The Committee on Drugs has reviewed the pharmacology of marihuana with special emphasis on effects in man because of the enormous impact of this drug on society. Much of modern day society's reaction to and attitudes about this psychoactive agent does not reflect its pharmacology, and it is only recently that pertinent biologic facts about marihuana have become known. The Committee reports these facts here, in part, to inform the Academy membership of these facts and, in part, to provide a perspective with which to consider the various societal controls (i.e., laws) on the use of marihuana.

**COMPOSITION**

Marihuana is a mixture of leaves and flowering tops of the plant *Cannabis sativa L.* It contains approximately 1% Δ-9-tetrahydrocannabinol (THC), the principal psychoactive substance in marihuana. Street preparations tend to vary in Δ-9-THC content; the range is 0% to 5%. An average marihuana cigarette contains 500 mg of marihuana and, therefore, about 5 mg of Δ-9-THC. Hashish, usually used in Eastern (Asiatic) countries and in North Africa, is the resinous substance of the flowers and leaves of *Cannabis sativa L* in which Δ-9-THC is found. Hashish contains 5% to 15% Δ-9-THC and is usually smoked as a mixture of the resin and tobacco. Generally, marihuana cigarettes do not contain tobacco, although some street preparations do.

**USERS**

In considering adverse effects of marihuana, it is important to appreciate some pertinent epidemiologic facts. It is estimated that 24,000,000 Americans have tried marihuana at least once and that there are 8,300,000 current users in this country.1 Approximately 70% of adults and youth (12 through 17 years) who were found by the National Commission on Marihuana and Drug Abuse1 to use marihuana used it so infrequently as to be considered experimental users. Individuals in this category have used marihuana at least once (most of them) but no more than once a month. Almost 20% of adult and youthful users take marihuana more than once per month, but no more than ten times a month (intermittent users). About 7% of the adults and youths surveyed indicated that they use marihuana more than ten times per month but less often than once daily (moderate users). Finally, about 4% of adults and youths who ever used marihuana use it more than once per day and are considered heavy users. A small fraction of these are extremely heavy users, and are almost continually intoxicated from smoking marihuana with a relatively high Δ-9-THC content many times a day.

**BASIC PHARMACOLOGICAL CONSIDERATIONS**

The main psychoactive ingredient of marihuana is Δ-9-THC. The isolation and recognition of this substance, the ability to assay for it quantitatively in natural materials, and its synthesis have allowed more precise psychopharmacologic studies of marihuana. Delta-9-THC is rarely available for use outside of a research setting. Delta-8-THC is another psychoactive substance in cannabis but usually occurs in negligible concentrations. Other neutral and acidic cannabinoids are found in cannabis, but they probably exert little biologic effect. However, they may
modify the effects of Δ-9-THC and thus confound the comparison of the actions of purified preparations of this compound with those of cannabis.

Smoking marihuana is a most effective route of administration, although the amount of Δ-9-THC absorbed into the bloodstream from the lungs varies considerably among smokers. Psychoactive and physiologic effects appear in two to three minutes, sometimes less, after smoking. The peak effect occurs in 10 to 20 minutes, and the duration is about 90 to 120 minutes after smoking a single cigarette (approximately 5 mg of Δ-9-THC). The pharmacologic effects of Δ-9-THC are delayed when administration is oral. Onset is usually 30 to 60 minutes after ingestion; peak effects occur in two to three hours, and the effects last for three to five hours. It requires approximately three times more marihuana or Δ-9-THC when administration is oral to obtain effects equivalent to those from smoking.

Studies with Δ-9-THC tagged with carbon 14 have provided information on its pharmacokinetics and metabolism in man. For instance, it has been found that THC is almost completely metabolized; less than 1% is recovered unchanged in urine or feces, regardless of the route of administration. Animal and in vitro studies indicate that nonspecific hepatic microsomal oxidases rapidly transform Δ-9-THC into 11-hydroxy-THC (11-OH-THC). This metabolite is psychoactive,being as potent as Δ-9-THC. 11-OH-THC is further rapidly metabolized to the inactive 8, 11-dihydroxy-THC. A good correlation exists between the time course of pharmacologic effects and plasma levels of Δ-9-THC and its immediate metabolites. Peak effects and blood levels were noted 10 to 30 minutes after smoking and about three hours after oral administration. It is not clear whether the parent compound or psychoactive metabolites were most psychoactively effective because the blood levels were determined by measuring radioactivity (reflecting unchanged Δ-9-THC and metabolites), administered initially as carbon 14 tagged Δ-9-THC.

Once Δ-9-THC is absorbed, there is an initial rapid decline of plasma Δ-9-THC concentration in about two hours. Delta-9-THC is transported in the lipoprotein fraction of plasma while the more polar 11-OH-THC is bound to albumin. After the initial two hours, Δ-9-THC disappears from the plasma at a slower rate for several days. The different rates of disappearance of Δ-9-THC from the plasma suggest rapid uptake and slow release by certain tissues. In the rat, Δ-9-THC is accumulated in fat much more than in any other tissue and persists for two weeks.

The initial distribution of Δ-9-THC is probably a function of vascularity and lipid content of the various organs. Thus, in rats, lung, salivary glands, jejunum, kidney, adrenals, muscle, liver, and testis (in decreasing order of concentrations of Δ-9-THC and metabolites) are the most prominent tissues for the early distribution. Brain levels of Δ-9-THC (and metabolites) persist for as long as seven days, and at that time concentrations are as high or higher than for other organs. Studies on the distribution in monkey brain indicate that there is an early concentration of radioactivity in gray matter, especially of the visual and frontal cortex. This radioactivity may reflect the more polar metabolites of THC. A later phase of organ distribution probably reflects excretion of the cannabinoids; some 60 minutes after administration of Δ-9-THC, relatively high concentrations (of radioactivity) are found in liver, bile, the gastrointestinal tract, kidneys, and bladder. Of interest is the fact that there is enterohepatic cycling of the metabolic products of Δ-9-THC. Delta-9-THC crosses the placental barrier in pregnant animals, and sizeable concentrations are found in the fetus. Effects on viability of the fetus are under investigation. Delta-9-THC metabolites are principally excreted in the urine and feces. Radioactive metabolites persist in urine and feces for days after administration of a single large dose. The use of cannabis appears to be detectable for a longer period than that of alcohol.

The physiologic responses to the administration of Δ-9-THC or marihuana include a dose-dependent increase in heart rate. Pretreatment with propranolol (a β-adrenergic blocking agent) has been reported to inhibit the effect of Δ-9-THC on heart rate. Another response to Δ-9-THC is conjunctival reddening, irrespective of route of administration (smoking or ingestion). It has been noted that Δ-9-THC may effect a decrease in intraocular pressure. There are no evident changes in body temperature, respiratory rate, or deep tendon reflexes after administration of marihuana or Δ-9-THC. Pupillary size is affected almost imperceptibly; a decrease can be recorded by careful measurement. Delta-9-THC does not usually affect fasting blood sugar levels or plasma levels of free fatty acids.

Physiological and biochemical measurements are being used to document the neurologic effects of cannabis in man and animals. Electroencephalographic changes, detected by computer rather than visual analysis, have been reported in volunteers who smoked marihuana in high or low doses and placebo cigarettes. The principal
changes noted were an increase in the percent of alpha time with decreased theta and beta bands. Young chronic users of marihuana, when acutely intoxicated, showed a decreased auditory-evoked EEG response. Studies on biogenic amines and neurotransmitter substances in the brain of experimental animals administered Δ-9-THC seem most promising in understanding the mechanism of action of cannabis. Effects on serotonin and catecholamine concentration in localized brain areas are being studied. The technique of autoradiography has been used to detect accumulations of radioactive Δ-9-THC or metabolites in specific brain areas at the time of maximal behavioral activity in the monkey. The lateral geniculate nuclei, the amygdala, the hippocampus, and the inferior and superior colliculi accumulated the labeled compounds at the peak of behavioral activity. Relatively large concentrations were also found in the cerebellum.

**PSYCHOLOGICAL EFFECTS**

The subjective effects of marihuana have been reported by many sources. Common and characteristic subjective effects in nonlaboratory settings have repeatedly indicated that the perception of the external environment is changed in all sensory modalities. Visual imagery is more vivid than usual; the subject sees forms and meaningful patterns in ambiguous visual material. There is an awareness of subtle qualities of sound rhythms, purity, and distinctness. Touch, taste, and smell are subjectively enhanced. Time perception seems changed; subjects report slowing down or stopping of time. Marihuana seems to potentiate social interaction; however, high doses tend to remove the user from the group, perhaps because of the enhanced psychoactive effects. Other typical components of the marihuana high are a feeling of lightness of the limbs, uncontrollable laughter without provocation, and difficulties in remembering from moment to moment the thread of what is being said in a conversation.

Almost invariably users report a pleasant, positive, emotional state. The temporarily overwhelming negative emotional state, known as "freakout," occurs infrequently in about 20% of experienced marihuana users. Almost always this state can be handled by reassurance and support. "Freakouts" may occur more frequently in new users, especially with potent preparations.

The attitude and expectations of the subject determine the subjective response of using marihuana. Even with experienced users, a placebo effect is common, especially in double-blind studies. Apparently, this reflects a learned set of expectations in the user. The interpersonal situation also is a determinant of the subjective response to marihuana. There is a greater variety of subjective symptoms when marihuana is smoked in a group setting. Sedative effects seem to predominate when the same subject smokes alone.

Marihuana and Δ-9-THC affect motor and mental performance in a dose-dependent manner, especially when dosage is carefully controlled. Motor performance (on various standardized tests) deteriorates with the dose of marihuana administered by smoking. Testing of mental performance has shown dose-related impairment of verbal output, counting, and color discrimination. Short-term memory seems to be the mental faculty most significantly affected by marihuana. Moderate amounts of marihuana seem not to interfere with the information retrieval component of this mental faculty but more likely with initial learning, thus affecting the acquisition process involved in the storage of information.

Comparative studies of the effects of marihuana, alcohol, and other drugs on mental and motor performance are especially interesting. Delta-9-THC in doses of 2.5 to 5 mg (the content of one half to one marihuana cigarette) provided the same performance decrements as three bottles of beer or 3 oz of 100-proof whiskey taken half hour before testing (equivalent to a blood alcohol level of 0.05%). When alcohol (first) and marihuana (second) were consumed together, an additive decrement on mental and motor performance was noted.

There is a significant effect of smoking experience on mental and motor test performance. In general, individuals with more experience seem to score better than those with little or no smoking experience after administration of standardized doses of marihuana.

Of particular importance is the effect of marihuana on driver performance. A significant dose-related increase in brake time has been found after ingestion of marihuana. An increased amount of time is required for recovery from glare when driving at night. This effect lasted for several hours after smoking marihuana. It was not related to pupillary size. Sedation and effects of marihuana which increase complex visual reaction time and variability in performance because of occasional lapses of attention would be expected to impair driving performance.

**TOLERANCE**

It is now generally agreed that physical dependence on cannabis comparable to that for the opiates, alcohol, and barbiturates does not exist (i.e., withdrawal from the drug is not followed by
a characteristic abstinence syndrome). On the other hand, tolerance to cannabis has been conclusively demonstrated in several species of animals and probably develops in man with prolonged use of potent preparations. When increasing drug doses are required to obtain the same degree of effect in an individual, tolerance has developed. The concept of tolerance should be restricted to a specific action of a drug rather than to all the effects of the drug. Dispositional tolerance refers to changes in absorption, distribution, metabolism, and excretion which result in a decreased intensity and duration of contact between the drug and its target tissue. Any change in the target tissue which makes it less sensitive to the same dose of the drug results in functional tolerance.

Tolerance, probably dispositional tolerance, to various pharmacologic and behavioral actions of marihuana and Δ-9-THC occurs in a number of animal species (pigeons, rats, dogs, mice, monkeys, and chimpanzees). This tolerance develops rapidly and is long-lasting. Hundredfold increases over the initially effective dose produce little effect in tolerant animals of some species. Cross tolerance for various effects has been demonstrated between Δ-9-THC and Δ-8-THC, but not LSD, morphine, and mescaline. Dispositional tolerance to the behavioral actions of THC may result from the animal learning to adapt to effects of the drug (a type of functional tolerance). However, there is clear evidence for metabolic tolerance as shown by an increase in the lethal dose during the course of tolerance development. SKF-525-A, an inhibitor of hepatic microsomal enzymes which interferes with THC metabolism, has been shown to possess a blocking action on tolerance in laboratory animals. Animals develop tolerance to some effects of THC but not others. Thus, differential tolerance is an important consideration for interpreting the results of various studies dealing with the development of tolerance.

A number of reports from Asian and Middle Eastern populations describe the daily use of enormous amounts of cannabis by chronic users. That tolerance has developed for psychoactive effects is suggested by the fact that the quantities consumed produce dysphoria in less experienced users but do not interfere with the usual daily activities of some chronic, heavy users. Smokers in these Eastern groups have increased the initial daily consumption some five to six times over a 20- to 30-year period to achieve the same degree of psychologic effect.

The development of tolerance has been studied and compared in long-term, intermittent, and moderate marihuana users given free access to the drug over a 21-day period. The investigators concluded that tolerance developed for the depressant and some physiological (pulse rate) and psychological effects (impaired recent memory, time estimation, and psychomotor coordination) of cannabis and that the duration of the desired high shortened with continuing exposure to the drug. Other more recent studies have tended to confirm one or more of these observations.

Of special interest have been reports suggesting “reverse tolerance” for marihuana. The basic observation has been that of a novice smoker requiring more marihuana initially to achieve psychologic effects than after his first few trials with the drug. It is as if an individual has to acquire the ability to perceive the desired effects of the intoxicated state. Supporting this phenomenon are observations of experienced users becoming high after receiving the same amount of Δ-9-THC or marihuana which was psychologically ineffective for naive subjects. Behavioral factors seem to account for such increased sensitivity.

**ADVERSE PHYSICAL EFFECTS**

Interest in and debate over the adverse effects of marihuana have stemmed from legal prohibitions and have raised questions concerning the appropriate stance of society and, in turn, the law with regard to this drug. Any consideration of the pharmacology of cannabis should include information concerning acute and chronic physical toxicity and psychiatric illness. In general, manifestations of acute physical toxicity are minimal, even with administration of large doses. Death from overdose has rarely been reported, and critical analysis of reports of fatality make it possible to conclude that definite incrimination of marihuana is lacking in most instances. For instance, although a cannabis metabolite was found in the urine of one victim recently reported to have succumbed from an overdose of marihuana, no cannabis was found in body tissues. Large amounts of cannabis were found in the room of the victim, and no other cause of death was apparent. Acute toxicity studies in animals and human case reports all indicate a high ratio of lethal to effective dose for marihuana; this ratio is more favorable than for alcohol and barbiturates.

Uneventful recovery from coma following overdose with hashish (nine to ten large pipefuls were smoked) has been reported. The most commonly reported physical reactions to marihuana are nausea, vomiting, and dizziness. These manifestations tend to occur most often in inexperienced smokers or with oral administration.
The intravenous administration of street preparations of marihuana has resulted in severe toxicity.\textsuperscript{26} Hypotension, chills, fever, leukocytosis, hepatosplenomegaly, and anuria have been reported following intravenous administration, which results in injection of insoluble particles and perhaps bacteria into the bloodstream.

Reports of chronic, physical effects of marihuana must be judged from the perspective of the population group under scrutiny. Heavy, long-term patterns of marihuana use in Eastern (Asiatic) populations have not yet been matched in Western groups where only small numbers of chronic users have been observed. Populations associated with heavy, chronic use of cannabis differ from Western groups in such important variables as nutritional status, patterns of disease, and perhaps in the potency of the cannabis preparation (e.g., hashish in the East, marihuana in the West).

In view of the usual route of administration of cannabis preparations, it is not surprising to encounter a relatively large number of reports dealing with the respiratory tracts of chronic users. High frequencies of chronic bronchitis have been encountered in heavy, long-term users from Eastern populations.\textsuperscript{27} Because mixtures of cannabis and tobacco are smoked in these populations, disentangling the respiratory effects of each of these agents poses a difficult problem. A group of 22 American soldiers in West Germany who smoked huge quantities of hashish (100 gm or more monthly) for 6 to 15 months exhibited a high frequency of upper and lower respiratory complaints: bronchitis, sinusitis, asthma, and nasopharyngitis. Twenty-one of the 22 soldiers also smoked tobacco.\textsuperscript{28} Five of nine patients with bronchitis were studied for pulmonary function and showed mild obstructive changes which improved on diminished hashish exposure, irrespective of tobacco smoking. It is difficult to relate these findings to the usual chronic user of marihuana in the United States because enormous amounts of a preparation containing about five times as much THC as in marihuana were smoked by soldiers. The clinical observations seemed to implicate hashish; but, it is not clear what level, if any, of marihuana exposure can affect pulmonary physiology. An attempt to define a pathologic effect on the lungs of marihuana smokers was undertaken by Mann \textit{et al.}\textsuperscript{29} who studied structure and function of alveolar macrophages obtained by pulmonary lavage from heavy users (3 to 20 cigarettes per day for at least one year). These investigators demonstrated no differences in phagocytic capacity (for \textit{Candida albicans}) of macrophages from marihuana or tobacco smokers and nonsmokers. Twenty-five percent fewer macrophages were recovered from the lungs of marihuana smokers as compared to recovery from nonsmokers (other studies have shown recovery of increased numbers of pulmonary macrophages from tobacco smokers than from nonsmokers). The investigators concluded that macrophages, a primary pulmonary defense against inhaled organisms and particles, were apparently replaced by other cell types. Thus, this finding may be reflected in the clinical respiratory picture described here for chronic and heavy exposure to cannabis preparations. Although there is little information on the respiratory status of intermittent and moderate users, the respiratory tract may be a potential target for adverse effects of long-term cannabis use. The information on pulmonary effects must be weighed, and tar from marihuana cigarette smoke has a carcinogenic effect on mouse skin similar to cigarette tobacco tar.\textsuperscript{30}

A high frequency of obliterative arteritis involving the lower extremities has been reported for young Morrocan males who are heavy cannabis users. Unfortunately, this is a clinical report and there are no control data.\textsuperscript{31} There is no definite evidence that long-term use of cannabis causes liver dysfunction.

Of note is the claim by British physicians that regular use of cannabis produces cerebral atrophy in young adults.\textsuperscript{32} These physicians reported evidence of ventricular dilatation by air encephalography in ten young adult males who used marihuana consistently for 3 to 11 years; other drugs (amphetamines, LSD) were also used, but reportedly less frequently. Normal values for ventricular measurements were obtained from age-matched patients with normal air encephalographic examinations and follow-up confirmation of a neurologically normal state. There was no attempt to control for exposure to marihuana and other psychoactive agents. This clinical observation is not enough to prove that long-term use of marihuana predisposes to or results in cerebral atrophy. There are variables other than marihuana which also must be controlled (e.g., the role of the other psychoactive drugs). The reliability of the histories of drug abuse given by the subjects of this study is questionable. Carefully controlled studies are needed to substantiate this clinical report.

The effects of long-term use have been studied in a small sample of cannabis users in Jamaica.\textsuperscript{33} Thirty long-term smokers of ganja (3\% THC, on average, usually smoked with tobacco) and 30
matched nonusers were selected for intensive hospital investigation. The ganja smokers in this study had used the drug for a mean duration of 17.5 years. No significant differences were found between users and controls for neurologic and EEG abnormalities, liver function tests, abnormal chest x-rays, and chromosomal aberrations. Ganja smokers, 90% of whom also smoked tobacco, showed significantly higher hemoglobin concentrations and hematocrits than did nonusers (19 of 30 nonusers smoked tobacco). These differences may reflect the effects of chronic ganja and/or tobacco smoking on the lungs of users; the hematological changes may be related to functional hypoxia. However, the results of pulmonary function tests did not differ between ganja smokers and nonusers.

New findings concerning the possible adverse effects of chronic intensive marijuana use (at least four days a week for a minimum of six months) on the endocrine system have recently been reported. Plasma testosterone levels were found to be significantly depressed in 20 marijuana smokers. More significantly, a suggestion of a dose-related response was noted in that there was an inverse relationship between amount of marijuana used and plasma testosterone concentrations and hematocrits than did nonusers (19 of 30 nonusers smoked tobacco). These observations may reflect the effects of chronic ganja and/or tobacco smoking on the lungs of users; the hematological changes may be related to functional hypoxia. However, the results of pulmonary function tests did not differ between ganja smokers and nonusers.

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MUTAGENESIS AND TERATOGENESIS

Results of studies seeking evidence of chromosomal abnormalities in peripheral blood lymphocytes of marijuana smokers are inconclusive. Two studies have suggested that abnormalities do not occur, at least for “light” marijuana users (one to two cigarettes per month or less) and a small group of smokers including both light and heavy users. Neither study would detect a low frequency of chromosomal abnormalities in heavy marijuana users. A more recent study has shown increased chromosome breakage in marijuana users.

Another aspect of this recent study, dealing with the effect of chronic marijuana smoking on cell-mediated immunity, exemplifies the application of newer knowledge and techniques to learning about the effects of this drug in man. Mixed lymphocyte culture (MLC) and phytohemagglutinin (PHA) responsiveness of the lymphocytes of 51 individuals who smoked marijuana at least once a week for at least one year was investigated; no other drugs were used by these subjects. MLC and PHA responsiveness reflects the status of cell-mediated immunity in man. Eighty-one healthy volunteers were used as controls, and the results of these tests were also compared to data from groups of patients with impaired cellular immunity (e.g., patients with uremia or malignancy and those receiving immunosuppressive therapy). The results of this study indicated that the mean response of the lymphocytes of marijuana smokers to allogenic cells (MLC) or PHA was significantly less than that of the control group and about the same as for the patients exhibiting impaired cellular immunity.

The basis for the depressed MLC and PHA responses of the marijuana smokers’ lymphocytes is unknown. The investigators suggest that DNA synthesis is impaired, but their own summarized evidence for this hypothesis—chromosome breaks, micronuclei, and a decreased number of cells synthesizing DNA in studies on four marijuana smokers—was not presented in a form permitting analysis. The data on chromosome breaks are controversial because, as indicated here, other groups have failed to find an increased frequency of chromosome damage among marijuana users. Unless this finding is consistent among different laboratories, extrapolation to mutagenesis and teratogenesis is extremely tenuous.

The design of this investigation suffers from flaws common to many other studies on adverse effects of marijuana. The assumption that marijuana is the only variable differentiating the control and study groups cannot be accepted. Variables correlated with marijuana smoking are unexamined in this (and other) studies, even though one or more of these may be depressing the MLC and PHA responses. Evidence of a “dose-response” relationship which demonstrates increasing frequency of chromosomal aberrations and increasing impaired MLC and PHA responses with increasing marijuana exposure should be sought. Although this type of evidence would not completely rule out the etiologic significance of other correlated variables, it would tend to suggest a causal role of marijuana.

The evidence is minimal for incriminating marijuana as a teratogen in man. The three clinical case reports of children born with birth defects to mothers who used marijuana can hardly be used as such evidence; multiple drugs...
were used by the mothers and there is relatively high frequency of birth defects in the general population. If marihuana were a human teratogen, we might expect more than three clinical case reports of association because of the large number of users in this country. However, it is extremely difficult to demonstrate cause-and-effect relationships for mutagens and teratogens in man so animal studies can provide useful information. Indeed, reports of congenital malformations in offspring and decreased litter size in various experimental animals exposed to (usually extremely large doses of) cannabis, certainly indicate that avoidance of exposure to marihuana during pregnancy would be wise.

ADVERSE PSYCHOLOGICAL EFFECTS

Perhaps one of society's greatest concerns with marihuana has been its possible relationship to mental illness. Clinical observations provide most of the information on this relationship; unfortunately, critically devised and analytic epidemiologic studies utilizing control groups and well-founded frequency data are lacking. In addition to the pharmacologic properties and dose received of a psychoactive drug, the psychologic state of the individual and the setting in which the drug is taken are two important variables which determine effect. Adverse psychologic effects may be dependent on these two variables and make it difficult to isolate the role of the psychoactive agent. Much of the information on cannabis-related mental illness originates in developing nations where the relatively low standards of medical care have resulted in low priorities for dealing with mental illness, few well-trained psychiatrists, and poor facilities for dealing with psychiatric disorders. Careful diagnosis and evaluation of the mentally ill patient is probably lacking. Chronic illness in these countries, especially infectious diseases and malnutrition, may affect mental function. Data from these countries on the frequency of mental illness among users and nonusers of marihuana are unavailable. Thus, there are reasons for using caution in relating much of the seemingly relevant information to Western populations.

If lack of critical information hampers delineation of a cause-and-effect relationship between marihuana and mental illness, the nonspecificity of the adverse psychologic reaction(s) attributed to cannabis does not improve the chances for critical analysis. For instance, there are no specific manifestations which distinguish between cannabis psychosis, an acute toxic state which occurs after heavy use, and other types of toxic psychoses. There is an acute onset of confusion, visual and/or auditory hallucinations, paranoid ideas and excitement or aggressive behavior; this state is self-limited (days to a few weeks). The diagnosis has given important weighting to a history of heavy cannabis intake, a situation which could lead to a biased inflation of the frequency of cannabis-induced psychosis. The similarity among cases reported from Eastern populations as cannabis psychosis may suggest that this is a diagnostic entity; however, this says nothing about the role of the psychoactive agent.

Administration of relatively large doses of Δ-9-thc isolated from cannabis can produce acute toxic psychosis and hallucinations in a controlled setting. Thus, it is not surprising to find various reports of toxic psychologic reactions following use of marihuana in Western populations. Smith and Mehl of the Haight-Ashbury Clinic (San Francisco) believe that the ingestion of large amounts of drugs, inexperience of the user, and personality factors predispose to such reactions which are manifested by panic, fear, depersonalization, confusion, disorientation, depression, and paranoid ideas. Among case reports associating panic reactions and psychotic states with use of marihuana, other factors (possibly) predisposing to the mental disturbance can often be found—a severe degree of stress, schizophrenia in the patient or his family, and preexisting psychopathology. Again, the host and the setting in which cannabis is taken are significant in understanding the etiology of these adverse reactions. The use of marihuana, especially heavy use, apparently can precipitate adverse psychologic effects, from mild reactions to psychotic episodes. Host and situational factors appear to contribute to many of these adverse effects. Fortunately, the psychotic episodes tend to be self-limited and of short duration if marihuana use is terminated.

A consideration of the frequency of toxic psychologic reactions associated with marihuana use soon indicates the poor quality of the data on which such estimates are based, even in Western populations. The reports of widespread cannabis use in American soldiers in Vietnam suggested that a useful source of data was available. This source provided an estimate of five cases per 45,000 troops per month of (acute onset) psychosis associated with a history of marihuana use. (The authors reporting this estimate indicated the presence of predisposing personality factors.) Of course, such an estimate provides no indication of the risk to a marihuana user of developing a psychosis because the actual number of such users among American troops in Vietnam was

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not reported; the estimate was based on the total American military population. Other similar estimates, from the student health service at Yale (11 cases per 8,500 students for the 1968-1969 academic year) and from Los Angeles County Hospital (nine admissions resulting from the use of marihuana out of 700,000 admissions during the period from 1961 to 1969—most of these patients were admitted after intravenous injection of marihuana) are again uninformative.

The recurrence of psychoactive effects when not under the influence of marihuana has been described by the term “flashback.” Euphoria, anxiety, or hallucinations may be features of the flashback, often depending on the psychologic manifestations of previous (especially recent) intoxications. These recurrences are intermittent, usually occur within days to a few weeks after using marihuana, and tend to disappear with time. Although flashbacks have been reported in individuals who have used only marihuana, these phenomena seem to occur more frequently in individuals who have used hallucinogenic drugs previously. The repetition during marihuana intoxication of hallucinations previously experienced with our psychoactive drugs is another phenomenon, perhaps related psychopharmacologically to flashbacks, which has been reported. The basis for these types of recurrent phenomena are poorly understood.

The amotivational syndrome refers to the loss of conventional motivation and to preoccupation with drug-taking and its subculture. The regular long-term use of marihuana may produce this syndrome (the marihuana hypothesis). Individuals who are constantly and chronically intoxicated cannot be expected to show conventional levels of motivation, although their desire to remain in the intoxicated state will motivate them to obtain sufficient amounts of the drug. Such individuals have been the subjects of reports from countries where the most potent preparations of cannabis are used. A less severe form of this syndrome may be manifest in this country in youths who are dropping out of school and refusing to prepare themselves for traditional adult roles and in young adults who, after a number of years of regular marihuana use, show subtle personality changes as indicated by diminished drive, lessened ambition, loss of effectiveness, apathy, and introversion. An important issue appears to be the role of marihuana in the etiology of the amotivational syndrome.

There is no objective evidence for or against the hypothesis that the amotivational syndrome results from organic brain changes brought about by chronic use of large amounts of cannabis. Pre-existing personality traits of heavy marihuana users which attract them to the drug must be considered in the etiology and pathogenesis of the behavior complex known as the amotivational syndrome. The emphasis in our present day society on reexamining traditional values and roles, which correlates with youthful rebellion and interest in “dropping-out,” indicates that interaction of the drug and social variables must also be considered in any examination of the amotivational syndrome. In the absence of data which provide insight into this possible adverse effect, an hypothesis equally suitable to the marihuana hypothesis is that psychosocial variables bring individuals into the counterculture, one of whose characteristics is use of cannabis.

**CONCLUSIONS**

Various adverse effects have been attributed to marihuana and other cannabis preparations. Most of these claims cannot be well substantiated because they are based on uncontrolled observations, improperly controlled studies, studies with small sample sizes, and retrospective analyses. Comparative studies of users and nonusers purporting to demonstrate physiologic or psychological adverse reactions usually fail to differentiate between a marihuana effect and effects of other variables correlated with the use of this drug. Demonstration of a specific adverse effect of marihuana (by studying users before and after abstaining from the drug) and of a dose-response relationship may tend to overcome this flaw in comparative studies.

Repeated clinical observations, properly executed investigations, and controlled animal studies are now documenting certain adverse effects of marihuana. Present knowledge indicates that, except for the effects of long-term smoking of potent cannabis preparations on the upper and lower respiratory tract, acute and chronic physical toxicity is rather low in man. The clinical significance of altered MLC and PHA responses and depressed plasma testosterone levels of marihuana users remains to be demonstrated. Animal studies indicating a teratogenic potential for cannabis are sufficient to recommend avoidance of exposure to marihuana by women who are or may become pregnant.

Observations on psychologic and physiologic effects of marihuana indicated that, as with alcohol and other psychoactive drugs, individuals who are “high” should not drive. Use of marihuana, especially heavy use, can precipitate adverse psychologic reactions. Host and situational...
factors appear to contribute to many of these adverse effects.

Tolerance to cannabis develops with prolonged use of potent preparations. A relationship between marihuana tolerance and adverse effects is not evident.

The biomedical aspects of the use of marihuana are being monitored, and we can expect more information on its adverse effects. As more information becomes available, the Committee on Drugs will bring it to the attention of the Academy membership.

The Committee on Drugs continues to adhere to its conclusion stated in 1971. Namely, that there should be no criminal penalties for simple possession and use of marihuana. When adequate methods for detecting concentrations of cannabis in the body (blood, urine, etc.) become available, the Committee would favor appropriate legal penalties for driving while intoxicated by marihuana.

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ports on marihuana research, Amsterdam, September 30-October 1, 1971.


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