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Health Aspects of Cannabis*

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I. Introduction

THE MODERN era of research into the effects of cannabis in man began less than 20 years ago. Many issues about its health hazards, as they are with all drugs, remain controversial and ambiguous. Many adverse reactions to drugs were not recognized until after much exposure had occurred. Often these are idiosyncratic or allergic reactions. On the other hand, adverse reactions due to extensions of the pharmacological action of a drug may be recognized both early and late. A similar pattern holds for cannabis.

The ambiguity currently surrounding the health hazards of cannabis may be attributed to a number of factors besides those which ordinarily prevail. First, it has been difficult either to prove or to disprove health hazards in man from animal studies. When such studies of cannabis reveal possible harmful effects, the doses used are often large and treatment is generally short. Second, cannabis is still used mainly by young persons in the best of health. Fortunately, the pattern of use is more often one of intermittent rather than regular use, the doses of drug usually being relatively small. This factor might lead to an underestimation of the potential impact of cannabis on health. Third, cannabis is often used in combination with tobacco and alcohol, among licit drugs, as well as a variety of other illicit drugs. Thus, potential health hazards from cannabis may be difficult to distinguish from those of concomitantly used drugs. Finally, the whole issue of cannabis use is so laden with emotion that serious investigations of the health hazards of the drug have been colored by the prejudices of the experimenter, either for or against the drug as a potential hazard to health.

Assessment of the therapeutic potentials of marijuana is also clouded by prejudices, either for or against the drug. Virtually every claim of therapeutic benefit made for marijuana is for a condition for which there are already many effective treatments. Thus, to justify the use of the new agent, it must be subjected to the same elements of proof as a brand-new drug. Thus far, none of the potential indications has been officially recognized.

This report will focus on three main areas: (*a*) acute and chronic effects of cannabis in humans; (*b*) issues regarding its possible adverse effects on health, including its effects on driving ability; and (*c*) the therapeutic potential of cannabis constituents or synthetic homologs of such constituents.

II. Acute and Chronic Effects of Cannabis in Humans

A. Acute Studies

The availability of synthetic trans-delta-9-tetrahydrocannabinol (THC), the major component of cannabis, and chemical techniques for quantifying its content in cannabis preparations and in blood have made possible for the first time pharmacological studies which provide some precision in dose. When the material is smoked, as it is most commonly used in North America, a variable fraction of THC is lost by smoke escaping into the air or exhaled from the respiratory dead space. Relatively little is lost by pyrolysis, since it is likely that the cannabinoid is volatilized in advance of the burning segment of the cigarette. The efficiency of the delivery of a dose by smoking has been estimated to be about 18%, but frequent smokers obtain 23%, while infrequent users obtain only 10% (110). THC and marijuana extracts are also active by mouth; the systemic bioavailability of oral administration is only about 6%, one-third that from smoking (130).

When smoked, THC is rapidly absorbed, and effects appear within minutes. If marijuana is of low potency, effects may be subtle and brief. Seldom do they last longer than 2 to 3 h after a single cigarette, although users prolong effects by repeated smoking. Oral doses delay the onset of symptoms for 30 min to over 2 h, as well as prolonging the span of action of the drug. These time schedules are consistent with knowledge of the pharmacokinetics of the drug. Smoking is similar to i.v. administration in producing maximum plasma concentrations early, while p.o. administration produces slower rises of maximum plasma concentrations, which are also lower than those for smoking (105, 130). Although the route of administration affects the time course and intensity of cannabis effects in man, the pattern of these effects was well established by early investigators (84, 88).

All observers have commented on the constant increase in pulse rate, often one of the first effects of the drug. Blood pressure tends to fall slightly or remains unchanged; at higher doses, orthostatic hypotension occurs. Conjunctival reddening is also consistently observed. Both this symptom and the increased pulse rate correlate quite well in time with the appearance and duration of psychic effects of the drug, as well as the plasma concentrations of the drug (6). Muscle strength is decreased. Appetite is inconsistently augmented, along with an increased food intake (80). Observed physiological effects have not included changes in pupil size, respiratory rate, or deep tendon reflexes.

Perceptual and psychic changes are biphasic. An initial period of euphoria or "high" is followed by drowsiness. Time sense is altered, hearing is less discriminant, and vision is apparently sharper with many visual distortions. Depersonalization, difficulty in concentrating and thinking, and dream-like states are prominent. Many of these symptoms are similar to those produced by psychotomimetics.

The effects that users derive from cannabis are extremely variable. Some of this variability depends on individual variation in degree of tolerance to the drug, based on prior use. Although it is customary to ascribe some variability to difference in setting, i.e., the type of

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conditions and surroundings which prevail during drug use, or to set, i.e., the expectations of the user, proving the effects of either has been difficult. One study indicated that, with pharmacologically active doses of the drug, extreme variations in setting produced little alteration of drug effects, which were clearly different from those produced by placebo (82).

B. Chronic Studies

The effects of chronic use of cannabis are more to the point when considering the issues of its status as a possible social drug. Three large-scale field trials of cannabis users have been implemented, but the results of these trials have done little to allay apprehensions about the possible ill effects of chronic use. Objections have been made about the small samples used, the sampling techniques, and the adequacy of the studies performed.

Jamaica is a country in which cannabis is widely used, under the name ganja. The content of the THC in native cannabis is generally high, estimated at several-fold that of cannabis generally available to users in North America. The average Jamaican user smokes seven to eight cannabis cigarettes a day, such use not being considered deviant in that country. Sixty adult workers, all men, were selected for study. Thirty were ganja smokers, and 30 were not, although the latter may have used cannabis tea. Extensive studies in the hospital revealed no significant physical abnormalities between the two groups. The smokers were found to be at greater risk of functional hypoxia, which might have been due to the fact that tobacco was also used by this group. Smokers claimed to use cannabis so as to work better, but evidence in a selected subgroup supported slightly decreased performance. The small sample and the fact that impairment may be difficult to detect in unskilled workers make it difficult to be sanguine about these generally negative results (147).

A similar study was done in Costa Rica, another country in which cannabis use is prevalent. Two groups of 80 subjects, users of cannabis and nonusers, were compared by a variety of clinical and laboratory examinations. Essentially no difference between the two groups was detected (34). Forty-seven chronic users of hashish in Greece were compared with 40 nonusers, focussing primarily on tests of brain damage. No evidence of abnormality in function as judged by a variety of tests could be detected in the hashish group as compared with the others. The hashish users had a higher prevalence of personality disorders, probably unrelated to their use of hashish but possibly contributing to it (49).

If field studies fail to provide evidence of harm from prolonged use of cannabis, it is unlikely that experimental studies will do better, and such has been the case. The results of a 30-day high-dose cannabis study in which doses up to 210 mg of THC per day were administered p.o. to volunteers were most remarkable in how well the subjects tolerated such large doses (93). Tolerance was probably present in most subjects prior to the study, but it was rapidly augmented during it. Under these conditions, a mild withdrawal reaction was found when the drug was abruptly discontinued. Additional unanticipated findings were weight gain, bradycardia, and an absence of psychotomimetic effects. As the amount of drug absorbed from p.o. administration may be small, these results are only partially applicable to smoking.

A longer experimental study in which cannabis was smoked rather than taken p.o. exposed subjects from 35 to 198 mg of THC daily for 78 days. The unique contribution of this study was the discovery of the effects of cannabis in lowering intraocular pressure. Other effects noted were lowering of serum testosterone levels, airway narrowing after heavy use, lack of chromosomal alteration, and unchanged immune responses (35). Other effects of chronic cannabis use are related in a specific publication of the New York Academy of Sciences on chronic cannabis use (31).

In summary, we have a very good idea of the acute effects of cannabis, although these are tempered by the dose of THC, the route of administration of the previous exposure of the user to the drug, and possibly by their past experiences with it. The effects of chronic use are somewhat less certain. Experimental studies suggest that tolerance develops rapdily, that a mild withdrawal reaction may occur, and that some acute effects may be reversed (for instance, a slow heart rate with chronic use rather than a rapid one as seen with acute use). Field studies have failed to detect any major health consequences from chronic heavy use of cannabis, but these studies have many deficiences, most studies being far too small to pick up unusual or rare consequences that could be of great importance. Nonetheless, one is forced to conclude that cannabis is a relatively safe drug as social drugs go. To date it compares favorably with tobacco and alcohol, if not with caffeine. One should bear in mind, however, the very long time that it took to determine the ill effects of health of these accepted social drugs.

III. Possible Adverse Effects of Cannabis on Health

A. Immunity

A number of in vitro studies, using both human and animal material, suggest that cell-mediated immunity may be impaired after exposure to cannabis. Clinically, one might assume that sustained impairment of cell-mediated immunity might lead to an increased prevalence of opportunistic infections, or an increased prevalence of malignancy, as seen in the current epidemic of acquired immune deficiency syndrome (AIDS). No such clinical evidence has been discovered. Despite some degree of impairment of immune responses, the remaining immune function may be adequate, especially in the young persons who are the major users of cannabis.

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An impairment of cellular immunity in 51 chronic users of cannabis was shown by inhibition of lymphocyte blastogenesis from the mitogen, phytohemagglutinin (171). A decrease in T-lymphocytes was found in 9 of 23 chronic cannabis users, employing rosette formation as a way of quantifying T-lymphocytes; the number of total lymphocytes was not different from nonusers (66). Thus, two early studies suggested that T-lymphocytes might be decreased in number as well as in ability to respond to an immunologic challenge. Immunosuppression was shown in animals by prolonged allogenic skin graft survival, inhibited primary antibody production to sheep erythrocytes, and a diminished blastogenic response (109).

Further studies have tended to confirm an immunosuppressant action of cannabis in animals, whether the material was given p.o. or injected i.p. (144, 185). Mice treated with THC and challenged with gram-negative bacteria showed enhanced susceptibility (19). However, others, using in vitro techniques for studying lymphocytes, have found no alteration in nucleic acid synthesis in the presence of as much as 10.6×10^{-4} M concentrations of THC (137).

Effects of cannabis on T-cells may be transitory. Smoking of cannabis temporarily decreased T-cell function in 13 chronic users as compared with 9 matched nonsmokers, but the effects varied from subject to subject and were closely related to the time at which the blood samples to be tested were drawn (134). Although early T-cell rosette formation was impaired in ten chronic cannabis smokers, despite a normal total of circulating T-cells, the absence of clinical evidence of greater disease susceptibility among such subjects makes this observation of dubious clinical importance (45, 126).

Other studies cast doubt on some of the earlier positive observations of impaired cellular immunity. Dinitrochlorobenzene is used as a skin test for intact delayed hypersensitivity, mediated by cellular immunity. No differences were observed in 34 chronic marijuana smokers as compared with 279 nonsmokers (152). The response of cultured lymphocytes from 12 long-term smokers of cannabis to two mitogens was not impaired as contrasted with lymphocytes from nonsmokers (178). Even the ingestion of cannabis in amounts of 210 mg daily of THC failed to alter the response of the subject's lymphocytes to mitogen stimulation (103).

In summary, evidence is difficult to interpret concerning a possible suppressant effect of cannabis on cell-mediated immunity. If suppression occurs, it may be only transient, in the sense that recovery can occur. Further, the degree may not be clinically significant as the reserve capacity of the body to respond to immune challenge may not be exceeded. We simply do not know how much impairment is necessary to make someone vulnerable. Clinical experience has not yet indicated an increased vulnerability of cannabis users, but further observations of the possible contribution of marijuana use to the susceptibility to develop AIDS must be awaited.

B. Chromosomal Damage

Adverse effects on chromosomes of somatic cells have been especially controversial. The techniques of human cytogenetic studies still leave much to be desired. Assessing damage to chromosomes is more of an art than a science. Interpretations are highly subjective, and it is often difficult to get agreement between any two readers of the same slide. Further, processing of cells to make the chromosomal preparations may differ from one laboratory to another, so that it is possible to get conflicting results from the same blood specimen even when read by the same reader. One needs only recall the controversy about chromosomal damage from lysergic acid diethylamide (LSD) a few years ago to interpret any reports of chromosomal damage with great caution. As similar types and degrees of chromosomal alteration have been reported in association with other drugs commonly used in medical practice, without any clinical evidence of harm, the significance of such changes remains unclear. Early reports were positive, but more recent reports were negative. A significant increase (3.4 *versus* 1.2%) of chromosomal abnormalities was reported in marijuana users as compared with nonusers (155). Changes were largely breaks or translocations of chromosomes. More of the latter were found in chronic cannabis users than in nonusers, but when breaks were included in the counts, the differences vanished (76). No increase in chromosomal breaks was found in cells from subjects taking p.o. hashish extract (which contains THC as well as cannabinol), marijuana extract (containing only THC), or synthetic THC (128). After 72 days of chronic smoking of cannabis, no increase in break frequency was found over that which existed prior to the study (116).

Both the retrospective and prospective studies have flaws, and one simply cannot conclude that the issue is settled. For that matter, it has not yet been settled for a variety of drugs, including aspirin, in which an increased number of chromosomal abnormalities have been described. One must conclude for the time being that, even if a small increase in chromosomal abnormalities is produced by cannabis, the clinical significance is doubtful.

C. Pregnancy and Fetal Development

This is another area of great uncertainty about the meaning of data. Virtually every drug that has been studied for dysmorphogenic effects has been found to have them if the doses are high enough, if enough species are tested, or if treatment is prolonged. The placenta is not a barrier to the passage of most drugs, so the assumption should be made that they will reach the fetus if taken during pregnancy (3).

This assumption is well validated for THC, based on autoradiographic studies (87). A high incidence of stunting of fetuses was seen in mice treated on day 6 of

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pregnancy with a single i.p. dose of 16 mg of cannabis resin per kg. No reduction in litter size or apparent malformations were seen. When the same dose was given repeatedly from days 1 to 6 of pregnancy, fetal resorption was complete (133). Treatment of mice from days 6 to 15 of gestation with THC at doses of 5, 15, 50, and 150 mg/kg had no effect on fetal weight, prenatal mortality rate, and frequency of gross external, internal, or skeletal abnormalities (50). Exposure of pregnant rats to either cannabis smoke or smoke from extracted marijuana throughout gestation produced less fertile offspring with smaller reproductive organs in the cannabis-treated animals (12, 54).

Pregnant rabbits treated p.o. with daily doses of THC at 15 mg/kg on days 6 to 18 of gestation delivered infants without visible abnormalities (36). Injection s.c. of doses of THC up to 100 mg/kg daily on days 6 to 15 of gestation had no teratogenic effect (97). Fetal resorption was seen in rats treated with s.c. doses of THC at 100 mg/kg for days 1 to 20 of gestation, but lesser doses had no effect (18).

Clinical studies have also not elucidated the question. An epidemiological study found more meconium staining of the fetus and more disturbances of the duration of labor (either short or long) among 35 users of marijuana as compared with 36 nonusers (63). However, no significant difference was found between 19 moderate to heavy users and many more nonusers in regard to several neonatal outcomes (53). Small sample sizes reduce the confidence in the results of either study. A much larger study involved 12,424 women of whom 1,246 (11%) were marijuana users. Lower birth weights, a shorter gestation period, and more major malformations were found among the offspring of users (111). No changes in serum human chorionic gonadotropin, placental lactogen, progesterone, estradiol, and estriol were found in 13 women who smoked marijuana during their pregnancy, compared with a matched control number who did not (20).

In summary, it is still good practice in areas of ignorance, such as the effects of drugs on fetal development, to be prudent. While no definite clinical association has yet been made between cannabis use during pregnancy and fetal abnormalities, such events are likely to be rare at best and could easily be missed. The belated recognition of the harmful effects on the fetus of smoking tobacco and drinking alcoholic beverages indicates that the same caution with cannabis is wise.

D. Cell Metabolism

Information currently available for the effects of cannabis on cell physiology and metabolism is limited. Smoke from both cannabis and tobacco increased the size of the cytoplasm, nuclei, and nucleoli along with an increase in DNA content of human lung cell explants. Mitotic abnormalities were also noted with an increase of 10 to 25% over those of controls. Combination of both smokes produced greater abnormalities than either one alone. Malignant cell transformation of hamster lung culture was observed after administration of both types of smoke (108). These findings suggest that cannabis smoke is harmful to lung cells in cultures and contributes to the development of premalignant and malignant lesions.

Cannabinoids may also interfere with the normal cell cycle. Experiments with the protozoan, *Tetrahymena*, synchronized in culture, showed a reduction in growth rate during log phase and a lengthening of the mean division time upon exposure of THC. These changes were dose dependent (183). Addition of THC to various human and animal cell cultures has been shown to decrease synthesis of DNA, RNA, and protein (17).

The clinical implication of some of these findings is obscure. On the one hand, exposure to smoke from cannabis may be carcinogenic. On the other, the changes in nucleic acid synthesis, were they to be specific for rapidly dividing cells, such as those of malignancies, might be useful therapeutically in their treatment.

E. Psychopathology

Cannabis may produce directly an acute panic reaction, a toxic delirium, an acute paranoid state, or acute mania. Whether it can directly evoke depressive or schizophrenic states, or whether it can lead to sociopathy or even to the "amotivational syndrome" is much less certain. The existence of a specific cannabis psychosis, postulated for many years, is still not established. The fact that users of cannabis may have higher levels of various types of psychopathology does not infer a causal relationship. Indeed, the evidence rather suggests that virtually every diagnosable psychiatric illness among cannabis users began before the first use of the drug. Use of alcohol and tobacco, as well as sexual experience and "acting-out" behavior, usually antedated the use of cannabis (68). When the contributions of childhood misbehavior, school behavioral problems, and associated use of other illicit drugs were taken into account, it was difficult to make a case for a deleterious effect of regular marijuana use (69). Thus, it seems likely that psychopathology may predispose to cannabis use rather than the other way around.

1. Acute panic reaction. This adverse psychological consequence of cannabis use is probably the most frequent. About one in three users in one high school and one in five in another reported having experienced anxiety, confusion, or other unpleasant effects from cannabis use. These unpleasant experiences were not always associated with unfamiliarity with the drug; some subjects experienced these adverse reactions after repeated use (7). The conventional wisdom, however, is that such acute panic reactions occur more commonly in relatively inexperienced users of cannabis, more commonly when the dose is larger than that to which prior users may have become accustomed, and more commonly in older

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users who may enter the drug state with a higher level of initial apprehension (67).

The acute panic reactions associated with cannabis are similar to those previously reported to be caused by hallucinogens. The subject is most concerned about losing control, or even of losing his or her mind. Reactions are usually self-limited and may respond to reassurance or "talking down"; in the case of cannabis use, sedatives are rarely required as the inherent sedative effect of the drug, following the initial stimulation, often is adequate. Occasionally one may see a dissociative reaction, but this complication is readily reversible. Depersonalization may be more long-lasting and recurrent, somewhat akin to "flashbacks" reported following hallucinogens; the electroencephalogram shows no abnormality (158).

2. *Toxic delirium.* Very high doses of cannabis may evoke a toxic delirium, manifested by marked memory impairment, confusion, and disorientation (120). This nonspecific adverse psychological effect is seen with many drugs, but the exact mechanism is not clear in the case of cannabis as it is in the case of *Datra stramonium* smoking, for instance, which produces potent anticholinergic actions. As high does of any drug tend to prolong its action, delirium is self-limited and requires no specific treatment. Highly potent preparations of cannabis are not as readily available in North America as in other parts of the world, so these reactions are less commonly observed in the United States and Canada.

3. *Acute paranoid states.* It is difficult to gauge the frequency of these reactions. In a laboratory setting, they are frequently encountered. Quite possibly the experimental setting creates a paranoid frame of reference to begin with. That this reaction is not peculiar to the laboratory is evident from reports in which it has been experienced in social settings (96). The illegal status of the drug might contribute in such instances, for while intoxicated, one might be more fearful of the consequences of getting caught. Undoubtedly, the degree of paranoia of the individual is also an important determinant, so that this reaction may represent an interplay between both the setting in which the drug is taken as well as the personality traits of the user.

4. *Psychoses.* A variety of psychotic reactions have been ascribed to cannabis use. Many are difficult to fit into the usual diagnostic classifications. Two cases of a kind of manic reaction were reported in children who were repeatedly exposed to cannabis by elders. Both required treatment with antipsychotic drugs but ultimately showed a full recovery (16). Hypomania, with persecutory delusions, auditory hallucinations, withdrawal, and thought disorder, was observed in four Jamaican subjects who had increased their use of marijuana (71). Twenty psychotic patients admitted to a mental hospital with high urinary cannabinoid levels were compared with 20 such patients with no evidence of exposure to cannabis. The former group was more agitated and hypomanic but showed less affective flattening, auditory hallucinations, incoherence of speech, and hysteria than the 20 matched control patients. The cannabis patients improved considerably after a week, while the control patients were essentially unchanged (146). Thus, a self-limiting hypomanic-schizophrenic-like psychosis following marijuana has been documented.

Psychoses in a group of East Indian marijuana users were predominantly instances of toxic delirium, but those who had "schizoid" features became overtly schizophrenic during the period of intoxication (30). The aggravating effect of marijuana on preexisting schizophrenia has been documented (169). However, it was impossible to distinguish retrospectively those individuals who exhibited behavioral changes in association with marijuana smoking from those who did not (114).

A controversial clinical report of 13 adults with psychatric disorder associated with the use of cannabis included some who had schizophrenic-like illnesses and one with depressive features. The majority of these subjects had used only cannabis, which was thought be the major precipitant of their disorders (98). A similar report from South Sweden involved 11 patients observed over a 1-year period. None had previous psychosis or abused other drugs. A mixture of affective and schizophrenic-like symptoms, as well as confusion and pronounced aggressiveness, was observed. The mental disturbances were self-limiting and rare (132).

It is impossible to think of any controlled trial that could be designed to detect adverse psychiatric effects from chronic use of a drug. Thus, clinical reports have long served as the surest way to detect adverse effects of both social and medically used drugs. Imperfect as such reports are, they can never be ignored.

Chronic use of hashish among a group of military personnel was tolerated quite well. Panic reactions, toxic psychosis, and schizophrenic reactions were infrequent occurrences among this group of 720 smokers, except when hashish was used in conjunction with alcohol or other psychoactive drugs. Rather, these 110 subjects who used the highest doses (over 50 g/month) developed a chronic intoxicated state characterized by apathy, dullness, lethargy, as well as impaired judgment, concentration, and memory (163).

The paranoid psychosis associated with long-term cannabis use was contrasted with paranoid schizophrenia in groups of 25 Indian patients with each syndrome. The cannabis psychosis was characterized by more bizarre behavior, more violence and panic, an absence of schizophrenic thought disorder, and more insight than was seen in the clearly schizophrenic group. The psychosis with drug use cleared rapidly with hospitalization and antipsychotic drug treatment and relapsed only when drug use was resumed (164). If there is a true cannabis psychosis, this description is probably the most accurate.

It would seem reasonable to assume that cannabis

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might unmask latent psychiatric disorders and that this action probably accounts for the great variety that have been described following its use. On the other hand, evidence for a specific type of psychosis associated with its use is still elusive. Hallucinogenic drugs have a similar property of unmasking latent illness, but a drug such as LSD, being much more disruptive to mental functioning than cannabis, is much more likely to precipitate a true psychosis or depression. Needless to say, use of cannabis should be discouraged (as would probably be the case with most socially used psychoactive drugs) in any patient with a history of prior emotional disorder (5).

5. *Flashbacks.* This curious phenomenon, in which events associated with drug use are suddenly thrust into consciousness in the nondrugged state, has never been satisfactorily explained. It is most common with LSD and other similar hallucinogens but has been reported fairly often with cannabis use. At first, it was thought that the phenomenon occurred only in subjects who had used LSD as well as cannabis, but more recent experience indicates that it occurs in those whose sole drug use is cannabis (153). One possibility is that flashbacks represent a kind of *deja vu* phenomenon. Another is that they are associated with recurrent paroxysmal seizure-like activity in the brain. The most unlikely possibility is that they are related to a persistent drug effect. They may occur many months removed from the last use of either LSD or cannabis, so that it is highly unlikely that any active drug could still be present in the body. Further, the interval between last drug use and the flashback is one in which the subject is perfectly lucid. For the most part, the reactions are mild and require no specific treatment.

6. *Violence.* The myth dies hard that cannabis makes otherwise docile subjects violent. Virtually every experimental study of cannabis that has tried to measure violent or aggressive behavior or thoughts during cannabis intoxication has come to the same conclusion; they are decreased rather than increased. A study of 40 college students focussed specifically on this problem, comparing cannabis with alcohol. Expression of physical aggression was related to the quantity of alcohol taken, but not to any dose of THC (64). Similar findings have resulted from surveys (162). Aggressive and sexually assaultive behavior in delinquent adolescents was more common following use of alcohol, even in those who also used cannabis (168). A review of the whole subject of cannabis and violence came to the consensus that cannabis does not precipitate violence in the vast majority of users. The possibility was entertained that a rare individual with some special predisposition to aggressive or violent behavior may be triggered into expressing such behavior under the influence of the drug (2).

7. *Amotivational syndrome.* Whether chronic use of cannabis changes the basic personality of the user so that he or she becomes less impelled to work and to strive for success has been a vexing question. As with other questions concerning cannabis use, it is difficult to separate consequences from possible causes of drug use. It has been postulated that the apparent loss of motivation seen in some cannabis users is really a manifestation of a concurrent depression, for which cannabis may have been a self-prescribed treatment (102).

The demonstration of such a syndrome in field studies has been generally unsuccessful. Cannabis use among working men in Costa Rica did not impair to any detectable degree their ability to function (26). Much the same was found among Jamaican laborers. No signs of apathy, ineffectiveness, nonproductiveness, or deficits in general motivation were found (38). Each of these approaches has been criticized on the basis that those surveyed were unskilled workers in whom subtle impairment might be difficult to detect. However, a study of college students came to similar conclusions (117). Little evidence was adduced that dropping out of college was associated with cannabis use. Family background, relationship with parents during high school, and social values were stronger forces than drug use. Thus, in subjects with moderate use patterns of cannabis, no evidence of the amotivational syndrome was detected (18). A similar survey of college students found no significant relationship between marijuana use and achievement, orientation, or actual performance (123).

Laboratory studies have provided only scant evidence for this concept. A Canadian study showed a decrease in productivity following the smoking of cannabis. The decreased building of stools was due to less time worked than lessened efficiency at work (122). Using an operant paradigm, volunteer subjects on a research ward worked less as their consumption of cannabis increased. The decreased work output might have been due to decreased ability to work rather than decreased motivation (119). The former possibility is not suggested by neuropsychological testing of long-term users. No generalized decrement was observed in adapative abilities or cerebral functions (24). Similar results were found in members of a United States religious sect that relies on cannabis use. They showed no impairment of cognitive functions on a number of neuropsychological tests (150).

If this syndrome is so difficult to prove, why does concern about it persist? Mainly because of clinical observations. One cannot help being impressed by the fact that many promising youngsters change their goals in life drastically after entering the illicit drug culture, usually by way of cannabis. While it is clearly impossible to be certain that these changes were caused by the drug (one might equally argue that the use of drug followed the decision to change life style), the consequences are often sad. With cannabis as with most other pleasures, moderation is the key word. Moderate use of the drug does not seem to be associated with this outcome, but

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when drug use becomes a preoccupation, trouble may be in the offing.

8. Residual psychomotor impairment. Almost any task, if it is made difficult enough or if a large enough dose of drug is given, can be shown to be impaired by acute administration of cannabis. More to the point is whether following chronic use impairment remains a problem. Experimental studies in rats suggest that it does, but such studies are always difficult to extrapolate to man (47). A comparison of 23 chronic users of bhang (equivalent to about 50 mg of THC daily for at least 5 years) with 11 nonusers revealed some evidence of impairment in the users. The latter had lower intelligence and memory quotients with lower scores on psychomotor tests (179). For whatever reasons, studies of cannabis done in India tend to show more evidence of impairment or other adverse effects than those done elsewhere.

9. Brain damage. The startling report of cerebral atrophy in ten young men who were chronic users of cannabis aroused a great deal of controversy (22). The subjects selected for the study were ones who had come to psychiatric and neurological attention, besides which they had used other drugs. Even the validity of the method of measuring atrophy by comparing pneumocephalograms of the patients with negative controls was questioned. A study in monkeys provided some support for this observation. After 2 to 3 months of heavy to moderate exposure to marijuana smoke, electrographic recording changes were noted in the septal region, hippocampus, and amygdala which persisted 1 to 8 months after smoke exposure stopped. Ultrastructural changes were seen in synapses, as well as destruction of rough endoplasmic reticulum and the presence of nuclear inclusion bodies. No such changes were observed in animals exposed to smoke from extracted cannabis (73).

The advent of computerized tomography reopened the question. Two studies using this technique have effectively refuted the original claim of brain atrophy. Nineteen men with long histories of heavy cannabis smoking were examined, and none was found to have brain atrophy as determined by this sensitive technique (101). A similar finding was noted in the other study (33). On the other hand, alcohol has long been thought to cause brain atrophy, but recent studies suggest that it may be partially reversible (23). As brain atrophy from alcohol requires a substantial amount of use, it is possible that with longer exposure, heavy users of cannabis might show a similar pattern, but at present this seems unlikely.

Thus, the issue of brain damage is not totally resolved, although the original observation of brain atrophy seems to have been disproven. The issue is of tremendous importance and probably can only be settled by some suitable animal model, as studies in man are confounded by too many other variables.

F. Tolerance and Dependence

Tolerance to cannabis has long been suspected to occur during its continued use. Narrative accounts indicate that chronic users of the drug either show very little effect from moderate doses or require very large doses to produce the characteristic intoxication. A pioneer study of subchronic administration of cannabis and synhexyl, a synthetic cannabinoid, suggests at best some degree of tolerance to the euphoriant actions (180). Yet it has only been in the past few years that tolerance to cannabis has been clearly documented experimentally.

The demonstration of tolerance in man was delayed by ethical restrictions on the amount of exposure permissible to human subjects. For instance, in an early study subjects were exposed only to a test dose of 20 mg of THC p.o. and then given the same doses or placebos repeated at bedtime for 4 more days, followed by the same THC dose as a challenge on the fifth day. Using such small doses and relatively infrequent intervals, it was impossible to show tolerance to the psychic effects of the drug, although tolerance to the tachycardia and dizziness produced by the drug were evident (85).

Other early studies likewise suggested tolerance without definite proof. Tolerance to both tachycardia and "high" was reported following 21 days of consecutive smoking of only one cigarette a day by experienced smokers. It was possible that these subjects may have already been tolerant to the drug (46). Another study, in which subjects smoked a cannabis cigarette containing 14 mg of THC for 22 days, revealed a progressive decline in the increase of pulse rate following smoking, an increase in alpha rhythm on the electroencephalogram, and more decrement in the performance of short-term memory and reaction time tasks (49).

A number of other early studies provided less evidence of tolerance. Little evidence of tolerance to clinical effects of cannabis was found from daily smoking of marijuana cigarettes over a period of 10 to 28 days (51, 142). Free choice of marijuana cigarettes for 21 days also provided little evidence to support the concept of tolerance in man (165). Meanwhile, substantial evidence had accumulated that tolerance could be shown in various animal species, especially with high doses of THC given for prolonged periods.

Definite evidence of tolerance to the effects of THC in man was adduced only when it became permissible to use comparably large doses over longer periods of time. Subjects in one 30-day study were given high doses (70 to 210 mg/day) of THC p.o. around the clock. Tachycardia actually became bradycardia, and a progressive loss of "high" was noted (49). Similar tolerance to cannabis smoking was observed in a 64-day study in which at least one cigarette daily had to be smoked with smoking as desired later in the same day. Additionally, in this study tolerance developed to the respiratory depressant effect of THC (13).

The pattern that has emerged in man, therefore, is that tolerance is not a problem when doses are small, or infrequent, or where the pattern of use of the drug is not

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prolonged. Tolerance only becomes a major factor with high, sustained, and prolonged use of the drug. It is interesting that no study in man or animals ever revealed any evidence for "reverse tolerance" or sensitization, such as had been reported in an early, rather naive clinical study of marijuana (176).

1. Cross-tolerance. THC has effects which in man somewhat resemble those of hallucinogens and strongly resemble those of alcohol, while in animals it slightly resembles morphine. No cross-tolerance to mescaline or lysergide (LSD) could be shown in rats (151). Rats tolerant to the effects of THC were also tolerant to ethyl alcohol, but when the situation was reversed, less tolerance to the THC was seen in alcohol-tolerant animals (127). Perhaps this difference in sequential tolerance is why THC has never become established as a treatment for alcohol withdrawal, despite some early clinical trials that suggested a favorable effect. Cross-tolerance between THC and morphine has been shown in rats using customary tests of analgesia (95).

2. Physical dependence. Evidence from both animals and man indicates that physical dependence can be induced by abuse of THC. All monkeys given automatic injections of doses of THC of 0.1 to 0.4 mg/kg showed abstinence signs when withdrawn. When monkeys were allowed to self-administer the drug for 3 to 8 weeks, the majority had an abstinence syndrome when the drug was abruptly discontinued. The syndrome appeared approximately 12 h after the last administration and lasted about 5 days. It was characterized by irritability, aggressivity, tremors, yawning, photophobia, piloerection, and penile erections (95).

In man, a somewhat similar, though mild, withdrawal reaction was uncovered after abrupt cessation of doses of 30 mg of THC given every 4 p.o. for 10 to 20 days. Subjects became irritable, had sleep disturbances, and had decreased appetite. Nausea, vomiting, and occasionally diarrhea were encountered. Sweating, salivation, and tremors were autonomic signs of abstinence (49). Relatively few reports of spontaneous withdrawal reactions from suddenly stopping cannabis use have appeared, despite the extraordinary amount of drug consumed. Five young persons experienced restlessness, abdominal cramps, nausea, sweating, increased pulse rate, and muscle aches when their supplies of cannabis were cut off. Symptoms persisted for 1 to 3 days (15). The rarity of reports of these reactions may reflect the fact that they are mild, and seldom is a user completely cut off from additional drug.

Cannabis would have been an exceptional centrally acting drug if tolerance/dependence were not one of its properties. The fact that tolerance was not strongly recognized as an effect of chronic use of the drug until fairly recently was due to the narrative nature of previous accounts of tolerance in man and the lack of systematic animal experimentation. Tolerance has now been proven for most of the actions of THC. It develops at varying rates for different actions, but it is rapidly reversible. Large doses of THC are required over long time periods for tolerance to develop. As most social use of the drug does not meet these requirements, neither tolerance nor dependence has been a major issue in its social use.

G. Endocrine and Metabolic Effects

Changes in male sex hormones have been a source of controversy ever since the first report of a cannabinoid-induced decrease in serum testosterone level. Decreased levels were associated with morphological abnormalities in sperm and with decreased sexual functioning (100). Such changes must require long-term exposure to cannabis, for subchronic studies in experimental subjects have generally failed to confirm these findings (118). During the first 4 weeks of a chronic administration study, no major changes in hormone levels were detected, but with subsequent exposure a decrease first occurred in luteinizing hormone (LH) followed by decreases in testosterone and follicle-stimulating hormone (FSH) (99). Testosterone synthesis by Leydig cells was decreased in rats, both by THC as well as by other cannabinoids (21). A similar finding had been reported earlier (57). A review of the literature on this subject concluded that no significant effect was found in regard to serum testosterone and that sperm production was decreased but without evidence of infertility. Ovulation was inhibited, and luteinizing hormone was decreased. Cannabinoids had no evidence of estrogenic activity, which had been postulated earlier (4).

The meaning of such changes in man is uncertain, as the hormone levels generally remained within the accepted limits of normal. Further, a single hormone level may not be truly representative of the prevailing levels of hormones that tend to be secreted episodically or which are subject to many extraneous influences.

Data on the effects of cannabis on the female reproductive system are sparse. Preliminary unpublished data indicate that women who use cannabis 4 times a week or more have more anovulatory menstrual cycles than do nonusers of the same age. Animal work tends to support this observation. THC administered to rats suppressed the cyclic surge of LH secretion and of ovulation (11).

Gynecomastia has been thought to be a complication of cannabis use, especially when it was also possible to stimulate breast tissue development in rats with THC (72). Eleven soldiers with gynecomastia of unknown cause were matched with 11 others with similar characteristics except for gynecomastia. No difference in cannabis use was found between the two groups (27). Such a finding does not disprove the relationship between cannabis and gynecomastia. Indeed, if cannabis increases peripheral conversion of testosterone to estrogens, then it is possible that the increased estrogens could stimulate breast tissue in a few susceptible men. Increased estro-

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gens might also account for some reports of diminution in sexual desire or in performance in men.

These endocrine changes may be of relatively little consequence in adults, but they could be of major importance in the prepubertal male who may use cannabis. At least one instance of pubertal arrest has been documented. A 16-year-old boy who had smoked marijuana since age 11 had short stature, no pubic hair, small testes and penis, and low serum testosterone. After stopping smoking, growth resumed and serum testosterone reached the normal range (41). As recent surveys of cannabis use indicate that some boys (and girls) may be exposed to it even as early as the prepubertal years, this question is of more than academic interest.

Although cannabis has been said in the past to cause hypoglycemia, this error has been pointed out in numerous studies. On the contrary, some subjects showed impaired glucose tolerance following experimentally administered i.v. doses of 6 mg of THC. Such a dose is probably greater than one generally attains from usual cigarettes but might be obtained from high-grade hashish. The deterioration of glucose tolerance was accompanied by increased levels of plasma growth hormone, as well as by a normal plasma insulin response. These findings suggested that growth hormone might be interfering with the action of insulin (83). A study in rabbits indicated that blood glucose was increased by single doses of THC but that this increase could be prevented by adrenalectomy. Increased release of epinephrine following THC was postulated as a possible cause for the hyperglycemia (70). Although large doses of THC might aggravate diabetes, the rarity of this phenomenon in clinical practice may be due to the lower doses of THC used socially or the development of tolerance to this specific pharmacological effect.

H. Lung Problems

Virtually all users of cannabis in North America take the drug by smoking. As inhaling any foreign material into the lung may have adverse consequences, as is well proven in the case of tobacco, this mode of administration of cannabis might also be suspect. Smoking is a most efficient method for administering the drug, due to the enormously high lipid solubility of THC. The pulmonary surfactant is a perfect trap for THC which is then rapidly absorbed into the blood. The kinetics of the THC administered by smoking are similar to those of its i.v. administration.

Heavy use of hashish by soldiers produced a number of bronchopulmonary consequences, including chronic bronchitis, chronic cough, and mucosal changes of squamous metaplasia, a precancerous change (74). Although at first THC was thought not to be a respiratory depressant, more careful studies indicated that it was when given p.o. in doses of 22.5 mg (14). Thus, its use in any form by patients with impaired pulmonary function would be hazardous. Young, healthy volunteer subjects in a chronic smoking experiment had pulmonary function tests before and after 47 to 59 days of daily smoking of approximately five marijuana cigarettes a day. Decreases were found in forced expiratory volume in 1 s, in maximal midexpiratory flow rate, in plethysomographic specific airway conductance, and in diffusing capacity. Thus, very heavy marijuana smoking for 6 to 8 weeks caused mild but significant airway obstruction (161).

Quite possibly such dramatic early changes are not progressive with continued smoking (171). Compared with tobacco, cannabis smoking yields more residue ("tar"), but the amount of smoke inhaled is very likely to be considerably less. The study in which five cigarettes were consumed daily represented heavy use of the drug, compared with 20 to 40 tobacco cigarettes which might be consumed by a heavy tobacco smoker. Low values for specific airway conductance were found in marijuana smokers, a change not observed in tobacco smokers. This change indicates mild impairment of large airway function. No differences were found between marijuana smokers and nonsmokers in spirometric indices, closing volumes, or nitrogen concentrations between 750 and 1250 ml of expired air (159). Marijuana smoke inhibits pulmonary antibacterial defense systems, mainly alveolar macrophages, in a dose-dependent manner. The cytotoxin involved is not related to any psychoactive component (86). One would assume that marijuana smokers might be more susceptible to bacterial infections of the lung, yet such increased susceptibility has not been clinically documented.

The issue of damage to lungs from cannabis is somewhat confounded by the fact that many cannabis users also use tobacco. As yet, it is far easier to find pulmonary cripples from the abuse of tobacco than it is to find any evidence of clinically important pulmonary insufficiency from smoking of cannabis.

I. Cardiovascular Problems

Tachycardia, orthostatic hypotension, and increased blood concentrations of carboxyhemoglobin from cannabis smoking would undoubtedly have deleterious effects on persons with heart disease due to arteriosclerosis of the coronary arteries or congestive heart failure. Although a slight trend toward increased use by persons over age 30 years has been detected in recent epidemiological studies, it is unlikely that many persons with serious heart disease will be exposed to this hazard from cannabis use.

Tachycardia is a consequence of almost every acute dose of cannabis, although some degree of tolerance develops to this effect. Evidence suggests that it is mainly due to an inhibition of vagal tone (32). Increasing the heart rate and thereby cardiac work might be harmful to patients with angina pectoris or congestive heart failure. A direct test of the effects of marijuana smoking in exercise-induced angina proved this harmful effect of the drug. Smoking one cigarette containing 19 mg of THC

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decreased the exercise time until angina by 48%. Smoking a marijuana placebo cigarette decreased the exercise time until angina by only 9%. Thus, smoking marijuana increased myocardial oxygen demand and decreased myocardial oxygen delivery (9). A subsequent study compared the effect of this type of marijuana cigarette with that of a high nicotine cigarette. The marijuana cigarette decreased exercise time to angina by 50%; the nicotine cigarette decreased the exercise time to angina by 23% (10). Clearly, smoking of any kind is bad for patients with angina, but the greater effect of cannabis in increasing heart rate makes this drug especially bad for such patients. Fortunately, few angina patients are devotees of cannabis.

A rapid heart rate might be expected to aggravate congestive heart failure. Actually, little is known about the direct effects of THC on myocardium. A single study using an isolated rat heart reported a negative inotropic effect from THC, i.e., weaker contractibility of the muscle (115). If so, the use of cannabis by patients in congestive heart failure could make matters even worse.

Premature ventricular contractions have been reported following marijuana smoking (91). However, when subjects were continually monitored electrocardiographically while smoking cigarettes containing approximately 20 mg of THC, no increase in such premature beats was found (145). Ventricular premature beats are rarely observed and do not seem to be of any great clinical importance.

J. Eye Problems

Eye complaints of cannabis users are vague and mild. All of 350 cannabis users had some eye complaints. Several consistent findings were (*a*) photophobia and belpharospasms; (*b*) injection of the globe; (*c*) increased visibility of the corneal nerves; and (*d*) accommodative or refractive changes. Visual acuity was preserved, but pupillary reactions were sluggish. Both alcohol and cannabis produced moderately debilitating effects on lateral phoria and abduction. During smoking, lacrimation may be observed along with the characteristic marked conjunctival injection. Despite the fact that numerous and complex changes occur in the eyes of cannabis users, these effects are confined to the anterior segment and in most respects mimic an irritative process of that region. They are transient and not cumulative. They are probably of little clinical significance (60).

Reduction in intraocular pressure is a characteristic effect from cannabis. This action provides distinct therapeutic possibilities and will be discussed later.

K. Contamination of Cannabis

The most definite health hazard was contamination of cannabis, largely of Mexican origin, by the herbicide, paraquat. Inhalation of toxic amounts of this material could lead to severe lung damage, and some instances of acute toxicity have occurred. Paradoxically, this hazard stemmed from efforts to save cannabis users from less well-documented hazards to their health.

Estimates of the amount of contaminated cannabis reaching North America may have been grossly exaggerated due to false positive results in testing for paraquat. Formerly as much as one-third to one-half of Mexican cannabis was assumed to be contaminated. The results of later analyses suggest that only about 10% is contaminated. The problem still remains for the user as to how to identify such a contaminated product.

One thought has been to look for red spots on the marijuana leaves. This approach may be difficult for the leaves usually are available in a finely ground form. A red fluorescence is seen under ultraviolet light, such as is commonly used in discotheques. A similar red fluorescence may be seen on the lips of the smoker of paraquat-contaminated cannabis.

After the experience with paraquat in Mexico, its use was temporarily discontinued. Recently, the possibility that it may be used against cannabis crops in California and Hawaii has resurfaced. One would hope that overzealous law enforcement would not once again pose a serious health risk to marijuana users.

Cannabis is generally harvested like any other crop. The final product of ground leaves and stems look very much like grass cut by a mower. Usual insecticides and fungicides are rarely used, as the plant grows abundantly with minimal care. Other sources of contamination may include insects and fungi.

L. Possible Accumulation of Drug

The major if not the sole active component of cannabis, THC, is highly lipid soluble. As the human body has a high lipid content, which includes not only body fat, but also brain and most cell membranes, lipid-soluble drugs tend to leave the blood rapidly to be distributed to fatty tissues. It is characteristic of such drugs that the action of a single dose is terminated not by the elimination of the drug through metabolic processes, but by redistribution to sites in the body where it cannot act. The prime example of such a drug is pentothal sodium, which rapidly produces anesthesia when given i.v., but which has a very short span of action. The drug still remains in the body, but in places where it cannot act. A similar situation applies to the widely used sedative drug, diazepam.

An early study of the pharmacokinetics of THC examined its tissue distribution following a single s.c. injection in rats. Following a single injection of radiolabeled material, the concentration of THC in fat was 10 times greater than for any other tissue examined and persisted in this tissue for 2 weeks. Thus, there is good evidence that THC and its metabolites might accumulate not only in fat, but also in brain (107).

Obviously, similar studies could not be done in man. One can measure in man the extraction of cannabis metabolites following single or repeated doses, to get some idea of their persistence. Following both single and

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repeated doses (at least single doses for several days), metabolites of cannabis can be found in the urine for varying periods, up to several days following the last dose (94). All of these metabolites are ones that are known to have no mental effects, except for a miniscule amount of unchanged THC which is excreted during the first 4 h following a dose, while the drug is having definite clinical effects. The excretion of these metabolites is not accompanied by any evidence of cannabis-like effects.

We may conjecture that THC rapidly leaves the blood to be sequestered in fatty tissues. It is either gradually metabolized in these tissues to inactive metabolites which are then excreted in the urine, or it may be gradually released from these tissues in small amounts to be metabolized by the liver before attaining effective plasma concentrations. In either case, there is no evidence of a continuing drug effect from this accumulation of drug in the body.

No one has yet reported on the excretion of metabolites following prolonged exceedingly high dose administration of THC. In one study in which doses of up to 210 mg of THC were given p.o., abrupt discontinuation of the drug led quickly to mild signs of a withdrawal reaction (49). As the development of withdrawal reactions is contingent upon a rapid decline to the point of absence of active drug in the body, one must assume that no accumulation of active drug occurred, even under extreme circumstances.

In short, the apprehension about accumulation of THC from repeated use is based on evidence indicating only the accumulation of drug that is either in inactive form to begin with or which is rendered inactive before reaching the circulation in any pharmacologically active amount. We do not know the full toxicity of many of the possible metabolites which might accumulate, but generally toxicity studies of cannabis and its constituents lead to the inescapable conclusion that it is one of the safest drugs ever studied in this way.

M. Effects on Driving an Automobile

If marijuana is to become an accepted social drug, it would be important to know its effects on driving ability. Fully one-half of the fatal car crashes in the United States are associated with another social drug, alcohol. Neither experimental nor epidemiological approaches to the marijuana question have yet provided definitive answers.

Many studies have used acute doses of marijuana or THC to study various psychomotor functions. These can be summarized by saying that, if the dose of drug was high enough or the task difficult enough, impairments were shown. It is difficult to determine how pertinent these tests are to the actual driving of an automobile. Furthermore, it is difficult to relate the effects of acute consumption of marijuana, often in relatively naive subjects, to the effects that may be found in chronic users, who may have developed some degree of tolerance.

Studies on the acute effects of marijuana on simulated driving have shown mixed results. The first compared smoked marijuana (doses uncertain) with ethanol in sufficient quantities to produce alcohol levels of 100 mg/dl. Marijuana increased speedometer errors but produced no deviation from the norm on accelerator, brake, signal, steering, or total errors. Alcohol had a far more deleterious effect (43). Marijuana administered p.o. in doses of 8, 12, and 16 mg was compared with a dose of 70 g of alcohol in eight volunteer subjects performing a simulated driving task. Both marijuana and alcohol increased the time to brake and to start, but these changes were confined to the 16-mg dose of THC (138). Marijuana was smoked with the intention of administering doses of 0, 50, 100, and 200 μg/kg, a most dubious assumption. No significant deviations from the norm were noted in car control and tracking aspects (124).

Actual driving in normal traffic conditions would more closely mimic real-life situations, including the dangers. Sixty-four volunteer subjects smoked cigarettes containing 0, 4.9, or 8.4 mg of THC. Oddly enough, THC had a biphasic effect, causing deterioration of driving skills in some subjects and improvement in others. A recently completed study compared the effects of smoking a marijuana cigarette with or without alcohol, alcohol alone, and placebos for each drug. Actual driving was done over a course rigged with various traffic problems. Both drugs produced impairment of driving performance, the combination being worse than either alone (141).

Fifty-nine subjects smoked marijuana cigarettes until "high" and then were tested periodically by highway patrol officers on the roadside sobriety test. Overall, 94% of subjects failed to pass the test 90 min after smoking and 60% after 150 min, despite the fact that by then plasma concentrations of THC were rather low (81). It appeared that establishing a clear relation between THC plasma concentrations and the degree of clinical impairment will be much more difficult than has been found in the case of alcohol (140). The exact prevalence of persons who might be picked up while driving under the influence of marijuana is uncertain. One survey found at least 5 ng of THC per ml in the blood specimens of 14.4% of a random sample of 1792 drivers detained for erratic driving. Many were also associated with blood levels of alcohol as well (184).

Flying an airplane is much more difficult than driving an automobile, but the general principles of impairment are similar. Ten certified pilots who smoked marijuana or placebo were tested on a simulator. The results were highly variable from pilot to pilot and from skill to skill. It was assumed that the pilots had regained full function after 4 h (90). Somewhat contrary results were obtained in another similar study which found, however, some degree of impairment in flying skills as long as 24 h after an exposure to marijuana. The subjects were unaware of any such impairment (182).

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The issue is not clearly settled, but common sense would suggest that it would be unwise to try to drive an automobile soon after exposure to marijuana. In our first study with the drug, the subjects were asked during the period of their intoxication, "Would you be able to drive a car now?" Their uniform answer was, "You've got to be kidding." The biggest areas of doubt are how long the impairment, even though subtle, may last and how to deal forensically with driving while under the influence of marijuana. The best evidence at present would be to assume that any amount of THC more than 10 ng/ml in plasma is presumptive evidence of impairment. Such a decision is arbitrary, but so have been forensic decisions about the presumed level of intoxication with alcohol.

IV. Therapeutic Uses

For many centuries, cannabis was used as a treatment, but only during the 19th century did a particularly lively interest develop for exploiting its therapeutic potential. Cannabis was reported to be effective in treating tetanus, convulsive disorders, neuralgia, migraine, dysmenorrhea, postpartum psychoses, senile insomnia, depression, and gonorrhea, as well as opium or chloral hydrate addiction. In addition, it was used to stimulate appetite and to allay the pain and anxiety of patients terminally ill with cancer (64, 121). However, the advent of modern pharmacology beginning in the 20th century discovered many other drugs more definitely effective in these disorders, with a subsequent decrease in the enthusiasm for cannabis as a therapeutic agent.

Advances in the chemistry of cannabis during the 1940s established tetrahydrocannabinol (THC) as the major active component. A semisynthetic THC-like material, synhexyl, was tested as a therapeutic agent during the late 1940s and early 1950s. Initial trials reported efficacy as an antidepressant and as a treatment for alcohol or opiate withdrawal, but subsequent clinical evaluations were negative (156, 166).

The exact structure of THC was shown in 1964 to be delta-9-trans-tetrahydrocannabinol, which was soon synthesized. The relative abundance of this material permitted extensive laboratory and clinical studies from 1968 onwards. These studies have included potential therapeutic uses.

At the present time, a number of pharmaceutical houses have programs to develop cannabinoids as therapeutic agents. The major problem is to separate the specific desired pharmacological effect from the pronounced mental effects of cannabinoids. A number of reviews of the potential therapeutic uses of cannabis have been published recently (36, 92, 104). We will now discuss some indications of current interest.

A. Antiemetic for Patients in Cancer Chemotherapy

Cancer chemotherapy, especially with the agent cisplatin, produces severe nausea and vomiting, which is extremely difficult to treat with ordinary antiemetic drugs, such as prochlorperazine. This complication is so severe that many patients forego effective cancer chemotherapy. The antiemetic effects of cannabis had been suggested as early as 1972 (6). THC was first tried as an antiemetic in a controlled trial comparing it with placebo in 20 patients undergoing cancer chemotherapy. Fifteen mg were given to some patients and 20 mg to the others in the form of gelatin capsules containing THC dissolved in sesame oil. The initial dose was started 2 h before chemotherapy and repeated 2 and 6 h later. Fourteen of the 20 patients in whom an evaluation could be made reported a definite antiemetic effect from THC, while none was observed from placebo during 22 courses of that drug (149).

Since then, studies have been largely confirmatory but not entirely so. Fifty-three patients refractory to other treatments were studied in an uncontrolled fashion. Ten had complete control of vomiting when THC was administered prior to chemotherapy and for 24 h thereafter. Twenty-eight had 50% or more reduction in vomiting, and only 15 patients showed no therapeutic effect whatsoever. However, four patients were dropped from the study because of adverse effects (113). Fifteen doses of 15 mg of THC were compared with 10-mg doses of prochlorperazine in a controlled cross-over trial in 84 patients. THC produced complete response in 36 of 79 courses, while prochlorperazine was effective in only 16 of 78 courses. Twenty-five patients received both drugs, of whom 20 preferred THC. Of the 36 courses of THC that resulted in complete antiemetic response, 32 were associated with mental effects characterized as a "high" (148). Another comparison between THC in 15-mg doses and prochlorperazine in 10-mg doses *versus* a placebo control was made in 116 patients who received p.o. doses 3 times a day. The THC regimen was equal to prochlorperazine, and both were superior to placebo. However, many patients who received THC found it to be unpleasant (55). A comparison of THC with placebo was made in 15 patients with each patient acting as his or her own control. Fourteen of the 15 patients given THC obtained more relief of nausea and vomiting than from placebo during a course of high-dose methotrexate chemotherapy (28). Best results were obtained when plasma concentrations of THC were more than 120 ng/ml. Such concentrations would ordinarily be expected to produce rather definite mental effects. THC was compared with two other antiemetics, thiethylperazine and metoclopramide, in a controlled cross-over trial. No difference was found between the antiemetic effect of these three agents. However, adverse effects of THC were sufficiently greater than those from the other two drugs, which raised questions about its clinical utility (37). When THC was compared with prochlorperazine and placebo, the latter two treatments were not found to differ, but THC was superior to either one (131).

In summary, it would appear that THC has definite

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antiemetic effects, that these are comparable to many other commonly used antiemetic agents such as prochlorperazine, thiethylperazine, and metoclopramide, but that the major disadvantage of the drug is the mental effects produced by the doses given.

A synthetic homolog of THC, nabilone, was developed in 1972 and has been tested extensively for antiemetic activity. A cross-over study comparing nabilone with prochlorperazine in 113 patients revealed significantly greater response rates following nabilone therapy. However, side effects from nabilone were also more common (77). Although it was hoped that nabilone separated the antiemetic effects from the mental effects of THC, this goal was not totally achieved. Levonantradol and BRL 4664 are two other synthetic THC homologs which showed antiemetic effects in open studies (43, 154). The exact role of synthetic homologs of THC as antiemetic agents remains to be determined.

Currently, a large amount of data on the clinical use of THC as an antiemetic is being accumulated in therapeutic situations monitored by the Food and Drug Administration. Unfortunately, this massive amount of clinical experience has no control, so that it may be impossible to conclude more than what is already known. Meanwhile, extremely promising results have been obtained with larger than usual i.v. doses of metoclopramide. When this drug was compared with prochlorperazine and placebo, it was more effective than either, the only disturbing side effect being sedation (59). The doses used of metoclopramide were 1 mg/kg i.v. before treatment with cisplatin (perhaps the most emetic anticancer drug) and several times after treatment. Protection was total in 48% of courses and major in another 23% (157).

This experience with metoclopramide suggests that the whole issue of the antiemetic effects of THC may become moot, as there are other drugs such as domperidone, which may also be effective in this situation.

B. Glaucoma

Discovery of the ability of cannabis to lower intraocular pressure was more or less fortuitous. Intraocular pressure was measured as part of a multifaceted study of the effects of chronic smoking of large amounts of cannabis. Intraocular pressure was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking (75). Lowered intraocular pressure lasted 4 to 5 h after smoking a single cigarette. Its magnitude was unrelated to the total number of cigarettes smoked. The maximal effect on intraocular pressure was produced by the amount of THC absorbed in a single cigarette containing 19 mg of THC. When patients with ocular hypertension or glaucoma were tested, 7 of 11 showed a fall of intraocular pressure of 30%. Confirmatory evidence was obtained from a trial in which i.v. injection of THC in doses of 22 μg/kg and 44 μg/kg produced an average fall in intraocular pressure of 37%, with some decreases as much as 51% (40). Many experiments done in rabbits using various routes of administration, including instillation of cannabinoids into the eye, have confirmed the ability of cannabis to reduce intraocular pressure.

Topical administration would be especially desirable for treating glaucoma as with the other drugs used for this purpose. Smoking cannabis or taking THC i.v. would be totally unsuitable for ptients with glaucoma. Rabbits have been used traditionally for studying topical eye medications. The lipid solubility of THC has been overcome by using mineral oil as the vehicle for its instillation into the eye. The degree of lowering of intraocular pressure is at least as great as that with conventional eye drops, such as pilocarpine, and the duration of effect is often longer. Some minimal systemic absorption of the drug occurs when it is applied to the conjunctivae, but it is of no consequence in producing mental effects. Other cannabinoids besides THC, such as cannabinol or 8-alpha- and 8-beta-11-dihydroxy-delta-9-THC, have also produced this effect in rabbits (62). These agents have no mental effects, which makes them of considerable interest for this therapeutic use.

An extract of nonpsychoactive components of cannabis whose composition is still uncertain has been tested both alone and in combination with timolol eye drops in patients with increased intraocular pressure. The effects of the two agents are additive and are said to be effective when other measures have failed (177). BW 146Y, a synthetic THC homolog, has been given p.o. to glaucomatous patients. Unfortunately, mild orthostatic hypotension and subjective effects were noted in addition to reduced intraocular pressure (167).

No psychoactive component of cannabis can be considered as a feasible therapeutic agent in this situation. Intraocular pressures, although they are reduced acutely, have not been shown to be reduced following long-term treatment, nor has there been any demonstration that visual function is preserved by the use of cannabinoids in glaucoma. Some of the problems associated with the development of cannabinoids as treatment for glaucoma have already been cited (61). The exploitation of cannabinoids for treatment of glaucoma will require much further developmental work to ascertain which cannabinoid will be lastingly effective and well tolerated. The potential benefits could be great, as present-day glaucoma treatment still does not prevent blindness as often as it might. If the effects of cannabinoids are additive to those of other drugs, the overall benefit to patients may be greater than is currently possible with single drugs.

C. Analgesia

Smoking of material estimated to deliver 12 mg of THC increased sensitivity to an electric shock applied to the skin (78). Single p.o. doses of 10 mg and 20 mg of THC were compared with codeine (60 mg and 120 mg) in patients with cancer pain. A 20-mg dose of THC was comparable to both doses of codeine. The 10-mg dose, which was better tolerated, was less effective than either

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dose of codeine (129). THC given i.v. in doses of 44 μg/kg to patients undergoing dental extraction produced an analgesic effect, which was less than that achieved from doses of 157 μg of diazepam per kg i.v. Several of these patients actually preferred placebo to the dose of 22 μg of THC per kg because of anxiety and dysphoria from the latter drug (139).

The apparent paradox is that THC both increases and decreases pain. Traditionally, aspirin-like drugs, which work peripherally by inhibiting the synthesis of prostaglandins, are used to treat pain derived from the integument. The initial mental stimulation from THC might increase sensitivity to this kind of pain. Visceral pain, such as that of cancer patients, is usually treated by opiates, which have both peripheral and central sites of action. Recent evidence suggests that opiates may act directly on pain pathways in the spinal cord as well as reducing the affect that accompanies pain. Cannabis could conceivably modify the affective response. Thus, when the two types of pain are distinguinshed from each other, the apparent paradox is solved.

THC, nantradol, and nabilone shared some properties with morphine in the chronic spinal dog model. Latency of the skin twitch reflex was increased, and withdrawal abstinence was suppressed. Naltrexone did not antagonize these actions, suggesting that they are not mediated through opiate receptors (56). Levonantradol i.m. was compared with placebo in postoperative pain, and a significant analgesic action was confirmed. No dose-response relationship was observed, and the number of side effects from levonantradol was rather high (89). It seems unlikely that any THC homolog will prove to be an analgesic of choice, when one considers the present array of very effective new analgesics of the agonist-antagonist type. It is too early to be sure, however.

D. Muscle Relaxant

Patients with spinal cord injuries often self-treat their muscle spasticity by smoking cannabis. Cannabis seems to help relieve the involuntary muscle spasms that can be so painful and disabling in this condition. A muscle relaxant or antispastic action of THC was confirmed by an experiment in which p.o. doses of 5 or 10 mg of THC were compared with placebo in patients with multiple sclerosis. The 10-mg dose of THC reduced spasticity by clinical measurement (135). Such single small studies can only point to the need for more study of this potential use of THC or possibly some of its homologs. Diazepam, cyclobenzaprine, baclofen, and dantrolene, which are used as muscle relaxants, all have major limitations. A new skeletal muscle relaxant would be most welcome.

E. Anticonvulsant

One of the first therapeutic uses suggested for cannabis was as an anticonvulsant. Such an effect was documented experimentally many years ago (112). Subsequent studies in various animal species have validated this action. THC in cats temporarily reduced the clinical and electrographic seizure activity induced by electrical stimulation of subcortical structures (175). Mice were protected by cannabidiol against maximal electroshock seizures but not against those caused by pentylenetetrazole. Its profile of activity more resembled that of phenytoin than that of THC (170). THC and cannabidiol both potentiated the anticonvulsant effects of phenytoin against electrically induced seizures in mice. The two cannabinoids in combination produced the most effect (29). Kindling involves the once-daily appliction of initially subconvulsive electrical stimulation to culminate in generalized convulsive seizures. THC given chronically to rats prevented the kindling effect (174).

Clinical testing has been rare, despite all these various lines of evidence supporting an anticonvulsant effect of cannabinoids. Better control of seizures following regular marijuana smoking was reported in a not very convincing single case (39). Fifteen patients not adequately controlled by anticonvulsants were treated with additional cannabidiol in doses of 200 or 300 mg or placebo. Cannabidiol controlled seizures somewhat better than the addition of placebo (25). Cannabidiol has little if any psychoactivity, making it a good candidate for this use.

F. Bronchial Asthma

A general study of the effects of marijuana on respiration revealed a bronchodilating action in normal volunteer subjects. Marijuana smoke was calculated to deliver 85 or 32 μg of THC per kg. A fall of 38% in airway resistance and an increase of 44% in airway conductance occurred in the high-dose group. The low-dose group showed lesser changes, but they were still significant as compared with baseline. The sensitivity of the respiratory center to carbon dioxide was not altered by either dose, indicating no central respiratory depression (172).

Asthma was deliberately induced by either inhalation of methacholine or exercise in asthmatic patients. They were then treated with inhalation of placebo marijuana, of saline, of isoproterenol, or of smoke derived from marijuana containing 1 g of THC. Both marijuana smoke and isoproterenol aerosol effectively reversed both methacholine- and exercise-induced asthma, while saline and placebo marijuana had no effect (160). Aerosols of placebo-ethanol, of THC (200 μg) in ethanol, or of salbutamol (100 μg) were tested in another study of ten stable asthmatic patients. Forced expiratory volume in 1-s forced vital capacity, and peak flow rate were measured on each occasion. Both salbutamol and THC significantly improved ventilatory function. Improvement was more rapid with salbutamol, but the two treatments were equally effective at the end of 1 h (181).

Both delta-8 and delta-9-THC have bronchodilating effects, while neither cannabinol nor cannabidiol has such actions. Thus, this action resides only in the psychoactive material. No evidence of tolerance to this effect developed over 20 days of continual administration (58).

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The treatment of asthma is much more chronic; further studies of tolerance will be needed.

Some patients might experience bronchoconstriction following THC. Doses of 10 mg p.o. produced mild and inconsistent bronchodilator effects as well as significant central nervous system effects. One patient of the six studied developed severe bronchial constriction (1). Mild but significant functional impairment, predominantly involving large airways, was found in 74 regular smokers of cannabis. Such impairment was not detectable in individuals of the same age who regularly smoked tobacco (64).

THC would best be administered by aerosol for this purpose, but whether effective doses would avoid the mental effects is uncertain. The mechanism of action by which THC increases airway conductance may be different from the usual beta-adrenergic stimulants. Resistance to repeated applications of beta-adrenergic stimulants does occur. Another type of bronchodilator might help some patients. The recent introduction of highly effective steroid aerosols, such as beclomethasone, meets that need to a considerable extent.

G. Insomnia

THC does not differ from conventional hypnotics in reducing rapid eye movement (REM) sleep (136). THC in doses ranging from 61 to 258 μg/kg produces in normal subjects increments in stage 4 sleep and decrements in REM sleep, but without the characteristic REM rebound which follows chronic treatment with hypnotics. When THC was administered p.o. as a hydroalcoholic solution in doses of 10, 20, and 30 mg, our subjects fell asleep faster after having mood alterations consistent with a "high." Some degree of "hangover" the day following was noted from larger doses (42). Another sleep laboratory study showed that a dose of 20 mg of THC given p.o. decreased REM sleep. After four to six nights of use, abrupt discontinuation of THC produced a mild insomnia but not marked REM rebound (52). REM rebound may not be apparent after low doses of THC. However, very high p.o. doses (70 to 210 mg) reduced REM sleep during treatment and were followed by marked REM rebound after withdrawal (48).

The sleep produced by THC does not seem to differ much from that of most currently used hypnotics. Side effects before sleep induction as well as the hangover effects make the drug less acceptable than currently popular benzodiazepines. It seems unlikely that THC will supplant existing hypnotics in the treatment of insomnia.

H. Miscellaneous Uses

1. Hypertension. Orthostatic hypotension occasionally follows use of THC (5). A dimethylheptyl side-chain derivative has more profound and constant effects on blood pressure. In man, this compound showed a marked orthostatic hypotensive effect, as well as tachycardia and some mental symptoms resembling those of THC. While the latter are less than from THC in proportion to the blood pressure-lowering effect, a definite separation of pharmacological effects has not really been attained (106).

Effective antihypertensive drugs have been one of the outstanding achievements of pharmacology over the past 30 years. A new antihypertensive based on orthostatic hypotension, perhaps the least desirable mode of lowering blood pressure, is hardly very enticing (8). The issue seems hardly worth pursuing further.

2. Abstinence syndromes due to central nervous system depressants. Synhexyl, the first THC homolog to be synthesized, was tested as a treatment for withdrawal reactions from opiates and alcohol with little evidence of efficacy. Withdrawal symptoms experienced by rats following morphine pellet implantation, followed by subsequent injection of naloxone, were reduced by THC. Cannabidiol, without any direct effect itself, augmented the action of THC (79).

This relatively weak effect of cannabinoids in opiate dependence is unlikely to be of clinical use. Detoxification programs using methadone have been highly successful and acceptable.

3. Antineoplastic activity. Both the delta-8 and delta-9-THC isomers, as well as cannabinol, have some antineoplastic effect on transplanted lung tumors in animals, as well as on tumors in vitro (125). THC may have a general ability to reduce the synthesis of nucleic acids, which may account for the reported immunosuppressant effects as well. Many agents are available that inhibit nucleic acid synthesis, so the possibility that THC or other cannabinoids might be advantageous seems rather unlikely.

4. Antimicrobial action. Both THC and cannabidiol inhibit and kill staphylococci and streptococci in vitro at concentrations of 1 to 5 μg/ml (173). Such concentrations are well above those reported for use of THC in man, even at the highest tolerated doses. Thus, this effect seems to have little practical application.

5. Migraine. This indication has not been studied systematically in recent years, although it has a long history. In one patient I treated, the mental effects sought socially caused the patient to abandon treatment. Innumerable successful treatments for migraine have been reported at one time or another.

6. Appetite stimulant. Most antipsychotic agents will stimulate appetite, but few other drugs do. THC as compared with ethanol and dextroamphetamine produced a variable response on appetite, both in fed and fasted subjects. The majority had increased appetite and food consumption as compared with placebo (80). Anorexia nervosa might be helped by an appetite stimulant. A test of the presumed appetite-stimulating properties of THC in patients with anorexia nervosa failed over a 4-week period. Doses of THC ranged between 7.5 and 30

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mg/day and were compared with 30 mg of diazepam per day and placebo. Three of the 11 patients treated with THC experienced severe dysphoria (65).

7. Alcoholism. Cannabis users are said not to drink, but most do. The prospect of changing an alcoholic into a cannabinolic has some appeal. A study showed that cannabis was not very attractive to alcoholics. Little difference in retention occurred among those given no medication, or a cannabis cigarette, or disulfiram or the combination of the cigarette and disulfiram (143).

V. Summary

Marijuana seems firmly established as another social drug in Western countries, regardless of its current legal status. Patterns of use vary widely. As with other social drugs, the pattern of use is critical in determining adverse effects on health. Perhaps the major area of concern about marijuana use is among the very young. Using any drug on a regular basis that alters reality may be detrimental to the psychosocial maturation of young persons. Chronic use of marijuana may stunt the emotional growth of youngsters. Evidence for an amotivational syndrome is largely based on clinical reports; whether marijuana use is a cause or effect is uncertain. A marijuana psychosis, long rumored, has been difficult to prove. No one doubts that marijuana use may aggravate existing psychoses or other severe emotional disorders. Brain damage has not been proved. Physical dependence is rarely encountered in the usual patterns of social use, despite some degree of tolerance that may develop. The endocrine effects of the drug might be expected to delay puberty in prepubertal boys, but actual instances have been rare. As with any material that is smoked, chronic smoking of marijuana will produce bronchitis; emphysema or lung cancer have not yet been documented. Cardiovascular effects of the drug are harmful to those with preexisting heart disease; fortunately the number of users with such conditions is minimal. Fears that the drug might accumulate in the body to the point of toxicity have been groundless. The potential deleterious effects of marijuana use on driving ability seem to be self-evident; proof of such impairment has been more difficult. The drug is probably harmful when taken during pregnancy, but the risk is uncertain. One would be prudent to avoid marijuana during pregnancy, just as one would do with most other drugs not essential to life or well-being. No clinical consequences have been noted from the effects of the drug on immune response, chromosomes, or cell metabolites. Contamination of marijuana by spraying with defoliants has created the clearest danger to health; such attempts to control production should be abandoned.

Therapeutic uses for marijuana, THC, or cannabinoid homologs are being actively explored. Only the synthetic homolog, nabilone, has been approved for use to control nausea and vomiting associated with cancer chemotherapy. While little doubt remains that marijuana, THC, and nabilone are effective for this use, the advent of other drugs that are equally effective but with fewer adverse effects may make this use moot. Use of marijuana to reduce intraocular pressure in patients with glaucoma requires a feasible topical preparation of cannabinoids. Although some cannabinoids have analgesic activity, the abundance of new opioid analgesics with little dependence liability provides tough competition. The use of marijuana as a muscle relaxant, though promising, has not yet been adequately studied. Clinical studies to establish the efficacy of cannabidiol as an anticonvulsant or to compare it with other anticonvulsants are still to be done. Other potential therapeutic uses, such as treatment of bronchitis, asthma, insomnia, hypertension, abstinence syndromes, migraine, anorexia, and alcoholism, are most unlikely prospects.

Compared with other licit social drugs, such as alcohol, tobacco, and caffeine, marijuana does not pose greater risks. One would wonder, however, if society were given a choice based on current knowledge, whether these drugs would have been granted their present status of acceptance. Marijuana may prove to have greater therapeutic potential than these other social drugs, but many questions still need to be answered.

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