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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 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 estrogens 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 [illegible]tion 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 c[illegible] almost every acute dose of cannabis, al[illegible] 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 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 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 insufficient 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).

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 (155, 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 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 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).

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. [illegible] the latter are less than from THC in proportion to [illegible] 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 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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Marijuana: An Overview

*Richard H. Schwartz, MD**

Of all illicit drugs popular in the United States and Canada, *Cannabis* (marijuana or hashish) is the most widely used. The potency of ordinary marijuana is now identical to that of hashish sold in the United States, and high-quality sinsemilla (seedless marijuana), much preferred by marijuana afficionados, is twice as strong as hashish.[10] Approximately 60 per cent of graduating high school seniors have smoked marijuana at least one time, and one in eight students who tried the drug even once progress to daily use. Many of these young people will continue to be psychologically dependent on the drug or will also abuse other mood-altering drugs (e.g., cocaine).

In 1985, marijuana was smoked daily by 120,000 (5 per cent) high school seniors nationwide.[15] In the most comprehensive statewide survey in the country, 3.5 per cent, 9.4 per cent, and 12.8 per cent, respectively, of eighth, tenth, and twelfth graders in Maryland smoked marijuana at least several times a week up to once or more per day; 12 per cent of tenth graders stated that they "got high" from an illicit drug more than ten times in 1984.[24] It should be emphasized that 28 per cent of all entering high school freshmen leave high school before graduation,[31] and frequent marijuana use is undoubtedly a significant factor in the decision to leave school.

CANNABIS: PHYSICAL PROPERTIES

Marijuana comprises the crumbled, cured leaves, small stems, and flower clusters of the resin-producing varieties of the hemp plant, *Cannabis sativa*. Indigenous to Asia, the plant originally was cultivated worldwide as a source of hemp fiber, oil, and homeopathic medicines. Varieties of the plant are often 5 to 8 feet tall and branched, [illegible] compound leaves composed of seven to nine serrated, slender, spe[illegible]shaped leaflets.

*Clinical Professor of Child Health and Development, [illegible]ashington University School of Medicine and The Children's Hospital Nation[illegible] Medical Center, Washington, D.C., Director of Research, Straight, Inc., Springfield, Virginia

Drug-producing varieties of the plant have glands that secrete a resinous substance containing about 60 unique compounds, called *cannabinoids*, the most psychoactive and prevalent of which is delta-9-tetrahydrocannabinol (Δ9-THC).

The ΔS-THC content of *C. sativa* is influenced by genetic factors, by the place and circumstances of its growth, by the method of storage of the plant material, and by the number of months elapsed since harvest time. The potency of Δ9-THC diminishes with time, especially for hashish.

In the United States, 60 per cent of all marijuana is grown in California, often by the sinsemilla method, which produces high-potency marijuana. Since 1975, the potency of "street pot" in the United States has tripled, from 1.2 to 4.1 per cent. The Δ9-THC concentration of the more potent sinsemilla type averages 7 per cent, but may be as high as 14 per cent.[10]

USE OF MARIJUANA AS A PSYCHOACTIVE DRUG

Mannner of Use

The primary mode of using marijuana or hashish in the United States is inhaling the smoke of marijuana cigarettes ("joints"), made by rolling 500 mg to 750 mg of marijuana in a thin paper. Smoking implements such as hollow smoking stones, miniature smoking pipes (bowls), or air-cooled or water-cooled smoking chambers (bongs) also may be used to cool and "sweeten" the highly irritating marijuana smoke, thus permitting the user to inhale a larger quantity. Adolescents often purchase marijuana in 4- to 5-gm packets, sufficient to make five or six "joints," each costing about one dollar. Prior to use, seeded marijuana must be cleaned of seeds and small woody stems, the combined weight of which is often 50 per cent or more of the "bag" as purchased. This "manicuring" is often done in the young person's bedroom on a smooth surface such as a record album cover; the seeds may then be discarded or may be collected for later cultivation.

To obtain maximal effect from marijuana, users must master a smoking technique somewhat different from that of smoking tobacco cigarettes or pipe tobacco. The experienced user inhales the smoke as deeply into the lungs as possible and holds his breath for 20 to 30 seconds or more in an effort to extract almost all the Δ9-THC into the capillary-rich pulmonary circulation. When this technique is followed, 50 per cent of the Δ9-THC contained in the crude marijuana is delivered into the smoker's bloodstream and practically no Δ9-THC remains in exhaled breath. Marijuana smoke has a pungent smell, resembling the smell of burning wet hay or leaves, and clings to hair and woolen garments. Consumption of the same amount of drug, of the same potency, even by an experienced user, may produce minimal effects on one occasion and, on another occasion, marked effects on cognition, mood, and performance.

"Hash oil" is street jargon for a viscous, black, oily liquid derived from marijuana mash by dissolving it in an organic solvent. Hash oil contains 20 to 30 per cent Δ9-THC, and one drop smeared on a marijuana rolling paper gives a "high" equivalent to one marijuana cigarette. Thus, users of hash

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oil add one drop to a joint to double its potency. Other drugs or chemicals[39] that may be mixed with marijuana to increase its intoxicating effects include phencyclidine, opium, cocaine paste, and even Raid insect spray. Not infrequently, naive marijuana-smoking adolescents may be given these laced joints without their knowledge, leading occasionally to serious psychiatric states of confusion and disorientation, intense anxiety, depersonalization, profound depression, acute paranoia, acute psychosis, or sheer panic.

Pharmacology

The minimal effective dose of Δ9-THC is 5 mg, of which 50 per cent is destroyed in the process of pyrolysis. The intoxicating dose for a 70-kg adult is 0.035 mg per kg. Merely smoking two sinsemilla cigarettes a day exceeds a total daily dose of 40 mg of Δ9-THC per day (considered to be a very heavy dose). Tolerance to the effects of cannabis has been demonstrated conclusively,[33] and experienced marijuana smokers require more potent cannabis, deeper, more sustained inhalations, or larger amounts of the crude drug to achieve the desired degree of euphoria. Mood-altering, intoxicating and cardiovascular effects of the drug become evident within a few minutes after deep and sustained inhalation of marijuana smoke, whereas oral administration of the drug has a 30-minute lag period. The subjective effects last 2 to 3 hours, somewhat longer if cannabis was eaten rather than smoked.

Δ9-THC is carried quickly by way of the bloodstream to the liver, and most of the drug is broken down (by hydroxylation and carboxylation enzymes in liver microsomes) to non–mood-altering carboxyacid analogues of THC (THC-COOH). These are carried by the enterohepatic circulation into the intestinal lumen, to be excreted in the feces (65 per cent), and through the renal circulation into the urine (35 per cent). Because the liver cannot remove all the Δ9-THC during the first pass through the hepatic circulation, and because Δ9-THC is intensely lipophilic, adipose tissues accumulate a substantial amount of the drug, which is then released slowly and unevenly into the bloodstream. The half-life of Δ9-THC is approximately 3 days.

The pharmacologic effects of ingested cannabis begin in 30 to 120 minutes, peak in 2 to 3 hours, and last 3 to 6 hours. About three times as much Δ9-THC must be ingested as smoked to obtain the same effects, and the psychoactive effects are much more variable with ingestion, even when the drug user is experienced.

Cannabinoid metabolites can be detected in the urine (presumably a result of sustained release from adipose tissue) for 2 or 3 days following one casual use of the drug.[47] The drug may be detected up to four or more weeks after monitored abstinence of daily chronic marijuana smokers.[34]

[illegible] alcohol intoxication, the "high" of marijuana can easily be [illegible] (worked through) by [illegible] "high" on marijuana may seem completely normal in appearance, [illegible] and content of speech, and [illegible]. After several hours of the "high," this [illegible] gradually merges, if the Δ9-THC [illegible] is sufficient, into a [illegible] physical and mental torpitude, irritability easily provoked to anger, drowsiness, and sometimes sleep. During this gradual "coming down" phase, there is a very strong hunger for high-calorie food such as cookies or "junk food" (known as the "marijuana munchies"), and an intense craving for sweet drinks such as carbonated beverages. Unlike alcohol intoxication, there is usually no "hangover" after the marijuana "high" is gone.

There are only two consistent physical signs of marijuana use: (1) increased heart rate and (2) conjunctival irritation or dilation. Because many adolescents are proficient users of Visine or other vasoconstrictive ophthalmic drops, the tell-tale reddened eyes following marijuana smoking may not be present.

ACUTE EFFECTS OF CANNABIS

Expected Effects

Primarily, the effect of marijuana depends on the concentration of Δ9-THC that reaches the bloodstream of the user (i.e., the potency of the Cannabis product). What has been termed "set" and "setting" also play a role.

"Set" is determined by the past experience, attitude, expectations of achieving euphoria ("shaping"), and underlying ego strength of the user. Thus, if the novice user is apprehensive and expects to be discovered by authority figures, he or she may experience a high anxiety level or even panic, and fear of losing control of thought processes may lead to intense discomfort instead of a pleasant experience. Adolescents who are known to have unstable personalities, particularly serious affective disorders such as prolonged depression, or a history of non–drug-induced psychosis, are at serious risk for adverse psychological effects from any psychoactive drug, permanent psychosis may be precipitated in such persons.

"Setting" refers to the degree of trust and congeniality between the user and others present, and to the comfort and safety of the surroundings. Marijuana is smoked alone or used with intoxicating amounts of alcohol, stimulant drugs (such as cocaine or amphetamines), other hallucinogenic drugs, phencyclidine, or inhalant drugs. Obviously, the complex pharmacologic interaction of these drugs is highly individual, and although users with an underlying explosive impulse-control disorder sometimes feel less tense and less angry when they smoke marijuana, they often become moody, irritable, and argumentative as the drug-induced euphoria dissipates. Such negative feelings may lead to hostile confrontation if the user is questioned in the posteuphoric state.

Adverse Effects

The acute effects of marijuana are usually pleasant, but adverse effects occur not infrequently, often unpredictably and even when the user is highly experienced.

Psychological Effects. Acute adverse (toxic) effects of marijuana include acute toxic psychosis, acute panic reactions, and flashback phenomena. Symptoms of acute toxic psychosis include excitement, confusion, disorien-

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tation, delusions, depersonalization, visual hallucinations, and full-blown delirium.[11] Acute panic reactions ("bad trips") may be accompanied by abdominal discomfort, headache, anxiety, depression, morbid fear of being "found out," fear of dying, restlessness, uncontrollable feelings of aggression, and paranoid ideation. Panic or psychotic toxic reactions are more frequent in the novice marijuana smoker. The occurrence of flashback phenomena after marijuana use has been reported, but flashbacks are uncommon.

Effects on Coordination and Reaction Time

Safe operation of a motor vehicle is often compromised if the driver is acutely intoxicated by marijuana.[2, 6, 7, 12, 19–21, 25–30, 31, 38, 42, 43, 48] It is estimated that 60 to 80 per cent of marijuana users who are licensed to operate a motor vehicle on occasion do so while intoxicated by that drug. Marijuana can impair motor activity in unpredictable ways, including altering reflex responses to sensory stimuli; decreasing attention to the "gestalt"; altering perceptions of the passage of time, of depth (e.g., distance to a traffic light or a pedestrian), or of colors; and impairing short-term memory. A person under the influence of marijuana also has impaired vigilance: in a recent study, marijuana was shown to cause impairment of eye-tracking skills that was roughly double that produced by alcohol. In addition, marijuana-intoxicated drivers of motor vehicles may fail to respond optimally to visual clues because of preoccupation with drug-induced imagery or music from the car radio or tape recorder.

Impairment of vigilance, coordination, and reaction time may persist for 12 to 24 hours[30] after the euphoria is gone: teenagers who drove after smoking marijuana on at least six occasions per month were 2.4 times more likely to be involved in traffic accidents. This lasting effect of marijuana intoxication has been demonstrated in a test using airline pilots: on a flight simulation, smoking a single marijuana cigarette containing 19 mg of Δ9-THC led 10 experienced, licensed private pilots to perform appreciably less well than before drug use. In addition, the pilots were unaware that they had performed poorly in the flight simulation tests.[48]

Physiologic Effects. Smoking marijuana affects the respiratory system, the heart, the eyes, and the brain (affect and perception). The mouth and throat feel parched, there is a sensation of pounding of the heart, the eyes become red and irritated, and there is a perceptible change in mood. Early effects include disinhibition and garrulousness (spontaneous laughter), and a sense of relaxation, pleasant reverie, and drowsiness. Many marijuana-intoxicated persons overestimate the passage of time and have impaired ability to process newly learned material and remember it a short time later. Auditory and visual enhancement or distortions may occur, particularly in the casual user. Coordination and balance may be impaired.

Aftereffects of smoking marijuana include lethargy, and changes in sleep patterns and in appetite. Adolescents especially may experience changes in mood (depression and irritability), be easily provoked to argumentativeness, and suffer posteuphoria depression.

Pulmonary System Effects. Stinging and burning sensations in the mouth and throat frequently occur after marijuana smoke is inhaled, and a dry, hacking cough may be present, particularly if an unscreened marijuana pipe or homemade smoking apparatus was used. Frequent hashish smokers occasionally have swollen, inflamed uvulae.[43]

Histologic changes may occur because marijuana smoke contains more carcinogens and more tar than does tobacco smoke; experienced cannabis smokers take longer and deeper draws on the marijuana cigarette and hold each inhalation in the lungs for a longer time, marijuana cigarettes burn at a higher temperature than do tobacco cigarettes, and marijuana cigarettes are smoked down to the very end (called a "roach"), which is more potent in Δ9-THC and polyaromatic hydrocarbons than is the rest of the cigarette. In addition, frequent cannabis smokers may have stuffy noses, bronchitis, and exacerbations of bronchial asthma. Only occasionally are these symptoms severe enough to prompt medical intervention.

Investigators at the University of California at Los Angeles[12] found that nontobacco-smoking heavy marijuana smokers had mild but significant functional impairment of airway conductance, whereas pathology investigations have shown diffuse infiltrations of mononuclear leukocytes into the alveoli and interstitium of the lungs.[27]

Possible Systemic Effects. Many published articles have detailed additional possible harmful systemic effects of marijuana. These include alterations in immune system function, cellular chromosomes, and cell metabolism; abnormalities in the reproductive system or in development of the fetuses of marijuana-smoking pregnant women[7]; cardiovascular system alterations; and changes in brain histology. All of the above findings have been challenged and all remain uproven, however.

CHRONIC EFFECTS OF CANNABIS

The Amotivational Syndrome

"Whether marijuana is a primary or a secondary factor in inducing amotivation is not a crucial issue. A drug that serves to support and reinforce passivity and withdrawal would make it an undesirable agent in predisposed individuals"[6] (e.g., the young, the learning disabled, and the emotionally immature).

There are seven consistent components of the amotivational syndrome: (1) loss of interest, general apathy, and passivity; (2) loss of desire to work consistently and loss of productivity, accompanied by a lack of concern about the poor work performance; (3) loss of energy and tiredness; (4) moodiness, sullenness, and inability to handle frustration; (5) impairment in concentration and in ability to process new material; (6) slovenly habits and appearance; and (7) a life-style revolving around procurement and use of marijuana and other drugs. A series of published studies of Egyptian prisoners,[37, 38] and of educated Nepalese young adults[36] provides strong evidence that links amotivation to heavy marijuana use by persons who perform highly skilled tasks or are employed in jobs demanding concentration and decision making.

In contradistinction, anthropologic studies in Greece,[1, 40] Jamaica,[33] and

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Costa Rica[4] have purported to show that the amotivational syndrome is not associated with frequent marijuana smoking. These studies were usually conducted among uneducated or poorly educated working-class adults, however, and the results were reported in all cases in nonpeer review publications. Thus, they provide no basis for disengaging marijuana use from the amotivational syndrome in marijuana-using American adolescents. Furthermore, in a study conducted in Costa Rica,[4] 41 marijuana-smoking city residents socioeconomically representative of most strata of Costa Rican society were compared to 41 matched controls. Users, when adolescents, had had higher rates of school absenteeism, delinquency, and sentencing to reformatories. Users also were more likely to leave the nuclear family prematurely and become "independent" (not infrequently before age 12 and usually by age 18), and were more committed to running with street gangs during late adolescence.

The Youthful Daily Marijuana Smoker

Marijuana use often progresses in a fairly predictable, stepwise fashion (in approximately one of three marijuana-smoking adolescents), from experimentation, to occasional social use, to regular social use, including actively seeking and buying quantities of marijuana. For some, preoccupation with a life-style focused on use of cannabis develops—the cannabis dependence syndrome.

If an adolescent begins to use marijuana during early adolescence, he or she is likely to use other illicit drugs such as cocaine and hallucinogenic drugs. Of 30 frequent adolescent cocaine snorters in the Straight, Inc. drug treatment program, 80 per cent had been daily marijuana smokers before they abused cocaine. The period of greatest vulnerability for initiation to marijuana is completed for the most part by the age of 22 years, with those who have not experimented with the drug by that age being unlikely to do so thereafter. Overall, patterns are similar for men and women before age 18.

Stepping-Stone Theory of Drug Use. Kandel has identified three stages between nonuse and frequent use of illicit drugs: use of beer or wine, use of cigarettes or distilled beverages, and use of marijuana (cannabis).[16, 17, 18] In almost all cases in that study, adolescents began to use illicit drugs only after becoming users of alcoholic beverages and of tobacco.

Adolescent Daily Marijuana Smokers in Treatment. In a survey of 180 primarily white adolescents in treatment for drug problems (Schwartz RH: unpublished data, 1986), 60 per cent had smoked marijuana on a daily basis. Thirty-seven of these middle class subjects aged 14 to 17 years were chosen at random for an in-depth interview. Approximately 40 per cent had divorced parents; 50 per cent of their fathers were college graduates. The median duration of daily use of the drug by those 37 young people was 1.25 years, and an average of 1.75 oz of marijuana was consumed per month at an average cost of approximately $80 per month.

About 75 per cent of the respondents, after 1 month in treatment, believed that they had experienced significant impairment in coping skills, memory and concentration, self-confidence, judgment, ambition, dependability, and relationships with parents, teachers, and employers as a direct result of chronic marijuana use. Social consequences of a serious nature began or worsened during the years of chronic marijuana intoxication. These consequences included more than ten violent quarrels with parents (44 per cent), running away for longer than 1 week (30 per cent), being arrested or detained by police (43 per cent), frequent stealing (32 per cent), involvement in an automobile accident while intoxicated (30 per cent), emergency medical care following drug use (27 per cent), and exchanging sexual favors for drugs (girls only–26 per cent).

Despite such significant psychosocial and behavioral problems, less than half of the 37 daily marijuana smokers believed that they had a drug problem on the day of admission to the drug treatment facility. Johnston[14] found that high-school seniors who used marijuana daily represented a cross-section of socioeconomic levels, and that daily use of the drug was only slightly higher among those from broken homes. Daily use correlated with declining grades, and also very strongly with truancy during high school.[14]

Follow-up of the Frequent Marijuana User. Weller et al.[12, 46] interviewed 100 frequent marijuana smokers and 50 nonmarijuana-smoking controls and reinterviewed the same group 6 to 8 years later. The group was composed of young white adults, 60 per cent men, mean age 22 years at the time of the first interview. Thirty per cent smoked marijuana once a week or less, 30 per cent smoked the drug three times a week or more, and only 12 per cent were daily users at the time of the *initial* interview.

At the time of the follow-up interview 20 per cent of the marijuana smokers were daily users. In addition, the proportion who abused alcohol had increased (18 per cent vs 3 per cent initially); furthermore, more subjects had antisocial personality disorders (21 per cent vs 6 per cent), anxiety disorders (11 per cent vs 0 per cent), and depression (44 per cent vs 29 per cent). With time, truly chronic users, instead of experiencing psychedelic effects of marijuana as they had during the earlier years of use, experienced sedative, depressant, or hypnotic effects of the drug as a rule.

CANNABIS ABUSE AND DEPENDENCE

The *Diagnostic and Statistical Manual* (3rd edition) (DSM-III), published by the American Psychiatric Association,[3] defines cannabis abuse as follows: (1) use nearly every day, several times a day, for at least one month, and (2) marked loss of (non–drug-using) friends, absence from work (school), marked loss of interest in (healthy) activities previously engaged in, and legal difficulties other than a single arrest for possession of cannabis.

Cannabis dependence is defined as abuse marked by repeated unsuccessful efforts to control cannabis use, and tolerance to the effects of the drug as evidenced by diminished psychoactive effects on regular use of the same amount of cannabis.

Urine Toxicology Tests for Cannabinoids

Various tests can be used to detect the products of marijuana metabolism in the urine, but they vary in availability, cost, complexity, and

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sensitivity.[35] One of the most often used screening tests is the enzyme multiplied immunoassay technique (EMIT, manufactured by Syva Co.). Two different levels of detection are available for screening for cannabinoids. The 20 ng per ml of urine level is more sensitive than the 100 ng per ml level (i.e., it can detect smaller amounts of carboxy-THC in the urine). The less cumbersome and simpler to use qualitative EMIT test detects recent marijuana use, but its 100 ng per ml level misses many weekend marijuana smokers and as any as 25 per cent of daily marijuana smokers unless the urine specimen is collected within 24 hours of last use. Analysis of 16 urine specimens from marijuana-smoking adolescents followed in a drug treatment program and tested with the EMIT instrument gave a sensitivity of 62 per cent of all proven-positive urine specimens.

A positive test result for marijuana byproducts in urine almost always means that the person used the drug recently. Only 2 of 161 urine specimens analyzed by two different methods by our laboratory had false-positive test results by EMIT tests (Schwartz RH: unpublished data, 1986).

Duration of Positive EMIT Test After Abstinence from Marijuana. Two days after smoking marijuana, more than 30 per cent of infrequent users of the drug will have no trace of carboxy-THC in the urine as measured by the EMITst test, EMIT-dau-100 test or radioimmunoassay-100 test, and by the third day after smoking the drug most novice users will have no carboxy-THC in the urine at all by radioimmunoassay (RIA-20), thin-layer chromatography (TLC), or EMIT-dau-20 tests. In contrast, those who use the drug in moderate amounts (three to four times a week, or 1 oz per month) will often have enough marijuana metabolites in the urine to give positive results on an EMIT test for at least 3 to 5 days after last use. However, we have determined that at least 25 per cent of such users have a negative test when the less sensitive EMIT (100 ng per ml threshold of sensitivity) is used. Chronic users of marijuana (those who smoke more than 2 oz of the drug per month and use it daily) will usually have positive results of the EMIT test for at least 3 days following last use but infrequently may have urine that tests positive for marijuana metabolites for as long as 5 weeks after cessation of drug use.[47] More sensitive toxicology tests, of course, are able to detect lower levels of cannabinoids in a urine specimen for a longer time, but the major variant in duration of excretion of the drug is frequency of its use beforehand.

Because of the level of sensitivity of the test, it is highly improbable or perhaps even impossible that a person who merely inhaled marijuana smoke passively (did not actually smoke the drug himself or herself) would take in enough of the drug to give a positive result on the less sensitive EMIT test.

Methods of Deceiving the EMIT Test. To obtain the highest concentration of marijuana metabolites in a urine specimen from a suspected user of the drug, the specimen should be the first voided urine, which is the most concentrated urine of the day. Specimens should be obtained the morning after likely "party" nights, should be observed for color, and tested for warmth if there is any possibility that the individual diluted it or substituted urine of a non–marijuana-smoking friend. The urine specimen should then be refrigerated, frozen, or even stored at room temperature for up to 3 days until it can be sent to a reliable and carefully supervised medical laboratory for testing. Cloudy urine from bacteriuria or crystalluria may cause a false-negative EMIT test result. If there is any question that the urine may have been adulterated (by blood, bleach, vinegar, ammonia, table salt, water, or soap solution), the specimen should be obtained under direct observation, as is done in the armed forces.

It is worthwhile to order a urine test for cannabinoids on any adolescent who is depressed, underachieving in school, or argumentative and belligerent, particularly before recommending psychosocial or psychiatric consultation. Although some physicians may disagree philosophically with the importance of such tests, the significant number of adolescents whose psychological problems are related to drug use warrants identification of this component as early as possible.

MARIJUANA AND Δ9-THC AS THERAPEUTIC AGENTS

Nausea and vomiting following administration of many chemotherapeutic drugs debilitate, discourage, depress, and dehydrate cancer patients and interfere with the treatment program.

Synthetic Δ9-THC, generically known as dronabinol, marketed as Marinol, a schedule II drug, is approved for oral use by the U.S. Food and Drug Administration for palliation of cancer chemotherapy-induced nausea and vomiting in patients who have not responded to conventional antiemetics. Dronabinol is definitely effective in precluding postchemotherapy nausea and vomiting, but no more so than metaclopramide administered intravenously. With repeated doses, most patients will experience effects typical of smoking marijuana: mood changes, as well as decreases in concentration, coordination, and ability to estimate time. Adverse physiologic effects include lightheadedness, orthostatic hypotension, tachycardia, conjunctival hyperemia, and dry mouth.

Nabilone and levonantradol are two other synthetic cannabinoids under investigation as antiemetic agents. Glaucoma affects more than one million people in the United States and is a leading cause of blindness. Timolol or pilocarpine can reduce intraocular pressure in 90 per cent of patients with open-angle glaucoma. THC can also reduce intraocular pressure in patients with open-angle glaucoma when administered as a topical eye drop, by the oral route, or when the crude drug marijuana is smoked.[5,26] For most people, however, THC is much less effective than some of the newer antiglaucoma drugs. In addition, regardless of the route of administration, marijuana or synthetic THC does not cure glaucoma and is not an indispensible palliative treatment for that disease. Furthermore, four to six marijuana cigarettes must be smoked each day to treat glaucoma, and this amount is sufficient to cause chronic marijuana intoxication, with adverse effects on psychosocial development, motivation, memory, motor function, and coordination.

THE PARAQUAT ISSUE

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completely removed from the plant by a strong rain, some greedy marijuana farmers harvest the plants before they have been exposed to sunlight, so that dessication of the leaves does not take place and the paraquat remains on the plant.[11, 33] Nevertheless, despite widespread spraying of paraquat, particularly in Mexico, there has never been a single documented case of human injury secondary to smoking paraquat-contaminated marijuana.[11]

CONCLUSIONS

Marijuana is a potent, crude, intoxicating drug that can alter mood and mind. Sinsemilla marijuana, used preferentially by frequent marijuana smokers, is 600 per cent more potent than the marijuana used in the previous decade. In 1985, marijuana was smoked on a daily basis by 120,000 American high school seniors and an unknown number of high school dropouts. Δ9-THC, the primary psychoactive chemical in marijuana, exerts pronounced adverse effects on the estimation of time, on short-term memory stores, and on complex performance tasks.

Experimentation with marijuana even once during adolescence carries with it at least an 8 per cent risk of one's becoming a daily marijuana smoker with attendant psychosocial consequences. For those adolescents with serious underlying genetic and developmental risk factors, the risk of progression from experimental use to the cannabis dependence syndrome appears to be much higher; furthermore, it is highly unlikely that adolescents will try cocaine or hallucinogens without prior experimentation with marijuana.

Parents of adolescents and physicians must be aware that any sustained deterioration in school performance, ethical values, interpersonal relationships, or a combination of these is often associated with frequent use of cannabis. There is also a real risk of serious accidental injury, running away, and suicide attempts in adolescents who develop the cannabis dependency syndrome. Urine toxicology screening tests, in selected cases, can help the physician to diagnose and manage deceptive adolescent drug users who deny or minimize the association of their drug use with their psychosocial problems.

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Marijuana's Effects on Human Cognitive Functions, Psychomotor Functions, and Personality

JOHN B. MURRAY
Department of Psychology
St. John's University

ABSTRACT. Marijuana is complex chemically and not yet fully understood, but it is not a narcotic. Like alcohol, marijuana acts as both stimulant and depressant, but it lingers in body organs longer than alcohol. Smoking marijuana can injure mucosal tissue and may have more carcinogenic potential than tobacco. Research has indicated that marijuana intoxication definitely hinders attention, long-term memory storage, and psychomotor skills involved in driving a car or flying a plane. Expectations and past experience with marijuana have often influenced results more than pharmacological aspects have. Marijuana has triggered psychc c episodes in those more vulnerable. Psychological and some instances of physiolo ical dependence on marijuana have been demonstrated. As a psychoactive drug, marijuana surely alters mental functioning. Although it is possible that chronic use of marijuana produces irreversible damage to mind or brain areas, this has not been determined by research.

ADOLESCENT USE OF MARIJUANA has peaked and in some areas declined (Maugh, 1982; Penning & Barnes, 1982; Relman, 1982). In a nationwide sample of 16,000 to 17,000 teenagers, the proportion that had tried marijuana dropped from 51% in 1979 to 42% in 1983, and daily use of marijuana was down from 10.7% in 1978 to 5.5%, according to the poll "Use of Drugs" reported in the *New York Times* on February 12, 1984. Although marijuana has been used since the third century B.C. (Talbot & Teague, 1969), it has become a worldwide problem, and its use may even be increasing with its users' age and among women (Kandel, 1984; Kandel & Adler, 1982; Lamanna, 1981; Lipp, Benson, & Taintor, 1971; Margolis & Popkin, 1980; *Marihuana Research*, 1974; "Marijuana and Health," 1971; Penning & Barnes, 1982; Relman, 1982)

Requests for reprints should be sent to John B. Murray, Department of Psychology, St. John's University, Grand Central and Utopia Parkways, Jamaica, NY 11439.

This review of research was limited to the studies of marijuana's effects, both physical and psychological, on human subjects. One of the methodological problems in research on marijuana is the lack of animal test procedures that adequately reflect many of the pharmacological properties of marijuana intoxication in human subjects, such as euphoria and hallucinations (Carlini, Kamiol, Renault, & Schuster, 1974; Harris, 1971; Thompson & Johanson, 1981).

Many studies have examined physical effects of marijuana, such as its impact on the cardiovascular system (Beaconsfield, Ginsburg, & Rainsbury, 1972; Tinklenberg, Roth, & Kopell, 1976). Tachycardia, for instance, is a consistent physiological effect of marijuana and, as such, is often used as a marker for the presence of marijuana versus placebo in controlled studies (Isbell & Jasinski, 1969; Kiplinger & Manno, 1971; *Marihuana and Health*, 1977). The second focus of this review of research, however, is the effect of marijuana on human cognitive and psychomotor functions and on personality patterns.

What Is Marijuana?

The flower and leaves of the female *Cannabis sativa* plant are the source of marijuana; stem and seeds may also be included in the mixture. *Cannabis sativa* has been grown throughout the world for the fiber that goes into rope, bags, and clothes, and it has been used as a by-product, a stimulant for work and a depressant for relaxation (National Commission on Marihuana and Drug Abuse [NCMDA], 1972). A pure, gummy resin obtained directly from the leaves contains the highest concentration of delta-9-tetrahydrocannabinol (THC; Abel, 1977; Mechoulam, Shani, Edery, & Grunfeld, 1970). Hashish from India is estimated to be 5 to 10 times more potent than marijuana, but estimates of potency of both hashish and marijuana vary with soil, climate, cultivation technique, and mixture (Smith, 1968; Weil, Zinberg, & Nelson, 1968).

Marijuana is a unique mixture of stimulation and depression of the central nervous system that is not mimicked by other classes of drugs (Consroe, Jones, & Laird, 1976). Scientific evidence has shown that marijuana is not a narcotic and should be treated differently from heroin and opiates (NCMDA, 1972). *Cannabis sativa* is one of the oldest intoxicants in use, but less is known about its pharmacology than about any other drug used. Varying mixtures of different parts of the *Cannabis sativa* plant have psychoactive properties that range from sedative in weaker forms and smaller doses to hallucinogenic in stronger forms and larger doses (*Marihuana and Health*, 1977; "Marijuana and Health," 1971). Lack of adequate supplies and of animal test procedures has delayed understanding of this fascinating group of drugs (Harris, 1971).

The marijuana plant is not a single, simple substance but is very complex, containing at least 419 individual compounds; 61 chemicals identified in the plant are specific to the *Cannabis* plant (*Marihuana and Health*, 1977, 1980; Paton, 1975; Zinberg, 1979). The exact chemical configurations of the most active materials did not become known until 1963, and synthesis was not accomplished until 1967.

Delta-9-tetrahydrocannabinol reproduces most if not all of the effects of the plant drug (Galanter et al., 1972; Hollister, 1973; Hollister & Gillespie, 1975; Isbell, 1971; Isbell et al., 1967; Mechoulam et al., 1970). The percentage of THC is a useful guide to the psychoactivity of a drug sample, but other chemical ingredients may prove to be important in modifying THC's effects as well as have their own impact on human physiology (Hollister, Richards, & Gillespie, 1968). Thus, some of the research on THC may prove to be only partially relevant to the effects of the marijuana plant itself (*Marihuana and Health*, 1980).

During the 1920s, marijuana surfaced as an intoxicant among migrant Mexican laborers and became a matter of public concern. In the 1960s, use of marijuana spread among college students and then among secondary school students, and it has been adopted by portions of the established middle class (Braucht, Brakarsh, Follingstad, & Berry, 1973; Penning & Barnes, 1982). In Eastern countries, marijuana has been used to relieve fatigue and to stimulate appetite. In the Middle East and Caribbean Islands, marijuana is mixed in beverages and drunk as tea (Goode, 1975; Haber, 1975; Hall, 1976; "Marijuana Smoking," 1933).

During the 19th century, *Cannabis* extracts were employed in the United States as therapeutics (Ungerlieder & Andrysiak, 1981). Recently, marijuana has proved helpful for some cases of glaucoma (*Marihuana and Health*, 1980; Relman, 1982; Tashkin, 1978), for the nausea associated with chemotherapy for cancer (*Marihuana and Health*, 1980; Relman, 1982; Sallan, Zinberg, & Frei, 1975; *Therapeutic Uses*, 1980), and for a few cases of anorexia nervosa (Zinberg, 1979).

Does marijuana have implications for the health of Americans, especially the young? Smoking marijuana as well as some plants growing with and contaminating marijuana may be hazardous to bronchial tissues and pulmonary systems, even more than tobacco smoking (Chusid, Gelfand, Nutter, & Fauci, 1975; Cohen, 1981; Kagen, 1981; *Marihuana and Health*, 1980; Maugh, 1982; Nicholi, 1983; Novotny, Lee, & Bartle, 1976; Relman, 1982; Schwarz, 1973b; Tashkin, 1978; Tashkin, Calvarese, Simmons, & Shapiro, 1980; Tashkin, Shapiro, & Frank, 1973; Tashkin, Shapiro, Lee, & Harper, 1976). Marijuana smoke may contain considerably more potential carcinogens than does tobacco smoke (Cohen, 1981; *Marihuana and Health*, 1980; Nicholi, 1983; Novotny et al., 1976). Marijuana may weaken the body's immunological defenses (Aaronson & Dunn, 1974; Lau et al., 1976; Relman,

1982) and may have a small, reversible suppressive effect on testosterone level and sperm count and motility (Kolodny, Masters, Kolodner, & Toro, 1974; Margolis & Popkin, 1980; *Marihuana Research*, 1974; Maugh, 1982; Mendelson, Kuehnle, Ellingboe, & Babor, 1974; Paton, 1975; Relman, 1982; Stuble & Raven, 1979). Marijuana does cross the placental barrier, and its use during pregnancy should be strongly discouraged because of many unknowns concerning its effects on ovulation, fetal development, and childbearing (Maugh, 1982; Petersen, 1980; Relman, 1982). It also enters into a nursing mother's milk.

The method of administration (oral, intravenous, or smoked) is one source of the variability of effects that limits conclusions in studies of marijuana. Smoking is the most common method of administration in the United States. Most users in the United States have smoked marijuana of relatively low potency, but its potency may be increasing (*Marihuana and Health*, 1977; Nicholi, 1983; Petersen, 1980).

Humans metabolize THC completely. When administered intravenously, THC may persist in plasma for more than 3 days (Lemberger, Silberstein, Axelrod, & Kopin, 1970). It disappears in 28 hr from the blood of experienced marijuana users but lasts for 57 hr in the blood of those unaccustomed to marijuana; metabolites of marijuana are excreted for more than a week in both groups (Dackis, Pottash, Annitto, & Gold, 1982; Lemberger, Tamarkin, Axelrod, & Kopin, 1971; Lemberger et al., 1972). Unlike alcohol, which is largely water soluble and may be washed out within 12 hr, marijuana is fat soluble and remains in the body, lodged in fat tissue, such as the brain, adrenal gland, liver, lungs, ovaries, and testes (Gill, 1976; Margolis & Popkin, 1980; Paton, 1975).

What Variables Must Be Controlled in Research With Marijuana?

Research for 50 years has examined marijuana's effect on human performance, but the variables involved are so complex that conclusions must be carefully stated. The statement of findings may displease those who prefer more forthright condemnation of marijuana lest the unwary, especially the young, might take up its use. It may also displease those who observe correctly that research evidence is not conclusive (Bennett & Milman, 1982; Hollister, 1971b; Kaplan, 1973; Kennedy, 1978; McGlothlin & West, 1968; Margolis & Popkin, 1980; *Marihuana and Health*, 1973, 1975, 1977, 1980; Maugh, 1982; Nicholi, 1983; Relman, 1982; Schwarz, 1973a).

First, there is the question of control of the potency and purity of the substance used as marijuana (Weil et al., 1968). Variation in potency among cannabinoids may reach a factor of 2,000; yet estimates of relative potency and quantitative analyses are difficult to make because of variability among subjects (Cocchetto, Owens, Perez-Reyes, DiGuiseppi, & Miller, 1981; Hawks, 1982; Hollister, 1976; Paton, 1975; Willette, 1976).

Since THC was synthesized, many investigations have employed it because its potency is more easily controlled and quantified (Hollister, 1971a; Hollister et al., 1968). THC reproduces most if not all of the effects of the plant drug (Isbell, 1971; Isbell et al., 1967; *Marihuana and Health*, 1980; Mechoulam et al., 1970; Rafaelsen et al., 1973). When this synthetic drug was administered with the natural marijuana to human subjects, however, the subjective, cognitive, and physiological changes tended to be greater for the natural marijuana. Marked placebo effects were suggestive of a learned subjective marijuana syndrome (Galanter, Weingartner, Vaughan, Roth, & Wyatt, 1973; Hollister, 1976). Recent authors have attempted to control for this factor by reporting the relative potency of the samples used in their studies, but potencies still vary from study to study.

The soil in which marijuana grows influences its potency (Abel, 1977). Carlini et al. (1974) used three samples of marijuana grown in Brazil. Their subjects were 11 physicians and 22 medical students who had never smoked marijuana. Each of the three samples of marijuana was burned in a pipe, and each of the subjects was exposed to the marijuana smoke in a room for 5 to 8 min; their noses were blocked. One sample of marijuana had no psychological effect, but the other two samples disrupted a time-estimation task and had effects two to four times greater than expected from the THC content.

Together with the potency of the marijuana used, the dosage is an important variable in marijuana research (Dornbush, 1974; Dornbush, Fink, & Freedman, 1971). Kiplinger and Manno (1971) and Kiplinger, Manno, Rodda, and Forney (1971) reported dose-related effects of THC. The latter authors had 15 volunteers smoke THC in different doses as well as a placebo dose in a randomized, double-blind design. Larger doses were associated with more interference in verbal tasks and rotor pursuit and unsteadiness on a test of stance. Most other investigations have also found more interference in human functioning traceable to larger doses of marijuana (Evans et al., 1973).

The route of administration—oral ingestion, intravenous injection, and smoking marijuana, which socially is the most common method in the United States—produces different effects (Cohen, 1981; "Marijuana and Health," 1971). The routes of absorption through lungs, digestive tract, or veins may filter the marijuana differently. Some 150 compounds have been identified in the smoke of marijuana; burning possibly transforms some of the chemicals into other compounds (*Marihuana and Health*, 1980). The effects of smoked marijuana appear within seconds to minutes, whereas in marijuana taken orally, the onset of effects is delayed for 30 min to over 2 hr (Hollister, 1973; Lemberger et al., 1972).

Some fraction of marijuana that is smoked may be lost into the air or exhaled before it is absorbed completely. Many investigations have attempted to standardize the routine of smoking by regulating the size of the cigarette, how long it was smoked, how long it was inhaled, and the number of grams of marijuana it contained, stated in terms of THC potency (Casswell & Marks, [illegible]a). The efficiency of delivery of a marijuana dose by smoking has been estimated to range from 20% to 80%; experienced and heavy marijuana users have smoked more efficiently than casual users (Hollister, 1971b, 1973; Lindgren, Ohlsson, Agurell, Hollister, & Gillespie, 1981). Inhaling gaseous and particulate products of *Cannabis* combustion exposes bronchial mucosa to polyaromatic hydrocarbons and other noxious compounds; some authors have been concerned that this may be a prodromal phase of another wave of lung cancer, as occurred with cigarette smoking (Cohen, 1981; Maugh, 1982; Relman, 1982). Potency is increased approximately three times by smoking THC, as compared with oral ingestion of the same material (Isbell et al., 1967).

The amount of marijuana entering the body can be controlled better in oral ingestion. Its fate within the body, however, is less certain because some active material might be lost through decomposition or other metabolic changes (Hollister, 1971b). Lemberger et al., (1972) studied the effects of three methods of administering THC—oral, intravenous, and smoking. The subjects were 12 young male volunteers who were long-term users of marijuana and were paid for their cooperation. Only 50% of the THC content of the smoked marijuana was delivered, but it took effect within 10 to 140 min, averaging at about 70 min. Of the marijuana taken in a cherry-flavored drink, 90% was absorbed, but the peak effect did not occur until 3 hr after the drug was taken. Excretion of marijuana in urine on the first day was similar for oral and intravenous administrations. Psychological effects, measured by a questionnaire and rated in observations at regular intervals, fitted temporally with the plasma levels of metabolites of marijuana ingested and inhaled.

The subjects employed are an important issue in research of marijuana's effects on human cognitive and psychomotor functions and on personality. Auditory thresholds of college students having smoked marijuana, as compared to those having smoked a placebo, were altered significantly on a standard hearing test (Caldwell, Myers, Domino, & Merriam, 1969a, 1969b). Meyer, Pillard, Shapiro, and Mirin (1971) tested six heavy and six casual marijuana users. Generally, research has revealed significant differences between performances of experienced and casual users of marijuana, although the criteria for selecting the two groups have not always agreed (Caldwell et al., 1969a; Greenberg, Mendelson, Kuehnle, Mello, & Babor, 1976; MacAvoy & Marks, 1975; Mendelson, Kuehnle, Greenberg, & Mello, 1976). In a double-blind study, all subjects smoked a placebo, marijuana in a dose fixed for the study, and marijuana in a dose that the subjects themselves selected. The four test sessions were a week apart. Casual smokers experienced more impairment on a psychomotor task, and their responses to a questionnaire checking their experience of the drug effects indicated that the placebo condition gave them more of a high than did either drug condition. Degree of impairment in a perceptual test was similar for both groups. The casual users made five times as many errors on a divided-attention task when they were smoking the ad libitum dose of marijuana as they did when they were smoking the placebo. Heavy marijuana users did not manifest any increase of errors in the ad libitum dose condition. In a similar study comparing heavy and casual users of marijuana, the heavy users manifested more hostility on the Psychiatric Outpatient Mood Scale and poorer work adjustment and interpersonal relations than did the casual users, although the two groups had been equated in educational background, racial distribution, and social class (Mirin, Shapiro, Meyer, Pillard, & Fisher, 1971).

Jones (1971a; 1971b) tested 100 users of marijuana in drug and placebo conditions. Frequent users (75 of 100 subjects) rated the placebo as higher in potency than did the infrequent marijuana users; the infrequent users significantly distinguished the placebo from the drug condition, but the frequent users did not. The frequent users seemed more likely to respond to cues of familiar taste and smell (i.e., psychological factors) than to the THC content of the cigarettes. Response variability seemed to be a function of users' expectations and their previous experience with marijuana (Carlin, Post, Bakker, & Halpern, 1974; Hollister, 1976; Hollister & Overall, 1975–1976).

The subjects were important considerations in the first research under U.S. auspices on marijuana's effects (Dornbush & Freedman, 1976). The first study examined use of marijuana by soldiers in the Panama Canal Zone. The dose was not specified, and control groups were not included. Appetite was increased, but no serious harm to soldiers' efficiency or corps morale was evidenced (Abel, 1982; "Marijuana Smoking," 1933). The second study, after the Marihuana Tax Act was passed in 1937 in the United States, was the LaGuardia report (*Mayor's Committee*, 1944) which was based on 72 prisoners in New York City, of whom 48 used marijuana. No control groups were described, the marijuana dose was not specified, and the scientific design was faulty ("Marijuana and Health," 1971). Intellectual functioning was impaired, body steadiness was decreased, but basic personality patterns remained unchanged (Clark & Nakashima, 1968; Weil et al., 1968).

The President's Commission on Law Enforcement and Administration of Justice in 1967 stated that no careful and detailed analysis of the experience with marijuana in the United States seemed to have been attempted (Weil et al., 1968). Three studies of those who had used marijuana alone for 10 years or more were conducted in Jamaica, Greece, and Costa Rica (Schaeffer, Andrysiak, & Ungerlieder, 1981). Subjects who had used marijuana exclusively for 10 years could not be identified in the United States. The marijuana users tested in the three other countries came from the lowest, least productive strata of society, in contrast to the well-educated, middle-class marijuana users who have been the subjects in most research in the United States (Dornbush & Freedman, 1976; Petersen, 1980). Research outside the United States has tended to be mostly anecdotal and deficient in scientific controls (Goode, 1975; Haber, 1975; Hall, 1976; Margolis & Popkin, 1980; Weil et al., 1968).

Both the set and setting must be controlled for consistent findings, but research with these variables has overlapped research with the variable of the subjects employed (Cappell & Pliner, 1974; Galanter et al., 1973; Hollister, 1976; Hollister & Overall, 1975–1976; Jones & Stone, 1970; Lamanna, 1981; Pihl, Shea, & Costa, 1979; Stark-Adamec, Adamec, & Pihl, 1981, 1982; Stark-Adamec, Pihl, & Adamec, 1980; Zinberg, 1979). Setting includes the environmental circumstances of the investigation. Hollister, Overall, and Gerber (1975) studied the effect of setting and found that it had less impact than either the drug effects or the reaction of subjects. Casual users of marijuana (*N* = 12) smoked cigarettes of either marijuana or placebo. The favorable environment included all the appurtenances deemed desirable by drug users, namely, mystical pictures, visual-centering devices, tapes of drone instruments that were suitable for meditation, burning incense, and small candies. Subjects were invited to remove their shoes and socks and lie on rugs or cushions placed around the room, which was in a private dwelling. The unfavorable environment was an austere laboratory in which were strewn odds and ends of medical equipment in a Veteran's Administration hospital.

Galanter et al. (1974) approached the influence of set and setting on marijuana effects in another way. Experienced users of marijuana (*N* = 36) joined sensitivity groups; 12 groups of three members each met for 90 min once a week for 26 weeks. The three conditions in the meetings were smoking marijuana, smoking a placebo cigarette, and using no drug. On questionnaires answered in Sessions 9 through 20, subjects' somatic experiences were consistent with the drug condition. The marijuana users had described previous experience with marijuana as happy, friendly, and warm and as occasions when they were not likely to become angry and defensive. Their questionnaire responses, however, did not reflect consistent affective change, increased insight, or increased feelings of cohesiveness in the sessions when they smoked marijuana. In their assessments of their own experience in the group and their perception of the group atmosphere, there were no significant differences between sessions in which they smoked a placebo and those in which they smoked marijuana. The marijuana users did not report themselves as more detached, but observers rated them as less involved with others. Subjective responses of marijuana users were at variance with the experiences they had anticipated in the light of their previous experience with marijuana. A strong learned component in the response to marijuana was suggested by subjective responses to placebo conditions (Galanter et al., 1973; Jones, 1971a, 1971b). To the extent that experienced users of marijuana were able to compensate for the effects of marijuana, the decrement in performance might have been less evident (Meyer et al., 1971).

Clopton, Janowsky, Clopton, Judd, and Huey's (1979) findings were in a similar vein. Experienced marijuana users were less aware of the emotions of others in a small-group setting after they smoked marijuana than they were in the placebo session. Their scores on the Affective Sensitivity Scale declined significantly after smoking marijuana. Janowsky et al. (1979) reported similar changes after their male subjects smoked marijuana. Twenty men were selected, all employed in mental health fields. Twenty women, controls, met with the men one-on-one for 25 min, during which they discussed difficult times they had experienced. Then the men smoked a marijuana or placebo cigarette. They returned to discussion for 25 min. After the marijuana cigarette, the men decreased significantly in interpersonal skills and in empathy. This change was noticed by the men themselves in their evaluations of their mood on an affective checklist as well as by judges who rated videotapes of the interviews between men and women.

As a further limitation on the results of investigations, Weil et al. (1968) considered the absence of negative control on placebo treatments one obstacle in marijuana research. For frequent users, the odor and taste of marijuana are so distinctive that an effective placebo is difficult to obtain. Placebo conditions are relatively easier to maintain with those who are unfamiliar with marijuana. Medical, legal, and ethical issues are also obstacles to be overcome if research with marijuana is to be scientifically controlled. Because women have not yet taken up marijuana in the same proportions as men, men predominate as subjects. College, medical, and graduate students also predominate. These factors, together with the small size of groups tested, limit the generality of conclusions from studies of the effects of marijuana (Glynn & Nelson, 1982).

Research Findings on Cognitive Performance

Does long-term substantial use of marijuana lead to impairment of cognitive functions? Intellectual function and immediate memory are impaired by marijuana, according to the statement of the secretary of health, education, and welfare (*Marihuana and Health*, 1975). Answers must usually be qualified in terms of not only the subjects' experience with marijuana, the potency and dosage of the substance used, and the method of administration but also the tasks employed, simple or complex (Cohen, 1981; Dornbush, 1974; Waskow, Olsson, Salzman, & Katz, 1970; Weckowicz et al., 1975; Wetzel, Janowsky, & Clopton, 1982).

Attention was the focus of early investigations of the effect of marijuana on human cognitive functioning. The Goal-Directed Serial Alternation (GDSA) was the task employed in several studies (Melges, Tinklenberg, Hollister, & Gillespie, 1970a, 1970b; Meyer et al., 1971). The GDSA required subjects to simultaneously hold in mind and coordinate information as well as perform mental operations relevant to pursuing a goal. Each subject was assigned a starting number in the range of 106 to 114 and was required to subtract 7 and then add 1, 2, or 3, continuing such alternate subtraction and addition until the number initially selected was attained. Casswell and Marks (1973a) compared nine male casual users and nine male heavy users of marijuana on the GDSA. Both groups obtained lower scores on the GDSA after smoking marijuana. On a vigilance task, Casswell and Marks (1973b) found that their two groups did not differ significantly. Confusion on the GDSA and loss of directedness usually occurred when marijuana was used (Melges et al., 1970a, 1970b). Smoking low doses of marijuana did not influence mental performance of 8 subjects on delayed auditory feedback, addition problems, color naming, or a task similar to the GDSA (Evans et al., 1973). Decrements in performance in connection with smoked marijuana were larger in Casswell and Marks's (1973a, 1973b) studies than were those Melges et al. (1970a, 1970b) found with orally ingested THC. Differences on the Digit Symbol (DS) were not altered significantly by smoking marijuana in Casswell and Marks's (1973a) investigation, in contrast to the significant results Melges et al. (1970a) obtained with THC orally ingested. Casual and heavy users were affected differently on different tasks by marijuana, ingested, smoked, or in the form of THC (Casswell & Marks, 1973a).

In Germany, Dittrich, Battig, and von Zeppelin (1973) also tested the effect of oral ingestion of marijuana on memory as well as on attention. They discovered that the effect of marijuana on attention varied according to the task and concluded that attention should not be considered a unitary trait. On 10 lists of two-syllable nouns, marijuana did not alter the retrieval of information already present in memory, but information stored in short-term memory was forgotten to a greater degree after the marijuana than after a placebo. They judged that their results supported the findings of Abel (1970, 1971) and Melges et al. (1970a, 1970b). Low doses of THC did not alter recall in short-term (6–18 s) memory of consonant trigrams for 10 first-year medical students, but high doses were followed by significant interference, especially in the longer delays. In his investigations of marijuana's effect on memory, Abel (1970, 1971) subjected 49 men and women to two experiments with the following three conditions: smoking marijuana, smoking a placebo, and being in the control group. In the first test, 18 lists of 10 words each were read aloud; 1 min was allowed for verbal recall of the list immediately after the words were presented. On a recognition test for immediate memory, the subjects had to circle 30 words that they recognized from 60 words, 30 from the first 3 lists and 30 new words. They also rated their confidence in the accuracy of their responses. One group smoked a marijuana cigarette for 5 to 10 min, and another smoked a placebo cigarette.

A second recognition test was made up of 300 items, 150 from the last 15 lists of words and 150 new words. Marijuana and placebo groups did equally well on both recognition tests; the marijuana group tended to be less cautious and to accept more incorrect words. In a second experiment, 10 subjects who were familiar with the effects of marijuana were tested twice, with 1 week between the two sessions; marijuana and control groups were reversed in the two sessions. After they smoked marijuana or the placebo, they were assigned the memory task of 10 lists of 12 words each. After the last list was read, they were given 5 min to write as many words as they could recall. All subjects remembered fewer words in the marijuana condition than they did in the placebo condition.

Marijuana affected recognition and the acquisition processes involved in the storage of information but not retrieval when the free-recall method was employed. In Abel's (1970) early study, eight men and women read through a book twice at their own speed after smoking two marijuana cigarettes. Those who smoked marijuana scored the same as the placebo subjects, but seven of eight marijuana smokers wrote significantly less and included fewer content words. Gianutsos and Litwack's (1976) results showed a significant reduction for chronic marijuana users in the movement of information from short-term memory to a more permanent level of information storage. Their subjects were college students, 25 chronic users and 25 nonusers, similar in sex, age, major, grade point average, and year in school.

Dornbush (1974) replicated the testing conditions of the two experiments conducted by Abel (1970) with 20 male first-year medical students. Specifying the THC content of the marijuana and having a placebo control were additions to Abel's research conditions. The results supported Abel's findings; that is, marijuana disrupted the storage phase of short-term memory (Dornbush et al., 1971). Miller, Drew, and Kiplinger (1972), including a placebo control and specification of the THC content, also replicated Abel's study. Students who were experienced users of marijuana ($N = 12$), having smoked either marijuana or a placebo in a random, double-blind design, were asked to relate all they could remember of a story read to them and to respond to the Stroop Color-Word Test. Marijuana did not alter performance on the Stroop test. Results on memory for narrative material supported Abel's (1970, 1971) findings but showed, in addition to memory deficits, that irrelevant material was intruded by those who had smoked marijuana, as had been noted in earlier research (Clark, Hughes, & Nakashima, 1970; Tinklenberg, Melges, Hollister, & Gillespie, 1970). Some of the irrelevant material added by those who had smoked marijuana was new and without any basis in the stimulus story, and some was arbitrarily unrelated and so strongly colored emotionally that the original story was altered.

In state-dependent learning research, marijuana intoxication did not alter the ability to accurately assess what information was available in long-term memory (Darley, Tinklenberg, Roth, Vernon, & Kopell, 1977; Parker et al., 1980). Stillman, Weingartner, Wyatt, Gillin, and Eich (1974) found that subjects recognized pictures better in the marijuana condition (smoking marijuana in a THC dose similar to that required for a social high) than in the placebo-marijuana or the marijuana-placebo condition. Placebo-placebo condition reproduction was substantially better than marijuana-marijuana condition reproduction, and marijuana produced some overall impairment in performance.

Rickles, Cohen, Whitaker, and McIntyre (1973) explored state-dependent recall with male subjects who had smoked two marijuana cigarettes within 20 min or a placebo and then learned paired-association lists. Those intoxicated on marijuana needed significantly more trials to reach criterional learning than did those in the placebo condition. Ten days later, the subjects who had been high on marijuana recalled better the material they had learned. Moderately high doses of marijuana interfered with learning new material in terms of subjects' needing more trials and more failures to reach criterion than did subjects in the placebo condition.

Impaired immediate memory and intellectual performance on a variety of tasks in connection with marijuana has been confirmed experimentally (Relman, 1982). Evidence has indicated that at lower doses, users are able to "suppress the marijuana high." Experimental research has not confirmed the enhanced visual, auditory, and tactual awareness and sensitivity claimed for marijuana by its users (*Marihuana and Health*, 1975).

Research Findings on Psychomotor Performance

Many of the studies in this area began as investigations of marijuana's effect on driving an automobile (Klonoff, 1974). Some researchers have reported that marijuana was associated with errors in estimates of time that might influence driving in traffic (Hollister & Gillespie, 1970; Jones & Stone, 1970; Kaplan, 1973; Melges, Tinklenberg, Hollister, & Gillespie, 1971; Vachon, Sulkowski, & Rich, 1974). Verbal and operative estimates of time, in which subjects press a key for an interval called for by the experimenter, involve functions different from those in reproductive time judgments, in which subjects press a key for 5, 10, or 15 s (Clausen, 1950). Similarly, smoking marijuana seemed to bring on errors in judgments of distance, important in parking and passing cars in traffic (Bech, Rafaelsen, & Rafaelsen, 1973). Tracking tasks and pursuit motor tasks were disrupted more by smoking THC than by taking a placebo, as evaluated by self-ratings and interpersonal judgments (Melges, 1976; Roth et al., 1973). Marijuana smoking affected reaction time and coordination of movements important for operating machinery at work and at home as well as for operating an automobile (Kvalseth, 1977;

Manno, Kiplinger, Haine, Bennett, & Forney, 1970; Manno, Kiplinger, Scholz, Forney, & Haine, 1971; Moskowitz, Shea, & Burns, 1974).

Bech et al. (1973) and Rafaelsen et al. (1973) fed cakes containing THC or a placebo to eight men. Marijuana affected estimates of time and distance in a simulated driving test. The car was equipped with steering wheel, accelerator, brake, and clutch; the men drove for about 25 min. They were asked how far they thought they had been driving. When the wheel was turned, the landscape moved at a speed determined by the drivers' pressure on the accelerator. Marijuana had a more marked effect on the subjective than the objective estimates. Moskowitz, Ziedman, and Sharma (1976) used film depicting moderate to heavy traffic for their investigation; alcohol disrupted visual search more than marijuana did.

Crancer, Dille, Delay, Wallace, and Haykin (1969) studied the comparative effects of marijuana and alcohol on simulated driving performance. Their 36 subjects, who were experienced with marijuana and mostly men, smoked marijuana until they reached a social high. More errors were recorded in the marijuana condition than in the normal condition, for reading the speedometer but not for using the accelerator, brake, or steering. Alcohol produced significantly more errors than marijuana did on driving tasks.

The research of MacAvoy and Marks (1975) in New Zealand also involved comparisons of effects of marijuana and alcohol, in this case on tracking accuracy and recognition of signals. Tasks required pressing a key when a central light signal flashed, breaking the sequence, and pressing a second key when a peripheral red light flashed. Marijuana reduced the accuracy in tracking and recognizing signals and impaired physiological and psychological functions involved in driving skills differently from alcohol.

In Casswell and Marks's (1973b) study, 10 male experienced marijuana users and 10 male nonusers, matched in age and education, were tested with two types of visual signals coming from different sources. Those who smoked marijuana missed significantly more of both the central and peripheral signals. The authors believed that their results applied to driving, which they construed as performing a task while processing information coming from more than one task. Visual-information processing in a tachistoscopic presentation was impaired significantly in 10 male experienced marijuana users after they smoked marijuana but not in a placebo condition (Braff, Silverton, Saccuzzo, & Janowsky 1981).

Clark, Hughes, and Nakashima (1970) studied the effects of oral THC on 18 college students who had never used marijuana. The students were tested on reaction time for four colors, singly or in combination, and on a digit-code memory task. After marijuana, responses to the reaction-time task were markedly inconsistent, especially in the more complex tasks. On the digit-code test, marijuana affected the students' accuracy and significantly reduced their hand steadiness.

Kvalseth (1977) reported an investigation in Norway in which six experienced marijuana users tested on linear and rotary movements made significantly more errors in the marijuana condition than they did in the placebo condition of testing. In two studies, motor performance was significantly decreased for 12 male volunteers who smoked marijuana in a double-blind design; alcohol also interfered with motor tasks of varied complexity; a combination of marijuana and alcohol induced significantly more performance decrement than did either drug alone (Manno et al., 1970, 1971). Both mental and motor performance of 15 male medical students, half of whom had experience with marijuana, showed deterioration after smoking THC, in comparison with the results of the placebo condition (Kiplinger et al., 1971).

Volunteers (N = 25, men and women about equally) responded to the following tasks: addition, subtraction, standing steadiness, pursuit rotor, and reaction time for red and white signal lights (Belgrave et al., 1979). Results were factor analyzed and indicated four factors; THC was associated with significant deterioration on all four factors. Comparisons of alcohol (ethanol) and THC showed that alcohol's effects on performance decrements were slower in onset than THC's but lasted longer. Apparently, the two drugs did not interact, but the combination of drugs as well as each drug alone impaired performance on tasks related to skills involved in driving an automobile.

Janowsky, Meacham, Blaine, Schoor, and Bozzetti (1976a, 1976b), in a double-blind study, investigated the effect of smoking marijuana on simulated-flying performance. Male certified pilots (N = 10, 7 professional and 3 private pilots), all of whom had used marijuana socially, took a simulated-flying test 30 min after smoking marijuana for 10 min; the tests were repeated 2, 4, and 6 hr after they smoked marijuana or a placebo cigarette. All showed significantly decreased flying skill in a 16-min test of flying in a simulated holding pattern sequence, involving straight and level flight and turns, and of instrument flying and navigation. Evaluation continued over the 6-hr period; flying performance was videotaped and analyzed in 10-s intervals for major and minor errors. Performance returned to normal 4 hr after smoking marijuana. Pilots rated the effects of marijuana as equivalent to a social high. They felt that flying was more challenging after smoking marijuana and that they were not able to compensate adequately. Analysis of their performance on videotapes by judges who did not know whether they had smoked marijuana or were in the placebo phase confirmed their self-judgments.

Hansteen, Miller, Lonero, Reid, and Jones (1976) reviewed the studies of marijuana and alcohol effects on automobile driving and psychomotor tracking. They concluded that under certain conditions of dosage and time intervals after smoking, marijuana impaired pursuit-tracking accuracy, hand and body steadiness, time needed to brake, signal detection, perception of danger and risk taking, and susceptibility to distraction or stress. Their own investigation of 16 licensed drivers, 12 men and 4 women, mostly college students, on driving tests was spread over four weekly sessions and included a high and low dose of marijuana, alcohol, and placebo. Both the doses of alcohol and the higher dose of marijuana induced poorer handling of the automobile. Early reports were more optimistic about driver performance after smoking marijuana than recent evidence (*Marihuana and Health,* 1975). The more complex the task was, the more disruptive the effect of acute marijuana intoxication generally was. Operation of an automobile and complex psychomotor skills are clearly impaired by marijuana (*Marihuana and Health,* 1977; Relman, 1982). In simulated-driving and actual-driving tests, in estimates of time and distance, in alertness to signals at the center of the visual field and on the periphery, and in stability of stance, it appears that marijuana in social doses can impair driving performance and complex psychomotor skills (Paton, 1975; Relman, 1982; Waller, 1965, 1971).

Personality Differences Attributable to Marijuana

Some studies have sought to identify personality traits that might identify those likely to take up drugs, marijuana in particular (Nicholi, 1983). Findings on personality characteristics of contemporary marijuana users indicate a greater diversity of personality patterns than in the more traditional hard-core heroin addicts of past generations (Austin & Lettieri, 1976; Blaine & Julius, 1977; Brill, Crumpton, & Grayson, 1971; Harmatz, Shader, & Salzman, 1972; Murray, 1967; Patalano, 1976, 1978, 1980; Penning & Barnes, 1982; Pope, Ionescu-Pioggia, & Cole, 1981). Gorsuch and Butler (1976), who reviewed the research on the predisposing social and psychological factors, and Sadava and Forsyth (1977) pointed out that a complex interaction of parent-child relationships, parental modeling, involvement with drug-using peers, and availability of illicit drugs made it difficult to distinguish clearly the path leading to initial drug use.

Another approach in marijuana study searched for a constellation of attitudes, values, and behavior representing a rejection of middle-class or establishment norms and activities or behavior reflecting a sense of alienation and dissatisfaction with family and school experience (Dembo, Schmeidler, & Koval, 1976; Ferguson, Lennox, & Lettieri, 1974; Hendin, Pollinger, Ulman, & Carr, 1981; Jessor, 1976; Rooney & Wright, 1982). Several studies employing questionnaires and interviews have looked into behavior patterns that preceded adolescents' use of marijuana (Lettieri, 1975). Family patterns rather than peer pressure appeared to be related to subsequent marijuana use in a study of 180 boys and girls from 13 to 17 years of age (Brook, Likoff, & Whiteman, 1980). Fathers' personalities and child-rearing practices, however, interacted with peer factors in influencing high school students' (Kandel, 1973) and male college students' patterns of marijuana use (Brook, Whiteman, Brook, & Gordon, 1981, 1982). Alcohol, in the form of beer and wine was often the first step in a sequence leading to tobacco and subsequently to marijuana (Kandel, 1975; Kandel & Faust, 1975; Maugh, 1982). The highest rates of marijuana use were observed in adolescents whose parents and friends both used drugs (Kandel, 1973). Cultural differences contribute to the mix of parental and peer influences on patterns of adolescent drug use (Kandel & Adler, 1982; Winfree & Griffiths, 1983).

In an early description of becoming a marijuana user, Becker (1953) emphasized not antecedent predispositions but the motives and changes in attitudes leading to the use of marijuana for pleasure, not as a compulsive response. It is probable that any excessive use of drugs for pleasure may decrease an individual's motivation. A frequent criticism of marijuana has been that it leads to an *amotivational syndrome* (Hendin, Pollinger, & Ulman, 1981–1982; McGlothlin & West, 1968; Margolis & Popkin, 1980; Miranne, 1979). This passive, inward-turning, amotivational personality change, reflected in rejection of previous achievement-oriented behavior, appeared more often in clinical studies with younger subjects and was more frequent in the late 1960s than recently (Creason & Goldman, 1981; Shean & Fechtmann, 1971; Toohey, Dezelsky, & Baffi, 1982). From their responses to questionnaires, college students' intellectual goals and academic performance seemed less impaired by marijuana than did those of high school students (Hochman & Brill, 1983; Jessor, Jessor, & Finney, 1973; Smith & Fogg, 1976). The question waits for an answer: Does marijuana have any specific capacity for inhibiting motivation not possessed by other drugs (Farnsworth, 1976)?

College students who were users of marijuana appeared to be less responsible, more nonconforming and more open and often possessed higher self-esteem (Cunningham, Cunningham, & English, 1974; Grossman, Goldstein, & Eisenman, 1974; Gulas & King, 1976; Hogan, Mankin, Conway, & Fox, 1970; Knecht, Cundick, Edwards, & Gunderson, 1972; Simon, 1974; Victor, Grossman, & Eisenman, 1973). Campbell (1976), reporting on the Canadian scene, and Mellinger, Somers, Davidson, and Manheimer (1976) found no conclusive evidence that generally moderate patterns of marijuana use produced amotivational symptoms sufficiently serious or long lasting enough to increase the risk of dropping out of college. Evidence connecting heavy use of marijuana to amotivational syndrome did not conclusively show whether the drug was a cause or an effect (Cohen, 1981; "Marijuana and Health," 1971; Relman, 1982).

Campbell (1976), as a member of the Canadian committee investigating the effects of marijuana, reviewed European, Canadian, and North American studies; the evidence did not conclusively support an amotivational-syndrome change in personality traceable to marijuana use. All the changes attributed to use of marijuana could be explained through membership in subcultures that did not stress academic success or the need for planning or through a general decline in motivation. A review of examinations taken and essays

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Does marijuana lead to violence? Early reports emanating from police records and stories in tabloids accentuated this relationship (Abel, 1977, 1982). Salzman, Van der Kolk, and Shader (1976), Colbach (1971), and Keup (1970) agreed that the setting of a crowd may bring on physical or sexual violence but that violence because of marijuana is rare. Tinklenberg, Roth, Kopell, and Murphy (1976) found that marijuana did not have as socially disruptive effects as alcohol, and no evidence that increase in violent crime was directly related to increase in marijuana use. The consensus is that marijuana does not precipitate violence in most of those who use marijuana and that aggressive behavior is not a common consequence of marijuana use in the United States (Petersen, 1980).

Marijuana intoxication, the high, may approach the hallucinogenic trips of LSD if dosage is high enough (Consroe et al., 1976; Fabian & Fishkin, 1981; Halikas, Goodwin, & Guze, 1971; Tart, 1970). About 17 of 42 (about 40%) marijuana users randomly selected from college students had experienced hallucinogenic ideation (Keeler, Ewing, & Rouse, 1971). Usually, as with other hallucinogens, marijuana users were able to recover as the drug left the system (Gersten, 1980). Hollister and Overall (1975–1976) and Pihl et al. (1979) factor analyzed the responses of several hundred marijuana users regarding their subjective experiences with marijuana; five factors that emerged made it clear that marijuana intoxication effects are multidimensional.

To what extent is the use of marijuana associated with psychotic episodes? Instances in which marijuana interferes with cognitive functioning, such as study or good judgment, have already been discussed, but sometimes these incidents blossom into anxiety states and, though temporary, may cause panic, which is a common reaction to the effects of large doses of marijuana, especially for first-time users (Bailos, 1970; Stanton & Bardoni, 1972; Weil, 1970). Accounts of psychotic episodes attributed to marijuana use have been reported more often in other countries than in the United States (Austin, Macari, & Sutker, 1972; Keup, 1970). Linn (1972) showed that psychopathology was a condition that developed prior to marijuana use.

Do marijuana users experience spontaneous recurrences? Keup (1970) found that 5% to 10% of newly admitted mental patients who had a history of drug abuse reported having had flashbacks after abusing marijuana. Marijuana had frequently been used along with other drugs by soldiers who had experienced flashbacks (Yager, Crumpton, & Rubenstein, 1983). Canadian high school students reported experiencing recurrences of marijuana effects at times when they were not using the drug (Annis & Smart, 1973). Keeler, Reifler, and Liptzin (1968) described 4 subjects who, in a drug-free state, had recurrences of unusual visual or somatic sensations that they had experienced while using marijuana. The subculture of marijuana users does believe in the reality of spontaneous flashbacks, but in most cases in which marijuana alone was the drug, the users diagnosed the flashbacks themselves, and few were legitimate instances of spontaneous recurrence (Brown & Stickgold, 1976).

Physicians, however, have been concerned with the number of patients who recover from mental illness only to relapse after using marijuana (Gersten, 1980; Nicholi, 1983). Marijuana has been known to push some into mania (Harding & Knight, 1973). Paranoid episodes and hallucinogenic effects occur in connection with marijuana use, especially with large doses and overdoses (Gersten, 1980; Relman, 1982; Treffert, 1978; Weil, 1970). Marijuana is especially ill-advised for those predisposed to schizophrenia (Casswell & Marks, 1973a; Gersten, 1980; Keeler et al., 1971; Keup, 1970; McGlothlin & West, 1968; Melges, 1976; Szymanski, 1981). When marijuana is used to treat nausea associated with chemotherapy for cancer, it sometimes triggers dysphoric reactions (Nicholi, 1983). Normally functioning individuals with no history of psychiatric illness but moderate underlying psychopathology may develop psychiatric disturbances associated with smoking marijuana, but these ordinarily clear up within a short time as the drug leaves the system.

Can marijuana lead to brain damage? Maugh (1974) outlined the arguments and research on the question of whether chronic and heavy marijuana use leads to brain damage. Marijuana seems to pass the blood-brain barrier (Wall, 1971). In England, Campbell, Evans, Thomson, and Williams (1971) reported cases of cerebral atrophy in 10 young men who had been heavy users of marijuana over a period of 2 or more years. Kolansky and Moore (1971, 1972a, 1972b) attributed the deleterious effects of long-time use of marijuana to damaged cerebral cortex. Cohen (1981) judged that long-term heavy use of marijuana and the process's taking so long to reverse itself pointed to organic brain impairment. Evidence in the United States has disputed the earlier judgments ("Marijuana and Health," 1971; Relman, 1982). Computerized transaxial tomography has provided a more comprehensive picture of the brain than Campbell et al. (1971) have. Computerized transaxial tomography of 12 men in St. Louis and 19 men in Boston revealed no evidence of cerebral atrophy (Co, Goodin, Gado, Mikhail, & Hill, 1977; Kuehnle, Mendelson, Davis, & New, 1977; *Marihuana and Health*, 1977; Relman, 1982). Surface electroencephalogram changes during marijuana smoking are minimal, but depth changes go on in the septal and amygdala areas in monkeys exposed to marijuana smoke. As a psychoactive drug, marijuana alters the brain functions of memory and time estimates, but the question to be resolved is whether impaired neurological functioning persists beyond the period of acute intoxication. The weight of evidence so far is that lasting brain impairment is possible but not inevitably associated with some undetermined level of heavy and chronic use of marijuana (Petersen, 1980).

Marijuana remains a drug with many attendant dangers and is potentially more harmful than was previously suspected (Margolis & Popkin, 1980). Marijuana use is inextricably tied to the use of many other drugs. Those who use drugs, licit and illicit, are far more likely to use marijuana; prior use of alcohol and tobacco by young people is clearly associated with later marijuana use. Heavy users of marijuana are more likely to use other drugs as well (Hochman & Brill, 1983; *Marihuana and Health*, 1975; *Marihuana Research*, 1974).

Discussion

Research supports the statement of the secretary of health, education, and welfare that marijuana impairs human intellectual judgment and short-term memory as well as human psychomotor function, particularly driving an automobile. The complexity of variables involved in research with human subjects' use of marijuana, however, precludes unqualified conclusions. The potency of the material used varies according to the part of the plant used, the soil in which it was grown, the method of cultivation, whether the marijuana is smoked or taken orally or intravenously, and whether the plant material or THC, the potency of which is believed to approximate the potency of plant material, is u: ed. Chronic users of marijuana probably respond differently to marijuana than do casual or naive users.

Still unanswered and crucial to programs of prevention of drug abuse are the questions of why some use marijuana and others do not and why some users of marijuana go on to become addicted to hard drugs and others, similarly at risk, do not (Blaine & Julius, 1977; Cunningham et al., 1974; *Marihuana Research*, 1974). Marijuana is used by groups younger than ever before; today's high school and college students have smoked marijuana longer than those who smoked it when it first became the fad. Marijuana use by women has increased. Will these changes in patterns of marijuana use be translated into damage, physiological or psychological, that was not evident in earlier studies of marijuana smokers (*Marihuana Research*, 1974; Penning & Barnes, 1982)? What effect if any does use of marijuana have on physical and intellectual development in the young, the adolescents and young adults who are prominent among the frequent users of marijuana (Petersen, 1980)? No research has addressed the effect of age in marijuana users. Concern has been expressed that the adolescent users of today may be handicapped later in life by deferring coming to grips with problems of living through frequent use of marijuana (Cohen, 1981; Maugh, 1982). Young people have reported that they fear that marijuana bought on the street might be laced with heroin or some dangerous substances, but assays of street drugs around the country by the United States government has shown little adulteration (Lamanna, 1981). As youth move into their adult years, will they trade in use of marijuana for traditional adult role behavior? Prediction of the future is more difficult because marijuana use is more widespread than ever before (Glynn & Nelson, 1982).

Because research on long-term physiological and neurological effects of chronic marijuana use remains modest, the information on marijuana's effects has limited relevance to long-term health implications (*Marihuana and Health*, 1977; "Marihuana and Health," 1971; Petersen, 1977). Marijuana has been used popularly in the United States for about two decades; other countries have had longer experience, but the scientific research is lacking (*Marihuana and Health*, 1975). Weller and Halikas (1982) resurveyed about 100 regular users of marijuana after 5 to 6 years; they averaged 27 years of age at the time of the second interview. Comparison of checklist ratings of subjective experiences indicated a decline in the effects initially classified as desirable. Perhaps this decline in experience with marijuana is behind the decline in use noted at the beginning of this report and offers some hope for spontaneous remission in use of marijuana. The major focus for explanations of centrally active drugs is their effects on neurotransmitters and neuropeptides in the brain. Animal studies with marijuana have implicated norepinephrine and serotonin, but the picture is not yet clear (Hollister, 1976; Paton, 1975). Some evidence has indicated that changes in the turnover or degrading effects of the catecholamines might be linked to oral doses of THC, but serotonin levels have been unaffected (Hollister, Moore, Kanter, & Noble, 1970). THC seems to function by an anticholinergic mechanism (Beaconsfield et al., 1972; Drew & Miller, 1974; and Freemon, Rosenblatt, & El-Yousef, 1975; *Marihuana and Health*, 1975; Paton, 1975).

Electrodes implanted in rhesus monkeys' brains may have revealed the brain areas involved in marijuana abuse (Cohen, 1981; Heath, 1973; Petersen, 1980). The hippocampal area of the limbic system of the brain, especially because of marijuana's disruption of immediate memory, has been connected to marijuana abuse through the similarity of behavior changes traceable to marijuana abuse and to the effects of hippocampectomy and temporal lobe resections (Drew & Miller, 1974; Paton, 1975). Perhaps marijuana's impact will be identified through its alteration of the speed of processing pictorial information in favor of the left hemisphere of the brain (Stillman, Wolkowitz, Weingartner, Waldman, DeRenzo, & Wyatt, 1977). Marijuana has chemical properties qualitatively similar to steroid anesthetics (Gill, 1976). Autonomic receptors seem not to explain the effects of THC (Bachman, Benowitz, Herning, & Jones, 1979).

Are there latent consequences of marijuana use due to the complex physicochemical properties of psychoactive cannabinoids? Will research 10 to 20 years ahead reveal consequences of marijuana smoking similar to those discovered with tobacco? Marijuana is more complex chemically than tobacco, and not all of its effects have been deciphered. Smoking marijuana intoxicates, and tobacco does not; smoking marijuana, unlike tobacco, interferes with intellectual functioning, alters time and distance perception and judgment of dangers, and impairs hand and eye coordination.

Like alcohol, marijuana is a drug, but the effects of the two differ in several respects. Marijuana had more deteriorating effect on some tasks than alcohol did, for example, subjective estimates of time and distance in some simulated-driving tasks (Bech et al., 1973; Crancer et al., 1969; MacAvoy & Marks, 1975). Marijuana's interference with performance was slower in onset than alcohol's but lasted longer (Belgrave et al., 1979). The effect of marijuana in oral form peaked after 30 to 60 min and culminated after 2 to 3 hr, whereas alcohol peaked later, between 1 and 2 hr (Rafaelsen et al., 1973). Marijuana did not have the socially disruptive effects of alcohol, nor was it directly related to violent crimes (Tinklenberg, Roth, & Kopell, 1976; Tinklenberg, Roth, Kopell, & Murphy, 1976). Hollister and Gillespie (1970) found that dextroamphetamines induced changes in behavior different from marijuana and alcohol, whose perceptual effects resembled those of hallucinogens.

Tolerance to some of the effects of marijuana, especially tachycardia and subjective highs, has been demonstrated (Jones, Benowitz, & Bachman, 1976; Mirin et al., 1971; Nowlan & Cohen, 1977; Petersen, 1980; Relman, 1982). Usually, large doses over a long period of time are needed to produce tolerance (Margolis & Popkin, 1980). Moreover, the literature includes a number of experiments where lack of tolerance has been reported (Cappell & Pliner, 1974; Krasnegor, 1978; *Marihuana and Health*, 1975). The following factors could have contributed to the conflicting results: the dosage, the active constituents, and the ingredients' potency (McMillan, Dewey, & Harris, 1971). Tolerance does not develop to all THC effects, and most of the tolerance seems to be lost rapidly. Evidence has not indicated that frequent use of marijuana leads inevitably to escalation of use and dose. Tolerance is not as likely to be reported in outpatient studies, in which drug histories are difficult to control (Jones et al., 1976; Lindgren et al., 1981; Petersen, 1980; Relman, 1982).

Dependence in the sense of experiencing definite physiological symptoms following withdrawal has been shown after heavy use of marijuana but not after the social high (Jones et al., 1976; Nicholi, 1983; Petersen, 1980). Withdrawal symptoms of mild nausea, restlessness, sleeplessness, and loss of appetite have been observed in the heaviest smokers (Lamanna, 1981; Nowlan & Cohen, 1977). Psychological dependence is not unusual (Lamanna, 1981). Where tolerance develops, mild physical dependence seems to be associated, but dosage and schedules of use are important variables (Jones et al., 1976; Petersen, 1980; Relman, 1982). No evidence has indicated that marijuana causes addiction to the extent that narcotics do or that physical dependence plays a significant role in persistent use of marijuana (Jones et al., 1976; Relman, 1982).

Probably no other drug has accumulated so much myth about it and so many unanswered questions. Factors of expectation and past experience with the drug may have influenced findings. The small samples that have been studied—mostly of healthy young male subjects who were well motivated and eager to demonstrate unimpaired performance—are serious limitations to broad conclusions. Until research includes more subjects, particularly those who are older and less healthy and women, the full picture of marijuana's effects will not be clear. Because widespread regular use of marijuana is relatively recent, the consequences of long-term use are less clearly documented than the short-term ones. Much remains to be learned about the effects of chronic use of marijuana. Cause for concern is the widespread use among the young of this drug, usually in addition to alcohol and tobacco, which has harmful known and unknown dangers. Many aspects of marijuana use are unknown. Enough is known, however, to state that use of marijuana is by no means harmless.

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The Chronic Cerebral Effects of Cannabis Use. I. Methodological Issues and Neurological Findings

Renee C. Wert, PhD

Michael L. Raulin,* PhD

State University of New York at Buffalo
Buffalo, New York

Abstract

This paper examines the research evidence relating sustained use of marijuana to chronic cerebral impairment. Evidence from both American and cross-cultural studies is reviewed, with a particular emphasis on methodological problems in the research. The focus of this paper is on neurological findings while another paper focuses on neuropsychological findings. On the basis of available research, it was concluded that there is no evidence that marijuana produces gross structural cerebral changes and little evidence that it leads to functional impairment, although subtle impairment cannot be ruled out.

Mind-altering substances have been used and abused throughout history, and their abuse continues to be a major social problem. Nevertheless, there has been relatively little study of their long-term effects on the central nervous system. Research on this question generally has used only one or two quasi-experimental designs, typically examining identified drug users for neurological impair-

*To whom requests for reprints should be sent at the Psychology Department, State University of New York at Buffalo, Julian Park Hall, Buffalo, New York 14260.

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ment or comparing the performance of drug users and a control group on some assessment instrument. Although these quasi-experimental designs are weak and lack the controls of a true experiment, ethical considerations have severely limited the degree of experimental control that an investigator can exercise. While a few true experiments on the effects of drugs on humans have been conducted (Hill and Belleville, 1953; Isbell, Altschul, Kornetsky, Eisenman, Flanary, and Fraser, 1950), most experimentation on the chronic effects of drug use has been conducted on animals. In the animal research, the issue is not one of experimental control, but rather one of generalizability. Since the cerebral cortex is less highly developed in animals than in man, impairments such as subtle biochemical dysfunctions which may affect only higher-level mental processes might go unnoticed in animals.

In this paper, research on the long-term cerebral effects of marijuana use is reviewed. The large amount of research on marijuana should provide enough data to draw some tentative conclusions and to suggest lines for further research. Only the research with human subjects is reviewed because of the limitations in generalizability already discussed. This review begins with a brief discussion of some methodological considerations in long-term drug effect research before reviewing the research studies themselves. The review ends with several suggestions for new lines of research on this question. A thorough understanding of the risks associated with cannabis is necessary if we are to develop reasoned policies and laws to regulate its use.

METHODOLOGICAL CONSIDERATIONS

Polydrug Use

Studying the chronic effects of any illegal drug presents some very serious methodological issues. Perhaps the most serious of these is the fact that the vast majority of drug abusers are polydrug users. A number of recent studies (Grant, Mohns, Miller, and Reitan, 1976; Grant, Adams, Carlin, Rennick, Judd, and Schoof, 1978; Grant, Reed, Adams, and Carlin, 1979; Judd and Grant, 1975) have provided evidence of neurological or neuropsychological impairment in heavy polydrug users relative to control subjects.

There are many possible factors which may account for these findings. First, the drugs themselves and/or their adulterants may be directly toxic to the central nervous system. Evidence suggestive of such toxicity has been presented for heroin and opium (Hall and Karp, 1973; Richter and Rosenberg, 1968; Schein, Yessayan, and Mayman, 1971; Thompson and Waldman, 1970), amphetamines (Citron, Halpern, McCarron, Lundberg, McCormick, Pincus, Tatter, and Haverback, 1970; Goodman and Becker, 1970; Kane, Keeler, and Reifler, 1969; Weiss, Raskind, Morganstern, Pytlyk, and Baiz, 1970), and inhalants (Grabski, 1961; Knox and Nelson, 1966; Layzer, Fishman, and Schafer, 1978; Prockop, 1977; Prockop and Couri, 1977; Schaumberg and Spencer, 1976; Valpey, Sumi, Copass, and Goble, 1978). Quinine, a substance used to dilute heroin, has been linked to optic atrophy in at least one case (Richter and Pearson, 1975) and is described as having "well recognized tissue toxic effects" (Pearson & Richter, 1975, p. 316).

In addition to the use of other illegal drugs, heavy alcohol use is common among drug abusers (Grant et al., 1979; Institute of Medicine, 1982). Alcohol consumption by drug users must be considered in selecting control groups since there is some evidence of neurological and neuropsychological impairment in alcoholics (for reviews, see Bolter and Hannon, 1980; Kleinknecht and Goldstein, 1972; Parsons, 1977; Parsons and Leber, 1981; Ron, 1977; Tarter, 1975; Wilkinson, 1982).

While the heavy use of alcohol by marijuana users can be addressed by including a control group of heavy alcohol (but not marijuana) users for comparison, there is no comparable way of controlling for the use of other drugs. At least in this culture, finding a group of polydrug users who do not use marijuana to serve as controls is extremely unlikely. An easier approach would be to study marijuana users who are not polydrug users.

Differential Vulnerability

Several authors have suggested the possibility of an interaction between drug effects and a preexisting vulnerability in some subjects. Goodman and Becker (1970) suggested that the hemorrhages in amphetamine users may have resulted from an interaction between the hypertensive and vasoconstrictive effects of the drug and a preexisting neurological vulnerability (such as an arteriovenous malformation or aneurysm which is assumed to have burst under the increased pressure). A recent study of polydrug users (Grant et al., 1978) also raised the possibility that individuals may be differentially vulnerable to drug-related cerebral impairment. Possible interactions between drug effects and some other factor(s) enormously complicate an already difficult research area, although such considerations are probably more realistic than assuming equal vulnerability to drug effects in all subjects. The hypothesis of differential vulnerability seems to be consistent with clinical experience which suggests that the effect of a lesion in a patient with a previous brain injury is often more severe than the same lesion in an unimpaired individual.

Secondary Effects

There are also a number of secondary factors associated with heavy polydrug use that may increase the likelihood of cerebral impairment. Heavy drug users may have a poor diet, and the resultant long-term nutritional deficiencies may produce impairment. The drug subculture is often violent, resulting in an increased likelihood of traumatic injuries. Falls due to impairment of coordination or loss of consciousness as a result of drug intoxication, overdose, or withdrawal may produce head injury. Head trauma may also result from errors in perception or judgment while in the intoxicated state. Local infections resulting from unsterile injections may spread to the central nervous system. Repeated anoxia resulting from overdose, withdrawal convulsions, or inhalation of solvents may increasingly destroy neurons.

It should be noted that all of the drug studies mentioned earlier as well as the marijuana studies described later in this paper have been retrospective. Thus it is unclear whether drug use predated cerebral impairment or whether the impairment predated drug use. For example, it is possible that the impairment in judgment sometimes seen in individuals with cerebral deficits may prevent them from being fully cognizant of the risks of heavy drug use, thus increasing the likelihood that cerebrally impaired individuals will abuse drugs. Although this possibility has not been studied with respect to marijuana or other illegal drugs, there is some evidence that alcoholics may be more likely than the general population to have been diagnosed as hyperactive or as having minimal brain dysfunction (MBD) in childhood (see Parsons and Leber, 1981, or Tarter, 1976, for reviews).

Even though polydrug use is not an insurmountable problem in marijuana research, there are other related issues which need to be considered. The purity and potency of any given street sample of marijuana may vary widely. Before gaining popularity as a drug in its own right, phencyclidine (PCP, angel dust) was used on occasion to strengthen poor-quality marijuana. Thus the central nervous system effects of PCP are also relevant. Another relevant drug is also one which the user might ingest unknowingly—the herbicide paraquat, which is sprayed on marijuana fields by U.S. Drug Enforcement agents in an attempt to kill the plants. While the central nervous system effects of paraquat are thought to be temporary, insufficient research has been conducted at the present time (Institute of Medicine, 1982).

Degree of Cannabis Use

Estimating the degree of past drug use is difficult since there are no standardized amounts of the drug in street samples. In addition, the self-report of drug users concerning the frequency of drug use is often suspect. In spite of these difficulties, getting some crude estimate of the level of use in the subjects under study is valuable and most studies report such information. However, few studies report how they gathered the information. The validity of such data can be enhanced if the questions used to gather the data are carefully standardized.

Well-worded questions could significantly reduce the effects of response-set biases such as social desirability and acquiescence.

Many studies use subjects who report a wide range of drug use from as little as once a week to as often as several times a day. Since light to moderate users, especially if the use is short term, would be unlikely to demonstrate impairment, their presence in a sample may serve to statistically mask impairment in the heavier users.

In many of the U.S. studies, the subjects were undergraduates or medical students who were often light cannabis users. The use of students as subjects does reduce the likelihood that secondary factors such as differences in motivation between the groups could lead to a false-positive finding of cerebral impairment. However, the likelihood of finding cerebral impairment in a group as select as medical or college students is small regardless of their level of cannabis use. Individuals with cerebral impairment are unlikely to perform as well as unimpaired individuals on standardized aptitude and achievement tests and other measures important for determining admission to college or medical school, and thus would have been selected out of the sample.

Preexisting Group Differences

Other variables provide some unique challenges in the study of the long-term effects of marijuana use. In general, many drug users tend to be transient, making it difficult to do repeated assessments. Many have a life-style that is not work oriented or competitive. Many resent authority figures. As a result, they may be poorly motivated and minimally cooperative during testing, which may produce spuriously low test scores. To the extent that they are isolated from society, they may fail to develop the knowledge and skill necessary for adequate performance on some of the tests. Many of these variables are difficult to control. In addition, lower educational levels, less prestigious occupations, and, in general, lower socioeconomic status are characteristic of adult heavy drug users. Since these variables are related to low scores on many performance measures, special care in selecting a matched control group should be taken.

Psychopathology may present a particularly difficult problem. Schizophrenics often score in the impaired range on neuropsychological measures (Golden, 1978). But often confirming evidence from other observations is lacking, suggesting that many of these low scorers are false positives. If the drug-using group shows more psychopathology than the control group, then drug use and psychopathology would be confounded. Any observed cerebral deficits in the drug users could be the result of either of these variables.

Preexisting group differences are particularly relevant in the cross-cultural studies. Poor nutrition and poor medical care in the cannabis users, and social class differences in the users and nonusers are common. Nonetheless, the cross-cultural studies are particularly relevant since the users in these studies typically consume considerably more and stronger forms of cannabis than is typical of American users, and polydrug use is less frequent in these individuals. Although there are a number of problems with many of the cross-cultural studies, the majority of the experimental problems would bias the study in favor of finding neurological deficits that are a function of factors other than cannabis consumption. Factors such as poor nutrition and medical care in the users, social class differences, and use of toxic or possibly toxic substances to enhance the effects of the cannabis (such as tobacco, opium, arsenic, strychnine, and dhatura—a poisonous alkaloid) would bias the study toward finding performance deficits in the cannabis users. One problem that might tend to bias the results of the cross-cultural studies in the opposite direction is the selection of the assessment instruments. In many cases the instruments were simply adaptations of tests used in the United States, with little or no normative data on the culture being studied. In some cases items were modified to make the test more relevant to the culture being studied (e.g., Bowman and Pihl, 1973), but those modifications were usually made solely on the basis of face validity. Another problem is the use of tests which are incapable of detecting real differences between groups. Tests which are too difficult (producing a floor effect) or too easy (producing a ceiling effect) may not detect real group differences in performance (Satz, Fletcher, and Sutker, 1976). Pretesting can reduce the likelihood of floor or ceiling effects.

Acute and Withdrawal Effects

Yet another factor is the acute or withdrawal effects of drugs on performance. Unless this factor is controlled, any observed deficit in performance in users might be an acute effect with no long-term consequences. A fairly long period of abstinence is required for some drugs. For example, Hill and Belleville (1953) found continued impairment in fine motor coordination 18 days after the abrupt withdrawal from heavy barbiturate use. Although the behavioral effects of marijuana appear to be short term, tetrahydrocannabinol (THC), the active ingredient in marijuana, remains in fatty tissue for up to 2 or 3 weeks (Mirin and Weiss, 1983). Approximately half of brain tissue is such fatty tissue (Grinker and Sahs, 1966). If the marijuana users use any other drugs, including alcohol, it is necessary to rule out the acute effects of all possible drugs. Behavioral observation is not sufficient since most heavy drug users can easily hide the effects of intoxication (Grant and Judd, 1976). Two ways of dealing with this issue are (1) to routinely use blood and urine screening of all subjects, or (2) to hospitalize drug users as a way of limiting drug use for the duration of the study. Both are expensive and neither is used very often. None of the marijuana studies reviewed in this paper utilized laboratory screening procedures for drugs other than marijuana, and only one study (Schaeffer, Andrysiak, and Ungerleider, 1981) used such a procedure to screen for the presence of marijuana.

Experimenter Bias

A major problem in most studies, and one which could be handled easily, is experimenter bias. The issue of the effects of illegal drugs is as much a social and political concern as a scientific concern, and the current social climate can have many effects on experimenters which can shape their expectations (Zinberg, 1972). Although experimenter bias is known to affect outcome in many experiments (Rosenthal, 1966), the possibility of its occurrence has been virtually ignored in the drug abuse literature. In only one study reviewed (Bowman and Pihl, 1973) were the preconceptions of the investigator stated directly and the possibility of bias considered. A few studies did test their subjects blindly as a way to control experimenter bias, but this was definitely the exception. In two recent reviews of the literature on the chronic cerebral effects of drug use (Grant and Mohns, 1975; Kornblith, 1981), experimenter bias was not even mentioned.

Summary on Methodology

Some of the problems that have been discussed are almost unavoidable given the nature of the problem, the population under study, and the ethical prohibitions which exist against direct experimentation. Some others are easily remedied (e.g., testing blindly to reduce experimenter bias) while others can be effectively dealt with if carefully selected control groups are used. Some control procedures may not be needed at all if preliminary research suggests no differences between users and nonusers since the uncontrolled variables would have likely led to the opposite results. There are times when rigorous adherence to methodological procedures must be sacrificed because of practical considerations and budget constraints. However, some of the methodological errors found in these studies do not seem to be the result of deliberate compromise, but rather seem to stem from oversight or perhaps ignorance. Several studies compared subjects on dozens of measures and, not surprisingly, found a few of them significant. Their interpretation of these results seemed to overlook the possibility that the differences were simply chance events. Satz et al. (1976) have argued that in many of these studies utilizing a variety of measures, a multivariate analysis of the data would have been much more appropriate. Another common error is the overinterpretation of a single or multiple case study (Altman and Evenson, 1973). The major methodological issues described in this paper are summarized in Table 1.

Table 1

Methodological Issues in the Study of Cannabis Users

Characteristics of the subjects:	Polydrug use Differential vulnerability Secondary effects Degree of cannabis use Preexisting group differences
Experimenter factors:	Experimenter bias
Experimental factors:	Acute and withdrawal effects

ASSESSING CEREBRAL DYSFUNCTION

There have been two basic approaches to the study of chronic cerebral effects in drug users: the neurological approach and the psychological-neuropsychological approach. Each has its strengths and weaknesses, and several of the methodological concerns described earlier affect one approach more than the other.

Neurological Approach

In the neurological approach, one or some combination of the following is employed: mental status examination; neurological examination; laboratory tests on blood, urine, or cerebrospinal fluid; electroencephalography (EEG); evoked potentials; echoencephalography (ultrasound); and neuroradiological techniques including skull X-ray, radionuclide brain scanning and flow studies, angiography, pneumoencephalography, and computerized axial tomography (CAT scanning). Most of these assessment techniques require considerable judgment and experience for accurate interpretation. In addition, such techniques have far from perfect reliability and validity (Filskov and Goldstein, 1974; Tsushima and Wedding, 1979), although this is rarely considered in interpreting research which has used these tests to provide evidence of brain impairment in drug users.

The mental status examination consists of clinical observation and questions relating to memory, cognitive processes, judgment, and so on. Many factors other than cerebral impairment, including psychopathology, may influence the results. The questions are not standardized, rating is subjective, and the specific behaviors leading to the conclusions are often not described. Socioeconomic status, race, and age may affect the responses, but these variables are often not taken into account when rating. Responses may also be affected if the individual is experiencing acute or withdrawal effects of drugs.

Table 2

Neurological Findings Organized by Test

Measures	Studies
Neurological examination	Grant et al., (1973) Mayor's Committee (1943/1966) Mendelson et al. (1974) Rodin et al. (1970)
EEG	Karacan et al. (1976) Rodin et al. (1970) Rubin & Comitas (1975) Stefanis et al. (1977)
Echoencephalography	Stefanis et al. (1977)
Pneumoencephalography	Campbell et al. (1971)
CAT scan	Co et al. (1977) Kuehnle et al. (1977)

The neurological examination consists of an assessment of the cranial nerves, reflexes, gait, and so on. Again, rating is subjective since there are no clearly defined empirical norms taking age and other important factors into account.

Laboratory tests may be helpful in the diagnosis of certain neurological conditions, especially those involving infectious processes, but are insensitive to the presence of other conditions, especially disorders in the early stages of development. The EEG, skull X-ray, brain scan and flow study, evoked potentials, pneumoencephalogram, and angiogram are each useful in the diagnosis of only certain neurological disorders. In all of these tests, abnormal findings occur in some proportion of persons lacking other evidence of neurological disorder (false positives). This is particularly true of the EEG (Cobb, 1963; Mayo Clinic, 1963; Vick, 1976) and the pneumoencephalogram (Bull, 1971). Finally, some of these assessment techniques have a significant morbidity and mortality rate, and are thus not appropriate for routine research.

In the late 1970s the CAT scan was developed and rapidly replaced many of the previously discussed tests as a result of its noninvasiveness, increased accuracy, and informativeness. Both the reliability and the validity of the CAT scan are quite high if an experienced interpreter reads the record (Tsushima and Wedding, 1979). Contrast enhancement, which aids in the differentiation of the various types of tissue and fluid, can further increase the validity of the CAT scan.

The neurological techniques that have been described, with the exception of those that assess behavior (i.e., neurological and mental status examinations), require no more than passive cooperation from the subject. Thus, an unmotivated subject will not present any particular problems in interpretation. Acute or withdrawal effects, psychopathology, or medication of any kind may affect the neurological or mental status examinations and the EEG but do not tend to affect the other tests. With the exception of the mental status examination, factors such as socioeconomic status and membership in a minority subculture should have a negligible effect. Table 2 lists each of the neurological techniques which have been used to investigate the cerebral effects of cannabis use and the investigators who have used them.

Neuropsychological Approach

The neuropsychological approach generally utilizes performance on standardized tests to determine the presence or absence of cerebral impairment. Over the years, there have been considerable changes in the particular tests used and in the signs on these tests thought to be indicative of cerebral impairment. Many of the earliest tests used for this purpose have been found to be invalid indicators of cerebral functioning (e.g., the Rorschach). Many other early tests were based on a unitary view of brain damage (e.g., the Bender Visual Motor Gestalt Test). Today, it is believed that there is no single deficit universally present in cerebral impairment and that proper assessment requires the examination of a wide range of cerebral functions (Golden, 1978). Tests from the unitary approach are now used as part of a comprehensive test battery. One such battery which has been widely used is the Halstead-Reitan Neuropsychological Battery, which has demonstrated reliability and validity comparable to the CAT scan when scored and interpreted by a trained neuropsychologist (Filskov and Goldstein, 1974; Schreiber, Goldman, Kleiman, Goldfader, and Snow, 1976; Swiercinsky and Leigh, 1979; Tsushima and Wedding, 1979). The Wechsler Adult Intelligence Scale (WAIS) and the Minnesota Multiphasic Personality Inventory (MMPI) are generally included in the battery as the WAIS can provide information on cognitive functioning and the MMPI can indicate the existence of factors such as psychopathology that may influence the test scores. For a more complete review of neuropsychological assessment, see Golden (1978) or Parsons and Prigatano (1978).

Neuropsychological testing relies on inferences from behavior to characterize the structural state of the brain. It is more vulnerable than neurological techniques to acute and withdrawal effects and to the effects of such variables as age, educational level, lack of motivation, and psychopathology. In particular, chronic schizophrenia frequently impairs performance on neuropsychological testing (Klonoff, Fibiger, and Hutton, 1970).

Neuropsychological testing can often detect the early stages of a neurological disorder, is sensitive to a wide range of etiologies, has no significant

Table 3

Psychological and Neuropsychological Findings Organized by Test

Type of measure and specific measures	Studies using the measure
Tests of intellectual functioning	
Ammons Full Range Vocabulary	Rubin and Comitas (1975)
Bhatia Battery of Intelligence	Agarwal et al. (1975)
General Aptitude Test Battery (portions)	Soueif (1976) Wig and Varma (1977)
Raven's Progressive Matrices	Grant et al. (1973) Schaeffer et al. (1981) Stefanis et al. (1977) Wig and Varma (1977)
WAIS (or portions)	Bowman and Pihl (1973) Carlin and Trupin (1977) Culver and King (1974) Mayor's Committee (1943/1966) Mendelson et al. (1974) Mendhiratta et al. (1978) Rubin and Comitas (1975) Satz et al. (1976) Schaeffer et al. (1981) Soueif (1976) Stefanis et al. (1977)
WISC (Indian adaptation)	Wig and Varma (1977)
Neuropsychological test batteries	
Halstead-Reitan (or portions)	Bowman and Pihl (1973) Carlin and Trupin (1977) Culver and King (1974) Grant et al. (1973) Mendelson et al. (1974) Rochford et al. (1977) Rubin and Comitas (1975) Satz et al. (1976) Schaeffer et al. (1981) Soueif (1976)
Tests of abstract reasoning and concept formation	
Embedded Figures	Bowman and Pihl (1973)
Wisconsin Card Sorting	Bowman and Pihl (1973)
Tests of attention and concentration	
Color Cancellation	Ray et al. (1978) Wig and Varma (1977)
Digits Backward	Ray et al. (1978)
Goal-Directed Serial Alternation	Grant et al. (1973)
Serial Arithmetic	Ray et al. (1978)
Symbol-Digit Modalities	Schaeffer et al. (1981)

(continued)

Table 3 (continued)

Type of measure and specific measures	Studies using the measure
Tests of memory	
Benton Visual Retention	Satz et al. (1976)
	Schaeffer et al. (1981)
Facial Recognition Memory	Satz et al. (1976)
Knox Cube	Bowman and Pihl (1973)
Paired Associates	Bowman and Pihl (1973)
Recognition	Mendhiratta et al. (1978)
Rey Auditory-Verbal Learning	Schaeffer et al. (1981)
Rey-Osterreith Complex Figure	Bowman and Pihl (1973)
Wechsler Memory Scale	Agarwal et al. (1975)
	Ray et al. (1978)
	Satz et al. (1976)
	Wig and Varma (1977)
Williams Memory Scale	Satz et al. (1976)
Tests of perceptuomotor and motor functions	
Benton Visual-Motor Gestalt	Agarwal et al. (1975)
	Mendhiratta et al. (1978)
	Rochford et al. (1977)
	Rodin et al. (1970)
	Soueif (1976)
	Wig and Varma (1977)
Card Rotation	Culver and King (1974)
Cube Comparisons	Culver and King (1974)
Graduated Holes	Rubin and Comitas (1975)
Hidden Patterns	Culver and King (1974)
Maze Steadiness	Rubin and Comitas (1975)
Minnesota Percepto-Diagnostic	Ray et al. (1978)
	Rochford et al. (1977)
Paper Folding	Culver and King (1974)
Pegboard	Rubin and Comitas (1975)
Pencil Tapping	Mendhiratta et al. (1978)
Pins	Bowman and Pihl (1973)
Reaction Time	Bowman and Pihl (1973)
	Mendhiratta et al. (1978)
	Soueif (1976)
Spatial Orientation	Culver and King (1974)
Speed and Accuracy	Mendhiratta et al. (1978)
Surface Development	Culver and King (1974)
Sensory-perceptual tests	
Distance Estimation	Soueif (1976)
Hooper Visual Organization	Schaeffer et al. (1981)
Laterality Discrimination	Culver and King (1974)
Time Estimation	Bowman and Pihl (1973)
	Mendhiratta et al. (1978)
	Rubin and Comitas (1975)

(continued)

Table 3 (continued)

Type of measure and specific measures	Studies using the measure
Sensory-perceptual tests:	
Time Estimation (continued)	Soueif (1976)
	Wig and Varma (1977)
Personality tests	
Lowenfeld Mosaic	Rubin and Comitas (1975)

medical risks, and provides direct information about behavioral deficits and assets. However, it may have a higher false-positive rate than most neurological techniques. In many ways, neurological and neuropsychological approaches are complementary, with different strengths and limitations. Unfortunately, there are few studies of marijuana (none of them recent) which utilize both techniques. Table 3 lists the various neuropsychological measures that have been used to evaluate the cerebral effects of cannabis and the investigators that have used them.

CHRONIC CEREBRAL EFFECTS OF MARIJUANA USE

Early Research

Until quite recently, little effort had been expended on understanding the effects of marijuana use. Over 80% of the published research on the chronic cerebral effects of marijuana has been conducted since 1970. However, to understand the context in which the current research is being conducted, one needs familiarity with early attempts to study the phenomenon.

The earliest known study of the effects of cannabis is that of the Indian Hemp Drugs Commission of 1893-1894, which had been commissioned by the British government to examine the physical, mental, and moral effects of cannabis use. The commission's report consisted of seven volumes and over 3,000 pages, but its findings have been virtually ignored by most researchers because so few copies of the report exist. In order to provide more access to this material, an article summarizing the findings (Mikuriya, 1968) and a book containing the commission's report while omitting many of the appendixes (Kaplan, 1969) have been published.

The Hemp Drugs Commission was a thorough attempt to study the effects of cannabis, especially considering the lack of auxiliary medical tests available at the time. The commission had no direct contact with the users and conducted very little experimentation. However, its members interviewed 1,193 individuals, including 335 physicians, and reviewed the records of all judicial proceedings for the previous 20 years in which cannabis had been thought to be a factor in violent crimes. They also reviewed the records of every mental hospital in India and thoroughly studied the files on each of the 222 individuals admitted in 1892 with a possible connection between cannabis use and mental illness.

The commission concluded that the moderate use of cannabis produced no injurious physical, mental, or moral effects, while excessive use was likely to be harmful. This conclusion represented the commission's best guess given the general inadequacy of their data. The commission did not clearly define moderate and excessive use, although it seems likely that even their moderate use would be considered heavy consumption by today's standards. Regardless of amount of cannabis use, however, they found no evidence of residual central nervous system effects, although they readily admitted that their evidence was often inadequate (Kaplan, 1969).

The commission may have been thorough in its work, but it is not clear that it was completely unbiased. For nearly 100 years, opium from India had been a major item in the trade between Britain and China (Hyde, 1973; McCoy, Read, & Adams, 1972). In 1895, 1 year after the report of the Hemp Drugs Commission, the report of a commission on opium was published. Its conclusions about opium were the same as those reported for hemp: that the moderate use of opium was not harmful and that its growth need not be prohibited. The Opium Commission's conclusions may well have been influenced by Britain's vested interest in maintaining the opium trade (Owen, 1934). The Hemp Commission findings may have set the stage for the opium report released the next year.

The next reported study, also conducted in India, was carried out 45 years later (Chopra and Chopra, 1939). Chopra and Chopra examined 1,238 cannabis smokers using interviews, physical examinations, and in some cases, extended behavioral observations. They concluded that moderate use was not harmful to the central nervous system while excessive use did lead to impairment. In a reanalysis of their data 18 years later (Chopra and Chopra, 1957), they questioned whether even moderate use of marijuana might be harmful. However, several problems plagued this study. These included the likelihood of poor nutrition and infectious disease in the sample (it was noted that 2.5% had a "history" of syphilis), and a probable overrepresentation of social deviates since it was unlikely that productive members of a higher social class would be referred to the investigators by medical and local governmental personnel. In discussing long-term central nervous system changes, they primarily reported symptoms that could as readily have reflected psychopathology, such as lability of affect, impairment of judgment and memory, habitual lying, and insomnia. The authors did report that many subjects demonstrated preexisting "neurotic tendencies" but felt that cannabis had been responsible for enhancing these tendencies. However, they presented no evidence to show that these individuals demonstrated less psychopathology before the onset of cannabis use.

The first study of the effects of marijuana on cerebral functioning conducted in the United States was carried out by the Mayor's Committee on Marijuana, more commonly referred to as the La Guardia Commission, which studied both the medical and psychological consequences of marijuana use (Mayor's Committee on Marijuana, 1943/1966). They studied 72 prison inmates, including 48 users, most of whom were under 30 years of age. User and nonuser subjects were given the Bellevue Adult Intelligence Test before and after the administration of various amounts of marijuana. Although there was a difference in mean score (97 for the user group and 104 for the nonuser group), the investigators felt that this difference could be accounted for by racial and cultural factors since the cannabis group contained a much larger proportion of Black and Puerto Rican subjects who often do more poorly on standardized tests. In addition, the general lack of subtest scatter in the user groups was considered evidence against cannabis-produced cognitive deterioration. More recent research suggests that neither intersubtest scatter nor deterioration in intelligence scores is characteristic of all types of cerebral impairment. Thus their conclusion that marijuana use does not seem to result in impairment appears premature.

In some ways, the La Guardia Commission was a forerunner of the modern marijuana studies. A smaller sample size was used with systematically gathered dependent variables measured for each subject. The conclusions were more clearly data based than in most of the other early studies. In general, the methodology was more in keeping with the empiricism and experimental control characteristic of modern Western science.

Benabud (1957) represents the last of the early marijuana studies. He studied 824 individuals who had been hospitalized for cannabis "addiction," although it was possible that there were additional reasons for their hospitalization. He expressed the opinion that cannabis itself produced a toxic effect which acted as a precipitant for psychosis or dementia, although again, it is not clear that this opinion is based on data.

These early research studies are summarized in Table 4.

Modern Neurological Approaches

Cerebral Atrophy

In the early '70s, a renewed interest in both the short-term and long-term effects of marijuana occurred, partly as a result of the increased use of the drug among high school and college-age subjects. One of the first reported studies, and also one of the most widely quoted, was conducted by Campbell, Evans, Thomson, and Williams (1971). They were the first to link cannabis smoking and

Table 4

A Summary of Early Research on the Effects of Cannabis Use

Author (year) [country]	Sample size and type: user/controls	Findings and comments
Indian Hemp Drugs Commission (1893-1894) [India] Mikuriya (1968); Kaplan (1969)	Medical and government data: ?/0	Moderate cannabis use produces no harmful physical, mental, or moral effects, while excessive use may be deleterious. Based on interview data ($N = 1,193$) and a review of judiciary and hospital records.
Chopra and Chopra (1939) [India]	"Known addicts": 1,238/0	Moderate use is not harmful to the CNS, while excessive use is harmful. Based on interviews and physical examinations.
Chopra and Chopra (1957) [India]	Mental patients: 600/0	Moderate use may be harmful to the CNS. Based on a study of mental hospital records.
Mayor's Committee (1943/1966) [USA]	Prison inmates: 40/20	A 7-point IQ difference between users and controls was found, but the difference was attributed to racial and cultural differences between the groups.
Benabud (1957) [Morocco]	Mental patients: 824/0	Cannabis may precipitate psychosis or even dementia. Based on interviews and mental hospital records.

cerebral atrophy. They administered pneumoencephalograms (a radiological procedure in which air is used to display the size and position of the cerebral ventricles) to 10 males between the ages of 18 and 28 who used marijuana consistently (not defined). Their results were compared with the pneumoencephalograms of persons of similar age who had been diagnosed as neurologically normal. They noted that all 10 of the marijuana users demonstated cerebral atrophy as determined by enlargement of the lateral ventricles.

However, a number of methodological flaws limit the conclusions that might be drawn from this study. First, the researchers may have been biased since they consistently referred to the users as "addicts," a term with a negative connotation which is generally not used in recent publications to describe marijuana users. The investigators did not report whether the pneumoencephalograms were interpreted blindly, making the bias issue that much more critical. Neither the user nor the control groups were randomly selected. The first four users were known to have abnormal pneumoencephalographic results (the study had been originally undertaken because of these findings), and the others were under psychiatric treatment for drug abuse. The controls were chosen from existing files on the basis of vague neurological complaints with a normal pneumoencephalogram. Thus, they were not actually control subjects, but rather provided a standard by which to compare the results from the users.

Alternative explanations for the cerebral atrophy were ignored by Campbell et al. (1971). For example, all 10 of the marijuana users were in fact polydrug users. All had taken LSD at least once, a few had used barbiturates and intravenous morphine, and seven had admitted the use of amphetamines. In some subjects, other drugs were used at least moderately often, but the investigators dismissed this polydrug use because the subjects used these drugs less often than they used marijuana and because the drugs were more rapidly metabolized than marijuana. In addition, all showed some evidence of psychopathology (Evans, 1974) and 3 of the 10 marijuana-using subjects had histories of head injury. In at least one subject, epileptic seizures began to occur following the injury. However, the investigators also discounted the head injuries as being too minor to result in cerebral atrophy.

A storm of articles followed the publication of the Campbell et al. (1971) study, most of which were critical of the methodology and/or conclusions (Brewer, 1972; Bull, 1971; Cannabis encephalopathy? 1971; Grinspoon 1972; Susser, 1972). However, Campbell et al. (1971) were not without their supporters who felt that "their evidence is amply sufficient to justify the continuation and strengthening of every possible measure to suppress cannabis" (Nattrass, 1971, p. 1314) and that cerebral impairment in cannabis users could also be observed through mental status examinations (Schwarz, 1972). In a second paper, Campbell, Thomson, Evans, and Williams (1972) attempted to justify their procedures and refute earlier criticisms, but their article failed to address the major criticisms of their earlier study.

Because of the risks associated with pneumoencephalography, the Campbell et al. (1971) study was never replicated. However, the development of the CAT scan in the late 1970s, which is painless and noninvasive, enabled investigators to safely test the findings of Campbell et al. Furthermore, the CAT scan is considerably more sensitive and valid than the pneumoencephalogram.

In two separate studies (Co, Goodwin, Gado, Mikhael, and Hill, 1977; Kuehnle, Mendelson, Davis, and New, 1977), the CAT scans of 31 marijuana-using subjects studied were all judged to be normal. These findings are particularly striking since in both studies, the marijuana users were predominantly polydrug users. While a normal CAT scan does not completely rule out the possibility of cerebral impairment, it is less likely than other neurological techniques (such as the pneumoencephalogram) to produce false negatives.

Thus, in spite of the Campbell et al. (1971) report, there seems to be no reason to believe that cannabis use results in cerebral atrophy. Although Campbell et al. is still widely quoted in some circles, its findings have not withstood replication efforts. Since significant cerebral atrophy invariably results in pronounced emotional, behavioral, perceptual, or cognitive deficits, it hardly seems possible that Campbell et al. could have been correct. If they had been correct, our mental and neurological hospitals would be filled with cannabis smokers, given the relatively wide use of the drug today (Zinberg, 1972).

Other Neurological Findings

A variety of other neurological approaches have been employed to study the effects of cannabis smoking. Several investigators found the EEG records to be normal in cannabis users (Karacan, Fernández-Salas, Coggins, Carter, Williams, Thornby, Salis, Okawa, and Villaume, 1976; Rodin, Domino, and Porzak, 1970; Rubin and Comitas, 1975; Stefanis, Dornbush, and Fink, 1977). All but one of those studies (Rodin et al., 1970) were cross-cultural, with users who were long-term, very heavy smokers. The typical cross-cultural study evaluated the cerebral functioning of users who smoked cannabis daily for several years. Stefanis et al. (1977) found no differences between users and nonusers on echoencephalograms, a technique described by the investigators as "a method of estimating ventricular size by a reflection of ultrasound signals" (Stefanis et al., 1977, p. 61). Mendelson, Rossi, and Meyer (1974) reported the only positive finding based on a neurological examination—a lateral gaze nystagmus which was present before, during, and after consumption of marijuana. However, these investigators did not have a nonuser comparison group. Rodin et al. (1970) found no abnormalities on either the mental status or neurological examinations for any of the 10 marijuana smokers in their study. However, their findings are hardly surprising since their subjects were first-year medical students

Table 5

A Summary of Neurological Studies on the Effects of Cannabis Use

Author (year) [country]	Sample size and type: users/controls	Findings and comments
Campbell et al. (1971) [Great Britain]	Neurology and drug abuse outpatients: 10/?	Users were administered pneumoencephalograms and all demonstrated cerebral atrophy indicated by enlarged ventricles. The control group was biased.
Co et al. (1977) [USA]	Paid volunteer users: 12/34	All subjects were found to have normal CAT scans. The control group was biased.
Kuehnle et al. (1977) [USA]	Volunteer users: 19/?	All subjects were found to have normal CAT scans.
Rodin et al. (1970) [USA]	Medical students: 10/0	All subjects demonstrated normal scores on EEG and on neurological and mental status examinations.
Karacan et al. (1976) [Costa Rica]	Heavy users: 32/32	No significant differences were found on sleep EEGs.
Rubin and Comitas (1975) [Jamaica]	Heavy users: 30/30	No significant differences were found on EEGs.
Stefanis et al. (1977) [Greece]	Heavy users: 47/40	No significant differences were found on EEGs or on echoencephalograms.
Mendelson et al. (1974) [USA]	Volunteer users: 20/0	Neurological examination of all users showed lateral gaze nystagmus before, during, and after ingestion of cannabis.
Grant et al. (1973) [USA]	Med students: 29/29	No differences found on neurological examination.

who had recently competed successfully for entrance into medical school. Kolansky and Moore (1971, 1972a, 1972b) did suggest that case study data from their psychoanalytic practice linked cannabis use with psychopathology and with cerebral impairment. However, unlike most of the other studies reviewed in this section, they had no control group and they did not use standard neurological measures in their diagnoses. Therefore, it is difficult to evaluate their contention.

Summary on Research Findings

The research reviewed in this section is summarized in Table 5. The available evidence suggests strongly that there are no gross structural or neurological deficits in marijuana-using subjects, although subtle neurological features (such as lateral gaze nystagmus) may be present. However, the type of deficit most likely to occur would be a subtle, functional deficit which could be assessed more easily with either psychological or neuropsychological assessment techniques. In Part II of this paper (Wert and Raulin, 1986), the research on the long-term effects of cannabis on psychological and neuropsychological functioning is reviewed.

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The Chronic Cerebral Effects of Cannabis Use. II. Psychological Findings and Conclusions

Renee C. Wert, PhD

Michael L. Raulin,* PhD

State University of New York at Buffalo
Buffalo, New York

Abstract

This paper examines the research evidence on the question of whether sustained use of marijuana may produce chronic cerebral impairment as measured by neuropsychological measures. Evidence from both American and cross-cultrual studies suggests that marijuana probably does not produce chronic cerebral impairment, although subtle impairment cannot be ruled out. Several suggestions for new lines of research are discussed including prospective studies, effects of cannabis use on later aging processes, and true experimental studies.

Mind-altering substances have been used and abused throughout history, and their abuse continues to be a major social problem. Research to uncover the risks involved in using drugs is needed if we are to establish reasoned policy on how to regulate these substances. In the first paper of this series (Wert and Raulin, 1986), we discussed some of the problems in studying the chronic cerebral effects of a drug such as cannabis and reviewed the neurological studies conducted to date. In this paper we review the psychological and neuropsycho-

*To whom requests for reprints should be sent at the Psychology Department, State University of New York at Buffalo, Julian Park Hall, Buffalo, New York 14260.

logical findings on the long-term effects of cannabis and suggest some directions for future study.

MODERN PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL APPROACHES

A number of psychological and neuropsychological studies of the long-term effects of marijuana, including several cross-cultural studies, have been reported. Fifteen studies of the chronic cerebral effects of cannabis have used psychological and neuropsychological assessment measures with varying results. Of the nine cross-cultural studies (Agarwal, Sethi, and Gupta, 1975; Bowman and Pihl, 1973; Mendhiratta, Wig, and Verma, 1978; Ray, Prabhu, Mohan, Nath, and Nekl, 1978; Rubin and Comitas, 1975; Satz, Fletcher, and Sutker, 1976; Soueif, 1976; Stefanis, Dornbush, and Fink, 1977; Wig and Varma, 1977), five found some evidence for impairment in the cannabis-using group. However, a closer inspection of the studies suggests that the evidence may not be as strong as these numbers might suggest.

Agarwal et al. (1975) claimed to have found evidence of impairment on three psychological tests (Weschler Memory Scale, Bender Visual Motor Gestalt, and Bhatia Battery of Intelligence) in 40 Indian cannabis users. No control group was used. However, on at least two of these tests, the proportions of scores in the "impaired" range as reported by the investigator are almost exactly what would be expected in a random sample from the general population. On the Bender, nearly half of the subjects received low scores, but without a comparison group it is impossible to determine whether this finding was abnormal for their population.

Stefanis et al. (1977) found four statistically significant differences on WAIS subtests between 47 Greek cannabis users and 41 controls. However, only one of these differences was on a subtest thought to be sensitive to cerebral functioning (Digit Symbol) while the others were on verbal subtests less sensitive to cerebral deficit.

Wig and Varma (1977) studied 27 Indian cannabis users and 11 controls on a number of tests including the EEG, Raven Colored Progressive Matrices, Bender Visual Motor Gestalt, and Indian adaptations of the WISC and the Weschler Memory Scale. Users performed significantly more poorly on 4 of the 8 psychological tests. Interestingly, Satz et al. (1976) found no differences between their 41 cannabis users and 41 controls on a very similar battery, and Rubin and Comitas (1975) found only three differences on a very large battery of similar tests.

Soueif (1976) studied nearly 1,700 incarcerated Egyptian cannabis users and controls, using a wide range of psychological tests (Tool Matching, Marking, Trail Making, Reaction Time, Digit Span, Distance and Time Estimation, and Bender Visual Motor Gestalt). He found that cannabis users performed significantly more poorly on 10 of the 16 measures. However, the differences were very small and significant primarily because of the extreme statistical power associated with such large sample sizes. They did not seem to reflect clinically significant differences. In addition, place of residence (rural vs urban) and degree of literacy were found to affect test scores at least as much as cannabis use. Finally, the test battery was heavily skewed toward tests of attention, concentration, and psychomotor speed; scores on these tests are heavily influenced by variables such as anxiety, psychopathology, lack of motivation, and acute drug effects (although subjects presumably had little access to drugs since they were incarcerated).

Mendhiratta et al. (1978) also administered a battery consisting primarily of tests of attention, concentration, and motor speed to 50 Indian cannabis users (25 of whom used less potent cannabis) and 25 controls. Groups were matched on age, sex, occupation, education, and level of psychopathology. They reported that one or both of the user groups scored more poorly than controls on 7 of the 9 measures. The authors concluded that chronic cannabis use may lead to deficits in concentration and attention. However, either acute effects (which were not considered) or motivational differences could have accounted for the obtained results.

It is interesting that Ray et al. (1978), using a test battery similarly skewed toward tests of attention, concentration, and motor speed, found only one significant difference between the groups of 30 Indian cannabis users and 50 controls. Ray et al. included a much smaller proportion of illiterate subjects in their sample than Mendhiratta et al.

Bowman and Pihl (1973) found no differences between 30 Jamaican cannabis users and 24 controls on a battery of tests despite the presence of a greater proportion of illiterate subjects in the user groups. The Bowman and Pihl study is distinguished by the use of several techniques to improve the validity of the findings, including a replication of the findings, an attempt to test subjects blindly, and the use of a monetary payment to increase subject motivation.

None of the studies conducted in the United States (Carlin and Trupin, 1977; Culver and King, 1974; Grant, Rochford, Fleming, and Stunkard, 1973; Mendelson, Rossi, and Meyer, 1974; Rochford, Grant, and La Vigne, 1977; Schaeffer et al., 1981) demonstrated statistically significant differences between cannabis users and controls. Rodin, Domino, and Porzak (1970) reported that cannabis users demonstrated "significantly" poorer Bender Gestalt performance (although still within the normal range) than non-drug users. We did not include this study because no results of statistical tests or even means were given, nor was there a mention that any statistical procedures had been performed. We can only conclude that they used the term "significantly" as a figure of speech rather than in the usual sense of *statistical significance*. Culver and King (1974)

Table 1

A Summary of the Psychological and Neuropsychological Studies of the Effects of Cannabis Use

Author (year) [country]	Sample size and type: users/controls	Findings and comments
Agarwal et al. (1975) [India]	Clients of cannabis shop: 40/0	Half of the subjects had abnormally high Bender Gestalt scores; 20% scored in the impaired range on the Wechsler Memory Scale; 25% had IQs < 90.
Bowman and Pihl (1973) Study 1 [Jamaica]	Volunteers with 10+ yr of cannabis use: 16/10	No significant differences between users and nonusers were found on the Embedded Figures, Paired Associates, Wisconsin Card Sorting, Finger Tapping, Digit Span, and Block Design.
Bowman and Pihl (1973) Study 2 [Jamaica]	Same as above: 14/14	The same tests as above were used, plus Time Estimation and Rhythm Tests. Again, no significant differences were found.
Mendhiratta et al. (1978) [India]	Volunteers with 4+ yr of cannabis use: 50/25	Tests used were Digit Span, Design Recognition, Tapping, Design Cancellation, Time and Size Estimation, Word Association, and Bender Gestalt. Users did more poorly on all tests except Digits Forward and Design Cancellation.
Ray et al. (1978) [India]	Rural males; 25% of each group were illiterate: 30/50	Tests used were Backward Digit Span, Serial Addition and Subtraction, Color Cancellation, Minnesota Perceptodiagnostic Test, and the Wechsler Memory Scale. Users scored significantly higher on 1 of the 10 subtests of the Wechsler Memory Scale.
Rubin and Comitas (1975) [Jamaica]	Paid volunteers with 10+ yr of cannabis use: 30/30	Only three significant differences found on a large number of tests including Ammons Vocabulary, Lowenfeld Mosaic, Maze Steadiness, Graduated Holes, Pegboard, and portions of the WAIS and the Halstead-Reitan Battery.
Satz et al. (1976) [Costa Rica]	Volunteers with 10+ yr of cannabis use: 41/41	No significant differences between users and nonusers were found on the WAIS, Benton Visual Retention, Williams Memory, Facial Recognition, Finger Localization, Finger Tapping, and Tactual Performance tests.
Soueif (1976) [Egypt]	Prison inmates: 850/839	Tests used were Tool Matching, Marking, Trail Making, Reaction Time, Digit Span, Distance and Time Estimation, and Bender Gestalt. Significant differences were found on 10 of the 16 measures with cannabis users scoring more poorly.
Stefanis et al. (1977) [Greece]	Volunteers with 10+ yr of cannabis use: 47/40	Gave WAIS and the Raven Progressive Matrices. Differences were found on Verbal IQ, Comprehension, Similarities, and Digit Symbol subtests.
Wig and Varma (1977) [India]	Volunteers with 5+ yr of cannabis use: 23/11	Cannabis users performed more poorly on WISC, Wechsler Memory, GATB Speed, Time Perception, and Bender Gestalt. No differences were found on Raven Colored Progressive Matrices or Color Cancellation.
Carlin and Trupin (1977) [USA]	Volunteers with 2+ yr of cannabis use: 10/10	Tests used were WAIS and Halstead-Reitan Battery. Controls were taken from Reitan's normative population. The control group did worse on Part B of the Trail Making Test.
Culver and King (1974) Study 1 [USA]	College seniors: 14/14	No significant differences between users and nonusers were found on Laterality Discrimination, the WAIS, Cube Comparison, Hidden Patterns, Paper Folding, and the Halstead-Reitan Battery.
Culver and King (1974) Study 2 [USA]	College seniors: 14/14	Tests were the same as above, plus Card Rotation, Spatial Orientation, and Surface Development. No significant differences were found between users and nonusers. Users were only casual users.
Grant et al. (1973) [USA]	Med students: 29/29	Tests used were Raven Advanced Progressive Matrices, Serial Alteration, and portions of the Halstead-Reitan Battery. Users did more poorly on the Location score of the Tactual Performance Test. Subjects were light cannabis users.

(continued)

Table 1 (continued)

Author (year) [country]	Sample size and type: users/controls	Findings and comments
Mendelson et al. (1974) [USA]	Volunteers with 2+ yr of cannabis use: 20/0	Tests included the WAIS and portions of the Halstead-Reitan Battery. No significant differences between casual and heavy users. Upon clinical examination, 2 heavy and 2 casual users showed impairment.
Rochford et al. (1977) [USA]	Med students: 26/25	No significant differences were found on Tactual Performance, Minnesota Perceptodiagnostic Test, and Bender Gestalt. Subjects were light cannabis users.
Schaeffer et al. (1981) [USA & unspecified Caribbean island]	Religious users of cannabis: 10/0	No evidence of impairment using the tests' published norms were found on the Benton Visual Retention, Trail Making Test, portions of the WAIS, Rey Auditory-Verbal Learning, Raven Progressive Matrices, Symbol-Digit Modalities, and Hooper Visual Organization.

conducted two studies with a total of 28 cannabis users and 28 controls, plus a group of LSD users, all of whom were college students. While there were some significant differences between LSD users and other groups, there were no differences between the cannabis users and controls on any of the measures. However, due to the inappropriate use of analysis of covariance (Lord, 1967) to minimize the effects of group differences in alcohol consumption, the results of their second study should be interpreted cautiously.

Carlin and Trupin (1977) compared 10 cannabis users to 10 members of Reitan's normative sample (Reitan, 1966) who had been tested a number of years earlier on the WAIS and portions of the Halstead-Reitan Battery. Clearly, this is not an adequate control group. Still, there were no statistically significant differences between the groups. Rochford et al. (1977) found no performance differences between 26 cannabis users and 25 controls, all of whom were medical students. Similarly, Grant et al. (1973) found only one difference among a large number of tests using medical students as subjects. Mendelson et al. (1974) found no differences between casual and heavy users of cannabis on a variety of neuropsychological measures.

Schaeffer et al. (1981) found and tested what might be considered an ideal experimental group: 10 members of a religious organization in which regular cannabis use was a part of their religious beliefs. Their subjects reported smoking cannabis virtually every waking moment, which was borne out by the observation of cannabis use during the test administration. In many studies, cannabis users were polydrug users and social deviants, often rebellious, resentful of authority, and unmotivated to perform on the basis of the usual social incentives. However, the cannabis-using subjects of Schaeffer et al. denied the use of alcohol and other drugs, and were described as productive members of society, thus minimizing the confounding effects of these variables. Unfortunately, Schaeffer et al. neglected to include a control group.

The following tests were administered: Benton Visual Retention, Trail Making, portions of the WAIS, Rey Auditory-Verbal Learning, Raven Progressive Matrices, Symbol-Digit Modalities, and Hooper Visual Organization. Despite the likelihood of acute drug effects, subjects' performances were not impaired when compared with the tests' published norms. In fact, mean WAIS scores indicated performance in the superior to very superior range.

Schaeffer et al. (1981) were the only investigators who attempted to estimate precannabis performance of their subjects for comparison with the present performance. They obtained early school achievement test scores for two of their subjects and compared the IQ conversion scores of these early tests with the subjects' present WAIS scores. No significant differences were found. While this use of achievement test scores provides only a rough estimate of the subjects' precannabis level of performance, it is a practical way of collecting information which otherwise would require a prospective study. In addition, Schaeffer et al. were the only investigators to use a laboratory test to detect recent marijuana ingestion. The use of this test in studies with positive results (i.e., impairment in cannabis users) would have been helpful in ruling out acute effects as the cause of the impairment.

Studies of the psychological and neuropsychological performance of cannabis users are summarized in Table 1.

Summary. Despite the large number of factors biasing most of these studies toward finding impairment in cannabis users (acute effects, polydrug use, poor nutrition, poor medical care, differences in literacy, etc.), only 1 (Wig and Varma, 1977) of the 15 studies found differences which could not be easily explained by these uncontrolled factors. One would expect a larger number of these studies, especially the cross-cultural studies using very heavy, long-term cannabis users, to have shown positive results if cannabis use indeed did produce cerebral impairment.

DISCUSSION

We have seen that the majority of studies have found no clinically or statistically significant differences between groups of cannabis users and controls on commonly accepted neurological and psychological measures of cerebral functioning. This finding is all the more impressive given the number of other variables (such as polydrug use, low motivation, and acute effects) which bias the results toward finding impairment in cannabis-using subjects.

This general finding of no clinically significant differences between cannabis users and controls may be interpreted in several ways. One possibility is that cannabis does not lead to chronic cerebral impairment. A second possibility is that cerebral deficits do develop but that the individual adapts and overcomes them through a process of relearning. It is well known that a chronic or slowly developing lesion will often be masked by the adaptation of the patient to the deficits produced by the lesion (Golden, 1978). A third possibility is that while the vast majority of cannabis-using subjects are not impaired, there may be a very small number of users who are vulnerable to cannabis-produced impairment. Such a possibility could explain the positive findings of a few studies: perhaps such studies used a larger proportion of vulnerable subjects. The possibility of differential impairment is an interesting one and is discussed later in this section. Fourth, it is possible that cerebral impairment does exist in the cannabis-using subjects, but that the tests are not sensitive enough to detect it. However, given that these same tests have demonstrated impairment in alcoholics (for reviews, see Bolter and Hannon, 1980; Kleinknecht and Goldstein, 1972; Parsons, 1977; Parsons and Leber, 1981; Ron, 1977; Tarter, 1975; Wilkinson, 1982) and heavy social drinkers (MacVane, Butters, Montgomery, and Farber, 1982; Parker, Birnbaum, Boyd, and Noble, 1980; Parker and Noble, 1977, 1980), this does not seem likely.

Directions for Future Research

Virtually all of the studies reviewed in this paper fit into a single research mold. They are all retrospective studies of preestablished groups (cannabis users and non-cannabis users). Although some of the studies made a commendable attempt to obtain suitable control subjects, this is still a very weak and vulnerable research design. In the remainder of the paper, we propose some alternative research designs and discuss their potential usefulness.

Prospective Studies

The greatest weakness of a retrospective study of preexisting groups is that one is never sure if observed differences between the groups are the result of the defining characteristic (in this case, cannabis use) or whether the differences existed prior to any cannabis use. While the experimenter may try to match users and controls on relevant variables, many times the relevant variables are not known or cannot be controlled for or matched. The prospective study, which uses the subject as his or her own control, is a sound method of dealing with many of the issues that cloud retrospective studies. For example, the possibility that cannabis users would have demonstrated poorer performance even before their use of cannabis is eliminated with this design. The notion that impairment might predate drug use has been expressed by some authors with respect to alcoholism (see Parsons and Leber, 1981, and Tarter, 1975, for reviews), although there has been little research to support or refute this hypothesis as yet.

Prospective studies have been recommended by a number of authors (Culver and King, 1974; Rochford et al., 1977; Wig and Varma, 1977; Institute of Medicine, 1982), although these authors have generally failed to address the complexities of such studies. Prospective studies are extremely expensive since a large number of people must be tested (to assure a large enough group of later cannabis users) and followed for a long period of time. The likelihood of maintaining a continuous funding source over such a long period of time is slim. Furthermore, a prospective study does not automatically deal with many of the experimental problems described earlier in this paper. The investigator would still need to control for variables such as polydrug and alcohol abuse, motivational differences, and acute and withdrawal effects. A prospective study, although it does assess precannabis performance, cannot in itself avoid the methodological issues inherent in research in this area.

There is one area where prospective studies could contribute a great deal to our understanding of possible chronic cerebral effects of cannabis. Prospective studies would be one of the few ways to adequately test the hypothesis of differential vulnerability in cannabis users. Such a hypothesis has been raised by a few authors (Carlin and Trupin, 1977; Jones, 1980). It might well be that some individuals are predisposed to cerebral impairment as the result of cannabis use, either because of structural or biochemical characteristics which accentuate the possible damaging effects of the drug, or because they have little of the "cerebral reserve" that most of us call on when we experience mild cerebral damage. That functional reserve can mask very real cerebral damage (Weiss, 1975). By having pre- and postcannabis performance scores for subjects, we can identify those subjects (if they exist) who show real impairment in functioning. By comparing those subjects who show impairment with those subjects who do not show impairment, we may be able to identify possible risk factors.

In our opinion, the results of the studies we have reviewed do not provide sufficient evidence of impairment to warrant the investment of time and money required for prospective studies. For those interested in ruling out previous impairment, we recommend the use of information that has already been gathered for other purposes such as school achievement or intelligence test scores or preinduction achievement testing for the Armed Forces. We agree with Schaeffer et al. (1981) that such information provides only a rough estimate of precannabis performance, but it would not appear to be cost-effective to gather more precise information through a prospective study. Indeed, a more worthwhile study might be to compare performance on such achievement tests with performance on neurological and psychological tests of cerebral functioning to determine just how "rough" such an estimate really is.

Studying the Effects of Cannabis on the Aging Process

Almost all of the studies reported in this paper used relatively young subjects. Of the 28 studies reviewed, 17 did not include a single subject over the age of 58. In the remaining 11 studies, either the age range was not given or the vast majority of the subjects were under the age of 60. While in most studies the lack of older subjects seemed to be a result of the population the investigators chose to study (students, volunteers recruited through street people, etc.), in at least one study (Agarwal et al., 1975) elderly people were excluded purposely to eliminate the possibility that any impairment seen in subjects was a consequence of aging.

We would like to suggest that the elderly may be the ideal population to investigate the chronic cerebral effects of cannabis use (Smith & Sethi, 1975). This approach has been used successfully in the study of cerebral effects of alcohol use (Blusewicz, Dustman, Schenkenburg, and Beck, 1977; Blusewicz, Schenkenburg, Dustman, and Beck, 1977). The data reviewed in this paper suggest that there are few if any detectable, long-term cerebral effects of cannabis use in young and reasonably healthy individuals. It is reasonable to conclude that any chronic effects that might result from the use of the drug are easily masked by the normal "cerebral reserve." However, the normal aging process

slowly erodes both our functional reserve and, in time, even our primary functional abilities. Chronic cerebral dysfunction is likely to become more noticeable in individuals experiencing additional cerebral deterioration. Thus, a premature intellectual deterioration (senility) might well be expected in long-term cannabis users if cannabis produces even subtle cerebral deterioration. So far, no one has investigated this possibility. Such a study would not be easy since a 60- to 70-year lifetime allows ample opportunity for numerous confounding variables to also affect cerebral functioning. Large sample sizes and some matching of samples on variables known to have chronic cerebral effects would be necessary. However, if any population is likely to show the results of a subtle cerebral impairment, it is likely to be a population of older citizens. Another reason for studying the possible effects of cannabis use on aging is that modern medicine is extending the life expectancy of people. As more people live longer, any variable which increases the level of dysfunction of the elderly will further strain our health care system.

Is It Time to Consider an Experiment?

All of the studies reviewed in this paper used a pseudoexperimental design in which preexisting groups (cannabis users and nonusers) were compared on measures of their cerebral functioning. Any research methods text will describe the weaknesses of such a design. Getting pretest measures (as in a prospective study) strengthens the design somewhat, but there are still numerous confounding variables which could affect the results. The alternative of conducting a true experiment where subjects are randomly assigned to the groups (cannabis users and nonusers) has not been an ethically responsible choice available to investigators. However, it may be time to reconsider the alternative of a true experiment.

We recognize that suggesting an experimental test of the chronic effects of cannabis is controversial, and we want to make it clear that we do not feel that such a test is warranted yet. But if further research were to show little or no effects in vulnerable populations such as the elderly and if the risks to other body systems are shown to be minimal, a carefully designed and executed experiment might add a great deal to our understanding of the long-term effects of cannabis use.

Summary

In this paper we have tried to review the available research on the chronic cerebral effects of cannabis use with a particular focus on methodological issues. Our general conclusion is that the current research does not support the contention that cannabis use results in chronic cerebral impairment. The possibility still

remains that such impairment exists, but it is likely to be either quite subtle or apparent in only a select group of vulnerable subjects. Those studies which did find cerebral effects were either fatally flawed [as in the Campbell et al. (1971) study] or biased in the direction of finding performance differences. For each study where significant impairment was found, several other studies with apparently equal methodological rigor found no impairment.

Any conclusion drawn from the studies reviewed here must be considered tentative because of the limitations inherent in the retrospective design. Although it may be possible to improve on many of the currently available studies in terms of methodology, it would probably make little difference in the conclusions we would draw. Therefore, we have chosen to focus our discussion on new directions for research using alternative designs and/or populations. We do not believe that more retrospective studies, even if they use the finest methodology available, are warranted given the data already available.

The issue of cannabis use is a highly emotional topic with serious political overtones. However, the fact remains that in spite of the illegal status of the drug, its use is widespread. To the extent that potential health risks exist, we have a continuing responsibility to identify them and communicate that information to those affected. Even though the current research does not suggest a risk for cerebral impairment, there are still some areas that have not been adequately investigated. Furthermore, there are areas of risk (e.g., cerebral effects of cannabis use by young children) which have received virtually no study. Now may be the best time to refocus our research efforts and explore these questions.

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THC-negative (No. = 10) (%)
10
0
50
20
20
50
50

produced little change in our results. is raised by the possibility that influenced the risk of spontaneous ult that users who carried long enough as ours were unrepresentative of users to interpret the lack of any important ifferences between the groups as argu- n that such a phenomenon was respon- nces observed in labor and neonatal investigation of this issue is beyond the owever.

small numbers involved in our study, is a severe problem. Many differences by chance alone we might expect statis- fferences to emerge even if marijuana observed differences are consistent in Because of the small size and other limi- we caution that accurate assessment of uana use during pregnancy must await tudies. Such studies will require extreme luct, and analysis.

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J. R. Soares. Validated direct blood Δ⁹-THC ntitation. *J. Analyt. Toxicol.* 2: 98–100, 1978.

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Epidemiology—Principles and

Marihuana Use by Pregnant Women and Effects on Offspring: An Update

P. A. FRIED

Department of Psychology, Carleton University, Ottawa, Ontario, Canada

FRIED, P. A. *Marihuana use by pregnant women and effects on offspring: An update.* NEUROBEHAV. TOXICOL. TERATOL. 4(4) 451–454, 1982.—This report is based on a previously described sample of 291 mothers-to- d on an additional 129 subjects. Among these 420 predominantly middle class pregnant women, approximately 3 ent used marihuana regularly during pregnancy. For assessing the effect of marihuana on pregnancy variables and the offspring, the mothers-to-be were matched in terms of nicotine and alcohol use. Marihuana use was associated with a shorter gestation period and a decreased maternal weight gain. No effect on birth weight, length of labor or difficulty in birth were observed. Consistent with the earlier report, babies born to women who smoked more than five joints per week during pregnancy demonstrated marked tremors and startles and altered visual responsiveness at 2–4 days of age. These symptoms had attenuated by 30 days and no developmental impairments were observed in any of seven babies who had reached one year of age born to women who had smoked 2 joints or more per week during pregnancy.

Marihuana Pregnancy Development Neurobehavior

THE present report is a brief update of aspects of an ongoing study started in 1978 involving the department of Psychology of Carleton University and the Ottawa Civic and Ottawa General hospitals. The purpose of the investigation is to examine, in a prospective fashion, the pattern of use of social levels of alcohol, cigarettes and marihuana during pregnancy and the effects of these drugs on the offspring. Details of the procedure and epidemiological information on approximately 200 subjects have been presented previously [4] and birth data and the results of behavioral testing of babies up to 4 days of age born to the marihuana users among 291 subjects in the Ottawa study have also been described elsewhere [3].

METHOD

The present report is based on a sample consisting of 420 subjects and includes several more infants born to marihuana users. As both the demographic data on the mothers and the results of the newborn are essentially the same as those found in the original cohort [3], the data will be described very briefly. Since the original report, a number of offspring of the marihuana users have been followed up and been examined using the Prechtl neurological examination [5] at nine (±1) and 30 (±2) days and the Bayley Scale of Infant Development [1] at 12 months. Although it is obvious, it must be emphasized that the sample size is small and these longitudinal results have to be viewed as quite preliminary.

trimesters remaining in their pregnancy. Information obtained included the volume and variability of alcohol consumption, cigarette smoking habits and marihuana intake for the year before pregnancy and each trimester of pregnancy. In addition to this "soft" drug report a general health history, previous pregnancy details, a 24-hour dietary recall and socio-demographic data were obtained.

The categorization for marihuana use for each of the four time periods (year before pregnancy and each of the trimesters) was: non-user; irregular user—one joint or less per week or exposure to the exhaled smoke of others; moderate user—two to five joints per week and; heavy user—more than five joints per week.

RESULTS

The socio-demographic characteristics of the new sample is essentially the same as that of the cohort described previously [4] and therefore will not be dealt with separately. Among the total sample of 420 women the average family income was $29,250±$13,050 and the average age and parity was 29±4 and 0.7±0.9, respectively. The economic figure was very similar to that of the general population of the Ottawa area reported by Statistics Canada and the age and parity figures were consistant with all the women giving birth in 1979 in the participating hospitals. Ninety-four percent of the women had at least a high school diploma and 63 percent had continued their education beyond high school

PULMONARY HAZARDS OF SMOKING MARIJUANA AS COMPARED WITH TOBACCO

TZU-CHIN WU, M.D., DONALD P. TASHKIN, M.D., BEHNAM DJAHED, M.D., AND JED E. ROSE, PH.D.

Abstract To compare the pulmonary hazards of smoking marijuana and tobacco, we quantified the relative burden to the lung of insoluble particulates (tar) and carbon monoxide from the smoke of similar quantities of marijuana and tobacco. The 15 subjects, all men, had smoked both marijuana and tobacco habitually for at least five years. We measured each subject's blood carboxyhemoglobin level before and after smoking and the amount of tar inhaled and deposited in the respiratory tract from the smoke of single filter-tipped tobacco cigarettes (900 to 1200 mg) and marijuana cigarettes (741 to 985 mg) containing 0.004 percent or 1.24 percent Δ^9-tetrahydrocannabinol.

As compared with smoking tobacco, smoking marijuana was associated with a nearly fivefold greater increment in the blood carboxyhemoglobin level, an approximately threefold increase in the amount of tar inhaled, and retention in the respiratory tract of one third more inhaled tar ($P<0.001$). Significant differences were also noted in the dynamics of smoking marijuana and tobacco, among them an approximately two-thirds larger puff volume, a one-third greater depth of inhalation, and a fourfold longer breath-holding time with marijuana than with tobacco ($P<0.01$). Smoking dynamics and the delivery of tar during marijuana smoking were only slightly influenced by the percentage of tetrahydrocannabinol.

We conclude that smoking marijuana, regardless of tetrahydrocannabinol content, results in a substantially greater respiratory burden of carbon monoxide and tar than smoking a similar quantity of tobacco. (N Engl J Med 1988; 318:347-51.)

WE have previously shown that the habitual smoking of 3 or 4 marijuana cigarettes a day is associated with the same frequency of the symptoms of acute and chronic bronchitis[1] and the same type and extent of epithelial damage in the central airways[2] as the regular smoking of more than 20 tobacco cigarettes a day. A possible explanation for these findings is that a greater quantity of smoke particulates and noxious gases is delivered to and deposited or absorbed in the lungs by marijuana than by a similar amount of tobacco, possibly as a result of differences in the way each type of cigarette is smoked. To investigate this possibility, we examined the dynamics of smoking a marijuana or a tobacco cigarette and measured the particulates delivered to the smoker's mouth during the smoking of a single cigarette of each type.

METHODS

We studied fifteen men who were habitual smokers (mean age [±SD], 31.5±7.1 years), each of whom smoked both tobacco and marijuana. The subjects smoked an average of 29.9±16.7 tobacco cigarettes per day and had smoked an average of 16.1±12.2 pack-years of tobacco (one pack-year equals one pack of tobacco cigarettes per day times the number of years of smoking); they smoked an average of 16.5±17.1 marijuana cigarettes per week, and had smoked an average of 54.8±34.8 joint-years of marijuana (one joint-year equals one cigarette [joint] of marijuana per day times the number of years of smoking). All were in good general health and had normal or nearly normal values for forced vital capacity (101±8.7 percent of predicted values[3]) and forced expiratory volume in one second (96±14 percent of predicted values[3]). None reported intravenous drug abuse or smoking other illicit substances besides marijuana.

Each subject was studied on a single day after refraining from smoking tobacco for at least one hour and marijuana for at least six hours. During the study session, each subject smoked his own brand of filter-tipped tobacco cigarette, followed, in single-blind fashion, first by a placebo marijuana cigarette (from which nearly all Δ^9-tetrahydrocannabinol [Δ^9-THC] had been extracted, so that the concentration was 0.004 percent) and next by a marijuana cigarette of similar weight containing 1.24±0.06 percent Δ^9-THC. An interval of approximately 30 minutes separated the smoking of each two cigarettes. The tobacco cigarettes weighed 900 to 1120 mg and had a tar yield of 4.6 to 23.1 mg (mean, 12.0±5.7 mg) and a nicotine yield of 0.4 to 1.4 mg (mean, 0.84±0.32 mg) by Federal Trade Commission analysis. The placebo marijuana cigarettes weighed 741 to 940 mg (mean, 840 mg) and those containing 1.24 percent Δ^9-THC weighed 849 to 985 mg (mean, 907 mg); both were supplied by the National Institute on Drug Abuse, were stored at 4°C to minimize chemical degradation, and were maintained in a humidifier at 60 percent humidity and 21°C for 24 hours before the study, to reduce harshness.

The subjects were asked to smoke both the tobacco cigarette and the two marijuana cigarettes in a manner as similar as possible to their usual pattern of smoking tobacco and marijuana. Peripheral venous blood was withdrawn anaerobically immediately before and two minutes after the first two cigarettes were smoked for measurement of the percentage of carboxyhemoglobin saturation, with use of a carbon monoxide–oximeter (Model 282, Instrumentation Laboratory, Lexington, Mass.). After smoking each of the marijuana cigarettes, the subjects were asked to rate their level of intoxication on a scale of 0 to 100 percent, with 100 percent representing the greatest "high" they had ever experienced.

The volume, duration, and number of puffs and the intervals between puffs were measured with a 00 Fleisch pneumotachygraph (linear from 5 to 100 ml per second) connected through a differential pressure transducer (Model MP45-3, Validyne, Northridge, Calif.) (range, ±2 cm of water) to an oscilloscopic recorder with a differential integrator–computer and a rapid photographic writer (Model VR6, Electronics for Medicine, Pleasantville, N.Y.). To prevent the pneumotachygraph screen from becoming clogged by smoke particles,[4] the pneumotachygraph was connected through wide-bore Tygon tubing (length, 70 cm; internal diameter, 1 cm) to the distal end of a glass cylinder (length, 12 cm; diameter, 5 cm) that contained two ventilation ports (each 1 cm in diameter) and was sealed at its proximal end by a rubber stopper. The tobacco or marijuana cigarette was held in a small plastic holder inserted through the rubber stopper. The ventilation ports were left open between puffs to prevent either the extinction of the lighted cigarette or the excessive accumulation of carbon monoxide. During a puff, the smoker covered the ventilation holes with his index and middle fingers so that the entire volume of air drawn through the cigarette could be measured by the pneumotachygraph. The resistance of the pneumotachygraph (0.0068 cm of water per milliliter per second) was considerably lower than that of the cigarette (0.51 cm of water per milliliter per second for tobacco; 0.17 cm of water per milliliter per second for marijuana); therefore, the pneumotachygraph itself was

From the Department of Medicine, University of California at Los Angeles School of Medicine, and the Departments of Psychiatry and Biobehavioral Sciences, Neuropsychiatric Institute, University of California at Los Angeles School of Medicine. Address reprint requests to Dr. Tashkin at the Department of Medicine, University of California at Los Angeles School of Medicine, Los Angeles, CA 90024.

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not likely to have a substantial effect on smoking dynamics. The duration of a puff was timed from the pneumotachygraphic flow tracing. The interval between puffs was defined as the period between the end of one puff and the start of the next.

To measure "wash-in" volume (the volume of air inhaled), inductive plethysmographic coils (Respitrace Ambulatory Monitoring Systems, Ardsley, N.Y.) were placed around each subject's rib cage and abdomen.[5,6] A demodulator converted changes in electrical inductance in the coils during respiratory movements into voltage signals proportional to changes in the volume enclosed by the coils. Changes in the volume of the respiratory system were calculated from the weighted sums of the signals from the rib cage and abdomen; the weights were determined by the least-squares calibration method.[7] The accuracy of the calibration was confirmed by comparing the inhaled volumes calculated from respiratory inductive plethysmography with spirometric values: the measurements obtained by spirometry and inductive plethysmography agreed within ±10 percent. The amount of time the inhaled smoke was retained in the lungs (smoke-retention time) was calculated as the interval between the times corresponding to one third of the maximum inhaled volume and two thirds of the maximum volume exhaled following breath holding (Fig. 1). The no-smoking interval was timed from the end of the smoke-retention time to the start of the next puff.

A previously described proportional smoke-trapping device[8] was connected to the apparatus for measuring the volume of puffs in order to measure the amount of smoke particulates delivered to the smoker's mouth. This device consisted of a plastic cigarette holder through which the mainstream smoke was diverted into two parallel pathways, one containing one capillary tube (pathway A) and the other seven parallel capillary tubes (pathway B). A Cambridge filter pad trapped the smoke that passed through pathway A. The tar trapped by the filter was extracted with methanol and analyzed by means of a spectrophotometer (wavelength, 400 nm). A constant fraction of the tar (12.5±0.53 percent) was retained in the filter over a wide range of puff volumes (30 to 60 ml), puff durations (1 to 4 sec), and puff flow rates (20 to 100 ml per second).[8] This apparatus, therefore, permitted the actual quantity of smoke particulates delivered to the mouth to be calculated by multiplying the amount of particulates trapped in the Cambridge filter pad in pathway A by seven. At the end of the period of breath holding after each puff, the subjects turned their heads slightly to one side and exhaled the smoke into the large end (diameter, 26 cm) of an adjacent megaphone device, the distal end (diameter, 4.5 cm) of which was fitted with a high-efficiency filter attached to a vacuum system as described by Hinds et al.[9] After the tar was extracted from the filter with methanol, the exhaled particulates were measured with a spectrophotometer. The amount of smoke retained (deposited) in the respiratory tract was expressed as a percentage of the amount inhaled: percentage deposited = [1 − (amount of exhaled particulates/amount of inhaled particulates)] × 100.

Each subject's measurements were averaged for each cigarette smoked. These mean values, as well as the number of puffs, the quantity of particulates inhaled, the percentage of inhaled particulates deposited, and the increment in carboxyhemoglobin saturation per cigarette, were averaged for all 15 subjects for each type of cigarette smoked. The subjects' ratings of their degree of intoxication after marijuana smoking were also averaged for all subjects for each type of marijuana cigarette (placebo and 1.24 percent Δ^9-THC). Two-way analysis of variance (for subject and type of cigarette) was used to determine the significance of differences in smoking patterns, the delivery and deposition of particulates, and the increase in carboxyhemoglobin saturation among types of cigarette.[10] Pairwise comparisons were then performed using testing for least significant differences[11]; differences were considered significant if P values were <0.05.

Results

Descriptive data about smoking in the group of 15 subjects are shown in Table 1. Placebo marijuana and marijuana containing approximately 1.24 percent Δ^9-THC were smoked in a similar manner. However, the average volume of puffs was about 70 percent larger ($P<0.001$) and the duration of puffs about 60 percent longer ($P<0.01$) during the smoking of marijuana than the smoking of tobacco, regardless of whether the marijuana contained 1.24 or 0.004 percent Δ^9-THC; significantly more puffs were taken from the tobacco cigarette than from either the placebo marijuana cigarette or that containing 1.24 percent Δ^9-THC ($P<0.001$). Although the interval between puffs was less for tobacco than for marijuana smoking ($P<0.05$), the no-smoking interval, which did not include the breath-holding time after

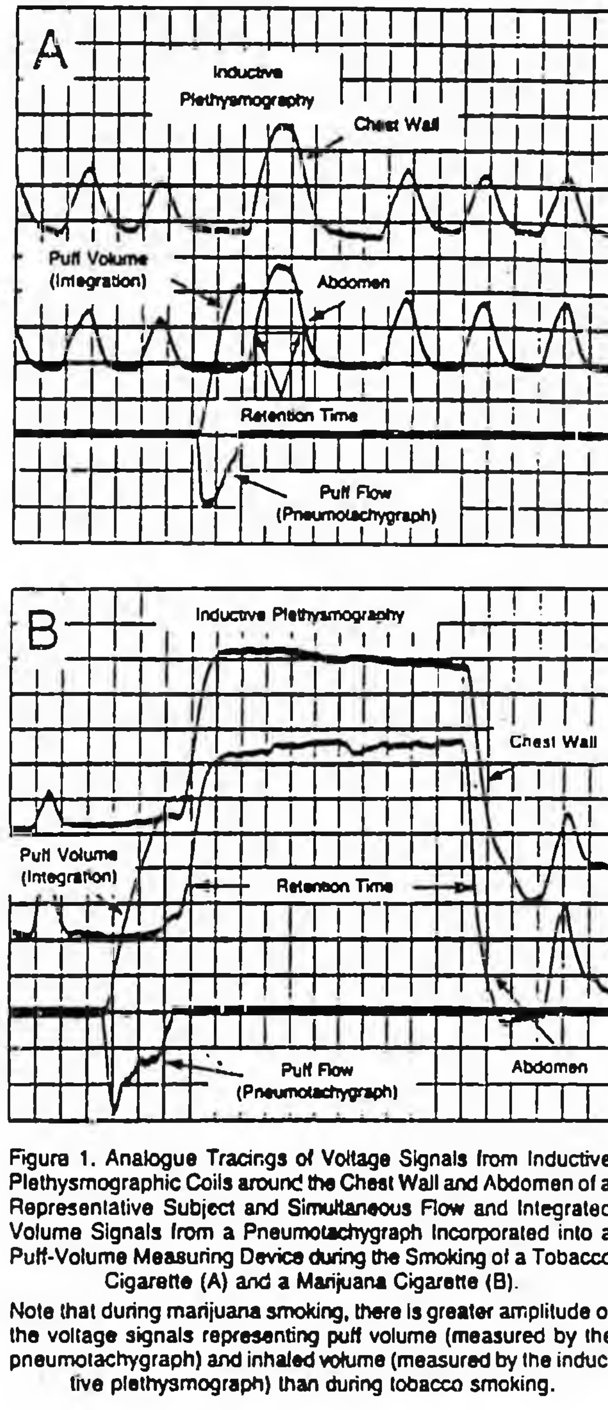

Figure 1. Analogue Tracings of Voltage Signals from Inductive Plethysmographic Coils around the Chest Wall and Abdomen of a Representative Subject and Simultaneous Flow and Integrated Volume Signals from a Pneumotachygraph Incorporated into a Puff-Volume Measuring Device during the Smoking of a Tobacco Cigarette (A) and a Marijuana Cigarette (B).

Note that during marijuana smoking, there is greater amplitude of the voltage signals representing puff volume (measured by the pneumotachygraph) and inhaled volume (measured by the inductive plethysmograph) than during tobacco smoking.

Table 1. Characteristics of 15 Subjects' Smoking of Tobacco, Placebo Marijuana (0.004 Percent Δ^9-THC), and Marijuana Containing 1.24 Percent Δ^9-THC.*

Index	Tobacco	Marijuana 0.004% Δ^9-THC	Marijuana 1.24% Δ^9-THC	P Value†
		mean ±SD		
Puff volume (ml)	49.4±15.2	88.3±24.8	78.0±22.8	<0.001
Puff duration (sec)	2.4±1.1	3.8±1.9	4.0±2.2	<0.01
No. of puffs	13.5±4.0	7.5±2.3	8.5±3.1	<0.001
Interval between puffs (sec)	27.0±8.2	35.3±12.2	37.6±14.5	<0.05
Inhaled volume (liters)	1.31±0.22	1.82±0.66	1.75±0.52	<0.002
Smoke-retention time (sec)	3.5±1.3	13.8±9.2	14.7±10.2	<0.001
[illegible] (sec)	23.5±8.5	21.5±6.4	23.0±8.8	NS

*All subjects were habitual smokers of both tobacco and marijuana. They smoked their own brands of tobacco cigarettes. Δ^9-THC denotes Δ^9-tetrahydrocannabinol; NS denotes not significant.

†The P values denote the significance of comparisons between tobacco and each strength of marijuana; none of the comparisons between the two different strengths of marijuana (0.004 percent vs. 1.24 percent Δ^9-THC) was statistically significant.

smoke was inhaled, was similar for both substances. The mean inhaled volume was 36 percent greater (P<0.002), and the smoke-retention time was four times longer (P<0.001) during marijuana smoking than tobacco smoking.

The volume of the portion of the proportional smoke-trapping device through which smoke was delivered was approximately 13 ml. After the first puff, this volume was filled with smoke that was delivered in subsequent puffs; thus, after the first puff, no additional volume of air not containing smoke was included in the measurement of puff volume. When the pneumotachygraph was disassembled from the proportional smoke-trapping device and used to measure puff volume, the difference in the mean volume was negligible (1.2±2.0 ml lower without the smoke-trapping device). Similarly, inhaled volumes determined directly from the cigarette by the inductive plethysmograph, without the attachment of either the pneumotachygraph or the proportional smoke-trapping device, were similar to (within 50 ml) the inhaled volume determined when the subjects smoked through these devices.

The amounts of particulates inhaled, the percentage of inhaled particulates deposited in the respiratory tract, and the differences between the carboxyhemoglobin levels before and after smoking each type of cigarette are shown in Table 2. The major significant difference between smoking marijuana cigarettes containing 0.004 percent Δ^9-THC (placebo) and smoking cigarettes containing 1.24 percent Δ^9-THC was that the latter caused a greater degree of intoxication. In addition, the amount of particulates inhaled from marijuana containing 1.24 percent Δ^9-THC was slightly but significantly greater (20 percent) than that delivered from placebo marijuana (P<0.05). In contrast, smoking either type of marijuana was associated with the inhalation of 2.8 to 3.3 times more insoluble particulates (tar) and with the deposition of 32 to 35 percent more of these inhaled particulates than smoking the subject's own brand of tobacco (P<0.001). Consequently, marijuana smoking resulted in a tar burden to the respiratory tract that was 3.5 to 4.5 times greater than that produced by tobacco smoking in the same subjects. Furthermore, smoking a single marijuana cigarette caused a fourfold greater increment in carboxyhemoglobin saturation (P<0.001) than did smoking a single tobacco cigarette.

Discussion

Long-term adverse pulmonary consequences of tobacco smoking have been shown to be related to dose.[12] For example, the incidence of chronic obstructive pulmonary disease or bronchogenic carcinoma in smokers of fewer than 5 to 10 tobacco cigarettes a day is substantially less than in habitual smokers of more than 20 tobacco cigarettes a day.[13] Although regular tobacco smokers consume more than 15 tobacco cigarettes a day, most current smokers of marijuana smoke less than 1 marijuana cigarette a day.[12] Even among the estimated 6 million daily smokers of marijuana in the United States,[14] smoking more than five marijuana cigarettes a day is unusual. In view of the many similarities in the smoke contents of marijuana and tobacco,[15,16] it has been argued that habitually smoking only a few marijuana cigarettes a day may have a proportionately less harmful long-term effect on the lungs than regularly smoking several times more tobacco cigarettes. This argument assumes that the number of cigarettes smoked is directly proportional to the dose of smoke contents inhaled; however, this assumption ignores the ways in which the characteristics of smoking may influence the delivery of the combustion products of cigarettes.[17,18]

Table 2. Inhalation and Deposition of Particulates, Increases in Blood Carboxyhemoglobin Saturation, and Levels of Intoxication Associated with the Smoking of Tobacco and Marijuana in 15 Smokers of Both Substances.*

Index	Tobacco	Marijuana 0.004% Δ^9-THC	Marijuana 1.24% Δ^9-THC
		mean ±SD	
Inhaled particulates (optical density)	4.9±2.0	13.5±6.0†	16.3±6.3†‡
Percentage of particulates deposited	64.0±8.9	84.4±6.9†	86.1±6.7†
Increase in carboxyhemoglobin saturation (%)	0.60±0.52	2.99±1.51†	—§
Degree of intoxication (maximum "high" = 100%)	—	15.3±16.9	63.9±18.3‡

*Δ^9-THC denotes Δ^9-tetrahydrocannabinol.

†Significantly greater than values for tobacco (P<0.001 by analysis of variance and testing for least significant difference).

‡Significantly greater than values for marijuana containing 0.004 percent Δ^9-THC (P<0.05 by analysis of variance and testing for least significant difference).

§Not measured.

Few studies have been carried out in which the actual dose of smoke contents delivered to and retained in the respiratory tract during natural smoking has been measured. In our study, both the amount of particulate matter that was inhaled and the amount that was deposited in the respiratory tract were quantified during tobacco and marijuana smoking by means of a simple, new, noninvasive device.[8] These measurements allowed us to compare the actual dose to the smoker of particulate matter from the smoke of marijuana with that from tobacco. At the same time, the characteristics of smoking were determined in order to ascertain the relation between behavioral variables in smoking and the delivery and retention of smoke contents in the respiratory tract for each type of cigarette. The proportional smoke-trapping device had little measurable influence on smoking dynamics.

Findings from the present study indicate that approximately three times as much particulate matter is delivered to the smoker's mouth during the smoking of a single marijuana cigarette than during the smoking of a single tobacco cigarette of the smoker's own brand. These results are similar to those obtained in studies that used smoking machines to simulate conditions thought to be representative of marijuana and tobacco smoking.[19,20] Our results also revealed that approximately one third more of the particulates inhaled from the smoke of marijuana are retained in the respiratory tract than is the case when tobacco is smoked. Consequently, the net respiratory burden of particulates was approximately four times greater during marijuana smoking than tobacco smoking.

Several explanations are possible for the greater burden of particulates to the lungs from marijuana than from a similar quantity of tobacco. First, in all cases, the tobacco cigarettes were more densely packed than the marijuana cigarettes and, unlike the marijuana cigarettes, were filter-tipped; therefore, the filtration efficiency of the tobacco cigarettes was greater. Second, the average residual length of the marijuana cigarettes (23±13 mm) was smaller than that of the tobacco cigarettes (37±12 mm), thereby further reducing the filtration efficiency of the marijuana cigarette. However, because the tobacco cigarettes were initially longer and because the filter tip was included in the tobacco butt, the actual quantities of tobacco and marijuana consumed were similar. Third, the subjects' patterns of inhalation in smoking the two types of cigarettes were markedly different: marijuana was smoked with a puff volume that was more than two thirds larger, an inhaled volume one third greater, and a retention time four times longer than the values for tobacco. Although the larger puff volumes for marijuana were partially offset by a smaller number of puffs, this factor may still have contributed to the greater mass of smoke particulates delivered to the mouth in marijuana smoking. The deeper inhaled volumes and, in particular, the severalfold longer retention times during marijuana smoking than during tobacco smoking may have accounted for the greater percentage of the inhaled particulates from marijuana smoke deposited in the respiratory tract.

The four-to-five-times-greater increments in carboxyhemoglobin saturation during marijuana smoking than tobacco smoking were probably due mainly to differences in how the cigarettes were smoked rather than in the amount of carbon monoxide produced, since syringe-simulated puffs of similar volumes and durations from lit cigarettes yielded approximately 25 percent lower concentrations of carbon monoxide from marijuana than from tobacco. This finding is consistent with the more complete combustion of the more loosely packed marijuana. On the other hand, the subjects' deeper inhalations and, in particular, their considerably longer retention of smoke in the lungs during marijuana smoking than during tobacco smoking made possible a greater uptake of carbon monoxide by the pulmonary microcirculation by means of passive diffusion. We measured the increment in blood carboxyhemoglobin after placebo marijuana (from which the cannabinoids had been extracted), and not after marijuana containing Δ^9-THC. However, we would not expect appreciable differences between the effects of real marijuana and those of placebo marijuana on blood carboxyhemoglobin levels, since the smoking dynamics and the carbon monoxide delivery of the two types of marijuana cigarettes were similar. The expected physiologic consequences of the markedly greater boost in carboxyhemoglobin levels from a single marijuana cigarette are a higher degree of impairment in oxygen transfer in the lung,[21] a reduction in the oxygen-carrying capacity of the blood, and impairment in the release of oxygen from hemoglobin in the tissues.[22] Moreover, the Δ^9-THC in marijuana causes dose-related increases in heart rate[23,24] and thus in cardiac work and myocardial oxygen requirements. Therefore, in persons with underlying coronary artery disease who smoke marijuana, the combined effects of a marked rise in the level of carboxyhemoglobin and the cardioacceleration induced by Δ^9-THC could lead to a critical imbalance between reduced myocardial oxygen supply and increased demand.

Interestingly, no significant differences in smoking dynamics were noted between placebo marijuana and marijuana containing 1.24 percent Δ^9-THC, despite marked differences in the subjects' perceived level of intoxication. These findings differ from previous observations in tobacco smokers that puff volume increases when low-nicotine cigarettes are smoked.[25] Our results in marijuana smokers are consistent with data from other studies,[26,27] however, and suggest that the pattern of smoking marijuana is not immediately adjusted to alter the inhaled dose of Δ^9-THC but, instead, probably represents a learned technique based on previous experiences and interactions.

In conclusion, our findings demonstrate that smoking behavior differs markedly between marijuana and tobacco smoking and that these differences are associ-

Table 1. Characteristics of 15 Subjects' Smoking of Tobacco, Placebo Marijuana (0.004 Percent Δ^9-THC), and Marijuana Containing 1.24 Percent Δ^9-THC.*

Index	Tobacco	Marijuana		P Value†
		0.004% Δ^9-THC	1.24% Δ^9-THC	
		mean ±SD		
Puff volume (ml)	49.4±15.2	88.3±24.8	78.0±22.8	<0.001
Puff duration (sec)	2.3±1.1	3.8±1.9	4.0±2.2	<0.01
No. of puffs	13.5±4.0	7.5±2.3	8.5±3.1	<0.001
Interval between puffs (sec)	27.0±8.2	35.3±12.2	37.6±14.5	<0.05
Inhaled volume (liters)	1.21±0.22	1.82±0.66	1.75±0.52	<0.002
Smoke-retention time (sec)	3.5±1.3	13.8±9.2	14.7±10.2	<0.001
Nonsmoking interval (sec)	23.5±8.5	21.5±6.4	23.0±8.8	NS

*All subjects were habitual smokers of both tobacco and marijuana. They smoked their own brands of tobacco cigarettes. Δ^9-THC denotes Δ^9-tetrahydrocannabinol; NS denotes not significant.

†P values denote the significance of comparisons between tobacco and each strength of marijuana; none of the comparisons between the two strengths of marijuana (0.004 percent vs. 1.24 percent Δ^9-THC) was statistically significant.

smoke was inhaled, was similar for both substances. The mean inhaled volume was 36 percent greater (P<0.002), and the smoke-retention time was four times longer (P<0.001) during marijuana smoking than tobacco smoking.

The volume of the portion of the proportional smoke-trapping device through which smoke was delivered was approximately 13 ml. After the first puff, this volume was filled with smoke that was delivered in subsequent puffs; thus, after the first puff, no additional volume of air not containing smoke was included in the measurement of puff volume. When the pneumotachygraph was disassembled from the proportional smoke-trapping device and used to measure puff volume, the difference in the mean volume was negligible (4.2±2.0 ml lower without the smoke-trapping device). Similarly, inhaled volumes determined directly from the cigarette by the inductive plethysmograph, without the attachment of either the pneumotachygraph or the proportional smoke-trapping device, were similar to (within 50 ml) the inhaled volume determined when the subjects smoked through these devices.

The amounts of particulates inhaled, the percentage of inhaled particulates deposited in the respiratory tract, and the differences between the carboxyhemoglobin levels before and after smoking each type of cigarette are shown in Table 2. The major significant difference between smoking marijuana cigarettes containing 0.004 percent Δ^9-THC (placebo) and smoking cigarettes containing 1.24 percent Δ^9-THC was that the latter caused a greater degree of intoxication. In addition, the amount of particulates inhaled from marijuana containing 1.24 percent Δ^9-THC was slightly but significantly greater (20 percent) than that delivered from placebo marijuana (P<0.05). In contrast, smoking either type of marijuana was associated with the inhalation of 2.8 to 3.3 times more insoluble particulates (tar) and with the deposition of 32 to 35 percent more of these inhaled particulates than smoking the subject's own brand of tobacco (P<0.001). Consequently, marijuana smoking resulted in a tar burden to the respiratory tract that was 3.5 to 4.5 times greater than that produced by tobacco smoking in the same subjects. Furthermore, smoking a single marijuana cigarette caused a fourfold greater increment in carboxyhemoglobin saturation (P<0.001) than did smoking a single tobacco cigarette.

Discussion

Long-term adverse pulmonary consequences of tobacco smoking have been shown to be related to dose.[12] For example, the incidence of chronic obstructive pulmonary disease or bronchogenic carcinoma in smokers of fewer than 5 to 10 tobacco cigarettes a day is substantially less than in habitual smokers of more than 20 tobacco cigarettes a day.[13] Although regular tobacco smokers consume more than 15 tobacco cigarettes a day, most current smokers of marijuana smoke less than 1 marijuana cigarette a day.[12] Even among the estimated 6 million daily smokers of marijuana in the United States,[14] smoking more than five marijuana cigarettes a day is unusual. In view of the many similarities in the smoke contents of marijuana and tobacco,[15,16] it has been argued that habitually smoking only a few marijuana cigarettes a day may have a proportionately less harmful long-term effect on the lungs than regularly smoking several times more tobacco cigarettes. This argument assumes that the number of cigarettes smoked is directly proportional to the dose of smoke contents inhaled; however, this assumption ignores the ways in which the characteristics of smoking may influence the delivery of the combustion products of cigarettes.[17,18]

Table 2. Inhalation and Deposition of Particulates, Increases in Blood Carboxyhemoglobin Saturation, and Levels of Intoxication Associated with the Smoking of Tobacco and Marijuana in 15 Smokers of Both Substances.*

Index	Tobacco	Marijuana	
		0.004% Δ^9-THC	1.24% Δ^9-THC
		mean ±SD	
Inhaled particulates (optical density)	4.9±2.0	13.5±6.0†	16.3±6.3†‡
Percentage of particulates deposited	64.0±8.9	84.4±6.9†	86.1±6.7†
Increase in carboxyhemoglobin saturation (%)	0.60±0.52	2.99±1.51†	—§
Degree of intoxication (maximum "high" = 100%)	—	15.3±16.9	63.9±18.3‡

*Δ^9-THC denotes Δ^9-tetrahydrocannabinol.

†Significantly greater than values for tobacco (P<0.001 by analysis of variance and testing for least significant difference).

‡Significantly greater than values for marijuana containing 0.004 percent Δ^9-THC (P<0.05 by analysis of variance and testing for least significant difference).

§Not measured.

ated with a [illegible] burden of smoke particulates and abs[illegible] of carbon monoxide that are approximately [illegible] times greater in the case of marijuana smoking. These results may account for previous findings that smoking only a few marijuana cigarettes a day (with[illegible] tobacco) has the same effect on the prevalence of [illegible] and chronic respiratory symptoms[1] and the [illegible] tracheobronchial epithelial histopathology [illegible] smoking more than 20 tobacco cigarettes a day ([illegible] marijuana). These observations justify [illegible] the potential long-term pulmonary con[illegible] the habitual smoking of only a few marijuana [illegible] a day.

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European Heart Journal (1985) 6, 637–638

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Myocardial infarction during marijuana smoking in a young female

J. S. A. Collins*, J. D. S. Higginson, D. McC. Boyle and S. W. Webb†

The Cardiology Department, Ulster Hospital, Dundonald and †Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, U.K.

KEY WORDS: Cannabis, normal coronary arteries.

Although marijuana smoking is popular among young adults, hospital admissions due to adverse effects of this drug are uncommon[1]. We report a case of a young female who developed an acute myocardial infarction while smoking the drug.

Case report

A previously healthy 33-year old secretary was admitted to the Casualty Department with severe central chest pain radiating to both arms. The pain had started one hour before, while smoking marijuana at a party. She had smoked 20 tobacco cigarettes per day for 16 years. There was no past history of cardiac disease, hypertension or diabetes. A paternal uncle had died of myocardial infarction age 59 years. She had taken marijuana on 3 occasions in the previous 3 years with no ill effects. She was not taking the oral contraceptive pill.

On examination, she was euphoric, pale and sweating profusely. Heart rate was 96 min^{-1} and blood pressure 110/70 mmHg. Heart sounds were normal and there were no signs of cardiac failure. The electrocardiograph showed ST elevation in leads 2,3 and aVF with reciprocal ST depression in leads V_2–V_6 (Fig. 1). Chest X-ray was within normal limits.

Fifteen minutes after admission, she developed ventricular fibrillation which responded to a 200 joule DC shock. She then developed 2:1 heart block, followed by complete heart block and a temporary transvenous pacing wire was inserted.

On the first admission day, serum creatine kinase and aspartate transaminase levels were elevated to 883 IU l^{-1} (normal 0–180 IU l^{-1}) and 78 IU l^{-1} (normal 6–35 IU l^{-1}), rising to 1701 IU l^{-1} and 208 IU l^{-1} on the second day, respectively. There was a corresponding rise in serum creatine kinase (MB) levels to 73 IU l^{-1} and 123 IU l^{-1} on these days. Blood urea, electrolytes and glucose were normal. Toxicological assay of the patient's urine within 6 h of admission, using a sensitive radioimmunoassay, showed 5·5 ng ml^{-1} of total cross-reacting cannabinoids. Electrocardiographs showed evolving changes of acute inferior infarction over the next week, but there were no further arrhythmias and she was discharged on the twelfth hospital day.

Three months later, she underwent treadmill exercise testing and completed stage 7 of Bruce Protocol, achieving a heart rate of 190 min^{-1} (>85% predicted maximal) with no haemodynamic or electrocardiographic abnormality. Random (non-fasting) serum cholesterol was 6·4 mmol l^{-1} (normal 3·4–7·8) and random serum triglycerides level was 1·58 mmol l^{-1} (normal 0·34–2·26) at this time. Subsequent selective coronary arteriography and left ventriculography showed normal coronary arteries with posterior hypokinesis of the left ventricle.

Comment

Marijuana smoking has been shown to affect the electrocardiograph of normal subjects[2] and a study in patients with ischaemic heart disease showed a significantly decreased exercise time to angina with the drug compared to high-nicotine cigarettes[3]. Two previous cases of acute

*Currently Senior Registrar in Gastroenterology, Royal Victoria Hospital

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Address for correspondence: Dr J. S. A. Collins, Senior Registrar in Gastroenterology, Department of Medicine, The Queen's University of Belfast, Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ, U.K.

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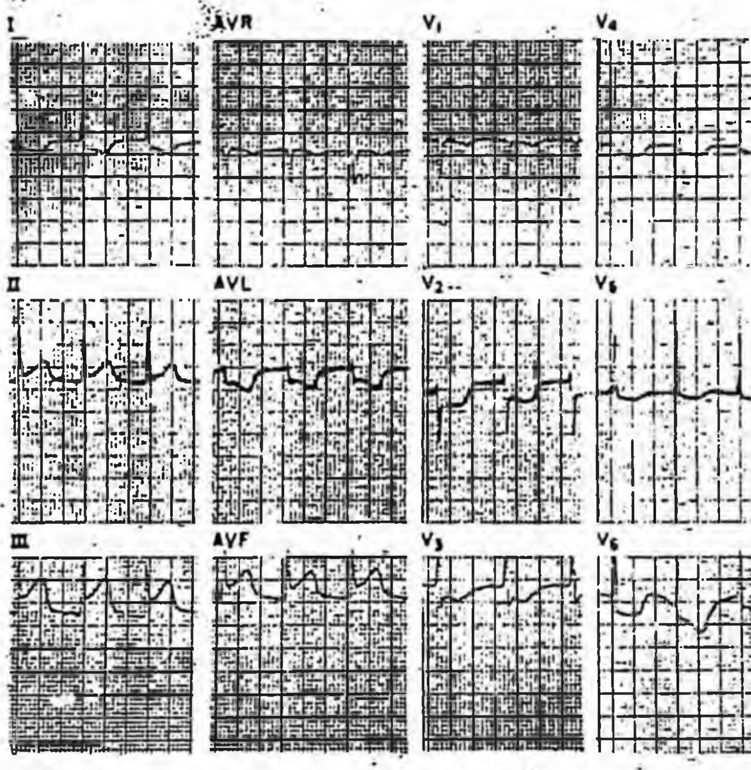

Figure 1 Twelve-lead electrocardiograph on admission.

myocardial infarction in close association with marijuana smoking have been reported[4,5]. In the most recent report, coronary atheroma was demonstrated at post-mortem. In neither case was toxicological evidence of marijuana exposure produced. In this case, the evidence of myocardial infarction is indisputable with classical electrocardiographic change, rise in cardiac enzymes and ventricular wall hypokinesis. The radiologically normal coronary arteries would suggest that coronary spasm was the cause of infarction in this case, in the absence of predisposing causes for thrombosis other than cigarette smoking. It was felt that ergometrine or marijuana challenge during angiography was not ethical in this case. Although the close relationship of drug exposure to acute infarction does not necessarily imply causation, an individual sensitivity to marijuana or an impurity in the preparation may have been present. Further non-invasive methods of investigation of myocardial perfusion in users of the drug would be of interest.

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Fatal coronary artery thrombosis associated with cannabis smoking

D. C. MACINNES, B.SC, MB, MRCGP
General Practitioner, Motherwell, Lanarkshire

K. M. MILLER, MD, FRC.PATH
Consultant Pathologist, Lanarkshire Health Board

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AN unusual case of coronary thrombosis associated with illicit drug use is described. It is suggested that general practitioners and casualty officers should consider the possibility of atypical presentations resulting from drug abuse not made known to the examining doctor.

Case report

A 32-year-old man complained of sudden onset chest pain but was unable to describe his pain in any detail or give any other information. He was distressed, unable to remain in one position for any length of time, and was rolling around his bed and onto the floor. Physical examination was not possible at first owing to lack of co-operation. The patient was sedated with 4 to 5 mg of intravenous diazepam with the remainder of the ampoule given intramuscularly. He became less distressed and was able to co-operate, complaining of central chest pain with tingling in the fingers of both hands. On examination the patient was not clammy, he was hyperventilating, his pulse rate was 100 beats minute and his blood pressure was normal; there were no signs of cardiac failure. Arrangements were made for the patient to be transferred to a casualty department, but unfortunately he died before the arrival of the ambulance.

Post-mortem investigations gave the following results. The heart weighed 430g; its configuration was normal and the chambers were in proportion. The myocardium was generally flabby in consistency, with early congestion of the anterior two-thirds of the intraventricular septum. There were numerous raised plaques of atheroma throughout both right and left coronary arteries; these were particularly prominent at the start of the circumflex branch of the left coronary artery where there was coarse focal stenosis of the lumen. One centimetre from the start of the descending branch of the left coronary artery one of the plaques showed ulceration of the intimal lining and adherent to it was a dark red thrombus 0.75 cm in length.

It was subsequently learned that the patient had been smoking cannabis earlier that evening.

Comment

This case demonstrates two possible adverse effects of cannabis on a person susceptible to ischaemic heart disease.

First, cannabis has a striking effect on heart rate, inducing a tachycardia up to 160 beats per minute or higher, which is achieved within a few minutes of drug absorption. Thereafter a slow decline in heart rate occurs which may take four hours or longer. Aronow has shown in a study of exercise-induced angina that smoking cannabis causes a decreased exercise time of 48 per cent, until angina is experienced, compared with a placebo reduction of 8.6 per cent.[1] This was ascribed to increased oxygen demand coupled with decreased oxygen perfusion leading to earlier experience of chest pain. Charles described one previous case of myocardial infarction occurring some 30 minutes after smoking cannabis;[2] a 25-year-old patient presented with cardiac failure and the infarction was confirmed by electrocardiography (ECG) and enzyme analysis.

Second, the psychological effects of cannabis appear to run in a continuum from mild dysphoria to acute psychotic reactions. Tart has shown that up to 36 per cent of regular cannabis users experienced symptoms during intoxication of distorted body image, acute pains or hallucinations.[3] Halikas has reported that 16 per cent of regular cannabis users experienced anxiety, fearfulness, confusion or aggressive urges as a 'usual occurrence'.[4] Controlled laboratory investigations have

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shown that acute psychological reactions tend to last up to four hours.

The smoking of cannabis causes changes in the cardiovascular system characteristic of stress. If cannabis were to increase the heart rate in a predisposed individual, it seems reasonable to suppose that angina could be precipitated, resulting perhaps in ischaemic damage. Furthermore, should psychoactive effects of the drug cause the patient to react in an atypical manner, he might not take suitable measures to relieve the angina, thus increasing the risk of damaging the myocardium or of precipitating an arrythmia. The problem of cardiovascular disease associated with cannabis smoking will surely become more common as younger cannabis smokers begin to enter the risk years of ischaemic heart disease.

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Address for correspondence

Dr D. MacInnes, 521 High Street, Newarthill, Motherwell.

SB

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file 6

ALASKA STATE OFFICE OF ALCOHOLISM AND DRUG ABUSE

STATEWIDE SUMMARY

DATE OF REPORT : 08/03/87
TIME OF REPORT : 09:19:35
BEGIN PERIOD DATE: 07/86
END PERIOD DATE : 06/87

CLIENT CHARACTERISTICS	PRIMARY SUBSTANCE ABUSED: ALCOHOL	SYN OPIATES	DEPRESSANTS	STIMULANTS	MARIJUANA AND HASHISH	HALLUCINO-GENS	POLYDRUG USE	OTHER SUBSTA[NCES]
SEX								
MALE	7517	123	13	454	468	21	2	
FEMALE	2428	88	20	219	111	5	1	
CLIENT AGE AT ADMISSION								
17 AND UNDER	422	2	6	20	170	11		
18-25 YEARS	2459	9	5	254	247	11	3	
26-40 YEARS	4938	182	19	376	149	1		
41-60 YEARS	1884	17	3	21	10	2		
61 AND OLDER	242	1		2	3	1		
RACE/ETHNICITY								
CAUSASIAN	4804	172	19	482	379	18	2	
BLACK	146	20	2	117	27			
AMERICAN INDIAN	162	2		5	3	1		
ATHABASCAN	1022	1		13	30	1	1	
TLINGIT	918	3	5	10	27			
HAIDA	110			2	5			
ALEUT	472		4	10	18	1		
INUPIAT	827	1		8	29	1		
YUPIK	907	2	1	2	21			
TSIMSHIAN	116			3	4			
OTHER ALASKAN NATIVE	267	1	1	10	16	1		
HISPANIC	110	5		6	11	2		
ASIAN	15	1	1		2			
OTHER	59	3		4	5			
UNKNOWN	11			1	2	1		
YEARS OF EDUCATION								
9 OR LESS	1772	16	11	80	162	12	1	
10 - 11 YEARS	2405	46	6	196	220	9	2	
12 YEARS	3960	80	13	241	143	4		
13 - 14 YEARS	1179	54	1	112	40	1		
15 - 16 YEARS	441	12	1	31	10			
17 OR MORE	118	2	1	9	3			
GED RECIPIENT	2308	60	8	202	158	7	2	
EMPLOYMENT STATUS								
EMPLOYED FULL-TIME	2049	53	4	117	56	2	1	

CLIENT CHARACTERISTICS BY PRIMARY SUBSTANCE USED

REPORT NO: HSSR.HAL.RP2325
VERSION :22.27.32AUG 22, 1985

STATEWIDE SUMMARY

ATE OF REPORT : 08/03/87
IME OF REPORT : 09:19:35
EGIN PERIOD DATE: 07/86
ID PERIOD DATE : 06/87

	P R I M A R Y		S U B S T A N C E		A B U S E D			
IENT CHARACTERISTICS	ALCOHOL	SYN OPIATES	DEPRESSANTS	STIMULANTS	MARIJUANA AND HASHISH	HALLUCINO-GENS	POLYDRUG USE	OTHER SUBSTANCE
FURLOUGH/REHAB LEAVE	170	2	1	18	8			
NON-CRIMINAL INVOL COMMIT	177		2	3	7			
INCARCERATED	874	34	5	180	163	7		
UNKNOWN	1167	16	2	58	35	1		
NO CRIMINAL CONVICTIONS	3508	125	24	280	240	12	1	2
NGLE CONVICTIONS								
CRIMINAL HOMICIDE	40			3	5			
FORCIBLE RAPE	45			2	3			
AGGREVATED ASSAULT	262	6		11	13			
ROBBERY	379	14	2	49	61	7		
NEGLIGENT HOMICIDE	42			3	4	1		
OTHER ASSAULTS	546	5		35	28	1		
WEAPONS	220	5		15	13	2		
SEXUAL OFFENSES	176		1	5	9			
OFFENSES AGAINST FAMILY	116			2	1			
OMVI/DUI	2165	10		54	33	2		
SALE OF MARIJUANA	41	6		8	23			
SALE OF OPIUM/COCAINE	46	14		44	10			
SALE OF SYNTHETHIC DRUGS	19	2		10	4			
SALE OF OTHER NON-NARCTCS	21	3		4	5			
MARIJUANA POSSESSION	144	8		17	37			
OPIUM/COCAINE POSSESSION	58	12		42	10			
SYN DRUGS POSSESSION	35	1	1	11	5	2		
OTHER NON-NARC POSSESSION	31	2		6	7			
YOUTH OFFENSES	434	3		19	23	1		
OTHER OFFENSES	423	3	3	71	52	2		
LTIPLE CONVICTIONS								
CRIMINAL HOMICIDE	3				1			
FORCIBLE RAPE	11				1			
AGGREVATED ASSAULT	123	1	1	1	3			
ROBBERY	133	7		32	21			
NEGLIGENT HOMICIDE	1							
OTHER ASSAULTS	319	1		7	11			
WEAPONS	70	1		5	4			
SEXUAL OFFENSES	42	1		3	3			
OFFENSES AGAINST FAMILY	43			2	2			
OMVI/DUI	1942	9	2	33	24		1	
SALE OF MARIJUANA	12			4	5			

ATE OF REPORT : 08/03/87
IME OF REPORT : 09:19:35
EGIN PERIOD DATE: 07/86
ND PERIOD DATE : 06/87

LIENT CHARACTERISTICS	ALCOHOL	SYN OPIATES	DEPRESSANTS	STIMULANTS	MARIJUANA AND HASHISH	HALLUCINO-GENS	POLYDRUG USE	OTHER SUBSTANCE
INSURANCE	529	8	3	31	28			
SOADA PROGRAM	4698	72	15	378	327	13	2	
VETERANS ADMINISTRATION	872	2	1	21	8			
OTHER THIRD PARTY	289	1	4	27	22	3		
UBSTANCE ABUSER								
CLIENT	9639	207	31	664	565	26	3	2
SPOUSE	52	1		3	4			
OTHER FAMILY MEMBER	134	2	2	6	8			
NON-FAMILY MEMBER	72				2			
RIMARY PROBLEM								
ALCOHOL	9946							
HEROIN		144						
METHADONE		6						
OTHER OPIATES & SYNTHETIC		61						
BARBITUATES			3					
TRANQUILIZERS			9					
SEDATIVES/HYPNOTICS			13					
INHALENTS			8					
AMPHETEMINES				18				
COCAINE				655				
MARIJUANA/HASHISH					579			
HALLUCINOGENS						26		
PCP								
OVER THE COUNTER								
OTHER DRUGS								2
POLYDRUG USE							3	
MARITAL								
FAMILY								
LEGAL								
MEDICAL								
PSYCHOLOGICAL/EMOTIONAL								
FINANCIAL								
POVERTY								
OTHER NON-DRUG								
ECONDARY PROBLEM								
ALCOHOL	50	24	10	261	349	2		1
HEROIN	35	17		31	2			
METHADONE	3	2		1	1			

CLIENT CHARACTERISTICS BY PRIMARY SUBSTANCE USED

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STATEWIDE SUMMARY

TE OF REPORT : 08/03/87
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GIN PERIOD DATE: 07/86
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IENT CHARACTERISTICS	ALCOHOL	SYN OPIATES	DEPRESSANTS	STIMULANTS	MARIJUANA AND HASHISH	HALLUCINOGENS	POLYDRUG USE	OTHER SUBSTANCE
	PRIMARY SUBSTANCE ABUSED							
LEGAL	41			1	4			
MEDICAL	8							
PSYCHOLOGICAL/EMOTIONAL	32	2			6			1
FINANCIAL	42	3						
POVERTY	8							
OTHER NON-DRUG	28	8		2	1			
VERITY OF PROBLEM								
NON-DEPENDENT	836	4	5	29	40	2		
DEPENDENT	5700	192	18	500	296	10	1	2
EPISODIC	1960	7	3	49	97	8	1	
DYSFUNCTIONAL	469	2	1	21	32	3		
UNKNOWN	847	6	6	68	104	3	1	
IMARY OTHER PROBLEM								
MARITAL	528	7	3	36	17			
FAMILY	811	16	3	65	80	4		
LEGAL	2361	32	7	207	142	5		
MEDICAL	393	9		21	4			
PSYCHOLOGICAL/EMOTIONAL	1468	24	13	155	85	8		
FINANCIAL	889	37	1	42	28			
POVERTY	203	1		7	4			
OTHER NON-DRUG	249	3	1	17	26			
CONDARY OTHER PROBLEM								
MARITAL	244	9		34	9			
FAMILY	632	24	3	71	62	3		
LEGAL	508	2		37	40	1		
MEDICAL	255	8	1	15	5	1		
PSYCHOLOGICAL/EMOTIONAL	915	19	5	99	62	4		
FINANCIAL	1012	26	3	71	38	1		
POVERTY	234			10	6			
OTHER NON-DRUG	336	4	3	12	16			
RTIARY OTHER PROBLEM								
MARITAL	95	2		15	3			
FAMILY	209	12		39	20	1		
LEGAL	175	4	1	20	24	3		
MEDICAL	108	4		10	3			
PSYCHOLOGICAL/EMOTIONAL	3[illegible]9	16	1	36	31	1		
FINANCIAL	416	12	2	44	17	2		

FACTS ABOUT DRUG USE IN JUNEAU

1983 UAA Survey showed that of 298 students in grades 7-12;

71% had tried alcohol

51% had tried marijuana

32% had tried stimulants

20% had tried inhalants

19% had tried cocaine

13% had tried depressants

1977 Juneau Youth Advisory Board random sample survey of 244 student in grades 5-12 learned that;

34% of students reported that some of their friends "have a problem with alcohol".

60% of those regarded the problem as "serious".

March 85 JDHS Student Survey indicates;

Alcohol is the #1 most commonly used drug

Marijuana is the second most commonly used drug

Speed is the #3rd most used drug

In a 1979 student survey for The Bird students reported the following:

20% drink "just on weekends"
11% drink "several times a week"

18% reported drinking"quite a few"
27% reported drinking "until I'm Drunk"

ALCOHOLISM AND OTHER ALCOHOL-RELATED PROBLEMS AMONG CHILDREN AND YOUTH

- ☐ Alcohol is America's No. 1 drug problem among youth. In 1985, an estimated 4.6 million adolescents aged 14 through 17 experienced negative consequences of alcohol use (e.g., arrest, involvement in an accident, impairment of health or job performance). (NIAAA, Projection of data in Alcohol and Health Monograph 1, Alcohol Consumption and Related Problems 1982, p. 85, updated with Bureau of the Census 1985 Population Projections.)
- ☐ Alcohol is over twice as popular among college students as the next leading drug, marijuana, and over five times as popular as cocaine. Ninety-two percent of college students reported using alcohol in a twelve-month period compared to 42 percent who had used marijuana and 17 percent who had used cocaine. (Institute for Social Research, University of Michigan, Ann Arbor, MI, Drug Use Among American High School Students and Other Young Adults 1985.)
- ☐ Only 42 percent of fourth graders know that alcohol is a drug, compared to 81 percent who consider marijuana a drug; the percentage of students considering alcohol a drug drops with age to 28 percent in the upper grades. (Weekly Reader Publications, A Study of Children's Attitudes and Perceptions About Drugs and Alcohol, Middletown, CT, Apr. 25, 1983.)
- ☐ The earlier in life a child starts using any dependence-producing drug, the more likely he or she is to experience dependence and other health problems, and go on to other dependence-producing drugs. (Robert L. DuPont, "Substance Abuse," Journal of the American Medical Association, Vol. 254, #16, Oct. 25, 1985, p. 2336.)
- ☐ Lower expectations for the future, alienation and boredom are associated with drinking among children in all socio-economic groups. (Nancy P. Gordon & Alfred McAlister, "Promoting Adolescent Health," Adolescent Drinking: Issues and Research, New York: Academic Press, 1982, p. 205.)
- ☐ Approximately 10,000 young people aged 16–24 are killed each year in alcohol-related accidents of all kinds, including drownings, suicides, violent injuries, homicides and injuries from fire. (US DHHS: NIAAA, Public Health Service, "Questions and Answers: Teenage Alcohol Use and Abuse," Prevention Plus: Involving Schools, Parents and the Community in Alcohol and Drug Education, Publication No. CADM 841256, Rockville, MD, 1983, p. xiii.)
- ☐ Alcohol-related highway deaths are the number one killer of 15- to 24-year-olds. (US DHHS National Center for Health Statistics, Public Health Service, Health, United States, 1980, Pub. No. (PHS) 81-1232, December 1980.)
- ☐ It takes less alcohol to produce impairment in youth than in adults. Younger drivers in fatal crashes have lower average blood alcohol concentrations (BACs) than older drivers. Blood alcohol concentration is the amount by weight of alcohol in a volume of blood, and is typically expressed as percent weight by volume. A BAC of .05 percent is equal to 50 mg of alcohol per deciliter of blood (approx. 3.5 fluid oz). ("Blood Alcohol Concentrations among Young Drivers, 1983," Morbidity and Mortality Weekly Report (MMWR),33:699-701, 1984.)
- ☐ Drivers 16–24 years old represent 20 percent of licensed drivers and less than 20 percent of total miles driven, and yet account for 42 percent of all fatal alcohol-related crashes. (US DOT Fatal Accident Reporting System, 1982, DOT No. HS-806-566, 1984 (h).)
- ☐ Of 27,000 New York public school students, grades 7 through 12, 11 percent described themselves as being "hooked" on alcohol, with 13 percent admitting to attending classes while "high," "drunk" or "stoned" on alcohol. (New York State Division of Alcoholism and Alcohol Abuse, Drug and Alcohol Survey, 1983.)
- ☐ Nearly 100,000 10- and 11-year-olds reported getting drunk at least once a week in 1985. Over 185,000 sixth graders have used hard liquor by age 10. Alcohol use at least once a week by sixth graders more than doubled from 1983 to 1984. (Ronald Adams and Thomas Gleaton, Parents' Resource Institute for Drug Education, PRIDE—Drug Usage Prevalence Questionnaire, 1985.)
- ☐ About one-third of fourth-graders (9-year-olds) said children their age pressured others to drink beer, wine or liquor; the figure increased to nearly 80 percent by high school. (Weekly Reader Publications, A Study of Children's Attitudes and Perceptions About Drugs and Alcohol, Middletown, CT, 1983.)
- ☐ Alcoholics are more likely than non-alcoholics to have an alcoholic father, mother, sibling or distant relative. Almost one-third of any sample of alcoholics had at least one parent who was also alcoholic. (Alcoholism: An Inherited Disease, US DHHS, Pub. No. (ADM) 85-1426, 1985, p. 3.)
- ☐ Children of alcoholics have a four times greater risk of developing alcoholism than children of non-alcoholics. There are 28.6 million children of alcoholics in the U.S. today, 6.6 million of whom are under the age of 18. (Children of Alcoholics Foundation, Children of Alcoholics: A Review of the Literature, 1985, Introduction and p. 2.)