However, their onset was more rapid and the intensity of effect more severe with anaesthesia, and convulsions noted after injection. The monkeys and dogs that survived the intravenous injection of THC recovered completely within five to nine days.

The only consistent pathological changes were noted in the animals which succumbed. Pulmonary changes including hemorrhage, edema, emphysema and generalized congestion were found and death resulted from respiratory arrest and subsequent cardiac failure. The investigators presumed one mechanism possibly accounting for these findings was due to the concentration of the THC solution and its insolubility in water. Presumably, when these highly concentrated solutions mixed with the blood, the THC precipitated out of solution. The precipitated foreign material then formed aggregates (or emboli) that were filtered out in the lung capillaries causing a physical blockage of pulmonary blood flow.

Subsequently, intravenous studies were repeated using Delta 9 THC emulsified in a sesame oil-Tween 80-saline vehicle at 15 mg/ml or 40 mg/ml. The emulsions were administered at a uniform rate of 2 ml/15 sec. Doses administered were 1, 4, 16, 64, 92,128, 192 and 256 mg/kg. All monkeys injected with 92 mg/kg or less survived and completely recovered from all effects with two to four days. All monkeys injected with 128 mg/kg or more succumbed within 30 minutes for all but one (180 minutes).

Histopathological changes found in the lungs of the deceased monkeys were like those described after the, previous intravenous experiment. All the monkeys that died exhibited severe respiratory depression and bradycardia within five minutes after the injection. Respiratory arrest and subsequent cardiac failure occurred within minutes. Behavioral changes preceding death were salivation, prostration, coma and tremors.

Behavioral and physiological changes described clinically in the surviving monkeys followed a consistent developmental sequence and were roughly dose related in severity and duration. Onset was 15 minutes following injection and duration was up to 48 hours. Huddled posture and lethargy were the most persistent changes. Constipation, anorexia and weight loss were noted. Hypothermia, bradycardia and decreased respiratory rate generally were maximal two to six hours post injection. Tremors with motion but not at rest were believed to be caused by peripheral muscle inadequacy.

In summary, enormous doses of Delta 9 THC, All THC and concentrated marihuana extract ingested by mouth were unable to produce death or organ pathology in large mammals but did produce fatalities in smaller rodents due to profound central nervous system depression.

The non-fatal consumption of 3000 mg/kg A THC by the dog and monkey would be comparable to a 154-pound human eating approximately 46 pounds (21 kilograms) of 1%-marihuana or 10 pounds of 5% hashish at one time. In addition, 92 mg/kg THC intravenously produced no fatalities in monkeys. These doses would be comparable to a 154-pound human smoking at one time almost three pounds (1.28 kg) of 1%-marihuana or 250,000 times the usual smoked dose and over a million times the minimal effective dose assuming 50% destruction of the THC by smoking.

Thus, evidence from animal studies and human case reports appears to indicate that the ratio of lethal dose to effective dose is quite large. This ratio is much more favorable than that of many other common psychoactive agents including alcohol and barbiturates (Phillips et al. 1971, Brill et al. 1970).

PHYSIOLOGICAL EFFECTS

Much research has been reported on the effect of single doses of marihuana or THC on a wide variety of indices of physiologic function in animals. Most animalt studies involved large doses a-rid produced profound changes similar in nature but less in magnitude than those described in the previous paragraphs. These have been comprehensively reviewed elsewhere (Secretary HEW 1972, Forney, 1971; Secretary HEW, 1971) and should be consulted if more detailed information is required.

Similarly, much research has been done in man. As discussed in the previous section on factors influencing the psychopharmacological effect in man, an acute dose-response relationship has been clearly defined over a dose range relevant to human usage patterns for these effects. Thus, with increasing dose, the larger the effect on the index being observed and the longer the effect persists. However, there is a wide variation between individuals' responses but each individual is quite consistent.

The most consistent physiological sign is an increased pulse rate (Mendelson et al., 1972; Johnson and Domino, 1971; Renault et al., 1971; Galanter et al., 1972; Domino, 1970; Hollister et al., 1968 Manno et al., 1970; Mayor's Committee 1944; Waskow et al., 1970; Isbell and Jasinski, 1969; Meyer et al., 1971; Weil et al., 1968; Jones and Stone, 1970; Clark and Nakashima, 1968). This does not appear to be a direct drug effect on the heart (Manno et al., 1970). Instead, the drug appears to cause complex changes in the autonomic nerves regulating heart rate. Thus, Kiplinger et al. (1971) demonstrated that the increase produced by marihuana in heart rate is prevented by pretreatment with a Beta-sympathetic nervous system blocking agent, propranolol. A comparable increase rate was produced by treatment with isoprotemol, a Beta-sympathetic like drug. One subject developed an

abnormal bigeminal rhythm after both marihuana and isoproternol.

Renault et al. (1971) noted a consistent effect of marihuana on the cardiac rhythm which also produced an increased heart rate. The effect was the suppression of the normal sinus arrhythmia usually produced by respiration. Respiration usually produces a slowing of heart rate mediated by the vagal parasympathetic nerve supply. This depression of normal vagal tone was further evidenced by the absence of heart rate slowing during forced expiration against a closed glotis (valsalva maneuver). This effect seemed to wax and wane over several minutes producing alternate periods of rapid and slowed heart rate.

Both autonomic nervous systems seem to be affected by marihuana; the sympathetic is stimulated while the parasympathetic is inhibited.

Kiplinger et al. (1971) clearly demonstrated that the amount of increase in pulse rate was directly related to the dose of THC administered as did Renault et al. (1971) and Johnson and Domino (1971) over a wide range of doses. Both experienced and inexperienced marihuana smokers demonstrated increases regardless of the subjective state described. Tachycardia is noted rapidly and reaches a peak about 15 to 20 minutes after finishing smoking. The pulse rate returns to normal within one to one-and-a-half hours.

Other than the one report of bigeminy (Kiplinger et al., 1971), little or no alteration of normal heart rhythm were noted by electrocardiogram (Isbell et al., 1967; Mayor's Committee, 1944) other than sinus tachycardia (Mendelson et al., 1972). Johnson and Domino (1971) noted premature ventricular contractions in a few of their subjects, but they felt this effect was more likely produced by the smoking itself rather than by the drug.

Conjunctival injection, reddening of the eyes due to increased prominence of the conjunctival blood vessel and dilation of the scleral vessels, (Hepler et al., 1971; Kiplinger, et al., 1971) is another highly consistent occurrence (Mendelson et al., 1972, Allentuck and Bowman, 1942, Ames, 1958; Hollister, et al., 1968; Isbell et al., 1967; Manno et al., 1970; Waskow et al., 1979; Weil et al., 1968) produced by orally ingested and smoked al., 1968). This finding is produced by orally ingested and smoked marihuana (or THC). And thus the effect must be a direct drug effect and not caused by irritation from smoke (Perez-Reyes and Lipton, 1971). Kiplinger et al. (1971) noted that this finding was dose-related although it develops slowly reaching a maximum about one hour after smoking.

Reported effects on blood pressure are inconsistent. Some investigators find lowered pressure (Hollister et al., 1968; Isbell et al., 1967; Waskow, et al., 1970) while others report a slight increase (Johnson and Domino, 1971; Domino, 1970; Mayor's Committee, 1944) and still others report increases and decreases (Mendelson et al., 1972; Perez-Reyes et al., 1971).

Preliminary results of a carefully performed study of the cardiovascular effects (Weiss, 1971) demonstrated orthostatic, hypotension in the erect position and hypertension when supine.

Little or no effect has been demonstrated in humans on a wide variety of parameters investigated. Body temperature is unchanged (Mendelson et al., 1971; Hollister et al., 1968; Isbell et al., 1967; Brooks, 1896) as is respiratory rate (Domino, 1970; Isbell et al., 1967; Weil et al., 1968), lung vital capacity and acute bronchospasni (Mendelson et O., 1972) and basal metabolism (Mayor's Committee, 1944).

Several studies (Mendelson et al., 1972; Mayor's Committee, 1944; Personal Communication, 1970) have examined changes in blood cells and blood chemistry. No

acute effects were demonstrated on red blood cell number, or structure; differential and total white blood cell count; platelet count; reticulocyte, count; serum electrolyte concentrations; calcium and phosphorous serum levels; liver function tests; uric acid concentration; type or quantity of serum proteins. Although increased frequency of urination is often reported, increased urine volume has not been demonstrated (Ames, 1958; Mayor's Committee, 1944) and no alteration of kidney function identified (Personal Communication, 1970; Hollister et al., 1968; Mayor's Committee, 194-4; Mendelson et al. 1972).

Reports of increased hunger, especially for sweets (Allentuck and Bowman, 1942; Ames, 1958; Manno et al., 1970; Mayor's Committee, 1944), have focused attention on blood sugar and food intake. No consistent significant change in blood sugar has been demonstrated (Dornbush and Freedman, 1971; Hollister, 1971; Hollister et al., 1968; Isbell et al., 1967; Manno et -al., 1970; Personal Communication, 1970; Weil et al., 1968) with some investigators finding decreases (Beringer et al., 1932; Lindemann, 1933-1934), others finding increases (Manno, 1970; Mayor"s Committee, 1944), still others finding both increases and decreases (Miras, 1965).

Podolsky (1971) found that although fasting blood glucose was unchanged by smoking marihuana, higher 30 and 60 minute glucose levels were noted after a standard dose of glucose. No corresponding alteration in insulin or growth hormone levels was demonstrated.

Hollister and Gillespie (1970) found an increased total food intake when the drug was administered after breakfast but not after an overnight fast. Half the subjects reported subjective increased hunger. Subjects' free fatty acid levels and blood glucose remained unchanged while the placebo controls' free fatty acid values decreased. Another study suggested increased appetite and food intake but was without adequate controls (Personal Communication, 1970).

An investigation of physiological parameters of stress after marihuana (Hollister, 1969; Hollister et al., 1970) revealed only a minimal increase in white blood cells and a minimal decrease in cosinophils but no changes in serotonin, cortisol level and urinary catecholamines. However, another investigator (Chopra, 1969) demonstrated increased catecholamine excretion especially those from the adrenal medulla.

Hepler and Frank (1971) and Frank et, al(1971) have carefully studied ophthalmological changes produced by marihuana. Swelling of the eyelids (Ames, 1958), ptosis (Isbell et al., 1967), photophobia and nystagmus (Allentuck and Bowman, 1942) and dilated, sluggish reacting pupils (Mayer-Gross et al., 1960; Mayor's Committee, 1944) were all mentioned in earlier discussions but were not demonstrated (Hepler et al., 1971).

Findings which were quantifiable (Hepler et al., 1971) were a slight pupillary constriction with normal responsiveness to light and accommodation and an increase in glare recovery time. No change was evident on near and far visual acuity, fundiscopic exam, visual field acuity and depth and color perception. However, a decrease in tear secretion and an increase in conjunctival injection was demonstrated.

Hepler and Frank (1971) reported an average of about 25% decrease in the intraocular pressure of most normal subjects after smoking marihuana. A preliminary trial in one patient with glaucoma demonstrated similar findings (Frank, 1971).

No objective impairment of improvement invisual acuity or brightness perception (Caldwell et al., 1970; Caldwell et al., 1969) nor effect on depth perception and duration of after image (Clark and Nakashima, 1968) was noted in other studies.

Neurological examinations have consistently revealed no major abnormalities during marihuana intoxication. (Mayor's Committee, 1944; Rodin and Domino, 1970; Rodin et al., 1970; Personal Communication, 1970). Subjects often report muscle weakness. Minimal decreased leg, hand and finger maximum muscle strength have been demonstrated objectively (Fere, 1901; Hollister et al., 1968; Mayor's Committee, 1944). However, electromyography was reported to be normal (Personal Communication, 1970

A slightly increased briskness in the knee jerk has been detected (Domino, 1971 - Rodin and Domino, 1973) while no change in threshold or elicitation of deep tendon reflexes is usually, reported (Hollister et al., 1968; Isbell et al., 1967).

Incoordination, fine tremor and ataxia are often experienced by the user (Ames, 1958; Beringer et al., 1932; Clark et al., 1970; Mayor's Committee, 1944). The presence of a fine tremor and decrements in hand steadiness and static body equilibrium leave been demonstrated with refined measuring devices when they are not grossly observable (Manno et al., 1970; Mayor's Committee, 1944; Mendelson et al., 1972). Kiplinger et al. (1971) using sensitive apparatus demonstrated these fine hand tremors and changes in body equilibrium are also dose related.

Cranial nerve function and somatic sensation have not been significantly impaired or improved. Subjective reports of increased auditory sensitivity contributing to greater esthetic appreciation of music (Winick, 1960) have been generally unconfirmed in objective tests of auditory acuity and pitch, frequency or intensity or threshold discrimination (Aldrich, 1944; Caldwell et al., 1970; Caldwell et al., 1969; Clark and Nakashima 1968; Mayor's Committee, 1944; Meyers and Caldwell, 1969). Objective improvement in auditory acuity in several subjects was noted (Walton, 1938; Williams et al., 1946).

Similarly, improvement in visual acuity and discrimination and altered depth perception reported by users has been unconfirmed objectively (Caldwell et al., 1970; Caldwell et al., 1969; Clark and Nakashima, 1968; Mayor's Committee, 1944; Hollister and Gillespie, 1970; Jones and Stone, 1970; Frank et al., 1971).

A slight improvement in vibratory sensation (Rodin and Domino, 1970), no change in touch or two-point discrimination (Rodin and Domino, 1970; Williams et al., 1946) nor olfactory and gustatory senses (Williams et al., 1946) have been demonstrated. Decreased sensitivity to pain has been objectively demonstrated (Personal Communication, 1970) which corroborates its past therapeutic use as an analgesic.

One of the most frequently reported subjective effects of marihuana intoxication is a distortion of time sense (Tart, 1971). Actual elapsed time is overestimated or perceived as being longer than actual clock time. Thus, present events are perceived as prolonged when intoxicated and isolated from the past and future. They are in the "hereand-now" (Melges et al., 1971). Many have confirmed this experimentally (Ames, 19.58; Clark et al., 1970; Mendelson et al., 1972; Dornbush and Freeman, 1971; Hollister and Gillespie, 1970; Weil et al., 1968; Williams et al., 1946). The over-estimate is much greater during periods lit which the subject is performing a task than for unfilled time, and the error is (greater as the

time period is longer (Clark et al., 1970).

Melges et al. (1971) have demonstrated that marihuana intoxication induces temporal distortions with a greater concentration on the present and a shortening of span of awareness into the past and future. They believe that under the drug's influence, as the, subject becomes less able to integrate past, present and future, his awareness becomes more concentrated on present events. These present events are experienced as prolonged or timeless because they no longer appear to the intoxicated individual as transitions from the past to the future.

Melges and Bowlby (1969) have described habitual marihuana smokers who specifically use the drug to achieve the "here-and-now" orientation. These smokers claim this focus on the present permits them to be more open to immediate experience while being less troubled by past and future concerns. This focus may also explain the belief that perceptions during intoxications are both unexpected and never experienced previously.

The effect of intoxication on the resting electroencephalogram are still unclear but generally have been minimal, inconsistent and within normal limits. In early studies (Wikler and Lloyd, 1945; Williams et al., 1946) a decrease in alpha activity was noted. More recently (Ames, 1958) noted a delayed alpha increase with concomitant increases in beta and theta activity. Rodin and Domino (1971) reported a slight shift toward slower alpha frequencies.

Three other studies (Jones and Stone, 1970; Hollister et al., 1971; Rickles et al., 1970), failed to find consistent changes but noted increased alpha frequency, increased synchronization and occasional paroxysmal activity. These effects were ascribed to relaxation and drowsiness.

Two investigators (Chopra, 1935; Miras, 1969) reported decreased fast activity and other variable effects. Most recently, Volavka et al. (1971) and Fink et al. (1971), reported a significant rapid onset effect occurring during the five-minute smoking period and of short duration (less than 30 minutes) in continuously alert individuals. The principal changes detected by computer analysis were a dose related increase in percent alpha time and an associated reduction in theta and beta hands.

Roth et al. (1972), demonstrated that auditory evoked responses were decreased in amplitude by marihuana and THC particularly during the first few minutes of stimulation. These results may indicate that the intoxicated individual may receive external auditory stimuli differently during the intoxication period.

The prominent and frequently reported sedative effects of marihuana and the dreamlike states occurring during intoxication directed several investigators to study the effects of marihuana on sleep. Fragmentary data from one sleep laboratory (Pivik et al., 1969) indicated decreased rapideye-movement (REM) sleep time. Another sleep lab (Rickles et al., 1970), in preliminary work demonstrated an increase in REM sleep time. Fink et al. (1971) noted that EEG defined sleep (stages one and two) were dose dependent but THC did not act like a classical sedative. The occurrence of EEG sleep was much more frequent in the placebo and low dose (10 mg THC) conditions than in the high dose condition (20 mg THC).

Mendelson et al. (1972) noticed an increased amount of total sleep as well as an increase in discrete episodes of sleep related to marihuana smoking. These findings correlate well with questionnaire data (Tart, 1970) indicating that at moderate doses, users found it easier to induce sleep and that sleep was considered to be more refreshing, while at higher doses both aspects were impaired.

In summary, marihuana containing Delta-9-THC is a pharmacologically active drug with minimal acute physiological effects at the low to moderate doses used by man.

Based on its few consistently observed physiological effects, marihuana is a rather unexciting compound of negligible acute physiological toxicity at the usual doses consumed by man. The subjective state characteristically described by the intoxicated user is far more interesting to both the user and the scientist than the objective one observed by the investigator.

EFFECTS ON MENTATION AND PSYCHOMOTOR PERFORMANCE

Characteristically, intoxication with psychoactive materials effec. psychomotor and mental functions. It is apparent from the subjective assertions of users and a wide range of experimental studies that marihuana is no exception (Clark and Nakashima, 1968; Clark et al., 1970; Dornbush and Freedman, 1971; Hollister and Gillespie, 1970; Manno et al., 1970; Mayor's Committee, 1944; McGlothlin et al., 1971; Melges et al., 1970; Meyer et al., 1971; Weil and Zinberg, 1969; Weil et al., 1968; Volavka et al., 1971; Galanter et al., 1972; Kiplinger et al., 1971; Mendelson et al., 1972; Dornbush et al., 1971).

Psychomotor tasks which have been tested include tapping speed, handwriting and free-hand writing and free handdrawing, simple and complex reaction time, pursuit rotor and tracking tasks and continuous performance tests. Cognitive tasks frequently tested are simple arithmetic problems, serial addition or subtraction, fine judgment tasks, 'digit-symbol substitution test, digit-code memory, reading comprehension, speech or verbal out-put, forward and backward digit spans, goal directed complex serial subtractions and additions to reach a set end sum, and short-term or immediate memory functions.

In general, Kiplinger et al. (1971) have clearly demonstrated that the degree of impairment is dose related and varies in degree during the period of intoxication exerting its maximal effect at the peak intoxication.

Naive subjects commonly demonstrate greater decrement in performance than experienced users but report less subjective effect (Weil et al., 1968). Experienced users appear to better compensate to the effect of the drug especially for ordinary performance at lower doses (Clark and Nakashima, 1968; Clark et al., 1970; Crancer et al., 1969; Jones and Stone, 1970; Meyer et al., 1971; Weil and Zinberg, 1969; Jones, 1971; Mendelson et al., 1972). Performance of simple or familiar tasks (i.e. simple reaction time) during intoxication is minimally effected. However, on unfamiliar or complex tasks (i.e., complex reaction time), performance decrements occur (Weil and Zinberg, 1969; Dornbush et al., 1971; Moskowitz et al., 1970).

Performance decrements are further enhanced when verbal tasks are performed during

delayed auditory feedback (Kiplinger et al., 1971). Also marked individual differences in performance are noted between similar subjects. (Clark and Nakashima, 1968; Clark et al., 1970; Manno et al., 1970; Kiplinger et al., 1971). A cyclical waxing and waning of the intensity of the intoxication and concomitant performance occurs periodically (Clark et al., 1970; Melges et al., 1970).

Finally, when subjects concentrate on the task being performed at "normal social high," objective evidence of intoxication is not apparent and the individual may perform better than when drug free (Rodin and Domino, 1970; Mendelson et al., 1972).

Obviously, these observations raise practical doubts regarding the intoxicated individuals' ability to function at jobs requiring memory, concentration, and organization of thinking.

THE INTOXICATED MENTAL STATE

Several investigators have suggested that shortterm memory is the mental function most significantly affected by marihuana and contributes to the subtle alterations of mental functioning noted. Generally an impairment of recent or short term memory is demonstrated (Abel, 1970,1971; Dornbush et al., 1971; Menges, 1970-71; Tinklenberg, 1970; Clark et al., 1970; Weil et al., 1968). Thus, mental tasks requiring immediate information acquisition (Abel, 1971) and/or retrieval (Weil et al., 1968) are effected.

Abel (1971) recently showed that marihuana blocks the acquisition process involved in the storage of new interferes with the retrieval of already stored information. Decrements are produced in decisions requiring recent memory or sustained alertness (Clark et al., 1970); conversation (Well et al., 1968); calculations, or reading which requires retention, coordinating and indexing sequential information termed temporal disintegration (Melges et al., 1970, 1971).

Melges eta]. (1970, 1971) theorizes that episodic impairment of immediate memory produces voids which are filled with perceptions and thoughts extraneous to the organized mental processes. He suggests that this leads to temporal disintegration producing a fragmented and disorganized temporal experience in which past and future time frames are blurred and the present is experienced as prolonged or boundless. Thus, depersonalization occurs a the individual experiences himself temporally in a strange and unreal manner during marihuana intoxication.

UNPLEASANT REACTIONS: "TOO STONED" AND "NOVICE-ANXIETY"

These substantial cognitive and psychomotor effect re probably responsible for many of the acute adverse reactions to marihuana. One, of the most common is the heavy, drugged feeling where the individual feels mentally and physically sluggish so that every motion and thought seems to require extreme effort (Smith and Mehl, 1970). This probably reflects impaired cognitive function and psychomotor retardation from getting "too stoned." This most frequently occurs after oral ingestion of a large dose of drugs or in inexperienced smokers who have, not learned to selftitrate their dose to achieve the desired high.

In these instances, depression, anxiety, fatigue, short-term memory loss, dizziness, nausea, incoordination, palpitations are experienced as generalized discomfort, and ill-being.

"Novice anxiety reactions" or panic reactions accoun: for a majority of acute toxic reactions to marihuana (Baker and Lucas, 1969; Baker-Bates, 1935; Gaskill, 1945; Grossman, 1969; Persyko, 1970; Bialos, 1970; Sonnenreich and Goes, 1962; Sigg, 1963; Dally, 1967; Hamaker, 1891; Marten, 1969; Smith and Mehl, 1970; Walton, 1938).

When dosage, set and setting are optimal the distortion of self (depersonalization) and temporal disintegration (timelessness of the present moment) common to marihuana intoxication is recognized by the individual as time-limited and drug-induced. It is usually experienced as pleasurable. But, if dose, set and setting are not optimal the experience may cause the intoxicated individual to fear that loss of his identify and self control may not end or that he is dying or losing, his mind. Acute, anxiety or panic results (Mel et al., 1970).

Non-drug factors of set and setting play a most important role in these, reactions. Of course, the great variability of individuals makes the effect of marihuana on any specific individual rather unpredictable.

The large majority of these anxiety reactions occur in novices who have intense underlying anxiety surrounding marihuana use such as fears of arrest, of disruption of family and occupational relations and of possible physical and mental dangers. Also, individuals with relatively rigid personality structures, whose values are more in line with those of the "straight"society and have little desire for new and different experiences, appear to experience these, anxiety reactions much more frequently than those, individuals who are members of the "counterculture" (Smith and Mehl, 1970).

In addition, simple episodes of neurotic depression may be observed in these, same types of individuals during periods of unusual psychological stress (Well, 1970). Both of these types of reactions are transient and abate as the drug effects wear off over a few hours. Treatment should consist of gentle but authoritative, reassurance that nothing is seriously wrong and that the drug effects will wear off and the individual will feel normal" again (Smith and Mehl, 1970; Well, 1970).

ACUTE PSYCHOSES

Rare cases of full-blown acute psychotic episodes precipitated by marihuana use are reported in individuals with histories of mental disorder, with marginal psychological adjustments or with poorly developed personality structures and ego defenses (Talbott, 1968; Heiman, 1968; Kaplan, 1971; Pernot, 1969; Keeler, 1968; Defer and Diehl, 1968; Wurniser et al., 1969; Allentuck and Bowman, 1942; Bromberg, 1939; Bromberg, 1934; Curtis and Wolfe, 1939; Hughes et al., 1970; Isbell et al., 1967; Keup , 1970; Keeler, 1967; Talbott and Teague, 1969 Mayor's Committee, 1944).

Marihuana intoxication may hinder the ability of these, individuals to maintain structural defenses to existing stresses, or, alternatively produce a keener awareness of personality problems or existing stresses (Smith, 1968). Psychotherapy and antipsychotic medications are useful in controlling and preventing this reaction (Weil, 1970).

Exceptionally rare reports from North America of nonspecific toxic psychosis or actite brain syndrome have occurred after extremely high drug dose consumption, although such reports are, more common in the eastern countries. These conditions are self-limited and clear spontaneously as the drug effect abates (Weil et al., 1968; Bartolucei et al. 1969 Ames, 1958; Isbell et al., 1967; Mayor's Committee, 1944; Williams et al., 1946).

Finally, marihuana intoxication may trigger delayed anxiety reactions or psychotic episodes in a small percentage of persons who have prior experience with hallucinogenic drugs (Ungerleider et al., 1968; Ungerleider, 1969; Weil et al., 1968; Favazza and Domino, 1969).

In summary, the acute psychomotor-cognitive effects of marihuana intoxication are, interesting academically to gain understanding of normal and abnormal mental function. Also, for practically determining the danger-risk factor for the individual including determination of his functional level personally, vocationally and socially in this society. The effect on personal-social-vocational function is highly individualized and difficult to predict at present.

Although reports of anxiety attacks and psychotic episodes are more frequent as marihuana use spreads, they are still exceedingly rare and their incidence appears to be decreasing as use becomes more acceptable to more diverse populations. For example, during the nine-year period of 1961 to 1969, out of 701,057 admissions to Los Angeles County Hospital, located in a city with very high marihuana use, only three patients required hospitalization for psychic sequelae of marihuana smoking (Lundberg, et al., 1971).

In contrast, many cases are being seen in Vietnam soldiers where a extremely potent material is available and daily stresses are high, but, these probably represent only a small fraction of marihuana, users (Talbott and Teague, 1969; Talbott, 1968; Heiman, 1968).

During the, academic year 1968 and 1969, eight students were seen in the mental hygiene division of a private Eastern University student population (8,500) with acute anxiety reactions (Bialos, 1970). The frequency of marihuana-associated acute adverse, anxiety reactions requiring attention at Boston University Student Health Service (student population 20,000) is between five and seven yearly (Pillard, 1970).

In a recent survey of newly admitted patients to a large mental hospital, marihuana was the direct cause of the hospitalization in only 0.9 per thousand admissions (Keup, 1970).

PERSISTENT EFFECTS AFTER ACUTE DOSE

Investigators have not noted persistent effects after smoking marihuana for periods of more than three to five hours (Fink et al., 1971; Weil et al., 1968; Pillard, 1970).

Users report only minimal hangover effects (Mayor's Committee, 1944; Haines and Green, 1970; McGlothlin et al., 1971) after very heavy use. Feelings of lassitude and heaviness of the head, lethargy, irritability, headaches and loss of concentration are reported especially when associated with lack of sleep (Chopra and Chopra, 1939; Indian Hemp, 1893). This may be related to preliminary data (Rickles et al., 1970) suggesting a subtle increase in REM sleep time primarily seen in the last one-third of the night in individuals who smoked one to two cigarettes per day usually at night for at least a year.

EFFECTS OF MARIHUANA USE ON CONCOMITANT BEHAVIOR

Mendelson et al. (1972), under contract to the Commission, analyzed the effects on behavior of acute marihuana intoxication on an extensive variety of assessine nts including a simple

operant task, mood states, individual and group observations before, during and after smoking and clinical psychological evaluations.

Sleep-inducing properties were confirmed. Increased amounts of total sleep were observed in both number and length of shorter and longer blocks of consecutive hours of sleep related to marihuana smoking.

Examination of mood assessments prior, during and after marihuana smoking indicates that the acute effects were a reduction of negative moods (anxiety, hostility, and guilt-shame) and an increase in the positive moods (carefreeness and friendliness). Examinations of the mood prior to smoking revealed that the subjects tended to smoke marihuana when they reported generally positive moods. The effect of the drug was to increase this positive mood. One paradoxical finding was that the subjects also reported feeling more depressed after smoking.

Acute effects of marihuana on cognitive and motor functions were studied with a battery of tests sensitive to brain function (Halstead Category Test, Tactile Performance Test, Seashore Rhythm Test, Finger Tapping Test, Trail Making Test and the Weschler Adult Intelligence Scale). No alterations in performance as a result of acute intake of marihuana were noted in any of these.

The acute effect of marihuana smoking on social behavior was investigated, by observing the individual and his interaction in small groups. The data indicated very strongly that marihuana smoking, in addition to being a subjective drug experience, is also a social activity around which verbal interaction and other types of social behavior are centered.

Although marihuana smoking tended to be, a group activity, subjects did not always engage in verbal communication while smoking. Subjects often were observed withdrawing from the social interaction and then participating in some type of noncommunicative passive activity, such as watching television, listening to music, reading or staring at objects or people. This decrement in total interaction appeared to be a drug effect.

Heavy marihuana users tended to be more withdrawn than the intermittent users, often listening to the stereo and focusing on the personal effects of the drug. The intermittent users tended to watch television which provided group entertainment, thus enhancing the social effects of the drug.

Verbal interaction in formal task-oriented discussion groups diminished when several group members were simultaneously intoxicated. How-ever, groups engaged in problem-solving tasks performed more efficiently because less suggestions and discussion ensued before proposing a workable solution. The groups tended to become more convivial and less task-oriented although none failed to arrive, at the goal. Marihuana did not appear to increase hostility during these sessions and furthermore tended to change the nature of hostile communication from direct criticism to indirect sarcasm.

Assessment of risk-taking behavior revealed that under the influence of marihuana, users tend to become more conservative in the decision making.

In summary, it appears that marihuana does exert subtle effects on measurable components of social behavior and interaction.

Effects of Short-Term or Subacute Use

ANIMAL STUDIES (PRECLINICAL)

Studies have only begun in this area in the last 10 years. Subacute toxicity studies in rats involving 30 daily intraperitoneal injections of up to 30 mg/kg THC were recently reported by Phillips et al. (1971). No fatalities were observed. Total body and organ weight (rains were significantly retarded over the period. However, no significant differences in organ histology were detected altnough in a few animals there were suggestions of change in liver and testicular cells. An interesting phenomena also observed was a suggestion of increased sensitivity to effects of Delta 9 THC occurring after two weeks of daily treatment.

Thompson et al. (1971) under contract to NIMH studied the toxicity in rats treated daily for seven, 28, 91 and then 119 days with oral Delta 9 THC, A" THC and crude marihuana extract at doses from 50 to 500 mg/kg. The findings were generally similar for all three preparations although A" effect was greater than All THC wnich in turn was greater than CME.

A bimodal pattern of behavorial toxicity was exhibited by the cannabinoids for all time periods of dosing ranging from five to 119 days. Initially, a dose-related generalized central nervous system depression was noted. This was characterized by huddled posture, inactivity, drowsiness, slow movements, unkempt appearance, loss of appetite, wide stance, constipation, weight loss, depressed respiration and heart rate and fall in body temperature. Tolerance gradually developed to the initial depressant effects starting after two to five doses and continued at different rates for different parameters.

Concomitant to the development of tolerance, rats exhibited progressively more hyperactivity, manifesting increased exploratory behavior, grooming and motor activity. The daily duration of the altered behavior progressively shortened. Tolerance to the hyperactivity was not seen in the rats. Later, in the experimental period, the rats became hyper-irritable and exhibited fighting behavior, especially at lower doses. Additionally, tremors and later chronic convulsions occurred in significant numbers of rats.

The onset and frequency of chronic convulsions were dose-related and the severity increased as the duration of dosage was extended. Cumulative toxicity, as evidenced by increased mortality, was observed in the rats but most deaths and maximal toxicity (central depression) occurred 36 to 72 hours following first treatment. Drug dose-related histopathological changes in all treated rats (in addition to decreased body and organ weight gains) were hypocellularity of the spleen and bone marrow, vacuolization of the adrenal gland and degeneration of the testes (seminiferous tubules) or ovarian stronia. Extended doses from five to119 days were not significantly more toxic except to the adrenals. No evidence of abstinence syndromes were noted upon abrupt cessation of these doses.

Similar behavorial and clinical findings were observed in monkeys given 50-500 mg oral Delta 9 THC, All THC and equivalent CME for up to 91 days. Cumulative toxicity was less

severe and all monkeys survived the initial moderately severe central nervous system depression. Tolerance to the depression occurred and the monkeys returned to their undrugged behavior. Mild hyperactivity was noted only in several of the median dosed animals.

Three of 28 monkeys studied became moribund on days 10, 14 and 16 respectively. These were sacrificed and the only histopathology seen was severe hemorrhagic and probably drug-related enterocolitis. The bone marrow and kidney changes seen probably were due to severe electrolyte imbalance resulting from the intestinal lesion. The thymus lesion is consistent with stress due to this electrolyte imbalance. Pancreatic atrophy was due to weight changes. Eight additional monkeys were sacrificed at 28 days in fair-to-good condition and no histopathology was demonstrable. Several other monkeys had bloody diarrhea, but recovered spontaneously without demonstrable histopathology.

The remaining 17 monkeys were all in fair-to good condition at 28 days and hyperactivity was no longer observed. They were treated at the same dose for an additional 63 days. Tolerance to the central depression continued to develop so that the effects lasted only one to two hours at 91 days. No additional monkey fatalities were recorded -and the remaining 17 monkeys were normal histopathological at autopsy. Urine and ophthalmological examinations were all within normal limits. Hematological and blood chemical changes after 28 and 91 days were minor and little affected in the surviving monkeys.

Thus, a. minimal toxicity in monkeys, either physical or behavorial, is evident after 91 daily doses orally of enormous amounts of Delta 9 THC. However, significant cumulative toxicity, primarily a generalized central nervous system depression, is evident in the first few days but tolerance rapidly develops to these effects. A dose-related hemorrhagic enterocolitis occurred which may lead to electrolyte imbalance and death in a few monkeys. This probably is a direct irritative phenomena.

Again, the enormous daily doses of THC that were administered to these animals cannot be compared to the daily doses used in man even by the heaviest users.

The effects were observed of 28 daily administrations to monkeys of intravenous Delta 9 THC in sesame oil-Tween 80-saline vehicle at doses of 5, 15 and 45 mg/kg. Behavioral, clinical, hematological and hemochemical changes were similar for monkeys given single or repeated injections. However, the duration was extended in the 28-day groups and tolerance gradually developed. Delayed death indicative of cumulative toxicity occured on days eight and 19 in two of four animals given the largest dose.

Histopathological changes, noted in the two animals which succumbed and in one of the highdose monkeys, were acute hemorrhagic pneumonia resembling the finding in the single-intravenous studies at doses of 128 mg/kg or greater. Additionally in the repeated dose study, edema, ulceration and fibrosis at the injection sites probably contributed to minor hematological and hemachemical alterations.

In summary, the 1972 Marihuana and Health Report to the Congress from the Secretary of HEW noted that these doses were employed in rodents and mammals to test the limits of toxicity. The doses are much higher than those used by man and the routes of administration substantially dif ferent. These studies have shown that the margin of safety between the lethal dose and the pharmacologically active doses of Delta 8 and All THC and crude marihuana extract is large. Consequently, it has been determined that these compounds could be safely administered to man for Phase I and early Phase II clinical studies (Secretary of HEW, Feb. 11, 1972, p. 158-160).

HUMAN EXPERIMENTS (CLINICAL)

Only a few investigators have studied the subacute administration of marihuana to man. Marihuana cigarettes of unknown potency were made available to 34 military prisoners in Panama by Siler et al. (1933). The mean daily consumption was five cigarettes (range one to 20). The usual behavior effects associated with marihuana use were noted. No ill effects were observed nor abstinence syndrome seen.

Williams et al. (1946) made available marihuana cigarettes of unknown potency to six prisoner addicts who were experienced marihuana users in the Public Health Service Lexington Hospital. The subjects were permitted to freely consume the drug in any quantity desired. The number of cigarettes consumed increased only slightly over a 39-day period. The daily range was from nine to 26 per day with a mean of 17. Only minimal evidence of tolerance was seen. There was no evidence of physical dependence; that is, no observable abstinence, syndrome was observed after abrupt termination of the drug.

In general, the following observations were made on these subjects: daily rectal temperature increased slightly; pulse, rate increased for three weeks, then returned to normal; no change was noted in respiratory rate, coordination, or rote memory ; increase was noted in sleep and body weight while caloric intake initially increased then progressively decreased; mild confusion was observed; general intelligence tests were slightly impaired while psychomotor tests were performed faster but less accurately; EEG showed inconsistent changes but returned to normal five days after cessation; and mood was euphoric for several days followed by general lassisitude and indifference.

In a recent uncontrolled preliminary study (Personal Communication, 1970), marihuana extract was administered daily to eight terminal cancer patients from four to 13 days (mean 8.5 days). Daily doses were purposefully raised by the investigator from 7.5 mg (mean daily dose 19.8 mg THC). The total dose per individual patient averaged 168 mg with a range from 75-210 mgs.

Euphoria was experienced by all eight subjects and one had a transient anxiety episode at a high dose. Three subjects demonstrated decreased-opiate analgesic needs indicating an analgesic-effect of the drug. Five subjects reported improved appetite and five, of six tested, demonstrated objective improvement in depression on Back scale. No new changes were seen in physiological parameters, neurological status, blood cell and chemistry values or urine examination. During the period of drug effect, drowsiness was common but not lethargy, lassitude or indifference. In fact, all became more active on the ward. No evidence of abstinence symptoms were seen after abrupt discontinuation of the drug.

Volavka et al. (1971) in preliminary experiments administered two marihuana cigarettes daily (13 mg Delta 9 THC) to four detoxified heroin addicts. Pleasant effects peaked during the second week and then leveled off. Prominent dysphoric effects and depressive reactions with paranoid thoughts appeared during the third to sixth days and persisted causing cessation of the study by one subject after 10 days and after 17 days by another. The other two subjects completed the entire planned 22 days.

Again no abstinence syndrome was seen and the dysphoric symptoms disappeared within five days after the last dose. Consistent electroencephalogram changes developed in three of four subjects indicating increased synchronization. Their EEG changes first appeared immediately after smoking.

In two of the f our subjects they were detectable, in the presmoking records after days 12 and eight, and did not begin to subside until 48 hours after the last dose in two subjects and persisted for the entire 72 hours follow-up in a third subject.

Fink et al. (1971) subsequently studied five medical and graduate students who had been almost daily marihuana smokers in college and were currently weekend smokers. Each subject smoked under laboratory conditions one marihuana cigarette containing 14 mg of THC each morning daily for 21 days.

No subject reported any adverse effects from smoking. The subjects were generally able to conduct their usual daily activities including jobs. However, they reported they did not function completely up to par during the several hour duration of the acute drug effect. There were no effects which persisted for more than three to five hours and cumulative effects were not noted day to day. No persistent decrements were seen in behavior, mental status, EEG, heart, rate, short-term memory, or psychomotor function tests. In sum, daily marihuana smoking for 21 days was well tolerated by well-adjusted graduate students.

Mendelson et al. (1972) performed a Commission-sponsored study of the biological and behavioral concomitants of 21 days repeated doses of marihuana. Subjects were individuals whose life style, activities, values and attributes were more characteristic of the unconventional youthful subculture than most of their peers in the general population. Their mean age was 23. Based on I.Q. testing they were superior intellectually although they had completed, on the average, two-and-a half years of college. Their job histories were rather erratic and characteristic of a pattern of itinerant living. Their family background was a middle or lower-middle socioeconomic status. In addition alcohol use was infrequent while use of drugs, especially hallucinogens and amphetamines, was significant.

Two groups of 10 subjects each were investigated over separate 31-day periods of confinement on a comfortably furnished research ward equipped with an array of recreational materials. A large, open yard was available for outdoor recreational activities. The research period was divided into three periods: a pre-drug period of five days during which the subjects were drug free; a, subsequent 21-day period when marihuana, could be earned by performing a, work-contingent operant task, then purchased and smoked on a free-choice basis; and a five-day post-drug period without access to marihuana.

All attempts were made to not interfere in any way with performance of the operant task or free choice marihuana smoking although the subjects were under constant observation. A vast array of behavioral and biological assessments were made during the experimental period to determine any effect of repeat doses of marihuana over this time.

Two groups of subjects, studied separately, differed primarily in the frequency of marihuana smoking over the past year. Both groups had averaged about five years of marihuana use (range two to 17 years). The first group studied, referred to as the "casual" users by the authors, reported an average frequency of marihuana use, of 7.7 occasions per month (range three to 15 occasions). The second group studied, referred to as the "heavy" users by the authors, reported almost daily use of marihuana (average 33 sessions per month; range 20+ to 75, including one substitute subject to fill the group who only smoked about 10 times a month).

During the first 20 days of the smoking period, the casual group's consumption averaged three cigarettes daily (individual average was one-half to six) while that of the heavy users

averaged six-and-a-half cigarettes daily (individual average three to eight-and-a-half). Both groups demonstrated a progressive trend toward increased daily consumption during the experiment. Close examination of the consumption patterns for individual subjects showed that the trend toward increased use occurred in the subjects who were initially the heaviest users. Several subjects who were initially the least frequent users did not increase their use of marihuana over the course of the study.

Subjects in both groups tended to smoke practically all of each cigarette including the butt. Each cigarette contained about 20 mg- Delta 9 THC. Therefore, the heavy users average daily intake was 130 mg of THC or a total of almost, Joni- -grams of THC over the 21-day period. The casual users average intake was slightly less than half this amount.

No abstinence syndrome or physical dependence was observed after abrupt termination of smoking. Signs of mild to moderate psychological dependence. were possibly seen in the heavy group but no evidence of psychological dependence was seen in the casual users.

No consistent clinically significant physiological or biochemical changes were demonstrated during or after the period of repeated use of marihuana.

Urinalysis, complete blood counts, cell morphologies and differentials, and blood chemistry determinations (calcium, phosphorous, glucose, blood urea nitrogen, uric acid, cholesterol, total protein, albumen, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and serum glutamic oxalacetic transaminase) were unaffected.

Weight gain occurred in all but one subject. Maximal gain was seen during the marihuana smoking period. The subjects were not judged to be clinically malnourished prior to the experiment.

Normal body temperature was not altered. No significant change, in pulmonary function (decreased. vital capacity or acute broncho spasm) was observed during the marihuana smoking period.

Variable inconsistent changes in upright blood pressure were noted. Effects on pulse rate were related only to acute drug administration and were more pronounced during the initial smoking phases. This suggests that tolerance developed to drug-induced tachycardia. No significant electrocardiographic changes were observed. Marihuana smoking had no apparent effect on exercise related cardiac vascular function.

Physical examinations revealed only the development of persistent conjunctival injection, lateral gaze nystagmus and fine, finger tremors. These findings were believed to be acute drug effects and of no clinical significance. No signs of neurological abnormality were observed. No cumulative effect of marihuana to cause, impairment of cognitive function was noted on a battery of tests sensitive to organic brain function.

An increased amount of sleep in both shorter and longer blocks of consecutive hours was observed. Also an increase in the number of discrete episodes of sleep, especially one to three hour episodes also occurred during the marihuana use period. Reappearance of pre-drug pattern was seen during the post-drug period. This reversion appeared to begin toward the end of the drug period which may be indicative of tolerance, to the acute depressant-like

effects of marihuana.

Generally, performances on short-term memory, psychomotor skills and time estimation suggests that repeated marihuana smoking had no discernible effect on the ability to improve performance with practice on these measures. Tolerance appeared to develop to the acute decrement in performance on these measures. On the time estimation task, a tendency appeared for the subjects to increasingly overcompensate for the acute drug effect with repeated testing in the nonintoxicated state.

Both casual and heavy users had a marked decrement in total social interaction during the first portion of the marihuana smoking period. Total interaction of the casual subjects continued to diminish subsequently. Heavy users subsequently tended to exceed presmoking levels of interaction indicating they accommodated to the depressant effects of repeat doses of marihuana.

Both groups became progressively more convivial and less task-oriented in group discussions. They offered less suggestions in problem-solving tasks but continued to efficiently solve the problem.

Casual users reported general relative increases in negative daily moods and decreases in positive daily moods during the course of the study. The trend began with the onset of smoking and persisted through the post-smoking period. This trend could be a sequelae of repeated marihuana use or related to non-drug variables (set and setting).

The heavy users did not evidence this trend toward relative increases in dysphoric mood until the post-smoking period. Again this may be related to repeated marihuana use, reflect psychological dependence or be related to set and setting variables, such as boredom and tension associated with the prolonged study period.

Finally, repeated use of marihuana over the 21day period did not decrease motivation to engage in a variety of social and goal-directed behaviors. Almost without exception, every subject earned the maximum number of points every day throughout all non-drug and drug periods. No consistent alteration in pattern of work could be related to repeated marihuana use. Subjects often performed very high work output while they were smoking marihuana and experiencing the maximum drug effects.

Repeated marihuana use, did not decrease subject's motivation to complete the study. Nor was any noticeable effect observed on interest and participation in a variety of personal activities, such as, writing, reading literature, keeping up with current national and world events, and participation in both athletic and esthetic endeavors.

Effects of Long-Term Cannabis Use

Patterns of marihuana use in Western countries, particularly the United States are primarily long term (two t o 10 years). Additionally, Western investigators have been able to observe those who use marihuana at most, daily and more often, moderately or intermittently. Consequently, observed effects are rare. Knowledge is incomplete but certain trends appear to be emerging in regard to American usage patterns.

The relevance of Eastern reports of heavy hashish use is uncertain. Nutrition, disease prevalence and quality of medical care impose limits on transferring Eastern observations to Western conditions of use.

DEPENDENCE AND TOLERANCE

Neither severe physical dependence, nor prominent withdrawal symptoms after abrupt termination of very heavy usage is suggested by some overseas experience (Charen and Perelman, 1946; Fraser, 1949; Ludlow, 1857, Marcovitz and Myers, 1944; Siler et al., 1933; Walton, 1938). Other studies, however, suggest marked psychological dependence from heavy use producing compulsive drug taking in very heavy users (Indian Hemp, 1893; Chopra and Chopra, 1957; Bouquet, 1944; Lambo, 1965).

Psychosomatic abstinence syndromes often reported were physical weakness, intellectual apathy, loss of appetite, flatulence, constipation, insomnia, fatigue, abdominal cramps and nervousness, restlessness, and headache. For most heavy users the syndrome of anxiety and restlessness seem to be comparable to that observed when a heavy tobacco smoking American attempts to quit smoking.

However, the psychological dependence appears to be severe as evidenced by the f act that one group of subjects were unable to cease their habitual use although the frequency of use, was only eight to 12 times per month (Soueif, 1967). This psychological dependence may have made some users claim physical dependence so that the government did not terminate dispensing them their drug. Studies in the United States using must lower doses for shorter periods of time have revealed little if any evidence of psychological dependence (Bromberg, 1934 Mayors Committee, 1944; Williams et al., 1946).

Tolerance to the subjective and depressant effects of the drug (discussed in an earlier section) does probably occur in man, with heavy use. Thus, increasingly larger and more frequent doses become necessary to experience the desired effects.

Several investigators have recently studied the question of physiological and psychological dependence to Delta 9 THC in monkeys using intravenous self-injection techniques.

Deneau and Kaymakcalan (1971) demonstrated that no monkey initiated self-administration over a three-week period when given the opportunity to self-inject a

behaviorly effective dose of 100 micrograms per kilogram of Delta 9 THC in a Tween solution. The researchers subsequently administered to these monkeys this dose every six hours. Tolerance developed to the behavioral effects within a few days. Dose administered was progressively increased up to 400 micrograms per kilogram over the course of a month. When the injections were abruptly discontinued, all six monkeys showed after twelve hours, behavioral and physiological changes described by the researchers as mild abstinence signs. Two of the six monkeys then initiated and maintained for several weeks the self-administration of THC.

The investigators believe these findings are evidence for mild psychological and physiological dependence on THC. However, vehicle controls were not included in the research design. Thus, the abstinence signs and subsequent behavior may possibly be accounted for by the biological effects in of the Tween vehicle.

Harris et al. (1972) utilized several procedures to maximize the possible conditions necessary for developing self-injection in monkeys. These procedures included: spontaneous Delta 9 THC self administration with no previous training to the technique; self-administration of A' THC after training, with cocaine alone and a mixture of cocaine and Delta 9 THC. Doses utilized ranged from 20 to 500 micrograms per kilogram suspended in polyvinylpyrrolidone. In all cases, monkeys failed to self -administer Delta 9 THC.

The researchers conclude that A' THC lacks the reinforcing effects of psychomotor stimulants and depressants which monkeys readily self infuse with no auxiliary incentives. Also Delta 9 THC lacks a reinforcing function even for monkeys that are well-trained with cocaine and have experienced several days of rather large quantities of Delta 9 THC during the early pleases of extinction of the cocaine reinforced response.

Finally, the results demonstrate that a two week period of exposure to Al THC (in a mixed solution with cocaine) does not result in the degree of homeostatic imbalance which occurs with morphine, ethanol, barbiturates and sometimes the amphetamines which accounts for the continued self-administration of these drugs.

PHYSIOLOGICAL EFFECTS

Permanent congestion of the transverse ciliary vessels of the eye and accompanying yellow discoloration is the only physical effect firmly linked to long-term marihuana use (Ames, 1958; Chopra, and Chopra, 1957; Dhunjibhoy, 1928). Although there are several suspected or reported effects, none has been conclusively demonstrated in a valid study. Some (Chopra and Chopra, 1939; Indian Hemp, 1893) claim that bronchitis, asthma and other respiratory problems may be produced by chronic and excessive use of potent compounds in India. Eastern smoking, preparations are often a mixture of tobacco and hashish.

Indian users reportedly exhibit digestive tract abnormalities, weight loss and disturbed sleep (Chopra and Chopra, 1939; Soueif, 1967). However, the contributing factors of poor living conditions, malnutrition and prevalence of communicable disease could not easily be separated.

A high percentage of heavy Moroccan users have developed obliterative arteritis of the lower extremities (Sterne, 1960) possibly related to the occurrence of tropic foot ulcers (Ganja -foot) (Miras, 1965). The progression of this abnormality is claimed to parallel prolonged use of the drugs.

Mendelson et al. (1972) were unable to demonstrate clinically significant abnormalities in the extensive battery of tests performed which could be attributed purely to the subjects long-term use of marihuana. No histories were obtained of neurological, hepatic, renal, pulmonary, cardiac, gastrointestinal, (renitourinary, or nutritional disorders. No history of psychotic illness was given.

All subjects were Judged to be in normal mental, health by psychiatric interview and psychological tests (MMPI and Edwards Personality Preference Inventory). Three subjects were felt to be neurotic.

Pre-drug complete physical exams, chest X-ray, electrocardiogram, urinalysis, complete blood count and blood chemistry profile did not demonstrate, any clinically significant abnormalities. No subject showed evidence of poor nutrition.

Pulmonary vital capacity and one second forced expiratory volume were reduced in 12 of the 20 subjects initially. These changes were not correlated with either current cigarette smoking or f requency or duration of marihuana smoking. Histories of past cigarette use, past patterns of marihuana use and past or present contact with environmental air pollutants were inadequate to attempt to account for these pulmonary findings.

Many of the subjects were in fair to poor physical condition as judged by a cardiac exercise tolerance test.

Four of the 20 subjects' initial performance on a battery of cognitive functions tests was poorer than would have been predicted by high average to superior I.Q. scores and educational backgrounds. One of the casual subjects demonstrated improvement with retesting consistent with good brain function. Thus, behavioral impairment was present in three subjects.

Whether the impairment is related to prior drug histories, particularly the excessive use of LSD by the two heavy users, cannot be ascertained. For the casual user nothing in the case histories possibly elucidated the reason for relatively poor performance based on the exceptionally high I.Q., 139 and 128.

Many Western investigators have suggested that smoking hashish or marihuana may possibly cause bronchitis, asthma or rhinopharyngitis (Bloomquist, 1967; Waldman, 1970; Tylden and Wild, 1967; Schwartz, 1969).

Tenant et al. (1971) described bronchitis, sinusitis, asthma and rhinopharyngitis in 22 American soldiers in Germany who smoked daily enormous quantities (100 grams or more) of hashish for six to 15 months. These conditions, believed to be caused by irritation of the respiratory tract by hashish smoke, seemed to improve, with diminished hashish use.

Twenty-one of the subjects were tobacco cigarette, smokers and occasionally smoked hashish rolled in a tobacco cigarette. Nine patients had symptomatic bronchitis. Five of these subjects underwent pulmonary function tests while consuming their usual daily amount of hashish and again three days after discontinuing use. A mild obstructive pulmonary deficit was demonstrated which was at least partially corrected with diminished hashish intake. Hashish contributed to rbinopharyngitis in 12 of the patients and this effect was not allergic in origin. Urticaria, acne, diarrhea and gastrointestinal cramps were less frequent complaints. Extensive hemotological and hentochemical studies including liver function tests were performed and were within normal limits.

Mann et a]. (1970, 1971) and Finley (1971) studied the effect of marihuana smoking on the pulmonary function of eight non-cigarette smoking marihuana smokers (20-27 years old). Marihuana smoking history was defined in marihuana cigarette-years, that is, one marihuana cigarette daily for one year or the equivalent over a longer or shorter period. The mean marihuana cigarette years for the group was 11 and the range from 2.5 to 26. Three of the marihuana users also used hashish. Chest X-ray, comprehensive spironietry deterinitiations, lung volumes and carbon monoxide diffusion studies were observed and retested with prednisone. Pulmonary functions were essentially normal for all of the non-cigarette smoking marihuana smokers and non-smoking controls.

These investigators were able to distinguish differences in quantity and structure and function in pulmonary macrophages and minor material between marihuana smokers and nonsmokers. In tobacco smokers more marked changes were noted. These changes do not indicate a diminution in defensive capacity of these cells.

Kew et al. (1969) has suggested a possible hepatotoxic effect of marihuana. right persons who smoked marihuana for two to eight years, at least six times a week, evidenced mild liver dysfunction by liver function tests and liver biopsy. Several of the patients admitted to the use of alcohol and oral amphetamines but denied use of intravenous drugs. The authors concluded that the findings were not unequivocally due to marihuana.

Hochman and Brill (1971) noted abnormal liver function tests in 10 of 50 frequent marihuana users. However. all admitted to long-term, regular and heavy use of alcohol. When these subjects abstained from alcohol for one month but continued their usual marihuana usage, evidence of disturbed liver function cleared in nine out of 10 subjects.

Recently, Liskow et al. (1971) reported the appearance of an anaphylactoid reaction in a 29year-old woman after smoking marihuana for the first time. Skin tests were positive for an allergy to marihuana, constituents. Allergy to marihuana, especially in areas of the country where it grows wild, may be more common than generally believed.

Campbell et al. (1971) presented evidence of ventricular dilatation consistent with cerebral atrophy by air encephalography in 10 young males (average age 22) with histories of consistent marihuana use for three to 11 years as well as less frequent use of LSD and amphetamines. The first four of the patients had been referred originally for neurological investigation of behavioral change, memory loss or headache. The remaining six subjects were selected from patients tinder treatment for drug abuse because of their long history of marihuana use and concomitant neurological and behavioral symptoms.

However, the patients showed personality behavioral and mental disorders, as well as histories of head trauma and psychomotor or grand mal epilepsy that are commonly associated with ventriculographic changes. Also alcoholism can be associated with these findings. Additionally, the authors compared their subjects ventriculograms with those of normal young adults originally referred for loss of consciousness, syncope and headache without subsequent development of neurological illness.

Thus, the authors demonstrated dilation of the third ventricle, of the frontal or temporal horn, or of the trigone of the lateral ventricle. All of these are commonly associated with personality and mental disorders such as these patients shelved. However, whether these changes are caused by marihuana is not proven beca..se no specific neuropathological cause for the cerebral atrophy was identified. Further carefully designed studies are required to clarify this finding.

The LaGuardia Report (Mayor's Committee, 1944) indicated no damage to the cardiovascular, digestive, respiratory and central nervous system, nor the liver, kidney or blood in individuals who had used from two to 18 cigarettes of unknown potency (average seven) for a period of two-and a-half to 10 years (average eight). However, this study was not up to modern standards as it lacked double-blind precautions and placebo controls and adequate statistical analysis of the data. Bias was present in reporting. Small numbers of prisoners were used as subjects.

Another less comprehensive American study of 310 individuals who used marihuana on the average of seven years was performed on soldiers (Freedman & Rockmore, 1946). It did not demonstrate any evidence of physical or mental deterioration.

Another team of investigators (Meyer et al., 1971; Mirin et al., 1970) examined a group of 10 male marihuana users (average age 25) who had consumed the drug about 20 to 30 times a month for all average of 4.4 years (one-half to five year range) and had smoked daily for three of the 4.4 years. Heavy use was correlated with psychological dependence, search for insight or meaningful experience, multi-drug use, poor work adjustment, diminished goal directed activity, decreased ability to master new problems, poor social adjustment and poorly established heterosexual relationship. No physical or neurological or psychiatric abnormalities were noted in their work-up.

Indeed, numerous American investigators have not reported abnormalities in baseline, examinations of their experimental subjects who have various patterns of marihuana use from very infrequent to many times a day.

GENETICS AND BIRTH DEFECTS

Much concern about possible effects on the unborn generations has arisen because of marihuana's use by persons in their reproductive years. Presently, most studies are preliminary.

There are three isolated case reports in man (Gelehrter, 1970; Carakiishansky et al., 1969; Heelit et al., 1968) of birth defects in mail in the offspring of parents who had used marihuana and LSD. However, due to their complex gestational histories and the high level of birth defects seen in a "normal" population, a causal relationship cannot be attributed to cannabis or anything else. At present, there is no substantial evidence indicating that marihuana at the dose commonly used is a teratogen in man.

Marihuana has been implicated as a teratogen in animals by several groups at high doses. One study (Miras, 1965) showed reduced fertility in rats impregnated after being fed a diet containing marihuana extract for several months. However, the offspring were normal. The reduced fertility may be related to the finding of marked decrease rate of cellular division, but without chromosomal damage, -when Delta 9 or All THC is added to white blood cell cultures (Neu et al., 1969 Martin, 1969).

Dorrance et al. (1970) and Gilmore et al. (1970) detected no significant difference in lymphocyte chromosomes in groups of users and nonusers. No significant differences were, found in lymphocyte chromosomes between heavy, long-term. Jamaican ganja users and matched nonusers. (Rubin and Comitas, 1972)

Pregnant mice injected with cannabis resin on day six of gestation caused stunted but not malformed offspring. Fetal reabsorption occurred when the dose was given on days one to six (Persand and Ellington, 1967). A second experiment using rats injected on days one to six produced a high frequency of malformed progeny. Another investigator (Geber, 1969; Geber and Schramm, 1969) demonstrated congenital malformations in fetal hamsters and rabbits after large multiple doses of cannabis extract.

Another group (Pace et al., 1971) have administered a wide range of dosages of Delta 8 and Delta 9 THC and marihuana extract by subcutaneous, intraperitoneal and intravenous routes at varying intervals pre- and post-conception to rats, hamsters and rabbits. Delta 9 THC up to 200 mg/kg in variety of dose schedules produced reduced average litter size and stunted pups at high doses but no birth defects. A low incidence of abnormalities occurred in rats and rabbits with marihuana extract, but a high incidence of neonatal deaths was observed apparently due to inadequate material lactation.

Studies with radioactive labeled THC (Idanpaaiini-Heikkila et al., 1969) indicated that it did cross the placenta in high concentrations early in gestation during the developmentally labile phase.

These studies suggest that Delta 9 THC itself is not a teratogen. Instead, perhaps some unidentified substance or substances in the plant extract may be causing the teratogenic effect noted by this group and others when injected. It is uncertain whether this theoretical substance(s) volatilizes during smoking or enters the pulmonary vasculature (Pace et al., 1971).

Consequently, the following FDA label required of many currently prescribed psychoactive drugs warning about use in Pregnant women and women of childbearing age, appeals indicated. "Safe use of the drug during pregnancy and lactation has not been established; therefore, in administering the drug to Pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results. . . . There have been clinical reports of congenital malformation associated with the use of this drug, but a causal relationship has not been confirmed."

ORGANIC BRAIN DAMAGE

Deterioration of mental functioning allegedly due to long-term use of marihuana can be subdivided into four major categories: organic brain damage, mental illness-psychosis, amotivational syndrome, and recurrent-pnuenomenia. As with alcoholism, it is quite often impossible to distinguish whether the described effects result from drug use or represent personality traits or changes which would have been present without the drug use.

When marihuana consumption was irregular, mental deterioration was not evidenced (Freedman and Rockmore, 1946) in 310 users with an average history of seven years of use. Sixty-seven heavy users in New York showed no evidence of dementia attributable to drug use although they did have underlying personality disorders. Another investigation (Mayor's Committee, 1944) of individuals who used a daily average of seven marihuana cigarettes (two to 18 range) for average of eight years (two-and-a-half to 16 range) showed no evidence of brain damage or mental deterioration.

Reports from India (Chopra, 1935; Chopra, 1940; Chopra and Chopra, 1939; Chopra, Chopra, and Chopra, 1942) relate minor impairment of judgment and memory, limited self - neglect and insomnia, when potent preparations are consumed regularly in large amounts for many years. No evidence for mental deterioration or brain damage has been noted.

Miras (1967) has described a Greek population of heavy hashish smokers who appear as outcasts from the community after 15 to 20 years of heavy hashish use. They appear mentally sluggish and depressed. They are reported to exhibit laziness, psychic instability, amorality and apparent lack of drive and ambition. Their speech and behavior has been described as -peculiar. Some degree of responsibility is retained in that some do work to cover their living and drug purchasing expenses. Some of them are still quite intelligent. Memory is not deteriorated except during the intoxication. They appear overly suspicious. Samples of their electroencephalograms were believed to demonstrate abnormalities.

However, Miras believes that this effect is related to the quantity and frequency of hashish use. He describes three categories of long-term hashish users. Type A uses low doses intermittently and is socially and mentally unaffected. Type B1 uses low doses daily and no interference is caused in function. Type B 2 uses high doses daily causing dependence and performance decrements. Type C uses very high doses daily allegedly causing mental deterioration and abnormal behavior described above. Fink and Dornbush (1971) are currently intensively studying this population. The results will be described in a later section.

Non-differentiated psychosis noted in foreign populations may also be included within this diagnostic category. These will be discussed with the psychosis.

PSYCHOSIS

The alleged connection between mental illness and cannabis derives from Africa, the Middle East and India. These areas are currently developing economically and scientifically, but for many years medical care and especially psychiatric care were given low priority. Many chronic illnesses still persist in these countries which may affect mental functioning. Furthermore, well-trained psychiatrists and methodologists are very rare in mental hospitals in these countries. Consequently, the findings of earlier studies are questionable due to lack of controls, biased sampling and poor data collection and failure to account for variables like nutrition, living standard, cultural factors and socioeconomic status.

India's mental institutions were widely quoted to support the, connection between excessive cannabis consumption and insanity. The Indian Hemp Commission performed a thorough and objective investigation of this question, although methodologically it was not up to modern standards. The Commission was unconvinced of the reliability of hospital statistics, where often the diagnosis was not made by a psychiatrist but by a referring policeman.

Therefore, the Commission examined all admissions to Indian mental hospitals for one year. They found that cannabis rise could not be considered a factor in more than seven to 13% of all cases of both acute and chronic psychosis.

Chopra et al. (1942) carefully performed the same examination of admission to Indian mental hospitals from 1928 through 1939 when cannabis use was extremely high. They found 600 cases of acute and chronic psychosis which could be traced to cannabis use. Other reports from India have produced varying estimates of the incidence of cannabis psychosis (Peebles and Mann, 1914; Chopra, 1971; Dhunjibhoy, 1930 Evens, 1904). In

Egypt 27% to 33% of mental hospital admissions were cannabis related (Ireland, 1893; Warnock, 1903).

Benabud (1957) reported that cannabis users comprised 68% of all mental hospital admissions in Morocco but only 25% of these admissions could be called cannabis psychosis. Watt (1936 and 1961) reported that 2% to 3% of mental hospital admissions in South Africa were due to the use of dagga (cannabis).

Boroffka (1966) and Asuni (1964) reported that 14% of psychiatric admissions in Nigeria used cannabis. Toxic psychosis accounted for half of these and cannabis was felt to aggravate underlying schizophrenia in the remainder.

Several statistical studies from other countries including Jamaica, Colombia, Algeria, Panama and Tunisia support this type of data (Prince et al., 1970; Beaubrun, 1971 Allentuck and Bowman, 1942; Bouquet, 1951; Chevers, 1870; Defer and Dielil, 1968; Fraser, 1949; Freedman and Rockmore, 1946; Porst, 1942; Siler et al., 1933; Reales-Aroyco, 1953; Medical Staff, 1938).

Very little information is available on the prevalence of psychosis in the overall population of cannabis users. Chopra and Chopra (1939) classified 2% of the ganja and charas smokers and 0.5% of the bhang drinkers in their sample of 1,200 as psychotic.

Roland and Teste (1958) estimated that no more than 0.5% of kif (cannabis) smokers in Morocco suffer from recurrent mental conditions.

Prince et al. (1970), in a study in Jamaica, noted that about 20 patients per year are admitted to mental or general hospitals with acute psychotic reactions allegedly precipitated by ganja. In one general and one mental hospital the, ganja smokers comprised 20% of the psychiatric admissions. Furthermore, the percentage of heavy ganja smokers in the community was significantly higher than 20%. Thus, a larger percentage of psychiatric admissions were, derived from non-ganja smokers in a comparable lower socioeconomic segment of the population.

This finding contrasts with the 68% prevalence of cannabis use among psychiatric admissions reported by Roland and Teste (1958) which is considerably higher than the prevalence of cannabis use in the general population of Morocco.

Studies based on several hundred cases indicate that the large majority of individuals hospitalized in mental institutions for "cannabis psychosis" have suffered acute toxic psychoses associated with a sharp toxic overdose or massive excesses among habitual users. Occasional smokers and moderate habitual users seldom had psychotic reactions and then only when there were substantial predisposing factors.

The acute clinical picture seen in these delirium with confusion, disorientation, terror, and subsequent amnesia is that of a severe exogenous psychosis. It does not typically involve the type of thought disorder characteristic of schizophrenia. Short recovery times ranging from a few days to six weeks are uniformly reported in sharp contrast to the lengthy recovery period of functional psychoses (Chopra et al., 1942; Roland, and Teste, 1958; Defer and Diehl, 1968; Beaubrun , 1971; Stringaris, 1939).

Consequently, the psychiatric literature on cannabis-induced chronic psychosis is quite confused. In general, it appears that cannabis use probably produces a specific psychosis, but this must be quite rare, since the prevalence of psychosis in heavy cannabis users, world-wide, is only doubtfully higher than the prevalence in general populations (Murphy,

1963). However, incidence and prevalence data for these countries on psychosis of users and non-users of cannabis does not exist.

A Morroccan investigator, Christozov (1965), studied 140 chronic heavy hashish users hospitalized in a mental hospital. Their behavior was characterized by a confusional state of consciousness, an impulsivity, an irresponsible attitude, and an instability of mood and character. The patients were often psychotic with persistent hallucinations. Intellectual functions were reduced in over half the cases although this was related to a low intellect prior to drug use. Electroencephalography showed no specific changes. In addition, it was noted that half of the patients were also alcoholics.

The majority of the patients were, sedated and showed a rapid improvement, allowing them to be discharged and be employed, Although it appeared that these characteristics are reversible, the patient often returned to heavy drug use again causing return of the syndrome.

Thus, the existence of a more long lasting cannabis-related psychosis is poorly defined. Some evidence indicates the existence, of a, quite rare slow-recovery, residual cannabis-psychosis following heavy chronic use. Patients often exhibit schizophrenic-like withdrawal, mental confusion and mild residual hallucinations; but there is little tendency for the, symptoms to become organized or proliferate. The symptoms develop gradually and then subside gradually before proceeding to full-blown psychotic symptoms. These may produce gradual psychic deterioration in the habitual excessive user after prolonged periods of time. Several authors theorized that the chronic psychosis consists of recurrent acute attacks with gradual deterioration in habitual excessive users (Roland and Teste, 1958; Chopra, et al., 1942; Stringaris, 1939; Sigg , 1963).

Most investigators, therefore, find it exceedingly difficult to distinguish a psychosis due to cannabis from other acute and chronic psychoses because, few, if any symptoms, are uniquely found in it and not observed in other psychoses. Often the diagnosis of cannabis psychosis is made because of the history of heavy marihuana or hashish use. Several have suggested that a characteristic cannabis psychosis does not exist and that marihuana will not produce a psychosis in a well-integrated, stable person (Allentuck and Bowman, 1942; Reales-Aroyco, 1953).

In addition, alcohol often played a part in producing the mental derangement (Medical Staff, 1938; Porst, 1942). Most data refers to any form of psychosis in marihuana users; not specifically cannabis psychosis.

Although it is fairly well-established that cannabis use attracts the mentally unstable, the prevalence of major mental disorder among cannabis users appears to be little if any higher than that in the general population. Therefore, true cannabis psychosis must be earlier, very rare or it must substitute for other forms of psychosis. Perhaps, cannabis use alternatively is protecting some less stable individuals from a psychosis (Murphy, 1963).

Because of these many difficulties, the role of cannabis use in acute and especially chronic psychoses in these countries is impossible to determine with certainty.

Finally, the Eastern literature often mentions the existence of a characteristic psychic degeneration among older habitues after prolonged excessive use (Chopra et al., 1942; Christozov, 1965; Indian Hemp Commission, 1893; Roland and Teste, 1958; Stringaris, 1939; Warnock, 1903). They are frequently described as showing a single minded, carefree

state, such as "Kif-happy vagabonds."

Soueif (1967) administered psychomotor and cognitive performance tests to imprisoned h..shish users and non-hashish users in Egypt. Preliminary results indicate that, on most of the tests, the hashish sample scored 10% to 20% below the control, and differences were larger for those with higher educational levels. These results do not necessarily indicate a causal relationship. Assessment of the significance of these findings must await further description of the samples utilized.

Experience in the U.S. and Western Europe has not involved a level of marihuana use comparable to the above-mentioned countries. Consequently, the associated chronic psychotic disturbances have not been seen.

In Western countries, Bromberg (1939) and Allentuck and Bowman (1952) reported on acute psychotic episodes with clear-cut onset during the marihuana intoxication. Most symptoms cleared within a few days although several had a prolonged illness. These rare acute psychotic episodes, discussed earlier, have been described recently by a variety of authors in scattered countries (Smith, 1968; Weil, 1970; Bialos, 1970; Keeler, 1967; Milman, 1971; Pesyko, 1970 Kaplan, 1971; Prince et al., 1970; Baker and Lucas, 1969; Grossman, 1969; Beaubrim, 1971; Spencer, 1970).

Some of these reported cases are quite transient and clear rapidly with support of others and may be more like acute panic reaction than psychosis. Still others appear to fit the picture of transient toxic psychosis.

A few cases of marihuana psychosis reported by Kaplan (1971) recovered very slowly after extensive psychotherapy. However, the high incidence of schizophrenia and borderline states described in these patients and their families may indicate that marihuana use merely aggravated or precipitated an underlying psychosis in these individuals.

George (1970) reported a case in Britain in which an acute episode of confusion, disorientation, hallucination, anxiety, paranoia, agitation and memory loss related to cannabis use was followed by a more chronic schizophrenic-like syndrome with thought disorder, incongruous affect and hallucinations. This individual was experiencing considerable financial and marital stress prior to these two separate acute episodes. The chronic condition eventually responded to psychotherapy.

Bernhardson. (1969) reported aggravation by cannabis of schizophrenic conditions in several Scandinavian patients. Perna (1969) reported a case in which marihuana appeared to aggravate an extended psychosis for which the patient had required psychiatric treatment prior to the use of marihuana.

Keup (1970) reported 14 cases of prolonged psychotic symptoms requiring hospitalization associated with the use of marihuana. He noted evidence for the existence of a high level of psychopathology in many of them which predated their marihuana use.

Kolansky and Moore (1971) in a widely publicized report of cases of individuals ages 13-to-24 has claimed profound adverse psychological effects from smoking marihuana two or more times a week.

Of 38 individuals reported, all had decompensated personalities, eight had psychoses (four

attempted suicide) and 13, according to the authors became sexually promiscuous due to marihuana. These clinical impressions were, all based on, at most, a few interviews with the, individuals who were referred to these psychiatrists for consultation for problems (including one-third by legal authorities after arrest for possession of marihuana).

Unfortunately, the authors made sweeping generalizations to all young adolescent marihuana users from this biased and non-representative sample. No attempt was made to interview other young marihuana users who have not been referred for psychiatric help, and the high prevalence of promiscuity and psychopathology in comparable adolescent populations was totally disregarded. In addition, case histories of previous mental health were obtained introspectively from the patient, their families or the referral source.

Thus, it is impossible, to state unequivocally, as the authors do, that since marihuana use and psychiatric problems occurred at the same time the former is causative of the latter.

Several authors have reported acute toxic psychosis following marihuana use by soldiers in Vietnam (Talbott and Teague, 1969; Colbach and Crowe, 1970, Bey and Zecchinelli, 1971).

All these cases represented transient reactions and cleared rapidly with treatment. In many cases, personality disorders or borderline personality states appeared to be predisposing factors in the development of the psychotic state. Often revealed were problems of identify diffusion, ego weakness, low self-esteem and inability to form close interpersonal relationships. Also the stressful conditions of the setting in which the drug was used deserves emphasis.

Halikas et. al. (1971, 1972) performed intensive psychiatric interviews on a population of 100 regular marihuana users and a control group of 50 of their non-using or casually using friends. Half of each group met the criteria for some psychiatric diagnosis. Psychiatric illness and antisocial behavior most often preceded marihuana use.

Some attempts have been made to estimate the incidence, of psychosis and other adverse reactions to marihuana in Western countries. Obviously, such estimates depend on how these reactions are defined-one questionnaire study of 2,700 psychiatrists, psychologists, internists and general practitioners in the Los Angeles area reported 1,887 "adverse reactions" to marihuana in an 18-month period (Ungerleider et al., 1968). Adverse reactions were not defined by the authors in the survey. Those reported ranged from mildly unpleasant parental objections to use to severe anxiety or acute psychosis.

Keeler (1967) reported on "adverse reactions" to marihuana (paranoid feelings, etc.) which are limited to the immediate period of intoxication. These phenomena occasionally occur in such a light proportion of regular users that they are of little interest in the present discussion, e.g., 80% of users report they sometimes have paranoid reactions during the marihuana intoxication (Tart, 1970).

Other estimates have been based on hospital admissions in which marihuana use was the recognized precipitating cause. Lundberg et al. (1971) reviewed the admission records for the Los Angeles County General Hospital for the period 1961-1969 and found marihuana use was listed as the reason for admission in only nine out of 700,000 cases, and five of these were for intravenous injections.

Keup (1970) reports that 0.9 per 1,000 of the 1968 admissions to a Brooklyn psychiatric hospital were directly related to cannabis use, and in another 1.9 per 1,000 it was found to be a contributory factor.

In 1966, psychiatric hospitals in England listed 82 admissions for which cannabis use was considered a factor (Baker and Lucas, 1969) in 1967, the number was 140 (George, 1970). For the 1966 data, further analysis revealed that eight of the 82 cases were acute psychotic reactions to cannabis, 20 were related to "cannabis addiction as a way of life," and cannabis could not be established as a definite factor in the remainder (Baker and Lucas, 1969).

Colbach and Crowe (1971) estimate that among a population of 45,000 U.S. soldiers in Vietnam in 1969, some 40 to 50 per month were hospitalized for psychiatric reasons and about five of these were associated with (usually heavy) marihuana use.

Among college populations, Pillard (1970) estimates five to seven marihuana-associated anxiety reactions are, seen per year by the Boston University Health Service which cares for a student population of 20,000; and Bialos (1970) reported 11 cases during a one-year period (1968-1969) for a student population of 8,500.

If it is assumed that about one-third of the Vietnam and college populations are using marihuana to some degree, the annual incidence of hospitalized cases in Vietnam would be about four per 1,000 users; the rate for student-health cases, 0.3 to 1.3 per 1,000 users.

The 1972 Secretary of Health, Education and Welfare's report on Marihuana and Health prepared by the National Institute of Mental Health noted in summary that marihuana can clearly precipitate certain less serious adverse psychiatric reactions, such as simple depression and panic, particularly in inexperienced users.

In these reactions, non-drug factors may be the most important determinants. Psychotic episodes may also be precipitated in persons with a preexisting borderline personality or psychotic disorder or those persons under excessively stressful conditions. These acute psychoses appear to share considerable clinical similarities with the acute toxic psychoses noted in the Eastern literature. Both these psychoses resemble an acute brain syndrome in that they occur primarily after heavier than usual usage and are self-limited and short-lived after the drug is removed from the body.

Some reports describing a prolonged psychotic course after an initial acute episode cannot rule out the role of pre-existing psychopathology. At the present time evidence that marihuana is a suf ficient or contributory cause of chronic psychosis is weak and rests primarily on temporal association. This issue may be clarified by extensive epidemiological and controlled clinical studies. (Secretary, HEW, 1972)

AMOTIVATIONAL SYNDROME

Another type of possible mental deterioration or subtle personality and behavioral changes associated with heavy long-term cannabis use is the amotivational syndrome.

This syndrome has been described world-wide in its extreme form when the most potent preparations are, used (Miras, 1967; Chopra. and Chopra, 1957; Chopra et aL, 1942; Christozov, 1965; Indian Hemp, 1893; Benabud, 1957; Warnock, 1903). Its most extreme form depicts a loss of interest in virtually all activities other than cannabis use. The resultant lethargy social and personal deterioration and drug preoccupation may be comparable to the skid row alcoholics' state.

Benabud (1957) describes the occurrence of this syndrome in individuals chronically intoxicated with hashish. These individuals are unlikely to show conventional levels of motivation. Also the time required to obtain and consume enough drug to maintain this state

is not likely to leave much time for other pursuits. The passive user tends to lose interest in work and other long-term goals.

The question of whether there exists a significant causal as opposed to an associative or correlational relationship, only attracted attention when the traditionally achievement-oriented Western youth adopted cannabis use. The traits of passivity or amotivation are commonly described among heavy cannabis user throughout the world.

A number of Eastern authors have expressed the opinion that this is a result of organicity from chronic cannabis use in large amounts, without objective studies being performed.

Recently the term has been used to describe the behavior of numbers of young Americans who are for a variety of reasons dropping out of school, refusing to prepare themselves for traditional adult roles and smoking marihuana.

This type of social maladjustment is not comparable in magnitude to that described in other cultures. However, the individual may lose the desire to work, to compete, to face challenges. Old interests and concerns are lost and the individual's life, becomes centered around his compulsive drug use. In addition, the individual may ignore personal hygiene, experience loss of sex drive and avoid social interaction (Mirin et al., 1970; Smith, 1968).

West (1970) and McGlothlin and West (1968) have described a clinical syndrome as a result of observations of regular marihuana users for four years. Their clinical impressions are that these individuals show subtle changes in personality over time which might represent an organic syndrome. These include diminished drive, lessened ambitious decreased motivation, apathy, shortened attention span, loss of effectiveness, introversion, magical thinking, derealization and depersonalization, decreased capacity to carry out complex plans or prepare realistically for the future, a peculiar fragmentation in flow of thought, and a progressive loss of insight.

Another psychiatrist, Powelson (1971), has also concluded on the basis of over five years clinical experience with drug users at the University of California, Berkeley, that the effects of marihuana are cumulative. He, feels that after a period of prolonged use a disorder of thinking characterized by a lack of coherence and a pathological thinking process results.

These disturbing findings are being reported more frequently, especially in adolescent and young-adult groups. Recently, tentative and preliminary data (Francois et al., 1970; White et al., 1970) has been presented on a group of 19 hospitalized 14-to-20-year-old patients with behavioral disorders who had used marihuana and other drugs heavily.

In addition to "amotivation," they showed primitive and magical modes of thought and low frustration tolerance. Subtle EEG patterns were detected although this finding is not uncommon in adolescents with behavior problems.

The researchers are presently carrying out a study in non-hospitalized adolescents without behavioral disorders who have similar patterns of drug use in order to clarify their findings.

Kornhaber (1971) believes that at least twice daily marihuana use for a year, in a 13-to-18-yearold population, has a deleterious effect upon the developing adolescent. The intoxicated state facilitates a regression from logical-mathematical thought processes to a more primitive conceptual mode of fantasy and magical thinking and impairs learning ability and judgment by decreasing attention and concentration. Thus, the developing youth turns away from reality toward fantasy and from structure and activity to passive dependency.

Kornhaber suggests that marihuana facilitates the development of normal adolescent turmoil into a pathological state. However, he feels that the existence of the syndrome depends partially on the individual's vulnerability to the drug influence.

A possibly milder variation of this syndrome has been clinically observed by Scher (1970) in individuals in the 20-to-30 age group who have used marihuana daily for five years while apparently functioning normally in society with good jobs, often creative ones. These individuals begin to experience a vague sense of functioning at reduced efficiency level. Thus, the disabilities experienced are personal and internal ,and constitute a vague neurotic depressive-like syndrome,.

In addition to the methodolcgical problems of (Establishing causative as opposed to associative relationships, it is also very difficult to obtain a sample of heavy cannabis users in the West who have not had substantial exp.rience, with other drugs, especially the strong hallucinogens.

Koridiaber (1971) has described a sample of 50 adolesc t psychiatric patients who used marihuana daily and also took other drugs. He concluded that marihuana exercised a "chronic, tranquilizing, psychomotor-depressant effect" among these patients, and facilitated regression, fantasy and magical thinking. School performance, participation in sports, and personal hygiene also declined. He reported improvement in school performance, mood and the underlying depressive symptoms for many patients four to six weeks after discontinuing marihuana use.

Given there is a fairly strong tendency for heavy cannabis users to be passive and apathetic, to emphasize the present over the future, and to choose fantasy over rationality, there are several ways by which this relationship might come about (McGlothlin, 1972).

First, persons who already exhibit these, traits may simply be attracted to the use of cannabis. Sociologists tend to favor this explanation, arguing that the relationship between cannabis use and various behavioral indicators is not causal, but simply one manifestation of a general pattern of youthful deviance or rebellion (Goode, 1970).

Utilizing a large sample, Johnson (1971) found that marihuana use is associated with impaired school performance and several forms of deviance; however, other indicators such as premarital sex and high school truancy predicted the dependent variable as well or better. Tobacco and alcohol use were nearly as good predictors as marihuana.

A second related explanation is that the illegal. context in which the drug is taken forces the adoption of a nonconforming life style. The users is thus further alienated from the dominant culture through his close ties with the cannabis-using group.

Third, cannabis use and associated activities may largely substitute for other interests. The individual may focus so much of his time and energy on cannabis that he has little time for other endeavors.

Fourth, heavy cannabis use may act pharmacologically to produce a chronic tranquilized state. Although the acute phase of intoxication is relatively short, there is some evidence of a lethargic hangover effect (Haines & Green, 1976).

Fifth, personality and behavior changes may result through the routine process of learning vi exposure. If an impressionable youth spends a great deal of his time in the world of cannabis intoxication, he may learn to think in a similar manner when not intoxicated. In particular, he may learn to choose the drug fantasy as an alternative to solving personal

problems and facing adult responsibility.

A related explanation is that cannabis acts as a catalyst, creating a condition which facilitates change, providing other necessary conditions are present. Cannabis, along with the strong hallucinogens, produces a kind of mind-loosening effect in which mechanisms providing structure and stability to perception of self-image, environment, time sense,, etc., are temporarily suspended.

The, more frequent users welcome this effect and report utilizing the loosening effect of the drug to achieve further personality change in the direction of less conformity and more spontaneity, that is, the "hang-loose ethic" (Suchman, 1968; Simmons and Winograd, 1966).

In addition, the cannabis intoxication produces a heightened suggestibility which likely makes the user more amenable to adopting the attitudes and values of the subculture in which the drug is taken. At a minimum, it may be concluded that the effects of cannabis can reinforce and provide a rationalization for previously existing tendencies.

Finally it is possible that chronic cannabis use can result in organicity (Soueif, 1967).

In summary, if cannabis use produces personality and behavior changes via one or more of the above mechanisms, the extent of such changes is likely to be strongly related to the amount consumed and the age of the user. According to evidence found in Western literature, frequent use may be quite disruptive during the formative years of adolescence.

On the other hand, the Eastern literature indicates that, although the very heavy user (200 mg. THC or more per day) is largely incapacitated, manual laborers often function adequately while consuming amounts containing 30 to 50 mg. THC per day (Roland and Teste, 1958; Chopra and Chopra, 1939). Similarly, many musicians and entertainers in the United States have lived productive lives while using marihuana (Winick, 1960).

RECURRENT PHENOMENON

Another poorly understood phenomenon is the spontaneous recurrence of all or part of the drug intoxicated state (somatic and visual sensations) when not under the influence of the drug. This phenomenon has been called a "flashback" when it occurs spontaneously or "a contact high" when it occurs in the presence of others who are intoxicated.

Flashbacks have been reported with marihuana use alone. However, these occurrences are apparently predominant in marihuana users, who have taken hallucinogenic drugs previously. These marihuana, users occasionally find that marihuana highs change for them after their hallucinogenic. experiences. For example, a simple hallucination experienced previously may reoccur while high on marihuana.

These flashbacks may be interpreted as pleasant, even desired experiences by some but unwelcome and disturbing to others. The recurrences are benign in most individuals and tend to disappear as the hallucinogenic experience recedes in time (Keeler, 1967; Smith, 1968; Weil, 1970; Bialos, 1970; Blumenfield, 1970).

Truly vivid experiences which recapture most of the elements of the original experience are extremely rare (Smith and Meld, 1970). More often they resemble an anxiety state occurring after an unpleasant high or the recurrence of a new perceptual awareness gained while high. It is difficult to differentiate these recurrences from the not uncommon deja vu phenomenon in which a person has the illusion that a perceived situation has occurred

before. These recurrences are intermittent and usually occur within a few days to weeks following the use of marihuana.

National Commission on Marihuana and Drug Abuse

Investigations of Very Heavy, Very Long-Term Cannabis Users

Proving a causal relationship between the use of any substance and an associated illness or condition is extremely difficult. Ideally, prospective longitudinal studies on large populations of both substance users and nonusers matched for socioeconomic and psychocultural variables should be performed for many years in order to detect subtle or cumulative effects. Unfortunately, the enormous expenditures of research effort and finances that would be required for a large scale investigation of this nature are prohibitive.

Consequently, carefully designed and controlled, clinical and epidemiological studies of very heavy, very long-term cannabis users in foreign countries must be relied upon to provide important data on possible effects because these populations are not obtainable in the United States.

GREECE

Preliminary results (Freedman and Fink 1971, Fink and Dornbush 1971, Fink 1971) from an intensive medical, neurological, and psychiatric study of 31 male chronic hashish users in Greece, performed under contract to the National Institute of Mental Health, have revealed few abnormalities in these individuals. Non-users matched for socioeconomic, and psychocultural factors including life style, alcohol and tobacco consumption and nutrition and general health have not been studied.

In collaboration with Professors Miras and Stefanis in Athens, Fink and co-workers are studying a population of chronic hashish users that Professor Miras has known for many years. The population studied is composed of 31 male subjects ranging in age from 26 to 69 years with a mean of 46 years.

The subjects report starting hashish use at 13 to 35 years of age with a mean of 19. They have -used hashish from 10 to 49 years, with a median of 28 years. In the past they used an average of eight grams of hashish daily with a range of 2 to 24: grams daily. (The hashish it estimated to contain 4% THC on the average. Therefore, average daily use was 320 mg. of THC).

In the past, 27 of the subjects were daily -users and four used every other day. Frequently of hashish use per day was: once per day-2 subjects, twice per day-6 subjects, three times per day-14 subjects, four times per day-4 subjects, and five, or more times per day-5 subjects.

The men reported a reduction in drug use with time ascribed to increasing difficulty in obtaining adequate supplies due to increased enforcement of the drug regulations. At

present they use an average of three grams of hashish daily (320 mg. of THC) with a range of one to 10 grams daily.

Twelve now use hashish daily, eight use, every other day and 11 use less frequently. Frequency of daily hashish use is: once per day-5 subjects, twice per day-12 subjects, three times per day-10 subjects, four times per day-2 subjects, and gve(sic) or more times per day-2 subjects.

The men are primarily hashish users. One has used opiates. Two are heavy users of alcohol and six report occasional to frequent use of alcohol at the present time. Tobacco is smoked by all subjects averaging 40 cigarettes per day.

Twenty-three of the subjects report periods of abstinence from hashish averaging ten months but up to three years. Hashish use is primarily social by 20 subjects, and 15 subjects smoke in solitude.

Pipes and cigarettes in which hashish is mixed with tobacco are used interchangeably. The usual time of smoking is after work (21 subjects) but 12 subjects smoke before work and five smoke anytime.

In this population, the median education is three-and-a-half years of school with a range of none to nine. Five of the men are illiterate. Twenty-one of the men are married, one is cohabiting, four are single and five are divorced or separated.

All of the married men are employed and support their families. The subjects report changing their jobs frequently and 11 had periods of unemployment from three to 120 months. Ten were classified as skilled workers and 21 as unskilled workers. Their jobs include selling scrap metals, general labor, cartage, messenger, maintenance assistants, etc.

Arrests are common and 19 report at least one non-hashish related arrest. Eighteen have been in regular military service, six were exempt because of hashish use and seven for other reasons.

Interestingly, 10 of the 15 wives interviewed prefer the behavior and attitudes of their husbands when they are using hashish compared to when they are drug-free.

In regard to family and personal background 20 had refugee parents, 13 had alcoholic or hashish using fathers, 26 had three or more siblings, 19 had dominant mothers. Fifteen of 21 had dominant wives. Seven reported broken homes under age 16.

Apparently, the subjects participation in society is consistent with their lower socioeconomic background. No gross behavioral deviation was detected I in this population.

Psychiatric status was evaluated by history and psychiatric interview. Nine have had psychiatric hospitalization of which three were in the military and related to hashish use. Two have, had psychiatric outpatient treatment. Eight had histories of neurotic traits during childhood. In their psychiatric evaluation, three men are considered to have psychiatric pathology. Two of these were considered sociopaths on the basis of homosexuality and criminal behavior. The third was diagnosed as a schizophrenic. No overt signs of any organic mental syndrome were detected. None of the three men were believed to require psychiatric intervention. The schizophrenic, although suspicious and withdrawal, is a successful business man and lives with his family on weekends.

Complete physical and neurological examination revealed three prominent findings. All had

very poor dentition which the men ascribed to hashish smoking. Chronic bronchitis was detected in 14 of the men and emphysema in three others. This finding is not surprising because all subjects were tobacco cigarette smokers averaging 40 cigarettes per day, in addition to their very heavy hashish consumption. Enlarged livers were also found in nine of the 31 subjects.

Because no extensive psychological test battery has been developed or standardized in Greece, American tests were used. These tests are not culture-free, and it is possible that certain items or subtests were inappropriate for the subjects because they had not acquired the type of knowledge or skills required due to their poor level of education.

The Wechsler-Bellevue I.Q. tests were translated into Greek and administered. Because of these, factors, comparison of level of performance between these subjects and white middle class Americans is meaningless.

The mean I.Q. is 86 with a range of 69 to 109. The mean verbal is 90.3 and the mean performance was 83.6. The group of subjects performed lower than expected on digit symbol, digit span and similarities but higher than expected on comprehension, arithmetic, vocabulary and picture completion. The Ravens Progression Matrices showed a similar pattern and mean I.Q. The significance of these findings will depend on a comparison with a matched nonuser population.

Resting electroencephalograms were obtained in 30 subjects and evaluated independently by four experts. Twenty-five were within normal limits.

Testing was incomplete in one record. One record in a subject who had a head injury within the prior three months showed focal slowing.

Two of the four experts judged the remaining three, records as showing low degrees of average to low voltage theta activity indicative of cerebral dysfunction. The remaining two experts judged these records as within normal limits.

This medical and psychological data suggests some effects of very long term, very heavy hashish use. Without a matched comparison group, factors independent of hashish use, such as age, socioeconomic conditions, or environmental conditions, may account for th observed changes.

However, the researchers note that these men have survived chronic hashish use in high doses without gross behavioral deviation.

JAMAICA

Another foreign investigation (Ruben et al., 1972) conducted in Jamaica (under contract for the National Institute of Mental Health) studied chronic cannabis users and matched nonuser controls. Preliminary findings have shown little evidence of significant differences between the two groups in the extensive anthropological, medical, psychiatric and psychological investigations.

Ganja use is widespread and endemic in the Jamaican lowest socioeconomic strata, and in particular in a millenial-religious sect known as the Rastafarians. More than 50% of all male Jamaicans are estimated to use some form of cannabis, and probably about 20% are regular heavy users of ganja.

The drug was brought to Jamaica from India over 130 years ago by indentured East Indian laborers. However, presently the heaviest ganja users are Afro-Jamaicans who comprise 90% of the population.

The Rastafarian religious sect, founded by Marcus Garvey, preach a "Back to Africa" destiny and claim Haile Selassie to be God. The Rastafarians have always worn. long hair and beards and dressed eccentrically. They believe that "the herb" was given them by God to help them to understand his wisdom exemplified in their greeting, "Peace and Love."

The Rastas reject the values of the dominant society and regard the government as "the powers of Babylon". They have, chosen to opt out of conventional society and instead work and live in a communal existence in poverty. They emphasize the value of ganja in achieving a new level of meaning in this existence.

The Rastafarians add ganja to their infant first bath and start feeding the drug to their infants from the time of weaning in an infusion known as ganja tea. They continue to smoke and drink the drug throughout life.

They, like many other Jamaicans, believe in its medicinal properties especially for asthma and indigestion and promotion of healing; that it gives protection from evil spirits; that it cleanses the skin and purifies the blood; that it promotes sexual vigor; that it gives energy for work and relieves fatigue and provides relaxation after work.

Extensive in-depth studies have been carried out by a team of anthropologists from The Research Institute for the Study of Man in conjunction with The Departments of Psychiatry, Pathology, Physiology and Medicine, of the University of the West Indies. Anthropology field workers lived for extensive periods of time in five rural communities (including fishing, farming and cane cutting areas) and two urban districts.

Over 2,000 people were observed and studied in these communities. Overall life styles of the ganja users were not notably different from nonusing individuals in the Jamaican lowest socioeconomic strata. Users are working, maintaining stable families and homes, and actively participating in their society. No evidence was noted of crime or aggressive behavior or drug use other than alcohol related to ganja use. No evidence of physical dependence was demonstrated. Minimal psychological dependence was observed but no drug craving was expressed.

Thirty long-term ganja smokers and 30 nonusers matched demographically to control factors other than ganja use, were chosen as representative of this functioning lower socioeconomic population and selected for intensive hospital study in order to determine, differences between the two groups.

The mean age of the subjects was 33 with a range of 23 to 51. The primary occupation of one-third of the subjects was farming. The next most common occupations were, fishing, skilled and semiskilled laborers. Half practiced no formal religion, five were Rastafarians and the remainder practiced a wide variety of traditional religious. Almost three-fourths of the males had stable "marriages" and the remaining single subjects were predominantly the younger ones.

The subjects were divided into three groups. Twenty-three were nonganja smokers, 28 were regular daily ganja smokers and 9 were occasional ganja smokers using the drug several times a we or less. Three types of regular ganja smokers were delineated: light smokers using one to four spliffs daily moderate smokers using four to seven spliffs daily; and

heavy smokers using eight or more spliffs per day.

Age of first use ranged from 8-36 years of age. Regular use of ganja occurred at a median age of 16 years with a range of 9-25 years. All ganja smokers had used the drug at least 7 years and some up to 37 years with a mean of 17.5 years.

The ganja users consumer on the average seven spliffs of ganja daily with a range of one to 24 per day. The typical ganja cigarette or cigar, termed a spliff is roughly a four-inch-long paper cone and contains about two to three grams of ganja with a delta 9 THC content of about 2.9% on the average (range of 0.7-10.3%) mixed with about half of a Tobacco cigarette. Also many smoke ganja in a Chillum pipe using very deep inhalation to fill their lungs with smoke. They consume 14 pipe fulls per week on the average, with a range of 1-25 per week.

No significant differences in neurological abnormalities, electroencephalographic abnormalities, hemochemical changes including liver function, urinalysis, chest X-ray abnormalities or chromosome damage in lymphocytes were found in the users or controls.

One user had a long history of bronchial asthma and another had a mild case of Jamaican neuropathy, but nothing suggests these disabilities were in any way related to ganja use. Minor electrocardiographic abnormalities were present in about one-third of both users and controls. This may be related to a syndrome of unknown etiology known as Jamaican cardiomiyopathy.

Thorough physical examination and hematological studies revealed only minimal significant differences between ganja smokers and non-ganja smoking controls. Comprehensive evaluation of red blood cell indices revealed that the ganja smokers had significantly higher hemoglobin levels and packed red cell volumes (hematocrit) than the non-ganja smokers.

These hematologic findings are compatible with those reported recently (Sangan and Balberzak, 1971) for heavy tobacco cigarette smokers. The authors noted that cigarette smoking causes a functional tissue hypoxia due to deficits in lung func tionwith resultant arterial oxygen unsaturation. Thus, an increased demand is placed on the bone marrow to provide more red blood cells to increase the oxygen carrying capacity of the blood.

In addition to the heavy smoking of ganja in spliffs and pipes, 27 of the 30 ganja smokers were tobacco smokers, and several have smoked tobacco cigarettes heavily. 19 of the 30 non-ganja smokers were tobacco cigarette smokers and tended to be light tobacco cigarette smokers.

Thus, the data appears to suggest that a combination of factors including number of years and quantity of cigarette smoking, ganja spliff smoking and ganja chilum pipe smoking is significantly correlated with the hematological changes indicative of functional hypoxia. However, pulmonary function studies did not demonstrate significant decrements correlated with ganja or tobacco smoking.

No significant differences were found between groups by a thorough psychiatric and psychological examination. All subjects were judged to be in normal mental health. Subjects were administered a battery of standardized reliable American psychological tests known to be sensitive to impairment in brain function. These tests were not culture free so that comparison of performance, between Jamaicans and Americans is meaningless Nineteen tests evaluating 47 variables were performed including one personality test, three tests of intelligence and verbal abilities, and 15 neuropsychological tests.

Two of 47 variables had statistically significant differences between ganja smokers and non-smokers. The smokers scored higher on the digit span subtest of the Wechsler Adult Intelligence Scale and bad a more centralized personality organization on the Lowenfeld Mosaic Test.

Non-smokers had the best performance on the number of edge contacts with the non-dominant hand on the Holes Test. These few significant differences were considered chance findings by the investigators.

In general no consistent differences were found on these psychological tests between ganja smokers and non-smokers. The data clearly indicate that the long-term ganja use by these men did not produce demonstrable intellectual or ability deficits when they were without the drug for three days. No evidence in these results suggest permanent brain damage.

The alleged role of ganja in producing personality change in the direction of a loss of competitive striving and an unwillingness to work, termed the amotivational syndrome was also investigated.

Based on clinical impressions gained from careful sociological and psycholo ical techniques, the investigators noted that the chronic ganja smoker differed little in work habits or record from his matched control. No evidence of an amotivational syndrome was found. In fact, the subjects believe ganja has a functional value as a work adjunct. It provides energy for work and helps them do arduous boring jobs.

In the Jamaican culture, ganja may produce a "motivational syndrome". In an objective videotape evaluation of work energy output and ganja smoking, ganja use did not lower productivity on simple repetitive tasks, such as woodcutting which requires compulsive concentrated effort.

A study of cultivators points up the relationship of population, land, and economic pressures to ganja use. In the area studied land resources are scarce, farms small and cultivation difficult on the hilly slopes. Market conditions determine income from cash crops and restrictions on migration maintain population pressures on limited resources.

For these farmers, the researchers suggest that ganja use. decreases total cultivated acreage and consolidates production while disruption of competition and social cohesiveness among the farmers is avoided.

These data may indicate that heavy ganja use during cultivation in farming situations with limited alternatives may serve to maintain the status quo. However, it is possible that the compulsive concentrated effort experienced by the cultivators with heavy ganja use may be productive in areas with good soil and climatic conditions where systematic weeding can increase crop yields.

As a result of the extensive anthropological study, the investigators believe that ganja use in Jamaica is a culturally determined phenomenon. '. "ganja complex" exists which consists of closely related, learned patterns of behavior manifested by the members of the society.

The ganja complex appears to be functional for the working-class Jamaican. Various elements Of the complex including economic, social and personal are interrelated in ways that contribute to operation of the whole culture.

AFGHANISTAN

Dr. Salamuddin Weiss (1971) studied 1011 chronic hashish users in Kabul in order to obtain a general picture of the charas habit in Afghanistan.

Cannabis is cultivated in this tropical country. A concentrated product, charas, the resin obtained from the flowering tops of the female plant, is the preparation generally used. The most common method of smoking charas is in a clay water pipe called a Chelum. Next most commonly used is a pipe or needle and straw. Infrequently, charas is smoked in tobacco cigars or cigarettes. Chewing the leaves or drinking a charas mixture as a confection is quite rare.

Although charas smokers are found throughout society, they are predominantly found in certain groups. The ages of the subjects studied ranged from 13 to 70 years old. More than 75% were, married. Almost all were males.

Socioeconomic status was as follows: 70%, lower, 28% middle and 2% upper. 82% are illiterate, 27% had a primary school education and less than 1% had any higher education.

Most smoking occurs in groups of two to 20 friends in quiet out of the way places. Most users smoke several times a day. The longer one has smoked charas, the shorter the duration of the high and the more often the individual can smoke each day.

Weakness, sexual difficulties and physical impotence are commonly reported by smokers. Most report they have a good appetite and eat more than normal, but malnutrition is common.

One hundred chronic smokers were selected at random and examined medically: 93 were malnourished; no evidence of illness was found in 79 subjects; 13 showed signs of respiratory illness (bronchitis) ; 7 showed sleep disturbances and one had pulmonary tuberculosis. No deaths have been reported from charas overdose. One subject out of the 1,011 was known to be chronically psychotic.

A review of over 150,000 outpatient and inpatient psychiatric visits per year over the past 10 years revealed 20 short-term psychotic episodes yearly involving charas alone and 16, short-term psychotic episodes yearly involving both charas and other drugs. An absence of chronic mental illness related to charas use was noteworthy.

Most charas smokers commence use during their teens, gradually increasing their use about five or six times until they reach their highest dose between the ages of 20 to 40 years.

At the extreme, smokers have raised their daily dosage up to 10 times their starting dose within the first two years. They then gradually decrease their daily requirement by about 50% upon reaching their 60's. Generally, most smokers cease charas use after their 60's, but some, use extremely low doses for the rest of their lives.

These patterns of use are consistent with the development of tolerance. Additionally, chronic smokers note they are able to use larger doses than they did when they began use without any significant signs of intoxication. Also after stopping charas use for a few days or months, the users report they restart use at smaller doses to achieve the desired effect.

No physical dependence was noted. Marked psychological dependence was present which

makes it difficult to stop their habitual use. Discontinuation of charas use produced mild psychologic abstinence signs. These signs, generally include restlessness loss of appetite, sleeplessness, nervousness, headache, and gastrointestinal upset.

Most smokers after discontinuation of use are quite able to live with their families and perform their jobs without discomfort. Most chronic smokers return to charas use within days or months. Out of a group of 100 randomly selected ex-smokers who had used for eight to 22 years, 42 have not returned to charas use, 16 use occasionally and 42 have returned to daily use within one to 13 months.

Most common explanation given by the subjects for restarting use were to continue close relationships with charas using friends and lack of a busy job.

A group of 100 opium addicts were selected at random from the community; 51 of these started their drug use with charas and later substituted opium for charas.

Generally, charas smokers report that they become faster in their daily jobs, but observation reveals a slowness in these activities. The ability to perform a non-complicated job is comparable to non-charas smokers. They tend to be cooperative but lazy persons. They tend to be more theoretical than practical and avoid making decisions. They do not demonstrate creativity or contribute significantly to the improvement of their community.

Summary

Marihuana has been used by man in countries around the world for many centuries. Scientifically, more is known about marihuana's effects than many other botanical substances consumed by man.

Marihuana is one of several preparations from the plant, cannabis sativa. The plant contains many different chemicals, but tetrahydrocannabinol appears to be the major active psychopharmacologic ingredient. The potency of the preparation is determined by the THC content, which varies according to the origin of the seed, the conditions of cultivation, and the extent of manicuring.

Several important factors exert significant influences on the psychopharmacological effect. These include dose, method of use, set and setting, and pattern of use including frequency and duration of use.

The acute subjective experience is dose-dependent. At low doses commonly used in this country a mild intoxication occurs, but at higher doses psychotomimetic experiences can occur. Few consistent physiological effects are noted. No pathologic bodily changes have been conclusively demonstrated from acute use. Subtle effects on recent memory, psychomotor function, and social behavior have been demonstrated.

The margins of safety between the effective dose and the toxic dose is quite large. No human fatalities have been noted in this country caused by marihuana. The most common adverse reactions are becoming too intoxicated, and the acute anxiety panic reaction. Both of these are transient and related to dose consumed as well as set and setting factors.

Acute psychotic, reactions are quite rare. They usually last a few days to weeks and occur in predisposed persons either with preexisting mental disorders or borderline personalities especially under stressful conditions. Transient acute brain syndrome or toxic psychosis is possible at extremely large doses.

Evidence has accumulated which indicates that differential tolerance does develop at least, in persons who smoke large amounts of marihuana several times a day. Development of tolerance to the depressant effects on behavior appears to precede development of tolerance to the intoxicant effect.

Physical dependence has not been demonstrated. Little, if any, psychological dependence is present in most intermittent marihuana users. Moderate psychological dependence occurs in moderate to heavy users and marked psychological dependence has been described in very heavy chronic users.

Some detrimental effects have been conclusively linked to short- and long-term marihuana use for very heavy users. The most frequently reported change in the heavy, long-term smokers of large quantities of potent preparations is chronic bronchitis comparable to that developed by a heavy, long-term tobacco cigarette smoker. A chronic cannabis psychosis probably occurs rarely in heavy chronic, hashish smokers in Eastern countries. Most psychotic episodes are the acute variety and clear in a few days to weeks. No objective evidence has been demonstrated that even very heavy, long-term hashish use causes organic brain damage.

Objective studies of chronic, heavy smokers of potent preparations have not causally linked this drug with the amotivational syndrome which has been described by many clinicians. Almost all chronic, heavy hashish smokers are indistinguishable from their peers in the lower socioeconomic strata of their respective societies in social behavior, work performance, mental status and overall life style.

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III. Marihuana and Public Safety

The significant role of the law enforcement community and the popular press in promoting the idea that marihuana use leads to undesirable and antisocial behavior has been discussed in the Report. The purpose of this chapter is to describe the genesis of the, perceived problem and the theoretical basis for these allegations.

The early campaigns against marihuana use can be viewed as an extension of the temperance and moral reform movements which swept the country during the 1920's. They were generally spearheaded by persons who opposed the use of opiates, alcohol and tobacco on the grounds that all such substances were physically, mentally and morally debilitating. The presumed dependence of the user on the drug, the loss of self-control and the unhealthy preoccupation with pleasure-seeking activities purportedly induced by these substances were seen as contrary to the traditional values of our society.

Reiteration of these themes by practicing professionals, respected members of officialdom and the popular press ultimately gave rise, to what Lindesmith (rev. ed., 1968: 188-189) has termed the "evil causes evil" fallacy, and which Goode (1972) has de-scribed as follows:

The impetus behind public and even expert conceptions of drugs and drug use is that a phenomenon so patently undesirable and universally condemned as the use of narcotics or marihuana must, inevitably, have both pathological causes as well as pathological consequences. Thus, the task of science and medical research is seen as "discovering" these negative concomitants of illicit drug use. In this way, we can all feel better about condemning the phenomenon itself because our moral and ideological feelings can thereby be, backed up and verified by the Indisputable data of positive science (p. 1).

This same philosophical leaning of persons who view marihuana as a significant danger to both the individual and society carries with it a corollary that use be prohibited and the user punished.

Perhaps the most persistent controversy with respect to marihuana use is the degree to which it poses a danger to public safety. Public and professional opinion surveys have repeatedly demonstrated the existence of a widespread belief that marihuana use leads to the commission of deviant, delinquent, criminal and violent acts. In addition, some persons have recently expressed concern that marihuana impairs driving skills and performance and, in this way, also constitutes a public safety hazards.

This chapter will review the evidence pertaining to the effects of marihuana on criminal and violent behavior, deviant and aggressive sexual behavior and driving skills and performance. Then an effort will be made to assess both the nature and strength of the purported relationships between marihuana use and these behaviors.

Problems in Assessing the Effects of Marihuana

The degree to which marihuana constitutes a danger to public safety is dependent, in large measure, upon the drug's observable, effects on the behavior of the user. No drug, including marihuana, produces the same effect at all times, under all conditions and in all individuals. Rather, the quality (form and intensity) and the quantity (extent and frequency) of the perceived effects are determined by the complex interaction of both pharmacological and extrapharmacological factors. As Goode (1972) has noted:

We should bear this qualification in mind when looking at the relationship between the ingestion of a drug and any subsequent behavior-with the latter supposedly "caused" by the effects of the drug. Drug effects vary, and, in addition, even standard effects do not automatically translate into specific forms of human behavior (P. 18).

In a paper prepared for the Commission, Tinklenberg (1971 : 1-8) has enumerated some of the basic factors which should be taken into consideration in evaluating the relationship between marihuana and crime. They are equally relevant, however, for the assessment of any behavioral effect presumably attributable to marihuana, and for that reason they are summarized below.

Definition and Congeners. The concentration of the principal active chemicals in cannabis (THC and their metabolites) in any given amount of marihuana varies widely according to where the plant is grown, how it is cultivated, harvested and cured. These variations permit a wide range of pharmacological potencies and unknown variations in their effects on behavior.

Drug-Drug Interactions. Given the strong possibility of intentional or inadvertent adulteration of marihuana with other psychoactive drugs, it may be that behavioral changes attributed to marihuana may actually derive from the adulterants or from the interaction of THC and the adulterants (which may well be occasioned by the deliberate rather than unknown simultaneous or sequential use, of other psychoactive drugs).

Dose-Response Functions. With respect to the question of how drugs affect behavior, it is likely that marihuana influences behavior in different ways and degrees, depending upon dosage levels. Although it is common to infer that higher doses of a given drug will induce more of a particular response and lower doses less, such inferences may be inaccurate in that drug effects can show a curvilinear dose-response relationship (as seems to be the case with alcohol).

Time-Action Functions. Time-action function describes the changing effects of marihuana during the course of the drug action. During the brief periods in which the drug effects are most intense, there may be a more pronounced alteration in behavior than during most of the points on the drug time-action continuum.

Individual Variation. Different individuals apparently respond quite differently to the same dose-time factors of marihuana as well as other drugs. In some laboratory studies, where, high doses of marihuana induced considerable euphoria and enhanced conviviality in most subjects, a few subjects who received the same dosage in the same setting experienced paranoia, excessive agitation and aggressive tendencies.

Cumulative Effects. The effects of marihuana on individual behavior have been shown to vary according to the amount of previous experience with the drug. There is increasing

evidence that chronic users respond quite differently to marihuana than do occasional users. The cumulative extent of previous experience may have an important influence on subsequent behavioral responses.

Psychological and Environmental Variables. The behavioral response to marihuana and to other drugs is at least partially dependent upon such psychosocial variables as the expectations of the user regarding its influence on his behavior. These expectations are in turn derived from. the personalities of the, individuals involved, recent events in their lives, and the physical, interpersonal and social milieu in which the marihuana use occurs. The behavioral responses to marihuana use are likely to correlate with such psychological and environmental variables quite independently of any pharmacological effects the drug may exert.

Personality Factors. A certain number of individuals in any given population demonstrate characteristic and relatively enduring patterns of antisocial behavior regardless of their immediate circumstances, possible drug use and the like. These individuals, variously described as antisocial, criminal or emotionally unstable, typically manifest, from childhood on, recurrent tendencies toward deviance in many areas of life. For some of these people, those predisposed toward both criminality and drug abuse, crime and drug use do coexist. However, the assumption that the drug causes crime or vice versa is not necessarily valid. One should not automatically conclude from this that the use of drugs has no influence on their criminal behavior. Drug use may possibly provide a form of reinforcement which may increase or decrease the likelihood of a criminal act.

Crime Process Factors. Crime process factors refer to the complexities of criminal behavior and the possible influence of marihuana on that behavior. A multifactored perspective of the etiology of crime , including personal, social and situational variables, allows for the possibility that at each step in the chain of events leading to the commission of a criminal act, marihuana use may contribute to enhance or diminish the possibility of this outcome.

In short, any interpretation of the data to be presented below which fails to take into account at least some of these variables will likely result in a "post hoc, ergo propter hoc" fallacy- that is, the invalid assumption that simply because one event occurs later than another event (one commits a crime after smoking marihuana) that the latter is caused by the former (marihuana caused the crime).

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Marihuana and Violence

(The evidence to be presented here applies not only to aggression and to violence but to marihuana's relationship to crime in general, and is therefore equally relevant to a later section on marihuana and non-violent crime. The effects of marihuana on sexual behavior, including the commission of sexual offenses will be treated in the following section on marihuana and sexual behavior.)

The popular and professional literature contains numerous unsupported and often emotionally charged accusations regarding marihuana's contribution to violence.

In at least two dozen comparatively recent cases of murder or degenerate sex attacks, marihuana proved to be a contributing cause (Anslinger, 1937).

In a recent study of thirty-seven murders in New Orleans in a year, seventeen were traced directly to marihuana. . . . Evil marihuana is pock-marking this nation with murders, sex attacks, suicides, and crimes in every category from bank stick-ups to petty thievery . . . (LaRoe, 1940).

Marihuana, while giving the hallucinations of cocaine, adds delusions of impending physical attack by one's best friend or close relatives. In addition, marihuana is intrinsically and inherently crime exciting. It has led to some of the most revolting cases of sadistic rape and murder of modern times (Rowell and Rowell, 1939: 67).

Even sex does not satisfy the abnormal urges induced by marihuana. There is still the necessity for further excitement, more emotional release. That is when the guns are grabbed, the knives waved and the razors swung. And all that is a marihuana user's idea of what is normal! (Williams, 1969).

To add greater credibility to their undocumented assertions, some persons describe the manner in which the drug purportedly leads to violence.

In the earliest stages of intoxication the willpower is destroyed and inhibitions and restraints are released; the moral barricades are broken down and often debauchery and sexuality result. Where mental instability is inherent, the behavior is generally violent. An egotist will enjoy delusions of grandeur, the timid individual will suffer anxiety, and the aggressive one often will resort to acts of violence and crime ... (Anslinger and Tompkins, 1953: 22).

Smoking of the weed is habit-forming. It destroys willpower, releases restraints, and promotes insane reactions ... Robberies, thrill murders, sex crimes and other offenses result (New York Daily Worker, 1940, in Solomon, 1968: 288).

Others simply deny these allegations or assert that there is no evidence to support the thesis of an independent causal relationship.

The fact that so many witnesses testified to the peaceable and orderly character of the excessive consumers goes far to prove that in this country experience shows that as a rule these (hemp) drugs do not tend to violent crime and violence (Indian Hemp Drugs Commission, 1969: 258).

A fair summary of the available evidence would be that very rarely do major (particularly violent) crimes follow upon the use of the drug, and that, in instances where they do, the relationship is an indirect one (Ausubel, 1958: 103).

One likely hypothesis is that, given the accepted tendency of marihuana to release inhibitions, the effect of the drug will depend on the individual and the circumstances. It

might, but certainly will not necessarily or inevitably, lead to aggressive behavior or crime (President's Commission on Law Enforcement and Administration of Justice, 1967: 13).

The relationship between marihuana use land the commission of aggressive acts or violent crime such as murder, rape and assault remains one of the most controversial issues relating to the drug. Persons who believe that such a relationship exists often argue that marihuana triggers the release of inhibitions and restraints, destroys the will power and heightens aggressive tendencies of the user, serving as a catalyst for the commission of aggressive or violent acts.

This argument raises several fundamental questions: Are the effects presumably induced by the drug commonly experienced by marihuana users? Are these effects, to the extent that they do occur, generally or frequently translated into overt behavior? And is the behavior which presumably manifests itself ordinarily violent or aggressive?

The answers to these questions may be obtained from several sources, including the results of laboratory experiments designed to measure certain physiological and psychological reactions and to identify observable behavioral effects; and retrospective self-reports of effects purportedly experienced by marihuana users. Additional clues may be gained from examination of the criminal records of known marihuana users and the incidence of marihuana. use among persons arrested for or convicted of violent crimes. However, while these latter methods may reveal statistical associations (which could prove to be spurious upon further analysis), they should riot be interpreted to demonstrate the existence of a causal connection between marihuana use and the offenses committed.

THE VIOLENT AND CRIMINOGENIC EFFECTS OF MARIHUANA

The empirical evidence gathered to date lends no support to the hypothesis that marihuana heightens aggressive tendencies in the user or that its effects significantly increase the likelihood of inciting the user to violence or crime. However, those findings summarized below do not mean that marihuana cannot be related to aggressive or violent behavior but merely suggest that the effects of the drug and the behaviors in question may operate independently.

The Mayor's Committee on Marihuana (1944) studied the psychomotor effects of marihuana on 72 prisoners, both users and non-users. Marihuana was administered experimentally as both an oral extract and as cigarettes. The data show that the degree of the drug's effect on psychomotor activities is dependent upon the complexity of the function and, in some cases, on the strength of the dose administered. Although simple reaction time and tasks were only slightly affected, more complex functions like static equilibrium and body and hand steadiness were significantly and adversely affected by both large (5 cc.) and small (2 cc.) doses of the drug.

In contrast to the ability of amphetamines to enhance muscular performance and to increase physical activity (Weiss and Laties, 1962; Tinklenberg and Stillman, 1970), marihuana has been found to decrease the inclination toward physical activity and to actually reduce both physical exertion and activity (Mayor's Committee on Marihuana, 1944; Hollister, et. al., 1968; Hollister, 1971), thereby decreasing the probability of inciting the user to assaultive behavior.

Although marihuana has been found to reduce inhibitions in some persons, it has not been shown to exaggerate extant aggressiveness to any appreciable degree; in some instances it has, in fact, been shown to reduce aggressiveness, and to induce timidity, fear and passivity in the user (Bromberg) 1934,1939; Chopra and Chopra, 1939; Allentuck, 1942; Chopra, and

Chopra, 1942; Charen and Perelman, 1946; Carstairs, 1954; Blumer, et. al., 1967; National Institute of Mental Health, 1970, 1972).

In recent years, a number of studies have been conducted in which marihuana users were asked to describe the effects they experienced while under the influence of the drug. On the whole, their findings are similar to those obtained from the results of laboratory experiments.

Halikas, Goodwin and Guze (1971) found that the majority of the users in their sample reported "usually" feeling relaxed (79%) and peaceful (74%).

Tart (1971) administered a questionnaire to college students in California, one item containing a list of 206 possible effects of marihuana. Respondents were asked to indicate whether, within the last six months, they had experienced the designated effects never, rarely, sometimes, very often or usually. Of the 153 respondents, 69% gave one of the latter three responses to the item: "My inhibitions are lowered so that I do things I'm normally inhibited to do."

To the item: "I lose control of my actions and do antisocial things (actions that harm other people) that I normally wouldn't do," 22% said rarely, 1% said sometimes, and the remaining 77% replied "never." With respect to other more specific effects, 23% of the users stated they "usually" felt physically relaxed, and 49% said they "very often" felt physically relaxed and did not want to get up or move around when high on marihuana (pp. 703-704).

In a study by Brotman and Suffet (1970) of 74 users in New York City (both students and nonstudents) no one mentioned any hostile feelings or actions when asked to describe what happens when they get high on marihuana (p. 264).

Goode (1970) asked 204 respondents to describe their experiences when high on marihuana. Table 1 illustrates the responses of the users to effects possibly related to aggression or crime (pp. 53-54).

In a more recent, Commission-sponsored survey of 15 to 34 year old male residents of Philadelphia, respondents were interviewed about the extent and frequency of their marihuana use, the extent to which marihuana figured in the commission of criminal or delinquent acts and the effects they generally experienced while under the influence of the drug (Goode, 1972). With respect to the effects experienced, nearly all the marihuana users (about 75% of the total sample reported that they had tried marihuana at one time or another) denied that the effects of marihuana on them could be interpreted as criminogenic or violent in nature. Table 2 below presents the subjective effects of marihuana related to crime and violence which were reported by the 559 respondents.

Table I.-CRIMINOGENIC AND AGGRESSIVE EFFECTS OF MARIHUANA

(Figures in Percentages)

More relaxed, peaceful, calmer; marihuana acts as

a tranquilizer - -- ---------- ------ -- ----- ---------- 46

Exaggeration of mood: greater subjective impact, emotional significance --- ------ ----- ------ ---------- -_ -_ 25

Time seems slowed down, stretched out, think more

time has passed ---------- ---------- ------ ---- -------- ------ 25

Become more withdrawn, introverted, privatistic-- - __ 22

Become tired, lazy, lethargic, don't want to move---- - 19

Feel freer, unrestrained, uninhibited --------- ---- --- ------ 18

Feel paranoid ----- ---------- -------- ------ ---------- ----- -- ------- 15

Have hallucinations ---------- - -- -- --------- -- ------- 15

Feel sleepy ------ ---------- --- ---- ---------- 14

More uncoordinated, clumsier, motor skills impaired 9

Other people annoy me more; find fault in others ------ 8

Become more active, want to move around more -_ __ - 6

Table 2.-REPORTED EFFECTS OF MARIHUANA AS RELATED TO CRIMINAL AND VIOLENT BEHAVIOR (Figures in Percentages)

Effects reported	Almost all the time	More than half the time	Less than half the time	Never or almost never
Feeling of wanting to hurt someone	0	3	96	
Feeling of wanting to do something violent.. *	4	95		
Feel more angry	1	3	8	88
Feeling of frustration	3	4	16	78
More willing to follow others' suggestions	4	12	25	59