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Research on the factors involved in cessation of the use of marijuana should also be carried out. Tobacco smoking is declining among youth (National Institute of Education, 1979). The reasons for this decline could be applicable to marijuana use and should be sought.

Studies should be undertaken to learn how peer influence can be reliably used to moderate or prevent marijuana use in young adolescents.

Properly planned longitudinal cohort studies should be conducted on both the behavioral and physiological antecedents and consequences of the use of marijuana. Detailed and continuing medical and psychosocial data are needed on the life careers of American adults who use marijuana "daily." Retrospective studies of middle-aged and elderly persons who have a history of chronic heavy use of marijuana would be systematically studied for medical and psychosocial attributes and for effects on job performance. These are especially needed for urban industrialized populations.

Little is known about the consequences of using marijuana in combination with other drugs. Inasmuch as the rates of use of other drugs are so high, this is of great salience. Interdisciplinary and collaborative efforts are crucial if the complexities of multiple drugs and intercorrelated behaviors are to be disentangled.

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3

EFFECTS OF MARIJUANA ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEMS

RESPIRATORY SYSTEM

Performance (Pulmonary Function)

The lungs are the natural target for the harmful effects of smoked materials. This is as true for marijuana as for tobacco. In both instances, smoke is drawn into the lungs where it can harm not only the cells that line the airways (trachea, nasopharynx, bronchi, and alveoli) and constitute the lung tissue, but also impair such cells as lung macrophages, which are part of the immune system. As a result, the smoke may inflict injury directly on parts of the system and also make the lungs vulnerable to agents that normally are held at bay by self-cleansing and self-protecting mechanisms.

Different effects would be expected from tobacco and marijuana smoking because of the striking differences in the way in which the two substances are smoked: marijuana smoke usually is drawn deeply into the lungs by one or a few deliberately deep breaths, whereas tobacco smoking is generally more automatic, repetitive, and variable in pattern. Moreover, because marijuana is a "street drug," it not only is inconsistent in its content but also is subject to contamination. Also, filters are not usually used by marijuana smokers, although water pipes are used occasionally. Consequently, under natural conditions it is difficult to judge dosage of active ingredients, to sort out the influence of contaminants, and to compare the consequences of marijuana and tobacco smoke.

Experience over the years with cigarette smoking has shown that continued exposure to tobacco smoke entails the risk of producing chronic bronchitis and/or carcinoma of the lung. But, although cannabis products have been smoked for centuries, remarkably little is recorded about their effects on the lungs. Whatever contemporary information exists is confounded by the fact that most marijuana smokers are also tobacco smokers.

In recent years, interest has heightened in the smoking of marijuana as a therapeutic measure. The inhalation route takes advantage of the large surface area afforded by the lungs for administering the effective constituents of marijuana. However, this

practice entails the disadvantage of administering a therapeutic agent in a cloud of air pollutants.

In brief, our appraisal must assess the impact of chronic bronchial irritation and inflammation on the airways and gas-exchanging surfaces of the lungs.

Acute Effects

Marijuana affects the control of the breathing pattern in different ways depending upon the dose, the preparation, and its psychotropic effect on the consumer. One marijuana cigarette generally stimulates ventilation (air exchange between the lungs and the ambient air) in conjunction with an increase in the metabolic rate and a heightened response to carbon dioxide (CO_2) as a regulatory stimulant (Vachon et al., 1973; Zwillich et al., 1978). On the other hand, larger doses of smoked marijuana may depress the ventilation and responsiveness to the CO_2 stimulus (Weil et al., 1968; Bellville et al., 1975). The intravenous administration of Δ-9-THC in equivalent doses has much less of an effect either on the ventilation or on the effectiveness of CO_2 as a respiratory stimulant (Malit et al., 1975).

Much more consistent and predictable is the effect of marijuana on the airways. The inhalation of small amounts of marijuana smoke causes bronchial dilation in persons without demonstrable lung disease (Tashkin et al., 1973; Vachon et al., 1973). The bronchodilation is easily demonstrable; the inhalation of isoproterenol (1250 μg), a potent bronchodilator, caused less of an improvement in airways conductance than the peak effect observed after smoking 2 percent marijuana (Tashkin et al., 1973). Ingestion of Δ-9-THC is less effective than smoking marijuana in producing bronchodilation; the bronchodilator effects of smoked marijuana last as long as 60 minutes; that of ingested Δ-9-THC up to 6 hours. Aerosolized Δ-9-THC has a local irritating effect on the airways, which often overrides the bronchodilating effect to the point of making it unsuitable for therapeutic purposes (Tashkin et al., 1977a).

Except for bronchodilation, acute exposure to marijuana has little effect on breathing as measured by conventional pulmonary tests. Thus, in young marijuana smokers (21-30 years of age) who smoked at least four cigarettes per week and no tobacco for at least 6 months before, ventilatory mechanics and gas exchange were normal by conventional tests (Tashkin et al., 1976). In contrast, heavy marijuana smoking, i.e., at least 4 days per week for 6 to 8 weeks did cause mild airway obstruction (Tashkin et al., 1976).

Acute smoking of marijuana, as well as the ingestion of Δ-9-THC, also causes bronchodilation in individuals with mild to moderate asthma (Tashkin et al., 1974). Marijuana smoking or ingestion of Δ-9-THC also dilated airways in asthmatics in whom bronchoconstriction was deliberately provided either by exercise or by the inhalation of methacholine, a bronchoconstrictor (Shapiro et al., 1976a). The mechanism by which bronchodilation is effected is not clear, but does not involve stimulation of beta-adrenergic

receptors or blockade of muscarinic receptors in airway smooth muscle (Shapiro et al., 1976a). Adding to the difficulties of interpretation are the psychotropic effects of marijuana: four of the individuals who had previously used cannabis could distinguish the marijuana cigarette from the placebo on the basis of the intoxicating experience afforded by the marijuana smoke. Although the four subjects without previous cannabis experience did not experience any central nervous system effects, they did note mild somnolence or light-headedness after marijuana use.

Among the experiments with induced asthma were some that employed the inhalation of cannabinoid-free marijuana smoke (Tashkin et al., 1975). The results indicate that the smoke of the marijuana cigarette does not prevent methacholine-induced bronchospasm (Tashkin et al., 1976). Smoking of marijuana did not aggravate or perpetuate bronchoconstriction in stable asthmatics, and it promptly reversed experimentally induced bronchospasm (Tashkin et al., 1978). Addition of Δ-9-THC to placebo smoke caused a prompt, complete, and sustained reversal of methacholine-induced bronchospasm. Although ingestion of Δ-9-THC in a sesame oil vehicle has produced bronchodilation in asthmatic patients, less dilation was noted than after smaller doses of Δ-9-THC delivered by smoking (Tashkin et al., 1974).

Although it appears that the mechanism of Δ-9-THC-induced bronchial dilation is mediated by the autonomic nervous system, the process of dilation is not understood (Gill and Paton, 1970; Cavero et al., 1972; Shapiro et al., 1973).

Subacute Effects

Pulmonary function tests in 28 healthy young experienced cannabis users before and after a 47-59-day period of heavier than customary marijuana usage (group daily average of 5.2 cigarettes, with a daily mean range of 1.7 to 10 cigarettes per subject) disclosed the development of mild but significant decreases in specific airway conductance and forced expiratory flow as well as in diffusing capacity (Tashkin et al., 1976). Cessation, by reduction in smoking, gradually restored the tests toward normal. The clinical significance of these abnormalities is uncertain. The marijuana smoked and the impairment in pulmonary function, coupled with the observation that reversibility of function was incomplete 1 week after marijuana smoking had stopped, suggests that heavy marijuana smoking over a much longer period could lead to clinically significant and less readily reversible impairment of pulmonary function.

Chronic Effects

A study of 31 American soldiers stationed in West Germany who smoked large quantities of hashish (100 grams or more per month for periods

of 6 to 15 months) found their ailments to be principally respiratory, including bronchitis, sinusitis, asthma, and rhinopharyngitis (inflammation of the nasopharynx) (Tennant et al., 1971). In one-third of the soldiers, sputum-producing coughs, difficulty in breathing, and wheezing followed 3 to 4 months of regular use of hashish. However, they had a normal chest radiograph and normal sputum. Antibiotics failed to relieve the symptoms. The symptomatic patients could not work and four required hospitalization. An unspecified decrease in hashish consumption improved their symptoms.

Pulmonary function tests in these individuals showed mild airway obstruction after 3 days of lessened hashish intake. Moreover, the response of these individuals to isoproterenol suggested that reversible bronchospasm and/or the accumulation of fluid in the bronchi was involved in the pathogenesis of the airway obstruction. Patch and serological tests failed to implicate allergy as a cause of the upper respiratory symptoms and signs.

In Jamaica (Hall, 1975), where marijuana usage is heavy, chronic bronchitis is frequent. However, marijuana smoking is usually associated with tobacco smoking, which confounds interpretation of the effects of marijuana alone. Adding to the uncertainty about the effects of marijuana as a cause of chronic regulatory abnormalities are two other studies, one in Jamaica (Rubin and Comitas, 1975) and the other in Costa Rica (Hernandez-Bolanos et al., 1976), which failed to find any difference in the prevalence of chronic respiratory disease between smokers and nonsmokers of marijuana. These results cannot be accepted as conclusive, because in each study the number of marijuana smokers was small, the subjects were not randomly selected, and the use of tobacco was not taken into account.

Much more convincing is a recent study (Tashkin et al., 1980) of 74 persons who smoked marijuana for 2 to 5 years, typically as frequently as several times per day, 3 to 6 days per week. Care was taken to obtain proper control groups. The results indicated that habitual smoking of marijuana causes a mild but significant increase in resistance to airflow in the large airways without an appreciable effect on conventional tests.

Another study was of 200 American soldiers stationed in West Germany who voluntarily sought medical attention for such respiratory symptoms as pharyngitis, sinusitis, bronchitis, and asthma related to chronic heavy hashish smoking (Henderson et al., 1972). Analysis of the hashish available and in use in the locale of this study showed concentrations of 5 to 10 percent Δ-9-THC. Two to 3 percent of samples were contaminated with cocaine, opium, morphine, spices, or feces. Two aspects of hashish smoking are relevant to the question of lung injury produced by hashish: 1) hashish is usually smoked in a pipe (occasionally in a water pipe), although it is occasionally eaten, drunk as a tea, or rolled into a cigarette and smoked, and 2) hashish smoke generally is regarded by users as burning much hotter than tobacco smoke.

Soldiers with pharyngitis usually smoked less than 25 grams of hashish monthly; those with bronchitis and asthma consumed more than 50 grams per month. The common complaint of sore throat in these

heavy hashish smokers occurred most often in those who smoked hashish in a pipe without a screen or cotton filter; in them, the roof of the mouth and the back of the throat were inflamed. Persistent rhinitis (inflammation of the nasal mucous membranes) was present in 26 patients. As a rule, allergy could not be implicated in the nasopharyngeal manifestations. Treatment with antibiotics, decongestants, and phenylephrine (a vasoconstrictor) relieved the symptoms, but they recurred in those who continued smoking hashish.

Twenty high-dose hashish smokers (more than 50 grams/month) had chronic bronchitis as manifested by a chronic sputum-producing cough, shortness of breath, and decreased exercise tolerance. On physical examination, abnormal respiratory sounds--rhonchi, wheezes, and rales--were present. Chest radiographs were consistently normal, but pulmonary function was abnormal; the vital capacity (the maximum volume of gas taken in) was 15 to 40 percent below normal. In six of these subjects who smoked 50 or more grams per month, biopsy of bronchial mucosa revealed changes that resembled the abnormalities that occur in older heavy smokers of tobacco (Auerbach et al., 1961). The biopsies also turned up atypical cells not found in tobacco smokers.

The study of a respiratory disease in hashish or marijuana smokers is difficult because the great majority also smoke tobacco cigarettes. Also, the illegality of marijuana smoking prevents people from volunteering information and cooperating in experimental studies. Baseline physiological or clinical studies are difficult, because the subject is not identified until he seeks medical help.

Rats (Fleischman et al., 1979) and dogs (Roy et al., 1976) have been exposed experimentally to marijuana smoke over long periods (1 year and 900 days, respectively) to determine its morphological effects on the lungs. At autopsy, the animals demonstrated damage of the airways and also of the lung substance. However, it is difficult to relate the results of these animal experiments, in which the artificial pattern of smoking differed markedly from that of the human smoker, to the effects that chronic marijuana smoking might elicit in man.

Defense Mechanisms (Alveolar Macrophages)

Little is known about the effects of marijuana on the defense mechanisms of the lungs. Although some observations have been made on the alveolar macrophage, an important element in this system, the results have been inconsistent. For example, some studies of the rat lung found that macrophages obtained by washing out the lung and exposing them to marijuana smoke manifested a depression in bactericidal activity (Huber et al., 1975, 1979a,b, 1980). On the other hand, another report failed to disclose a significant effect, not only of marijuana, but also of tobacco smoke on the bactericidal activity of macrophages (Drath et al., 1979). Finally, others have found that alveolar macrophages differ slightly in their morphological responses to tobacco and to marijuana smoke. The significance of

these differences, especially in terms of their long-term effect on pulmonary defense mechanisms, remains to be defined.

Explants of lung have also been examined after exposure in culture to marijuana smoke (Leuchtenborger et al., 1973a,b; Leuchtenberger and Leuchtenberger, 1976). Striking changes have been observed in the appearance and growth characteristics of exposed cells.

Carcinoma of the Lung

The effect of marijuana as a carcinogen for lung, airways, and upper respiratory organs has not been systematically explored. Evaluating the carcinogenicity of marijuana is difficult, because most marijuana smokers also are tobacco cigarette smokers and because such carcinogenicity could have a long period of latency; studies of tobacco carcinogenesis indicate that 20 to 30 years of exposure must occur before tumors appear in the lung. It is understandable that information concerning the carcinogenic properties of marijuana are not yet available, particularly in the United States, where the agent has come into extensive use only during the past two decades. An important problem in evaluating carcinogenicity is the fact that the leaf is used by igniting it and the inhaled products of its combustion may be carcinogenic, as in the case of tobacco products. Even if it proved to be carcinogenic, the question would still remain as to what constituent in marijuana smoke was at fault.

The potency of a substance as a mutagen (ability to change genetic material) can provide a clue as to its possible role as a carcinogen. Induction of genetic mutations by a substance in test strains of bacteria correlates with induction of tumors in test animals. Fractions from extracts of marijuana smoke particulates ("tar") have been found to produce dose-related mutations in four out of five test strains of bacteria (Busch et al., 1979; Seid and Wei, 1979; Wehner et al., 1980). By itself, Δ-9-THC was not active as a mutagen in bacterial strains (Glatt et al., 1979) or in mammalian test systems (van Went, 1978).

The extent to which marijuana smoke differs from tobacco smoke is discussed in detail in Chapter 1. In general, except for the presence of cannabinoids in one and tobacco alkaloids (nicotine) in the other, the combustion products of tobacco and marijuana are qualitatively similar. On occasion, however, differences that may be meaningful have been found. For example, one study (Hoffmann et al., 1975) reports that tobacco smoke contains more isoprene and volatile phenols, whereas marijuana smoke contains about 50 percent more carcinogenic hydrocarbons.

Tumorigenicity of marijuana and tobacco smoke condensates on mouse skin have been reported. In mice painted three times weekly with a tar suspension of smoke condensate, survival at 74 weeks was better in the marijuana group than in the tobacco group. Six of 100 mice painted with marijuana condensate developed skin tumors, all of which were benign, whereas 14 of 100 in the tobacco condensate group developed tumors, two of them malignant (Hoffman et al., 1975).

Because marijuana smoke has adverse actions similar to tobacco smoke on cell function in the respiratory and cardiovascular systems, it has been proposed that marijuana smoke, rather than only the cannabinoid, should be used to obtain information about effects on cell injury and response (Leuchtenberger and Leuchtenberger, 1971). Exposure of human lung cells in culture to freshly generated marijuana smoke for up to 2 months resulted in increased mitotic indices, stimulation of DNA synthesis, and an increase in the population of cells with four times the DNA content of control cells or those exposed to tobacco smoke (Leuchtenberger et al., 1973a,b). Long-term exposure of hamster lung cells to the smoke of either marijuana or tobacco led to abnormal proliferation and malignant transformation within 3 to 6 months of exposure (Leuchtenberger and Leuchtenberger, 1976). Since malignant transformation was also noted in unexposed lung cells after 12-24 months of culture, it appears that the smoke of marijuana or tobacco accelerates, rather than initiates, the malignant change.

Although no instance of human lung carcinoma attributable solely to marijuana smoking has yet been reported, abnormalities suggestive of cancerous lesions have been recorded. For example, in several of the U.S. servicemen who smoked 50 grams of hashish or more per month and developed upper respiratory disorders, mucosal biopsy showed extensive cellular abnormalities, including loss of cilia, proliferatior of basal epithelial cells, and atypical cells (Tennant et al., 1971; Henderson et al., 1972). Comparison of 30 American hashish smokers (25-150 grams/month for 3-24 months; 23 also smoked tobacco and 7 did not), 3 tobacco smokers (1.6 packs/day for 11.3 years) who did not smoke marijuana and 3 nonsmokers of tobacco or hashish, indicated exposure to combined marijuana and tobacco smoke produced more harmful effects than that produced by either substance alone (Tennant et al., 1980). In the hashish smokers who did not smoke tobacco, abnormalities in the tracheal biopsies were no more frequent or severe than in those persons who smoked only tobacco.

Exception has been taken to the idea of an additive effect of tobacco and hashish smoke. A Greek study that compared chronic hashish and tobacco users with tobacco smoking controls found that although the hashish smokers had considerably more throat irritation and cough, the prevalence of bronchitis in both groups was about the same (Boulougouris et al., 1976); no biopsies were taken. The differences between the Greek and American studies may reflect differences between the two populations: The American study, done in Germany, favored inclusion of men with severe respiratory disturbances (Tennant et al., 1980), whereas the Greek study (Boulougouris et al., 1976) appears to have included persons with less severe illness.

The finding of known carcinogens in marijuana smoke and the presence of epithelial abnormalities known to be the precursors of lung cancer in heavy smokers of tobacco suggest the possible development of lung cancer in chronic, heavy users of marijuana and/or hashish after a prolonged period of use, especially if they are also smokers of tobacco. However, evidence to support this hypothesis is not available. Because marijuana smoking is an ancient

custom in Asia and the Middle East, lung cancer would be expected to be more prevalent in these parts of the world if a causal relationship did exist. Unfortunately, no reliable data have been gathered to settle this question. Heavy smoking of marijuana, in quantities comparable to that of tobacco, has been relatively uncommon in the United States. Therefore, the contribution of marijuana smoking to the incidence of primary lung cancer cannot yet be answered with any authoritative data.

Summary: Respiratory System

Lung Function and Defense Mechanisms

The most important question about the effects of marijuana on the health of the respiratory system is whether acute or chronic marijuana smoking cause detectable structural or functional impairment of the lungs. Mild but measurable airway obstruction, affecting both large and small airways, can be shown to exist after 6 to 8 weeks of smoking marijuana daily, averaging five marijuana cigarettes a day; this decrement in function is reversible, but does not return to normal within one week of abstaining from smoking.

In persons with histories of heavy smoking, particularly of hashish, chronic inflammatory changes are seen in the bronchi and uvula, often in association with chronic sinusitis. These manifestations of upper respiratory disturbance have been described in individuals with histories of marijuana smoking usually in excess of 3 years and are reversible when marijuana smoking is stopped.

Acute exposure of alveolar macrophages *in vitro* to marijuana smoke causes a reduction in phagocytic activity, a cell defense mechanism. The agents responsible for this change in macrophage function are in the vapor phase of marijuana smoke and are not related to the presence of Δ-9-THC. Also, lung explants exposed to marijuana smoke *in vitro* show changes in the chromosomal structure of nuclei.

There is as yet no information about the effects of prolonged smoking of marijuana, that is, beyond 5 years. Although some populations have been examined for the effects of chronic marijuana smoking, controlled studies are sparse and populations exposed to marijuana smoke only--without exposure to tobacco--apparently are not available. Particularly conspicuous is the lack of information about the effect of chronic marijuana smoking begun in late childhood or adolescence and continued to adulthood. Such studies would require morphological examination of biopsy material from the bronchi and respiratory passages to determine the presence of structural changes that indicate the development of chronic bronchitis and/or lung cancer. Morphological changes associated with smoking marijuana could be compared with the morphological abnormalities associated with chronic tobacco smoking.

The acute response to inhalation of marijuana is an appreciable bronchodilation, both in normal subjects and in individuals with

bronchial asthma. However, the bronchodilator effects of marijuana are a response to acute exposure; chronic exposure usually evokes bronchoconstriction.

With respect to therapeutic application, the effects of smoking marijuana in producing bronchial dilatation do not exceed those that follow the inhalation of beta-agonist drugs. Moreover, the doses required for bronchodilatation usually elicit the psychotropic effects of marijuana and may be associated with changes in the structure of bronchial and parenchymal lung cells, the significance of which remains to be assessed. For these reasons therapeutic usefulness as a bronchodilator drug is open to serious question (see Chapter 7).

Carcinoma of the Lung

One of the great uncertainties about marijuana smoking is its neoplastic potential. No reliable data are available concerning the incidence of carcinoma of the lungs and upper respiratory passages in long-term users of cannabis.

But a variety of experimental studies has sounded the alert that marijuana smoking--just as tobacco smoking--may be carcinogenic and that a combination of tobacco and marijuana smoke may have greater neoplastic potential than either one alone. Although the experimental observations have raised the suspicion, long-term observations on human subjects--and possibly on smoking animals--will be necessary to settle the issue.

Recommendations for Research

Lung Function and Defense Mechanisms

With respect to the performance and defenses of the lungs, these studies would be informative:

- the physiological, biochemical, and morphological interactions of combined exposures of the respiratory tract to tobacco and marijuana smoke;
- the interactions of cannabis and alcohol on the function of the respiratory tract;
- the long-term effects, i.e., 10 to 30 years, of exposure of the respiratory tract to frequent use of cannabis in the absence and pressure of exposure to tobacco smoke (for this purpose, large-scale epidemiological studies may be required);
- the physiological effects and clinical consequences of exposure of alveolar macrophages and other lung cells to long-term exposure to marijuana smoke;
- the immunologic effects of marijuana smoke exposure on cells and on the entire body.

Carcinoma of the Lung

With respect to carcinoma of the lung, these studies seem essential:

- an epidemiological survey to determine over the next 20 to 30 years if there will be an increased incidence of primary lung, laryngeal, oropharyngeal, esophageal, nasal, or sinus cancer in chronic marijuana smokers;
- epidemiologic and pathological studies in humans and experimental studies in animals to evaluate the carcinogenic potential of chronic marijuana smoking on the lung, larynx, oropharynx, nasal, and sinus epithelium.

CARDIOVASCULAR SYSTEM

Normal Heart and Circulation

Heart (Direct Effects)

With respect to the heart and circulation, the most evident effect in human beings of smoking marijuana, or of ingesting the active ingredient (Δ-9-THC), is a brisk increase in heart rate (tachycardia). Although this is not threatening to the normal heart, the rapid heart action can be harmful to the heart in which the circulation is compromised by atherosclerosis or is on the verge of failing.

The responses of the cardiovascular system to acute exposure to marijuana differ between human beings and most other mammals in that the human subject typically responds with an increase in heart rate (Bright et al., 1971; Beaconsfield et al., 1972; Perez-Reyes et al., 1973), whereas most mammals show a slowing in rate (bradycardia) (Cavero et al., 1973; Graham and Li, 1973; Rosenkrantz and Braude, 1974; Vollmer et al., 1974; Adams et al., 1976; Hardman and Hosko, 1976; Kawasaki et al., 1980). Human blood pressure usually increases moderately on acute administration of Δ-9-THC, but in monkeys and dogs acute administration is followed by a decrease in systemic arterial pressure. Typical effects on heart rate and blood pressure have been attributed to altered autonomic function (Loewe, 1944; Joachimoglu, 1965; Ames, 1968; Gill and Paton, 1970).

Effects on the cardiovascular system are to some extent a function of dose, route of administration, and duration of exposure. Tolerance to some of the cardiovascular effects in human beings develops with chronic use (Benowitz and Jones, 1975, 1977a,b; Nowlan and Cohen, 1977), but continued use does not result in any persistent alteration in cardiovascular function after cessation of exposure (Dornbush and Kokkevi, 1976).

Effects on Heart Rate In healthy young adults, acute administration of marijuana by smoking (10 mg total dose) causes a prompt increase in heart rate (increasing by up to 90 beats/minute) for about 1 hour.

The change in heart rate caused by Δ-9-THC appears to result from alterations in both sympathetic and parasympathetic efferent activity to the normal cardiac pacemaker (Beaconsfield et al., 1972; Martz et al., 1972; Sulkowski et al., 1977). The results of studies designed to determine whether beta-adrenergic stimulation is responsible for the tachycardia have not been consistent: In one series of reports, prior administration of propranolol,* in a dose sufficient to block the heart's beta-adrenergic receptors, prevented the increase in heart rate (Bright et al., 1971; Beaconsfield et al., 1972; Perez-Reyes et al., 1973), whereas in other reports, propranolol failed to block the marijuana-induced tachycardia (Kanakis et al., 1976; Tashkin et al., 1978). Although part of the discrepancy may be attributable to differences in dosages, not all of it can be rationalized this way, leaving an unexplained disparity.

Hemodynamic Effects Effects of marijuana on blood pressure and cardiac output, as mentioned above, are a function of the nature of exposure (acute or chronic), of the dose, and of the body position; also, there are differences among human beings and a number of mammalian species. In human beings lying supine, acute exposure to Δ-9-THC typically causes a modest increase in blood pressure, although in some instances no significant change in pressure has been observed (Beaconsfield et al., 1972; Kanakis et al., 1976; Benowitz et al., 1979). On assuming the upright posture, blood pressure may drop considerably. Cardiac output, in the supine position following an injection of Δ-9-THC, has been found to increase by as much as 30 percent (Malit et al., 1975; Tashkin et al., 1977b). The increase in cardiac output in the face of only a modest increase in blood pressure clearly results in a substantial decrease in peripheral vascular resistance. The change in resistance varies among the different vascular beds, being greatest in the vessels to the skeletal muscles.

Chronic administration of quite large oral doses of Δ-9-THC exerts different effects (than the acute) on the circulation (Bernstein et al., 1974; Benowitz and Jones, 1975; Benowitz et al., 1979). Systolic and diastolic pressure usually fall slightly, but these changes are not always sustained. As the blood pressure falls, the heart rate slows from the high levels caused by initial marijuana administration. The decrease in blood pressure can be accentuated if the subject assumes an upright posture. The extent to which it drops appears to be a reciprocal function of the extent to which plasma volume has increased.

Effects on Heart Muscle Data about changes in human left ventricular function caused by marijuana are not entirely convincing because most studies have relied on noninvasive measurements and

*Propranolol is an agent that blocks beta-adrenergic neurotransmitters and is used in treatment of cardiac arrhythmias.

because it has not been possible to control separately the several variables that modify left ventricular function and are changed by administration of Δ-9-THC. Changes in heart rate, afterload (systemic vascular resistance, blood pressure), or preload (plasma volume, venous return) individually can cause changes in heart size and ventricular performance. In spite of these limitations, conclusions can be drawn from the observations on human beings. Definitive animal studies of Δ-9-THC effects on ventricular performance have not been done.

Indices of cardiac performance usually improve after marijuana or Δ-9-THC. Almost invariably this improvement can be attributed to the increase in heart rate (Gash et al., 1978). The acute administration of Δ-9-THC (25 μg/kg intravenously) to healthy young males elicits, in association with the increase in heart rate, changes in the ventricular contraction periods (an increase in ejection time and shortening of the preinjection period), while systemic arterial pressure is unaffected (Weiss et al., 1972; Kanakis et al., 1976). Beta-adrenergic blockade by propranolol is followed by less striking changes in the contraction time intervals. Another study of 17 subjects who smoked two to three cigarettes (20 mg Δ-9-THC per cigarette) found cardiac output increased by 28 percent and heart rate by 30 percent, in conjunction with a slight decrease in stroke volume, which affects pulse pressure (Tashkin et al., 1977b).

Autonomic Nervous System

Marijuana could influence autonomic function in several ways: (1) by changing the sensitivity of reflexes that influence and control cardiovascular function; this effect could result either from changes in the processing of nerve impulses in the central nervous system or autonomic ganglia (a group of nerve cells outside the central nervous system), from changes in the liberation or metabolism of transmitters at the autonomic nerve terminals, or from changes in the sensitivity of the pre- or postjunctional receptors; (2) by a change in the levels of neurotransmitters, the catecholamines (norepinephrine, epinephrine) in the blood as a result of actions on the adrenal medulla, which secretes these neurotransmitters; activation of the adrenals could be a direct effect or by reflexes or by a central action of Δ-9-THC; and (3) by exerting effects on dopamine activity (an intermediate product in the synthesis of norepinephrine) either in the central nervous system or periphery.

Unfortunately, it is unclear how the effects of Δ-9-THC are exerted on the autonomic nervous system (Truitt and Anderson, 1971; Beaconsfield et al., 1972; Weiss et al., 1972; Englert et al., 1973; Ho et al., 1973; Howes and Osgood, 1974; Ho and Johnson, 1976; Huot, 1976; Benowitz and Jones, 1977a,b; Gash et al., 1978; Stefanis, 1978). The data are insufficient to determine if the effects come by way of the central nervous system, or by peripheral neural structures, or by the adrenal medulla. It is also difficult to assess the role of

reflex adjustments in the heart and systemic circulation. Finally, other possibilities, such as desensitization or blockade of peripheral adrenergic receptors, have not been examined.

Although the data on human beings are not adequate to determine how marijuana influences autonomic function, evidence that it does has been obtained. For example, Δ-9-THC appears to reduce a number of autonomic reflexes: After marijuana, the typical changes in heart rate and blood pressure elicited by the Valsalva maneuver (a forced exhalation effort against the closed glottis) are decreased, and so are the reflex circulatory responses to immersion of the hand in cold water (Beaconsfield et al., 1972; Benowitz et al., 1979). However, during chronic administration of Δ-9-THC, no change occurs in the reflex decrease in heart rate caused by infusion of a dose of the vasoconstrictor phenylephrine sufficient to increase the blood pressure (Benowitz and Jones, 1975; Benowitz et al., 1979).

Exercise

Acute exposure to Δ-9-THC modifies exercise performance by human beings. Smoking (20 mg of Δ-9-THC) decreased the duration of exercise but caused no change in any cardiopulmonary parameter at any work load except for heart rate, which increased (Shapiro et al., 1976b).

Other Effects (Plasma Volume, Sodium Retention)

Acute administration of Δ-9-THC would not be expected to have prominent effects on sodium balance or plasma volume. Chronic administration, on the other hand, has distinct effects. With chronic ingestion of large doses of Δ-9-THC there is a consistent gain in body weight and plasma volume, the latter caused by sodium retention (Benowitz and Jones, 1975, 1977a,b). The change in plasma volume seems to be causally related to the decrease in orthostatic hypotension during chronic exposure. The mechanisms responsible for the retention of salt and water have not been explored and may include changes in renal perfusion, inhibition of prostaglandin (a substance that affects blood pressure) synthesis by Δ-9-THC (Burstein and Raz, 1972; Howes and Osgood, 1976), or some modification in pituitary-adrenal function (Birmingham and Bartova, 1976).

Abnormal Heart and Circulation

Although smoking marijuana or the introduction of Δ-9-THC into the body is apparently without deleterious effect on the normal heart and circulation, the possibility is great that the abnormal heart and circulation will not be as tolerant of an agent that speeds up the heart, sometimes unpredictably raises or drops the blood pressure,

and modifies the activities of the autonomic nervous system. Therefore, it is pertinent to examine the prospects that marijuana (or Δ-9-THC) may be harmful in individuals with coronary heart disease, cerebrovascular disease, hypertension, and heart failure. Moreover, it may be important to determine if Δ-9-THC interacts in its effects on the abnormal heart or circulation with other agents that are being administered for therapeutic purposes.

Coronary Heart Disease

Data on this topic are sparse, presumably because of the relatively short time that marijuana has been available in this country. Those who have smoked marijuana are just entering the age when coronary atherosclerosis is common. However, it has been shown both in normal individuals and in individuals with coronary artery disease that the acute administration of Δ-9-THC by smoking or injection can cause changes in the electrocardiogram (ECG) (Johnson and Domino, 1971; Beaconsfield et al., 1972; Kochar and Hosko, 1973). Premature beats have also been noted. The reasons for the changes are unclear. Also not understood is the contribution of the increase in heart rate itself to the ECG changes and to the premature beats.

In some patients with coronary artery disease, increased catecholamines can induce arrhythmias. It seems likely that in such patients Δ-9-THC could have the same effect. Also, in patients with coronary artery disease a large increase in heart rate can induce angina (pain) and even ischemic damage from insufficient oxygen as a result of an obstructed blood vessel. If Δ-9-THC were to increase heart rate markedly in such patients, and at the same time increase the need for cardiac perfusion because of the increased cardiac work and because of the intensified effect of catecholamines on the heart, it seems reasonable that there could be induction of angina and potentially precipitation of ischemic damage. Furthermore, if Δ-9-THC dulled the appreciation of pain and the appropriate responses to pain, the patient might not take suitable measure to relieve the angina, thereby increasing the risk of damage or arrhythmias.

A decrease in oxygen-carrying capacity of blood because of formation of carboxyhemoglobin could also be troublesome. Exercise tolerance has been reported to decrease in individuals with angina after smoking marijuana; this decrease is in contrast to the unaffected exercise tolerance after smoking a placebo marijuana cigarette (Aronow and Cassidy, 1974). Oral ingestion of Δ-9-THC or smoking marijuana apparently can cause marked hypertension in association with an increase in systemic vascular resistance (Benowitz et al., 1979), which would place the heart with coronary artery disease at risk of damage.

These observations concur in indicating that marijuana and Δ-9-THC increase the work of the heart, often in many ways. The conclusion seems inescapable that this increased work, coupled with stimulation by catecholamines, may tax the heart to the point of clinical hazard.

Cerebrovascular Disease

There are few, if any, indications that Δ-9-THC has direct effects on the cerebral circulation that would be important in patients with cerebrovascular disease. In the occasional patient who develops hypertension after smoking, there would be an increased risk of a cerebral vascular accident (stroke). Also, because Δ-9-THC administered after atropine can cause marked increases in blood pressure, this combination would place the patient with cerebrovascular disease at risk, as would smoking after ingestion of other muscarinic blockers. In some patients, postural hypotension could be a problem, not only for persons with abnormal cerebral circulations, but also with abnormal coronary circulations.

Hypertension

The factors that act to intensify angina would be of importance in hypertensive patients. Although data are lacking on the magnitude of change in blood pressure caused by Δ-9-THC in hypertensives, it seems reasonable to assume that hypertensives smoking marijuana might have a greater increase in blood pressure than normals do. The increase in plasma volume and sodium retention that are associated with chronic exposure to Δ-9-THC could increase blood pressure in hypertensives and the mechanisms responsible for these changes very likely would interfere with the action of a number of antihypertensive medications.

Heart Failure

Because marijuana can cause tachycardia, a decrease in systemic vascular resistance (required for increased cardiac output to sustain blood pressure) and salt and water retention might place patients with severe heart failure at a disadvantage by exposure to Δ-9-THC. Data on such patients are lacking. In older patients treated by Δ-9-THC or who have smoked marijuana for glaucoma or cancer, orthostatic hypotension has been both disabling and a threat of cardiovascular complications (Merritt et al., 1980). However, tolerance to orthostatic hypotension seems to develop during continued intake of Δ-9-THC or continued smoking of marijuana. Dehydration, as during vomiting or diuretic therapy, predisposes to the orthostatic hypotensive effects and resists the development of tolerance because it prevents expansion of blood volume.

Interactions with Cardioactive Drugs

Few studies evaluate interactions between Δ-9-THC and other drugs that act directly or indirectly on the heart. Propranolol usually attenuates the increase in heart rate caused by Δ-9-THC. Atropine

can greatly potentiate the ability of Δ-9-THC to increase systemic arterial pressure (Benowitz and Jones, 1977a,b). A number of possible interactions can be imagined. If a patient were taking a drug that blocked uptake of catecholamines by nerve terminals, then those effects of Δ-9-THC that are mediated by catecholamines would be intensified. Because a great many psychotropic and antihypertensive drugs modify metabolism of neurotransmitters in the central nervous system and periphery, a wide variety of interactions with Δ-9-THC seems possible.

Summary: Cardiovascular System

The smoking of marijuana causes changes in the heart and circulation that are characteristic of stress. But there is no evidence to indicate that it exerts a permanently deleterious effect on the normal cardiovascular system. Neither is there convincing evidence that marijuana would be of particular benefit in treating any of the major forms of cardiovascular disease.

The situation is quite different for those with an abnormal heart or circulation. Evidence abounds that marijuana increases the work of the heart, usually by increasing heart rate, and in some persons by increasing blood pressure. This increase in workload poses a threat to patients with hypertension, cerebrovascular disease, and coronary atherosclerosis. The magnitude and incidence of the threat remains to be determined because marijuana smoking has largely been confined to younger adults who are only now entering the age of serious complications of atherosclerosis on the heart, brain, and peripheral vessels.

Marijuana also can cause postural hypotension. This drop in blood pressure could be hazardous in those individuals with compromised blood flow to the heart or brain, especially if they are volume-depleted (dehydrated) or if other drugs have impaired reflex control of their blood vessels.

Marijuana appears to intensify the effects of the sympathetic nervous system on the heart, an undesirable consequence in patients with coronary artery disease and in those susceptible to arrhythmias. Many of the undesirable effects of marijuana on the cardiovascular system seem to become less severe following chronic exposure. Whether the relative paucity of reports of the ill-effects of marijuana on the abnormal cardiovascular system is a consequence of adaptation to chronic usage or to lack of exposure to marijuana of a population that is sufficiently advanced in years to be susceptible to its untoward effects remains to be determined.

Recommendations for Research

Additional studies are needed both (1) to provide information on the mechanisms responsible for the observed effects of marijuana on the cardiovascular system and (2) to provide new data on the effects of marijuana in patients with known forms of cardiovascular disease.

- The manner in which Δ-9-THC acts on the heart to change the rate and force of contraction needs clarification. Direct effects on the heart are not likely to differ among species, and thus experiments can be planned for a "standard" heart preparation.
- Direct effects on electrical activity, which might relate to reports of changes in electrical activity and production of premature impulses as well as changes in sinus rate, should be evaluated with standard methods and standard preparations.
- Direct effects of Δ-9-THC on vascular smooth muscle should be explored. For this purpose, it would be essential to use some vessels that did, and others that did not, have functioning nerve terminals. It would be important here to include studies on selected coronary vessels and on vessels which play a dominant role in the regulation of systemic vascular resistance.
- A number of related studies are needed before the effects on humans can be explained in full, particularly the effects of Δ-9-THC on the renin-angiotensin system in the kidney, which provides control of arterial pressure, and on the several sequences of prostaglandin metabolism.

Studies also are indicated to obtain new data about the effects of marijuana on:

- persons with hypertension, coronary artery disease, and cerebrovascular disease;
- increases in systemic arterial pressure in low- and high-renin hypertension and the interactions between Δ-9-THC and several classes of antihypertensive medications;
- the interactions between the salt and water-retaining effect of Δ-9-THC and diuretics that could be employed both in hypertensives and those with heart failure.

Additionally, studies should be done on the use of standard monitoring techniques to quantify any effect of marijuana smoking on tendencies toward arrhythmias, and on interactions of Δ-9-THC with drugs that modify synaptic transmission in the central nervous system.

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4

EFFECTS OF MARIJUANA ON THE BRAIN

The most clearly established effects of cannabis are upon behavior. These effects, described in Chapter 6, indicate that major actions of cannabinoids are upon the brain. The ways in which marijuana alters the brain to produce its behavioral effects are not known.

Efforts to discover the causes of the behavioral effects have included studies on brain morphology, physiology, and chemistry to be reviewed in this chapter. Effects of marijuana on brain electrical activity and on brain chemistry have been measured, but their significance for brain function is not known because of our limited knowledge of brain-behavior relations. Marijuana causes temporary intoxication and results in changes in brain physiology and chemistry similar to those caused by other intoxicating drugs. Although these kinds of studies may ultimately shed light on the way marijuana produces its behavioral changes, they do not provide answers to important clinical questions. Does marijuana cause long-term changes in the brain that lead to chronic psychiatric or neurological disorders? So far, the studies reviewed below provide no convincing evidence for long-term changes because of use of marijuana.

BRAIN MORPHOLOGY

There is substantial controversy about whether marijuana causes changes in brain structure or in brain cells. Two studies have reported that marijuana produces changes in brain morphology. Both suffer sufficiently from methodologic and interpretational defects that their conclusions cannot be accepted. Furthermore, other studies have not found changes in morphology.

Gross Morphology

Data suggesting that use of marijuana causes brain atrophy were obtained by pneumoencephalography (injection of air into spaces in and surrounding the brain) on 10 users of marijuana who had sought medical attention because of neurologic complaints (Campbell et al., 1971). The size of the largest brain cavities (ventricles) was

measured to determine whether loss of brain tissue had occurred. The authors interpreted their data as showing that atrophy was present.

One of the first critics of this report questioned the interpretation of the radiologic techniques used (Bull, 1971). The results also have been seriously criticized because of the marijuana users studied. They had neurological symptoms or signs sufficient to justify an invasive and painful diagnostic test, but there is no evidence that such neurological complaints occur with greater frequency in users of marijuana than in the general population. Further, Campbell's patients did not only use marijuana, but also used such behavior-altering drugs, as lysergic acid diethylamide (LSD) and amphetamines.

More recent evidence has been provided by computed tomography (CT) scans of the brain. This technique, which is noninvasive, painless, and yields more precise and quantifiable measures of brain atrophy, has replaced pneumoencephalography as a diagnostic test. Using CT methods, two studies failed to find evidence of cerebral atrophy in healthy chronic marijuana users (Co et al., 1977; Keuhnle et al., 1977). These latter results suggest that the earlier findings were attributable to the imprecision of conventional pneumoencephalography, or to the fact that a group with neurologic complaints was studied, or to the use of multiple psychoactive drugs by these individuals. This last possibility is reinforced by CT scans of animals who received a variety of psychoactive drugs. Marijuana alone produced no evidence of brain atrophy, whereas other drugs, such as amphetamines, did produce changes (Rumbaugh et al., 1980).

Microscopic Morphology

Three post mortem studies on monkeys in the same laboratory have reported changes in the microscopic morphology of the brain at the ultrastructural level (Harper et al., 1977; Meyers and Heath, 1979; Heath et al., 1980). No similar studies on human beings have been reported. The monkeys received either chronic exposure to marijuana smoke or chronic injections of Δ-9-THC. Changes reported to have occurred in the brains included alteration in synaptic* cleft width, increased density of synaptic cleft material, a decrease in volume of rough endoplasmic reticulum, presence of clumping of synaptic vesicles in axon terminals (where impulses travel away from the cell body), and an increase in intranuclear inclusions. These changes appear dramatic, but they must be interpreted with caution. The three studies are based principally upon examination of two limited brain areas only in three treated monkeys, two receiving marijuana smoke

*A synapse is the region of communication between nerve cells, forming the place where a nervous impulse is transmitted from one nerve cell to another.

and one intravenous Δ-9-THC; a fourth treated animal was added to the last study and more brain areas were analyzed in it (Heath et al., 1980). Further, although the material was evaluated "doubleblind" after electron micrographs had been made, it would appear that fixation, tissue preparation, and photography were carried out before these safeguards against bias were applied. It is possible that unknown but systematic differences occurred between experimental (treated) and control animals in fixation and preparation of tissue or in selection of samples for micrography. In addition, it should be noted that at least one of the changes noted, clumping of synaptic vesicles (Harper et al., 1977), is a normal variant in the synaptic morphology of axon terminals in mammalian brain (Sipe and Moore, 1977) and does not represent a pathological change. Also, these studies have not been replicated and, because the basis for interpretation is such a limited sample, it is concluded that no definitive interpretation can be made at this time. However, the possibility that marijuana may produce chronic, ultrastructural changes in brain has not been ruled out and should be investigated.

NEUROPHYSIOLOGY

One source of information on the mechanisms of action of a drug, such as marijuana, is the study of its physiological effects. Effects of marijuana on the electrical activity of the brain have been demonstrated by means of the electroencephalogram (EEG). The standard, or clinical, EEG measures tiny variations at the scalp of voltages produced by the electrical activity of the brain. Voltage differences between two points on the scalp, or between the scalp and an inactive reference site, are recorded on moving paper, producing a graph of voltage over time. The waves observed are classified according to frequencies as delta, theta, alpha, and beta. While the changes in EEG described below are of interest, their biological significance is unknown.

Acute (Short-Term) Effects in Waking EEG

Ingested marijuana or Δ-9-THC produces rather slight effects on the EEG of an awake subject. Relatively high doses (210 mg Δ-9-THC or its equivalent/day) have failed to produce measurable changes even though marked behavioral effects were observed. The EEG effect most frequently reported in recent studies has been an increased abundance of alpha waves associated with a slight slowing (about 0.25 Hz) of the alpha frequency (Rodin et al., 1970; Volavka et al., 1971; Fink, 1976). However, reduced alpha abundance and increased fast frequency activity (beta) have also been reported (Wikler and Lloyd, 1945; Jones and Stone, 1970). Most studies which report EEG changes have noted that tolerance develops with repeated drug administration. No significance with respect to hazard can be inferred from the effects

of cannabis on the waking EEG. For a further review of this literature, see Fried (1977).

Persistent Effects in Waking EEG

The occurrence of persistent (long-lasting) changes in EEG with use of marijuana would cause concern even if their significance for brain function was unknown. However, in attempting to investigate the question of whether such changes occur, there inevitably arise crucial issues of subject selection. If one selects only chronic marijuana users who are in good health, one may be eliminating systematically those who have been adversely affected by use of the drug and who might have shown EEG changes. On the other hand, if one includes in such studies marijuana users who suffer from various illnesses or behavioral disturbances, one might find abnormalities of the EEG that result from these conditions rather than from the marijuana.

Long-term use of marijuana, either in the modest doses customarily used in this country or the heavy doses of hashish and ganga used by certain studied populations abroad, has not been shown to produce changes in the EEG. No abnormalities were found in the EEG of 10 healthy students who had smoked marijuana regularly for 1 year (Rodin et al., 1970). Another study compared clinical EEG records of 46 hashish users and 40 matched controls in Greece (Fink, 1976). Each record was evaluated independently by four qualified neurologist-electroencephalographers. No differences were observed in the incidence of abnormal records in the users and controls, a result consistent with the absence of significant differences between the two groups in various tests of neurological function.

Essentially, the same negative results were obtained in studies of ganga users in Jamaica (Rubin and Comitas, 1975) and marijuana users in Costa Rica (Karacan et al., 1976). In these later studies subjects were carefully selected to include only those in good health who were functioning adequately in the community. As mentioned above, this method of selection runs the risk of eliminating subjects whose health or behavior were adversely affected by marijuana and who might have shown EEG changes. This methodological difficulty cannot be eliminated in any small sample investigation of marijuana users.

Acute Effects in Event-Related Potentials

One can employ computer averaging to retrieve from the EEG certain information that is not detectable by visual inspection. In this way, the electrical events that follow a stimulus may be studied in subjects who are at rest, asleep, or carrying out certain tasks. These computer-averaged potentials provide clues to the sequential processing of information by the brain.

Although the literature is inconsistent, it is clear that cannabis can produce effects on event-related potentials (EPs) (Herning et al., 1979). Effects on amplitude are more often reported than effects

on latency of the event-related waves. Several studies with inconsistent results have appeared; these inconsistencies result from differences in task, dose, or duration of administration. Thus, EPs in response to sensory stimuli are unaffected or even increased by cannabis if the subject is passive, but are decreased in amplitude if the subject is performing a task. One study found the first negative wave, a component of the auditory EP, was reduced at a dose of 180-210 mg per day, but not at a dose of 70-90 mg per day during acute (1 to 3 days) administration (Herning et al., 1979). After 2 weeks at the higher dosage, this effect was observed only for the more difficult tasks. This study demonstrates differences in marijuana effects on EPs according to dose, duration of administration, and task complexity.

Acute Effects in Sleep EEG

Drugs often produce marked effects on the EEG during sleep, but producing little or no change in the waking EEG. This is the case with marijuana and Δ-9-THC.

In relatively high doses (70-210 mg/day), Δ-9-THC and marijuana extract produced marked effects on sleep EEG (Feinberg et al., 1975, 1976). On initial administration, the time spent in REM sleep* (stage REM duration) was reduced below baseline levels (placebo) by 18 percent and the number of eye movements by 49 percent. Some tolerance (return toward baseline levels) was apparent during the period (12-16 days) of drug administration. On withdrawal, REM duration was increased above baseline by 49 percent and rapid eye movements were increased by 67 percent. While these effects are quite large, their clinical significance is unknown. They were not accompanied by such unusual behavioral changes as hallucinations or disorientation, although there was evidence of withdrawal--irritability, increased reflexes, and mild agitation. With much smaller doses of Δ-9-THC, either a small reduction in REM sleep (Pivik et al., 1972; Freemon, 1974) or no change has been reported (Barratt et al., 1974; Hosko et al., 1973; Pranikoff et al., 1973).

Persistent Effects in Sleep EEG

We are not aware of any investigation of sleep in abstinent long-term marijuana users. However, 32 male chronic marijuana users and matched controls were studied in Costa Rica (Karacan et al., 1976). The users habitually smoked 2.5 to 23.3 cigarettes per day (mean = 9.2) and had used the drug for 10 to 27 years; they continued their usual intake during the study (Costa Rican cigarettes contain about 200 mg

*A stage in sleep during which Rapid Eye Movements may be detected and vivid dreaming usually occurs.

of marijuana). The subjects selected for this study had normal medical, neurologic, and laboratory evaluations.

Sleep was recorded for 8 consecutive nights. Prior to each night's recording, the users described their marijuana intake during the previous 24 hours. This intake was not directly monitored or controlled by the experimenters, because the goal was to observe sleep patterns under "naturalistic" conditions. The subjects were forbidden to use marijuana during the 2-3 hours prior to sleep recording. (For further details of this extensive study, see Karacan et al., 1976.)

All of the major variables derived from visual sleep stage classification were examined. The only statistically significant differences between marijuana users and their matched controls were in one of the sleep latency measures and in REM percentage of total sleep and average REM period length. The differences were quite small and may have been due to the subjects experiencing early withdrawal at the time their sleep was recorded. This is a likely explanation for these findings according to studies described previously (Feinberg et al., 1975, 1976).

The Costa Rican study concluded there was a lack of evidence of major disturbances of EEG sleep patterns in user subjects studied in situ (Karacan et al., 1976). Thus, long-term marijuana use has not been demonstrated to cause marked and consistent abnormalities of sleep EEG that can be demonstrated in studies with small samples.

Electrophysiological Studies in Animals

Sleep Studies

The findings of several animal studies carried out to investigate the effects of marijuana on EEG differ in some respects to those in human beings. Species differences are thought to be responsible for some of the variations found from species to species. For example, 5 and 10 mg/kg Δ-9-THC administered acutely to rats suppressed REM, reduced slow-wave sleep, and increased wakefulness (Moreton and Davis, 1973). Chronic administration caused an initial suppression of REM, which returned to baseline after 4 days and remained at baseline levels for a further 16 days. In contrast to the human studies, there was no withdrawal increase in REM above baseline during a 10-day withdrawal period. Similar results were obtained in a short-term study that employed intravenous doses of Δ-9-THC (0.5 and 1.0 mg/kg) to rabbits (Fujuimori and Himwich, 1973).

Appreciable qualitative differences in sleep EEG response to Δ-9-THC have also been detected in primates when compared with human studies. When 1.2 mg/kg Δ-9-THC is administered to squirrel monkeys in a single oral dose, daily for 60 days, no significant effects on REM sleep duration occurred; instead, a decrease in EEG stages 3 and 4 was noted (Adams and Barratt, 1975).

EEG Studies in Subcortical Structures

Electrode implantation is rarely possible in man, but is a routine and essential technique for the study of brain electrophysiology in animals. Animal experiments also permit use of higher doses and more prolonged administration than is possible with human subjects. For these reasons, animal experiments can yield important data that cannot be obtained in human studies. In general, EEG recordings after short-term administration of marijuana are similar from surface (cortex) or from deep brain (subcortex) regions. However, after chronic administration of high doses of Δ-9-THC, abnormal recordings have been observed in subcortical regions of some animals, readings not seen in the cortex. Although these findings have not been replicated, they are of particular concern, because they raise the possibility that chronic exposure to high doses of marijuana produces long-lasting effects on brain physiology.

After intravenous administration of a range of Δ-9-THC doses (from 0.05 to 12.8 mg/kg) to rhesus monkeys, a general increase in EEG synchrony was observed; and at higher dose ranges, there were specific EEG changes in the limbic system, frontal cortex, thalamus and fastigial nuclei (Martinez et al., 1972). In this study, the increase in high-voltage activity showed a good dose-response relationship. In a second study, oral dosing of three rhesus monkeys with a crude marijuana extract containing 25 percent Δ-9-THC produced dose-related EEG changes, including slow waves in the hippocampus, amygdala, and septum (Stadnicki et al., 1974). Tolerance to the behavioral and EEG changes occurred with daily treatment, which was stopped after 51 days. Behavioral withdrawal effects were noted, but EEG changes during withdrawal were minimal and there was no evidence of EEG changes persisting beyond the period of Δ-9-THC ingestion.

Two studies that monitored EEG recording from deep brain sites after chronic administration of high doses of marijuana found changes in EEGs from deep brain sites that were not observed in surface areas after drug withdrawal (Fehr et al., 1976; Heath, 1976; Heath et al., 1979). Studies of two rats with electrodes implanted in the anterior neocortex, dorsal hippocampus, and mesencephalic reticular formation 1 year after exposure to 20 mg/kg for 6 months (Fehr et al., 1976) yielded hippocampal recordings with "epileptiform" abnormalities, in contrast to one control and two alcohol-treated animals.

The second study was carried out on thirteen feral-raised rhesus monkeys (Heath 1976; Heath et al., 1979). Ten monkeys had electrodes implanted in deep sites and in brain cortex. Four monkeys were made to smoke marijuana three times a day, 5 days per week for 6 months; two other monkeys with implants were given 0.6 mg/kg Δ-9-THC each day, 5 days per week for 6 months; still other monkeys were used as controls or received smaller doses of marijuana. In three high-dose monkeys, two smoking and one ingesting Δ-9-THC, changes in EEG could be detected in recordings from deep brain sites; the changes continued 7 months after cessation of marijuana exposure. No EEG abnormalities were present in recordings from the brain surface.

One of the major criticisms of both these studies is their use of small numbers of animals. Furthermore, there have been no attempts at replication by other workers. Nevertheless, because these findings provide some of the only evidence for a possible irreversible effect of chronic high doses of marijuana, they are mentioned here with a strong urging for additional studies in an effort to replicate these findings.

EPILEPSY

Because of the effects of marijuana on brain electrical activity, questions have been raised about its association with epilepsy. Two questions are raised in the literature. First, does marijuana produce seizures? Second, does marijuana or a derivative prevent seizures? The first question will be discussed here. The second is reviewed in Chapter 7, which is concerned with the potential therapeutic uses of cannabis.

There are anecdotal reports in the literature that suggest seizures may be induced by marijuana in some persons with a known seizure disorder. A rigorous study, using adequate numbers of patients with documented seizure patterns, has not been done. Reports of experimental animal studies are conflicting and varied (Feeney et al., 1973, 1979; Lemberger, 1980). There are some circumstances in which cannabis administration does not alter certain types of seizures such as the photosensitive seizures in the baboon (Meldrum et al., 1974), and others in which it seems that seizures are induced. A single rabbit that responded to Δ-9-THC administration with seizures was bred to establish a colony of rabbits with similar response (Consroe and Fish, 1981). It will be of considerable interest to determine mechanisms of seizure induction and pharmacologic response patterns in this unusual animal model. However, as described further in Chapter 7, the bulk of the animal literature and some data from human studies suggest that the more prominent effect of marijuana derivatives, especially cannabinol and cannabidiol, is to decrease rather than increase seizure susceptibility (see Karler and Turkanis, 1981, for review).

NEUROCHEMISTRY

Our knowledge of the effects of marijuana on brain chemistry has come largely from studies in animals. Cannabis and some of its derivatives have been shown to cause chemical effects in the brain, as demonstrated by effects on neurotransmitters and on nucleic acids. The evidence is reviewed below.

Neurotransmitters

The brain is composed of many information-processing networks of nerve cells. Within each of these networks the transfer of informa-

tion from one nerve cell to another is dependent upon chemicals called neurotransmitters. These substances are produced by nerve cells, released when the cells are stimulated and act to alter the excitability of neighboring nerve cells. Neurotransmitters play an essential role in the transmission and processing of information, and it is not surprising that many drugs that alter behavior do so by their actions on neurotransmitters. The understanding of the effects of marijuana on the brain must include knowledge of its effects on neurotransmitter systems.

Several different classes of chemicals act as neurotransmitters. The first chemical to be demonstrated to have this function was acetylcholine, and it is now established that acetylcholine is the neurotransmitter for several nerve cell networks in the brain. A number of studies in animals have examined the effect of marijuana on brain acetylcholine (see Domino, 1981, for a brief review of the extensive literature). The most clear-cut effects have been on acetylcholine turnover, a measure of the level of activity of neurons producing the chemical. Small doses of Δ-9-THC cause a reduction in acetylcholine turnover in the hippocampus (Domino et al., 1978; Revuelta et al., 1978; Domino, 1981) and this results from reduced activity of the acetylcholine neurons. It is noteworthy that the effect is produced by small doses and only by cannabinoids. Administration of physostigmine, a drug that enhances acetylcholine action by partially blocking its breakdown, to five healthy human volunteers (2 hours after ingestion of 20 to 40 mg of Δ-9-THC) produced enhancement of the lethargy and somnolence occurring late in the course of the Δ-9-THC intoxication (Freemon et al., 1975). The results of this study, and others in man and animals (El-Yousef et al., 1973; Low et al., 1973; Drew and Miller, 1974; Freemon et al., 1975), have led to the conclusion that Δ-9-THC acts to inhibit acetylcholine nerve cell networks. The exact nature of this action is not known, but it may be related to the memory deficits produced (Domino, 1981).

There have been studies of cannabinoids on several other neurotransmitters in brain, including catecholamines, serotonin, and gamma aminobutyric acid (Banerjee et al., 1975; Bracs et al., 1975). Although some effects have been reported, they either are produced by a very high dose or are so fragmentary that their implications are unclear. The effects of cannabinoids on neurotransmitters that have been studied to date, other than acetylcholine, are not striking. In particular, there is no evidence for any significant, long-term toxic effect of cannabinoids on any of the nerve cell networks that produce identified neurotransmitters.

Proteins, Enzymes, Nucleic Acids

A very few studies have examined the effects of marijuana on neurochemical variables other than neurotransmitters (Luthra and Rosenkrantz, 1974; Luthra et al., 1975, 1976). After chronic administration to rats either of Δ-9-THC or marijuana smoke (for

periods from 28 to 180 days), these investigators examined brain lipid, protein, and ribonucleic acid (RNA) content. With very high doses of Δ-9-THC (up to 500 mg/kg/day), some decrease in brain protein and RNA was noted; no decrease was noted in lipid content. However, with smaller doses, or administration of marijuana smoke, no consistent or marked changes were noted. The significance of these effects is unknown. Whether additional effects might be observed with more sophisticated and sensitive methods directed to more restricted analytical problems cannot be answered at present.

SUMMARY

There is no persuasive evidence that marijuana causes morphological changes in the brain. Computer tomography studies on users of marijuana reveal no gross changes in brain structure. Electron micrographic studies of monkey brains indicating morphologic changes are methodologically flawed and cannot be used as evidence for an effect of marijuana on brain cell morphology. Clear effects on brain electrical activity in human beings and in animals have been found after drug exposure. These effects have not been demonstrated to persist in human beings after the drug has been discontinued. Studies of EEG from deep brain structures in chronically treated animals have shown changes after the withdrawl of the drug. These limited findings need to be confirmed by further studies. Studies in human beings and animals indicate that, despite the neurophysiologic effects demonstrated in EEG studies, marijuana does not appear to increase epileptic seizure susceptibility. Current evidence has shown marijuana causes some chemical changes in brain. Cannabinoids affect several neurotransmitter systems, especially the cholinergic system. At high doses marijuana also has been shown to affect nucleoprotein synthesis. The significance of these findings for brain function as demonstrated by human behavior or their clinical relevance is unknown.

RECOMMENDATIONS FOR RESEARCH

In view of the widespread use of cannabis, it would be worthwhile to carry out further and more systematic studies of the effects of cannabis on brain structure, chemistry, and electrophysiology. Such studies should be closely correlated with behavior, e.g., learning, psychomotor coordination (see Chapter 6). One useful approach might be to investigate the effects of medium and high doses of cannabis (defined in terms of the patterns of human consumption) on juvenile and adult monkeys during and after long-term exposure. Juvenile monkeys should be included because the immature nervous system may be more sensitive to harmful drug effects; this issue is of great clinical concern, because marijuana use by human beings now begins quite early in life (see Chapter 2). Observations also should be made during long-term abstinence after previous long-term exposure to

determine whether any persistent abnormalities have been produced. A systematic approach to these questions using modern methods of measurement and analysis could extend our present knowledge substantially.

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5

EFFECTS OF MARIJUANA ON OTHER BIOLOGICAL SYSTEMS

This chapter covers what little is known about the effects of cannabis on male and female reproduction and endocrine systems, birth defects and teratogenic effects, genetics, the immune system, and body temperature.

MALE REPRODUCTIVE FUNCTION

A variety of studies indicate that marijuana and some of its derivatives have reversible, suppressive effects upon testicular function in animals and men. These have been measured in terms of diminished weights of the prostate gland, seminal vesicles, or testes, and in decreased levels of testosterone (the male hormone) in blood plasma or suppression of spermatogenesis following chronic or acute administration of cannabis or Δ-9-THC. Appropriate observations have indicated that the effects of cannabinoids on the male reproductive tract and on testicular function were completely reversed 1 month after drug withdrawal.

There is no general agreement as to the cause or magnitude of these effects. The major reasons for this lack of agreement relate to major differences in study design, including species studied (man, monkey, or rodent), route of drug administration, and purity of the drug used.

Human Studies

In 1974, a group of 20 men were studied who had used marijuana at least 4 days a week for a minimum of 6 months without the use of other drugs (Kolodny et al., 1974). Plasma testosterone levels in subjects smoking five to nine marijuana cigarettes per week were significantly lower than controls (however, only 2 had levels out of the normal range, i.e., below 400 ng/dl); all but 1 of the men smoking more than 10 marijuana cigarettes per week had testosterone levels below 400 ng/dl. These results suggest that there was a dose-dependent effect of marijuana on testosterone levels. Plasma levels of lutenizing hormone (LH) and follicle-stimulating hormone

(FSH), gonadotropins that control the growth of the ovaries or testes and their hormonal activities, were in the normal range; however, in men smoking more than 10 marijuana cigarettes per week, the FSH level was significantly lower than for those who smoked 5 to 10 marijuana cigarettes per week. Because only random samples of blood were obtained for gonadotropic measurements, small but significant changes could have been missed. Levels of prolactin, the female hormone involved in lactation and also present in small quantities in men, were all in the low normal range. In addition, the men who smoked more than 10 marijuana cigarettes per week had significantly lower sperm counts than those who smoked the lesser quantity (26 versus 68 million/ml). These individuals obtained marijuana from a variety of sources, and there was no way to determine whether they were taking other drugs that could lower plasma testosterone.

Later in 1974, another study reported that plasma testosterone levels were not suppressed in 27 men studied in a research ward (Mendelson et al., 1974) These individuals smoked marijuana cigarettes supplied by the federal government. For unexplained reasons, the mean testosterone levels in these individuals were greater than 1,000 ng/dl (higher than the normal mean) before and during the smoking periods. This is in marked contrast to the mean value of 742 ng/dl for nonsmokers in the study of Kolodny et al. mentioned above. There was no report of gonadotropic values or semen analysis in the Mendelson Study.

A study of 16 patients on a metabolic ward who smoked NIDA cigarettes (Hembree et al., 1979) showed that 5 to 6 weeks of high-dose (2 percent) marijuana administration (8-20 cigarettes/day) was associated with a decline in sperm count during the fifth and sixth weeks after initiation of drug exposure. This was preceded by a decrease in sperm motility and an increase in abnormal forms of sperm. Once a week during the study five blood samples were obtained at 15-minute intervals for measurement of testosterone, LH, and FSH. No change in these hormone levels was noted throughout the study (although no values were reported). The relationship in time of these samples to the last previous cigarette was not mentioned, therefore the test would not have excluded a transient decline in hormonal levels after each cigarette. However, because hormonal suppression of spermatogenesis takes longer than 4 weeks and usually is not associated with an increase in the number of abnormal forms and a decrease in motility, the authors concluded that the effect upon the seminiferous tubular epithelium was direct rather than by suppression of gonadotropins. This is the only reported study in man that measured the hour-to-hour fluctuations in gonadotropic levels.

Another study (Coggins et al., 1976) evaluated the health status of 84 marijuana smokers who had used the agent three or more times per week for a minimum of 10 years. Testosterone levels were measured in 38 users and 38 nonusers. The mean levels and ranges were virtually identical. This heterogeneous group of men patients studied in Costa Rica was not recruited for the purpose of studying the pituitary-gonadal axis. No gonadotropic levels or semen samples were studied.

Endocrine function studies are briefly mentioned in a paper by Cohen (1976). Subjects were recruited on the basis of heavy marijuana use and were studied in a metabolic ward. They smoked an average of five marijuana cigarettes per day, which was believed to be the equivalent of 103 mg of Δ-9-THC. During acute administration, mean levels of plasma testosterone declined from 754 to 533 ng/dl over a 3-hour period. After 9 weeks of smoking, plasma testosterone levels had declined from 740 to 509 ng. Plasma LH levels were reported to have fallen after the fourth week; however, no absolute values were given. In addition, no standard errors are given for any of the means presented in this paper. Therefore, it is impossible to evaluate the significance of the reported findings.

In Greece, a population of 47 chronic hashish users was studied. Electron microscope studies of the acrosome, the head of the sperm, showed abnormality in some patients (Issidorides, 1979). It is difficult to evaluate the study because no quantitative data were presented.

Animal Studies

All of the studies mentioned below are substantially different from those of human beings because, with one exception, the active agent (usually Δ-9-THC) was administered intraperitoneally at a dose of 2.5 to 25 mg/kg. Based on calculations given by Cohen (1976), 3 to 6 mg/kg/day would be considered a large dose in human beings.* Also, human beings self-administer the drug over many hours rather than as a single dose.

In castrated rhesus monkeys, plasma LH and FSH fell acutely following acute administration of Δ-9-THC (Smith et al., 1980). During this suppression period, both gonadotropins could be stimulated by lutenizing hormone-releasing factor (LHRF), which causes the release of LH. The effect of Δ-9-THC was to suppress prolactin release, which, in turn, could be stimulated by thyrotropin-releasing hormone (TRH). Studies in other species have tended to confirm these observations in monkeys.

The results are compatible with the hypothesis that the effect of marijuana and its derivatives is on gonadotropic secretion (Harclerode et al., 1979). Testicular cytochrome P-450 (an enzyme) decreased in the rat following 2 to 9 weeks of treatment. The concentrations of this enzyme, plus a variety of other testicular markers, were restored with FSH and LH therapy. The effect of various cannabinoids has been studied on sperm morphology in the mouse (Zimmerman et al., 1979).

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*Rosenkrantz (1981) considers 0.6-3.0 mg/kg by inhalation and 1.8-9.0 mg/kg orally to be large doses in human beings. For the monkey, 1.8-9.0 mg/kg by inhalation and 5-27 mg/kg orally would be considered a high dose. (These concentrations are equivalent to six cigarettes/day.)

Mice were given five daily intraperitoneal injections of Δ-9-THC, cannabidiol, or cannabinol at doses approaching or exceeding the LD_{50} (the dose necessary to kill 50 percent of the animals). Thirty-five days after the last treatment, animals were killed and sperm were evaluated by scanning electron microscopy. Control animals had 1.5 percent abnormal forms. Animals that received LD_{50} doses of the various derivatives had 2.4 to 5.0 percent abnormal forms.

Only a few studies have examined the effects of cannabis on spermatogenesis (Huang et al., 1979). Marijuana was administered to rats in a smoke machine. After 30 days of exposure, marijuana smoke lowered the sperm counts in animals significantly, as did cannabinoid-free smoke. By 75 days, however, only the marijuana smoke group maintained a low sperm count. In the marijuana-treated group, there was an increased number of abnormal forms, particularly with an increase in dissociation of sperm heads and tails. In the discussion of this paper, the authors reported elevated serum FSH levels following marijuana exposure, but did not present data. They concluded that marijuana has a direct effect on the testis. A variety of *in vitro* studies support this suggestion (Jakubovic et al., 1977, 1979).

Marijuana and its derivatives also have been shown to be antiandrogenic (antagonistic to male hormones) (Purohit et al., 1980). Several constituents, including Δ-9-THC, can bind to the receptor for androgen. Marijuana also has been demonstrated to be estrogenic (like female sex hormones) *in vivo*, and recent studies suggest that these effects may be mediated via the estrogen receptor. These observations have been disputed by others (reviewed by Purohit et al., 1980). The ability to inhibit or mimic the action of sex steroids provides one mechanism by which these agents can produce their effects. There obviously are many others.

FEMALE REPRODUCTIVE FUNCTION

The effect of cannabis on female reproduction has been studied in rats, mice, rabbits, and monkeys. The work in rhesus monkeys is of particular importance, because of the similarity in the menstrual cycle among primate species, including human beings.

Human Studies

There is only one study reported on the effects of marijuana on reproductive function in women. The work has appeared in print as a report of the proceedings of a 1978 symposium held in Mexico City (Bauman et al., 1979) and as part of the congressional record subsequent to testimony before a Senate committee hearing (Bauman, 1980). These publications do not provide details on methodology or on individual hormone values. Differences between the control and experimental groups, recognized by the investigators, could be of

importance; alcohol use, for example, was more frequent in the marijuana-using group. The study attempted to establish the endocrine (hormonal) profile and menstrual patterns of women who used marijuana on a chronic and frequent basis. Twenty-six women who used it at least three times a week for 6 months were compared with 17 women who had never used the substance. The number of cycles studied for each variable investigated is not clear from the publications. This difficulty notwithstanding, the report reveals no difference in plasma levels of LH and FSH between the two groups and no change in peaks and basal values of the female hormones estradiol or progesterone, the critical hormone levels controlling the process of ovulation. It would be expected that no major difference was found in the incidence of anovulatory cycles between the two groups. By combining anovulation and shortened luteal phase, however, the authors report a statistically significant difference in the marijuana-using group, which could be clinically important in causing subfertility. This evidence is, at best, only suggestive. The observation that testosterone levels in marijuana-using women are elevated is difficult to interpret in terms of clinical significance; apparently, the subjects did not report episodes of acne, abnormal hairiness, or other testosterone-dependent side-effects. According to the authors, serum prolactin levels are lower in marijuana users than in controls. The implications of this observation for fertility, lactation, or the development of breast cancer are not clear.

The absence of other studies on users of marijuana makes it difficult to draw conclusions on the implications of the data cited above. Several of the effects noted are different from the more extensive and experimentally controlled observations in rhesus monkeys and other laboratory animals. This situation calls attention to the urgent need for more comprehensive endocrine and gynecologic investigations of women who use marijuana.

Animal Studies

Administration of crude marijuana extract to rats or mice resulted generally in suppression of ovarian function and in various aspects of estrogen activity, such as uterine metabolism, weight, glycogen content, and levels of RNA and sialic acid (Chakravarty et al., 1975; Dixit et al., 1975).

The administration of crude marijuana extract for 30 days to rats and mice abolished the estrus cycle and caused a significant reduction in the size of the ovaries and in some primordial ova (Dixit et al., 1975). Intraperitoneal administration of Δ-9-THC to rats, appropriately timed, has also been reported to block ovulation (Nir et al., 1973). This effect of Δ-9-THC was exerted by suppressing the characteristic preovulatory surge of plasma LH. Other investigators have reported suppression also of plasma FSH and prolactin when Δ-9-THC is given just before ovulation (Ayalon et al., 1977). The substance was found to depress plasma concentration of LH in ovariectomized rats (Marks, 1973; Tyrey, 1978, 1980) and

rhesus monkeys (Besch et al., 1977). Asch et al. (1979) also showed in the rabbit, a reflex ovulator, that a precoital single dose of Δ-9-THC blocks the postcoital LH surge and ovulation.

Administration of LHRF was able to bring about the release of LH in Δ-9-THC treated rats and rhesus monkeys (Smith et al., 1979). These results indicate a direct effect of cannabinoids at the level of the hypothalamus, part of brain important in reproductive hormone regulation. The ovulation-blocking effect of the cannabinoids was further investigated by Cordova et al. (1980). Natural and chemically modified cannabinoids blocked ovulation in rats.

Administration of Δ-9-THC to rhesus monkeys during the follicular phase resulted in prolonged periods of amennorhea (absence or abnormal stoppage of the menstrual flow), absence of midcycle LH surge, and progesterone levels characteristic of anovulation (Asch et al., 1981).

BIRTH DEFECTS AND TERATOGENICITY

Because Δ-9-THC crosses the placenta it is a potential teratogen, an agent that causes defects in the developing embryo. This effect could occur in either of two ways: (1) exposure to cannabis prior to conception could harm the sex cells (the ova and sperm), or (2) the fetus could be harmed directly during organogenesis. In addition, Δ-9-THC can be secreted in breast milk and, therefore, can be toxic postnatally.

Human Studies

The evidence for teratogenicity in human beings is very difficult to interpret. Although there is widespread use of marijuana in young women of reproductive age, there is no evidence yet of any teratogenic effects of high frequency or consistent association with the drug. There are isolated reports of congenital anomalies in the offspring of marijuana users, but there is no evidence that they occurred more often in users than in nonusers and in those cases there was coincident use of other drugs. Subtle development effects in offspring, such as nervous system abnormalities, and reductions in birth weight and height may indeed exist (Finnegan, 1980; Friad, 1980; Hingson et al., in press). Additional carefully designed, prospective studies should provide valuable information in this area.

Animal Studies

Crude marijuana extract and Δ-9-THC are teratogenic at certain doses in animals.*

*Bibliography available upon request from the Institute of Medicine, National Academy of Sciences.

One study reported that subcutaneous injection of pregnant hamsters and rabbits with various doses of crude marijuana extract caused malformations of the brain, spinal cord, forelimb, and liver, as well as edema of the head and spinal region in developing embryos (Gerber and Schramm, 1969). In hamsters, significant embryocidal and growth retardation effects also were noted. It was concluded that doses greater than 200 mg/kg in hamsters and 250 mg/kg in rabbits were teratogenic. Caution in interpreting these findings must be exercised because the teratogenic effects may be caused by any combination of constituents of the cannabis extract.

In a study of mice, the teratological effects of Δ-9-THC were evaluated for doses ranging from 3.0 to 400 mg/kg by various routes of administration--intravenous, subcutaneous, and intragastric (Joneja, 1976). Significant fetal growth retardation was induced at higher dose levels and by some routes of administration. For example, a high dose of 400 mg/kg was significantly teratogenic by the intragastric route; 12.1 percent of the live fetuses were malformed.

In a study of female monkeys given an oral dose of 2.4 mg/kg Δ-9-THC for 1 to 4 years, a nonspecific pattern of reproductive difficulties was observed characteristic of "high-risk" pregnancies, including a high rate of offspring loss during pregnancy or in the early postnatal period (Sassenrath et al., 1979).

GENETIC EFFECTS

The potential genetic effects of marijuana are of major concern because of its prevalent use by young people in their reproductive years (see Chapter 2). Although there is a growing amount of evidence that drugs can induce mutations, and an improving ability to use toxicological methods to evaluate agents for their mutagenic potential (such as the Ames test, which detects changes or damages in the genetic material), the available information on the genetic hazards or even on the potential genetic hazards of the use of marijuana is extremely limited.

Mutagenicity

Elsewhere in this report (Chapter 3) the scientific evidence that marijuana smoke and tar are mutagenic has been discussed. Lung explants of mice and human fibroblast cultures exposed to fresh smoke showed abnormalities of cell division, as well as changes in chromosome structure and in DNA synthesis (Leuchtenberger and Leuchtenberger, 1971; Leuchtenberger, et al., 1973a,b). Moreover, extracts and smoke condensates of marijuana are mutagenic when evaluated by the Ames test (Busch et al., 1979; Said and Wei, 1979; Wehner et al., 1980). Animal studies on rodents painted with marijuana tar, three times weekly for 1 year, resulted in skin papillomas, carcinomas, and fibrosarcomas (Hoffmann et al., 1975).

However, extensive testing with Δ-9-THC using three established tests for mutagenesis failed to detect any mutagenic effect, or any effect as an inhibitor of DNA repair (Legator et al., 1976; Glatt et al., 1979; Zimmerman et al., 1978).

Cytogenetic Effects

The numbers and kinds of chromosomes (structures in a cell nucleus that contain and transmit genetic information carried in DNA) are highly characteristic for a given species. Structural variation and changes in numbers of chromosomes may be evidence for genetic damage produced by drugs and other chemical agents. Unfortunately, the literature on the effects of marijuana on chromosomes is limited and conflicting. Studies suggesting that marijuana probably does not break chromosomes are fairly conclusive. There is less evidence that marijuana may produce aneuploidy (abnormal numbers of chromosomes) in some daughter cells during cell division.

Does marijuana cause chromosome breaks? The weight of the evidence from in vitro cultures of human cells and from in vivo animal and human studies is that neither marijuana nor Δ-9-THC causes chromosome breaks.

In Vitro and Animal Studies

Cultures of human leukocytes, exposed to different concentrations of Δ-9-THC, showed no increase in the incidence of chromosome breaks or gaps when compared to controls (Stenchever and Allen, 1972). Studies of golden hamsters given subcutaneous injections for 10 days of marijuana extract distillate containing 17.1 percent Δ-9-THC (Nicholson et al., 1973), and of beagle dogs trained to smoke high doses of marijuana (3 g/day/week for 30 months), showed no significant differences in chromosome gaps or breaks when compared with control groups (Genest et al., 1976).

Human Studies

Cytogenetic analysis of chromosomes from peripheral blood leukocytes and cultures of subjects exposed to marijuana smoking, marijuana extract, or synthetic Δ-9-THC revealed no increase in chromosome breakage attributable to these compounds (Nichols et al., 1974; Matsuyama, 1976; Morishima et al., 1979). Doses ranged from 20 mg Δ-9-THC per day to 12-16 marijuana cigarettes per day. Studies that have reported chromosome breaks or gaps in cell cultures of users of marijuana have largely been carried out on multiple drug users, and the breaks and gaps may be due to other factors associated with a life of heavy drug use (Gilmour et al., 1971; Herha and Obe, 1974). However, in a retrospective study on college students, chromosome breaks were found in blood cultures of 49 light (one or

less exposure per week) and heavy (more than two exposures per week) users of marijuana (Stenchever et al., 1974). One problem in this study is the poor dose characterization. Furthermore, the increase in the numbers of breaks in both light and heavy users of marijuana was not dose-related; the same frequency of breaks was observed in both groups. Although the evidence is inconclusive, it suggests that marijuana does not cause chromosome breaks.

Does marijuana interfere with cell division and chromosome segregation, thereby resulting in abnormal numbers of chromosomes? There is conflicting evidence in the literature. On the one hand, no significant effects of marijuana smoke or Δ-9-THC on chromosome complement have been reported using the micronuclei test in mice or in cytogenetic studies in dogs (Genest et al., 1976; Legator et al., 1976). On the other hand, more extensive studies have demonstrated aneuploidy resulting from in vitro exposure of cells to marijuana as well as in vivo studies of animals and human beings.

In Vitro and Animal Studies

Exposure of mouse lung and adult human lung tissue culture to marijuana smoke in vitro resulted in abnormal cell proliferation and abnormalities in DNA content (Leuchtenberger and Leuchtenberger, 1971; Leuchtenberger, et al., 1973b). Addition of Δ-9-THC and olivetol, a compound with a ring structure similar to cannabinoids, to normal human leukocyte cultures induced hypodiploidy (defined as metaphase nuclei with a chromosome complement of less than 30 chromosomes--a normal human cell contains 46 chromosomes) (Morishima et al., 1976). Hybrid mice treated for 5 consecutive days with Δ-9-THC, cannabinol, and cannabidiol at a dose of 10 mg/kg had a three- to fivefold increase of micronuclei over controls. The number of micronuclei increased with increasing Δ-9-THC dosage. Examination of bone marrow mitosis in these same mice showed a five- to sevenfold increase in chromosome number aberrations during metaphase (Zimmerman and Raj, 1980).

Human Studies

Studies of lymphocytes cultured from human marijuana smokers defined either as "moderate" users (at least one marijuana cigarette per week, range 1-10 for a minimum of two years) or "heavy" users (more than three times per week) all of whom consumed between 12.9 and 15.3 marijuana cigarettes per day during the experiment, turned up a significantly larger number of cells with less than 30 chromosomes than would be found in normal control cultures (Morishima et al., 1979). These positive findings suggest that marijuana may affect chromosome segregation during cell division and result in cells with fewer than the normal number of chromosomes. What these findings mean in terms of risk for abnormalities in offspring or possible disease is not known. Findings in lymphocyte cultures may not be relevant to what is happening in the germ cells (sex cells).

THE IMMUNE SYSTEM

The immune system functions in protecting the body against viruses, bacteria, and other infections. It also plays a major role in preventing the growth and dissemination of cancerous cells.

There have been reports that cannabis is immunogenic, capable of activating components in the immune system. These components include such cells as lymphocytes, some of which produce antibodies in response to invasion by a foreign agent, and macrophages, which can be stimulated by inflammation to ingest invaders.

Human Studies

There have been reports that cannabis interferes with components in the immune system in man. Antibodies will develop in response to marijuana in some people, along with an allergic response, while others develop antibodies without apparent allergic reaction (Liskow et al., 1971; Shapiro et al., 1974, 1976; Lewis and Slavin, 1975). However, the studies reporting these effects were not designed to determine which components of the marijuana are immunogenic and which are allergenic.

Studies of various aspects of the immune system in persons who were chronic users of marijuana have indicated mild decreases in activity of one or another component of the system; however, other investigators have noted no changes outside of the normal range (Gupta et al., 1974; Petersen et al., 1975, 1976; White et al., 1975; Lau et al., 1976; Rachelefsky et al., 1976; Silverstein and Lessin, 1976; Cushman and Khurana, 1977; McDonough et al., 1980). These apparent inconsistencies may stem from the variability in the amount of marijuana consumed among users in different studies and the differences in the immune system assays. Hashish, as distinct from marijuana, was shown to have a slight temporary stimulatory effect on the immune system (Kaklamani et al., 1978; Kalofoutis et al., 1978).

Animal Studies

A number of studies have shown that Δ-9-THC and other cannabinoids induce immunological defects in rodents (Petersen and Lemberger, 1976; Lefkowitz and Klager, 1978, Lefkowitz et al., 1978; Preuss and Lefkowitz, 1978). The doses varied from 5 to 25 mg/kg (intraperitoneally) to 100 mg/kg (orally). At the higher doses there was a diminution of immune response, as measured by standard immunological assays. Delta-9-THC had the same effects on cells grown <u>in vitro</u>. Other cannabinoids also have been tested for their effects. Cannabinol, Δ-8-THC, and 1-methyl-Δ-8-THC had the same immunosuppressive effects as Δ-9-THC, but cannabidiol had no immunosuppressive effect. Immunizing rabbits with Δ-9-THC resulted in the production of antibodies (Chiarotti et al., 1980).

BODY TEMPERATURE

Regulation of body temperature is a complex process that can be influenced by drugs. In several species of animals, Δ-9-THC produces a lowering of body temperature (hypothermia). The effect is seen when animals are housed at normal room temperatures, and it is greater with colder ambient temperatures (Pertwee and Travendale, 1979). Marijuana apparently causes a decrease in heat production for reasons that are unclear.

In experiments with human subjects, marijuana has produced little or no change in body temperature when given in a cool environment (Beaconsfield et al., 1972; Hanna et al., 1976). In a hot environment (40°C) marijuana caused inhibition of sweating and a consistent rise in body temperature (Jones et al., 1980). Thus, there is evidence that marijuana does interfere with temperature regulation, although there is no currently known clinical significance to this finding.

Cannabis appears to interfere with temperature regulation, but the clinical significance is unknown.

SUMMARY

Male Reproductive Function

In animals, marijuana and its derivatives can acutely lower gonadotropic secretion when administered intraperitoneally. There is also some evidence in animals to suggest that these agents can directly affect the seminiferous tubule. In man, sperm number and motility are decreased during chronic marijuana use. From the available studies, it appears this was due to a direct effect of the cannabinoids either on the seminiferous tubular epithelium or the epididymal sperm. Due to conflicting and incomplete evidence, it is not possible to conclude at the present time whether marijuana smoking has a significant effect upon gonadotropic and testosterone concentrations in humans. Whether the decrease in sperm number or motility has any effect on fertility is not known.

Female Reproductive Function

There is only one study of human beings that attempts to establish the endocrine profile and menstrual patterns of women who used marijuana on a chronic and frequent basis. By combining categories of anovulation and shortened luteal phase, a statistically significant difference was noticed in the marijuana using group. It is not known if this leads to problems with fertility or lactation, or if it leads to cancer of the reproductive organs.

Animal studies have shown that Δ-9-THC lowers the serum gonadotropic levels. It is unknown if there is a direct effect on the reproductive tissues, particularly under prolonged use of cannabis products.

Birth Defects and Teratogencity

Cannabis is teratogenic at high doses in animals. There is no evidence of obvious teratogenicity or structural defects in the offspring of human users. But the data are not adequate to reveal a long-range functional impairment or a very low level of teratogenicity if one is present. It may be impossible to identify a distinct role for cannabis in the production of subtle effects in offspring, because of the confounding influences of malnutrition, smoking, and alcohol.

Genetic Effects

Marijuana and Δ-9-THC do not appear to break chromosomes, although there is some conflicting evidence on this point. Multiple drug use seems to be correlated with an increase in the numbers of gaps and breaks in the genetic material. Furthermore, marijuana may affect chromosome segregation during cell division, resulting in abnormal numbers of chromosomes in daughter cells. While these conflicting results are worrisome, their clinical significance is not known. Further investigations, especially controlled prospective studies, of human beings are needed.

The Immune System

The data from animal studies suggest that Δ-9-THC and some of its analogues have a mild, transient, immunosuppressant effect in both *in vitro* and *in vivo* systems; the effects are mild compared with known immunosuppressant drugs. The studies in human beings are contradictory; some demonstrated mild, immunosuppressive effects, but others, using the same or similar methods, did not find any differences in the immune system between normals and chronic marijuana smokers. At the present time, there have been no human or animal studies that have determined if marijuana smokers are more prone to infections or other diseases. Because of the widespread use of marijuana, even weak immunosuppressive effects are a concern. Since further research may not demonstrate definitive findings, immunologic effects should be studied along with other variables in a larger investigation. If marijuana is to be used on immunosuppressed patients (for example, for antiemetic purposes during cancer chemotherapy), even minor additional suppression might be dangerous.

RECOMMENDATIONS FOR RESEARCH

The committee recommends the following types of studies.

- Further observations should be made regarding the relation of marijuana use to reproductive defects in human beings, especially

on young users whose reproductive biology is undergoing rapid change. The principal need is for assessment of endocrine profiles and semen analysis in male users versus nonusers, with adequate control of confounding variables--for example, diet, alcohol, other drug use. In women, the principal need is for more data on endocrine and menstrual patterns in users versus nonusers, with particular attention to the length of cycles, the presence or absence of ovulation, and the existence or absence of subfertility. More studies are needed to detect subtle, low-frequency, or cumulative effects on reproductive function in long-term, heavy users.

- Although routine testing of teratogenicity in human beings is not recommended at this time, the collection of precise epidemiologic information on the outcome of human pregnancy in marijuana users is of great importance and must be carefully controlled.
- There are no good animal models for studying the effects of smoking marijuana, but cytogenetic studies in animals after exposure to Δ-9-THC by other routes than smoking would be of some value. The most relevant studies still would be in vivo human studies.
- Marijuana has been found to have mild immunological effects in a variety of test systems, but studies of its influence on the body's immune defense against microorganisms are lacking and need to be conducted.
- Critical experiments are needed to test the hypothesis that Δ-9-THC causes disruption of thermoregulatory effector responses rather than an alteration of the level of thermoregulation.
- Inherited variation in the way some drugs are metabolized is widely recognized. This type of variation must be evaluated in respect to susceptibility to marijuana.

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6

BEHAVIORAL AND PSYCHOSOCIAL EFFECTS OF MARIJUANA USE

The mind-altering effects of marijuana underlie its widespread and increasing popularity. Marijuana users who experience effects on mood, perception, and motivation report that they seek the "high" and the "mellowing-out." However, under some circumstances many of these same effects can be considered adverse. Perceptual distortions that are sought by users pose risks for driving cars or using other machines. There is reason to be concerned about effects on learning by students using marijuana in school. Older adults receiving Δ-9-THC as therapy may be highly intolerant of altered consciousness and perceived loss of control. Thus, it has become a matter of practical as well as scientific interest to learn more about the effects of marijuana on the brain and behavior.

Many psychological and neuropsychological studies have been conducted to investigate specific effects of marijuana on behavior. These include studies of intellectual functions, such as memory, attention, sequential information processing, and decision-making, as well as perceptual and psychomotor functions. There is a methodological challenge in trying to design experiments that will discriminate reliably among these functions and determine precisely which is being affected when a drug produces a particular behavioral outcome. For example, one's ability to process and respond to environmental stimuli represents a chain of events. The sequence begins with a sensation or perception. Drugs can influence the manner, speed, and accuracy with which this input is received. The information must then be stored in memory, even if only very briefly, and then retrieved from memory to be integrated with recalled prior experiences and other sensory inputs. The response from the subject is the result of the integration of new and old information. A drug acting at any point in this chain of events can alter behavioral performance.

Studies of the effects of marijuana on complex behavior must be carefully interpreted, because there are numerous variables that can influence the results. First, there is the drug itself. The dose, type of preparation, route of administration, and speed of administration must be specified. Next, the user--his personality, level of innate ability, motivation to perform, and especially his previous experience with marijuana, are powerful influences on test results. Finally, there is the type of behavioral test and the setting in

which it is performed. Simpler and well-practiced skills are less susceptible to disruption by drug effects than are novel or complex tasks. The studies in the literature vary in their attention to these factors.

Most of these studies have been carried out on male college students who volunteer for marijuana research. Although this age-group (19-25) represents a period of peak use of marijuana, it cannot be assumed that findings from a college population will generalize to other sectors of the youth population. The differing motives of student volunteers seriously confound the interpretation of results in intellectual areas, where it has been established that motivation plays a significant role in determining performance. Some dedicated users want to do well and demonstrate that marijuana has no harmful effect. Others are simply interested in obtaining the drug and enjoying its effects with little interest in the experiment. Additional methodological issues that recur in this body of research include: (a) reliance on self-reports by subjects regarding personal history of frequency and intensity of drug use, (b) occasional reliance on self-reports of drug dose and level of intoxication at the time of the experiment, (c) lack of standardized dosages and methods of administration of Δ-9-THC even when the drug is administered by the investigator, and (d) lack of attention to motives and beliefs of users and nonusers with whom they interact.

A representative sample of studies will be reviewed here, and a summary table of 88 reports of the relationship between marijuana use and behavioral and psychosocial functioning is available from the Institute of Medicine by request.

PERCEPTUAL AND PSYCHOMOTOR FUNCTIONS

Acute Effects

The studies reported here cover the range of commonly used doses* from very low up to 0.250 mg/kg of Δ-9-THC in marijuana cigarettes at a single sitting. These are acute effects--changes that can be seen after a single dose. The effects begin to be seen at about the same dose level at which a "high" is perceived (0.050-0.150 mg/kg Δ-9-THC). Generally the effects are dose-related. In other words, low doses have small effects; higher doses tend to have greater effects.

*Doses are reported in milligrams per kilogram (mg/kg) where provided by the authors or as total doses in milligrams with the route of administration.

Coordination

Marijuana has been found to impair motor coordination at doses commonly used in social settings by both naive and chronic users. The functions studied include: hand steadiness (Mayor's Committee on Marihuana, 1944; Clark et al., 1970; Milstein et al., 1975), body sway (Mayor's Committee on Marihuana, 1944; Kiplinger et al., 1971; Evans et al., 1973), and accuracy of execution movements (Rafaelsen et al., 1973; Milstein et al., 1975; Kvalseth, 1977). Studies have also showed a dose-related increase in impairment of postural stability as measured by increased body sway (Kiplinger et al., 1971).

Reaction Time

Reaction time is defined as the time lag between a signal and the response a subject makes to that signal. Most studies examine the time that it takes a subject to respond to a visual or auditory signal. The effects of marijuana on either speed of initial detection of the signal or speed of response have been inconsistent at doses commonly used in social settings ("low to moderate"). The same subjects are impaired at some times, but not at other times (Mayor's Committee on Marihuana, 1944; Clark et al., 1970; Dornbush et al., 1971; Moskowitz et al., 1972, 1974; Borg et al., 1975; Schaefer et al., 1977; Peeke et al., 1976; Stillman et al., 1977). The meaning of this inconsistency is uncertain, but it probably involves an effect on attention mechanisms. When a subject is intoxicated with marijuana, he is probably less likely to attend to the reaction time task. Perhaps it is when he does pay attention to the task that function on this test is not impaired.

Tracking

Tracking is the term used to describe the act of following a moving stimulus. It is an important component of driving and flying skills. Tracking behavior is highly sensitive to the effects of marijuana. Impairment of tracking occurs even at very low doses (4.5 mg by smoking) in naive subjects (Weil et al., 1968). Studies of experienced users have also demonstrated consistent impairment. The tracking impairment has been found to persist for 4 to 8 hours, well beyond the feeling of intoxication ("high") by one laboratory (Moskowitz and Sharma, 1979; Moskowitz et al., 1981). No other studies have measured the effects of marijuana beyond 2 hours. This finding on the long-lasting effects has very important implications, as will be discussed later when the effects of marijuana on driving are reviewed, and, therefore, such studies should be repeated by other investigators.

While reaction time studies (as noted above) showed inconsistent results, tracking behavior is regularly and significantly diminished by marijuana at doses usually used in social settings. Tracking

tasks differ from reaction time studies, because the subject must continuously pay attention to the task. Since reaction time tests are intermittent, continuous attention is not required, and this may explain why reaction time studies fail to show consistent marijuana effects.

Sensory and Perceptual Functions

Tests that measure a subject's ability to detect a brief flash of light show significant impairment by low to moderate doses (2-3 mg are examples) of smoked marijuana (Sharma and Moskowitz, 1972, 1973, 1974; Moskowitz et al., 1972, 1974; Casswell and Marks, 1973; Jones and Stone, 1970). Sustained attention is required in signal detection tasks, and the relation between this sustained attention requirement and motivation effects has not been explored. Signal detection tasks are prototypes of perceptual demands found in man-machine interactions. The large reductions in signal detection that occur under the influence of marijuana may suggest a substantial risk for users who are operating machines. Other visual functions, such as visual search, that depend on eye movements are not impaired.

Intellectual and Cognitive Functions

The effects of marijuana on such intellectual and cognitive functions as verbal fluency, short-term memory, learning ability, calculation skills, ability to follow complex directions, and time sense have been investigated and are reported below. However, this area of study has been hampered by the lack of standard measures of functioning in the intellectual and cognitive areas tested. Overall, the investigation of marijuana effects on intellectual and cognitive functioning has not followed a logical progression.

Learning and Memory When studying the effects of drugs on learning, it is difficult to control all of the factors that might influence the results; for example, as noted above, how hard a subject tries to perform can make a big difference even in the presence of a sedating drug. Thus, it is not surprising that early studies of marijuana's effects gave inconsistent results.

More recently, several studies have demonstrated that a single moderate dose of marijuana impairs short-term memory. This effect is especially noticeable in the phases of short-term memory that are heavily dependent on attention, such as information acquisition and storage (Abel, 1970, 1971; Dornbush et al., 1971; Dittrich et al., 1973; Melges et al., 1974; Belmore and Miller, 1980). Examples of the types of impaired tasks would be remembering a sequence of numbers or syllables or memorizing and following a sequence of directions.

Physiological changes have been monitored in some of the same studies in which intellectual impairment has been reported. Miller

and Cornett (1978) found that increases in heart rate are produced by marijuana to about the same degree as impairment on intellectual tasks. This linking of a physiological marker with studies of behavioral effects is a useful model for research in this field.

Time Sense Another intellectual function influenced by marijuana is time sense. Under the influence of moderate doses of the drug, most investigators report that subjects consistently overestimate the amount of time that has elapsed. Thus, under the influence of marijuana, a given event is reported to last longer than it actually does last (Clark et al., 1970; Vachon et al., 1974; Tinklenberg et al., 1976a).

State-Dependent Learning State-dependent learning refers to a situation in which material that is learned while under the influence of a drug is remembered best in the state of drug intoxication in which it was originally learned. A series of studies were conducted with oral doses of 20 mg (in a subsequent study this dose was calibrated to 0.3 mg/kg) of Δ-9-THC to investigate the extent to which learning and memory are linked to the state of intoxication (Darley et al., 1973a,b, 1974, 1977). This modest dose of marijuana caused learning to take place more slowly than when the subject was drug-free. Once learned, recall of the learning that occurred during intoxication was best when the subject was again under the influence of marijuana. Although state-dependent learning occurs with marijuana, the quality of learning and recall is impaired because the information or problem-solving skills learned in the marijuana-intoxicated state will be reduced or impaired. These investigators believe that the major deficit is in the attention-storage phase of learning.

Oral Communication

Marijuana use in low to moderate doses impairs oral communication, especially clarity of sequential dialogue with other persons (Dornbush et al., 1971; Paul and Carson, 1973; Zeidenberg et al., 1973; Crockett et al., 1976; Miller et al., 1977a-d, 1978a,b, 1979; Pfefferbaum et al., 1977; Miller and Cornett, 1978; Natale et al., 1979; Belmore and Miller, 1980). Marijuana at moderate doses disrupts continuity of speech by impairing short-term memory (6-18 seconds duration) (Belmore and Miller, 1980). Communication while intoxicated is also impaired by the intrusion of irrelevant words and ideas into the stream of communication. When a list of words is learned and then the subjects are asked to recall those words without regard to sequence, words that were never in the original list are inserted during recall more often by subjects given Δ-9-THC than by those who were drug-free (Pfefferbaum et al., 1977; Miller and Cornett, 1978; Miller et al., 1978a,b). Zeidenberg et al. (1973) administered 5 mg Δ-9-THC orally and found that, in a social context, phrases became shorter, speech became slower, and there was

greater lag time between the cue to talk and the actual onset of talking. These subjects were also less able to recognize three-letter nonsense syllables to which they had previously been exposed. Further, when experimental subjects were all given the same dose of Δ-9-THC, they reported different subjective levels of intoxication. Those who reported more intoxication showed greater disruption of two-person communication (Paul and Carson, 1973).

Experimental subjects who were asked to tell stories about ambiguous pictures (the Thematic Apperception Test) demonstrated drug impaired organization and integration of stories. The authors reported "a timeless, nonnarrative quality, with greater discontinuity in thought sequence and more frequent inclusion of contradictory ideas" (Roth et al., 1975). When asked to talk for five minutes on any topic, subjects under Δ-9-THC demonstrated decreased variability of language and an increase in personal references, as well as less detailing of items mentioned in the monologue and less critical evaluation of those items (Natale et al., 1979).

Auto Accidents

Simulator Studies

A driving simulator is a laboratory instrument that requires the subject to perform a sample of the behavior required in automobile driving situations. Simulators differ from most of the laboratory studies described above in that complex behavior is required. Although simulators are representative of the multitask character of driving, no one simulator is capable of presenting all aspects of driving simultaneously. The behavior sampled varies across simulators; however, in comparison to car driving situations, the simulator has the advantage of presenting a standard stimulus to all subjects.

Most simulator studies reveal impairment of driving skills following moderately intoxicating doses of marijuana such as 10-15 mg (Crancer et al., 1969; Dott, 1972; Ellingstad et al., 1973; Rafaelsen et al., 1973; Moskowitz et al., 1976; Smiley et al., 1981). These impairments have been reported in simulators that test the perceptual functions as well as those that test motor skills of car control.*

*Another type of simulator study examined marijuana's effect on performance in a flying simulator (Janowsky et al., 1976). Subjects smoked marijuana cigarettes with 0.09 mg/kg Δ-9-THC, a dose of Δ-9-THC commonly used in social settings. Significant impairment of short-term memory was noted. Subjects were unable to recall where they were in the execution of a task. On the simulator they tended to forget where they were in a given flight sequence.

Test Courses

Experimental studies of the effects of marijuana on closed course automobile driving performance show that this skill is impaired by marijuana. Car handling skills were reduced, as shown by objective measures (Klonoff, 1974; Hansteen et al., 1976; Attwood, in press). It should be noted that these studies, involving subjects under the influence of marijuana, examined performance in less complex situations than are actually met in real-life driving situations. However, a closed course has the advantages of standard conditions and safety factors. In real-life driving situations, the perceptual and cognitive demands are considerably more complex. The Klonoff (1974) study of driving performance on city streets indicates that smoked marijuana (5-10 mg Δ-9-THC) impairs judgment and concentration in addition to impairing car handling skills.

Accident Surveys

Experimental evidence of impairments caused by marijuana on psychomotor functions, judgment, and motor skills involved in driving has led to research on the relationship of the use of marijuana and automobile accidents. A strongly positive relationship between use of alcohol and increased driving risk has long been established. The techniques used to establish the relationship of alcohol to accidents might appear to offer an excellent paradigm for comparable marijuana-accident research. However, there have been practical reasons why the roadside survey model of using breath samples obtained from accident drivers and comparing those to breath samples of randomly selected drivers who are passing the accident site in the same direction, the same time of day, and same day of the week has not worked for marijuana studies. Whereas there has been 97 percent cooperation for alcohol breath analysis, marijuana determination requires a blood sample, and only a minority of drivers willingly cooperate. Further, marijuana has a quite different body distribution pattern due to its high fat solubility. Delta-9-THC is not only technically quite difficult to detect in samples of body fluid, but it may be active in the nervous system long after it is not detectable in blood. The detrimental effects on driving skills (Moskowitz and Sharma, 1979; Moskowitz et al., 1981) may even persist 4 to 8 hours beyond the time when the user has had subjective feelings or euphoria or sleepiness.

Several reports of accident surveys have recently been published (Teale et al., 1977; Cimbura et al., 1980; McBay and Owens, 1981), but all suffer from the problems discussed above and particularly from the lack of a reasonable comparison group. For example, one study reported that 16 percent of Boston drivers had Δ-9-THC in their blood (Sterling-Smith, 1975). There was no description of the group who declined to give a blood sample but provided breath or urine samples instead. Also, there is no information as to the frequency of finding Δ-9-THC in the blood of those drivers who have

not had an accident or otherwise come to police attention. In addition, many users of marijuana also use other drugs so that data are available on only a few subjects who only used marijuana.

In an effort to obtain some reference point for the association of marijuana with accidents as compared with other drugs, Warren et al. (in press) reanalyzed the Cimbura et al. (1980) data. Twelve percent of the fatally injured drivers and pedestrians in that study had been found to have Δ-9-THC in their blood. The presence of other drugs was also determined and a culpability index was developed. A culpability index compares the frequency that a drug is found in drivers assigned responsibility for causing a collision with the frequency in individuals from the same sample who had not caused an accident.

Aspirin was found to have a culpability index of 1.0. That is, it was no more frequent in individuals assigned responsibility for a collision than on those who were not. This is of some significance because it serves as an internal check on the technique, agreeing with the a priori assumption that it would be unlikely for aspirin users to be overrepresented among those responsible for accidents. In contrast, subjects with cannabinoids present in the urine were found to have a culpability index of 1.7, the same culpability level found for the presence of alcohol. This indicates an excess of Δ-9-THC-positive drivers in the category responsible for accidents. The presence of antihistamines produced a culpability index of 1.5, and tranquilizers/antidepressants, 1.8.

Given the difficulties in executing epidemiologic studies where it is so difficult to obtain adequate control groups, it would appear that only tentative conclusions about marijuana's role in accidents can be reached. Supportive evidence that marijuana is a contributing cause of accidents comes from surveys of marijuana users who report they receive a higher-than-average number of tickets for driving violations and are involved in a higher-than-average number of accidents (Johnston, 1980). Nevertheless, the problems described above are yet to be solved. But the culpability index model presents a methodology that may be refined and utilized in future studies.

Alcohol-Marijuana Interactions

Surveys show that marijuana and alcohol are frequently consumed together (Fishburne et al., 1980; Johnston et al., 1980). Thus, it is important to determine what interactions, if any, occur between these two drugs. As both drugs have sedative properties, an additive effect would be expected and has been found in the few systematic investigations of the effects of this combination. One study reported that 0.05 percent blood alcohol level concentration (BAC) increased the impairment produced by 5 mg of smoked Δ-9-THC on tracking behavior (Manno et al., 1971). In a study using two doses of alcohol and two doses of marijuana, even the low dose of alcohol (0.07 percent BAC) and the low dose of Δ-9-THC (1.4 mg) impaired complex tracking in an additive fashion (Hansteen et al., 1976).

Higher doses produced more pronounced decrements. A combination of Δ-9-THC (0.320 mg/kg) and ethanol (a dose that produces a peak blood level of less than 0.08 percent BAC) has also produced an additive effect on the ability to perform on a psychomotor test (Belgrave et al., 1979). This additive effect would be of concern to those operating a motor vehicle.

The issue of alcohol-marijuana interactions is an important one, but currently few data are available. Clearly, more studies of marijuana's interaction with alcohol and other commonly used drugs are needed.

Chronic Effects

Animal Studies

Studies of chronic effects are necessary to determine whether a drug produces changes that persist after administration has stopped. In view of the theoretical possibility of cumulative or persistent marijuana effects, it is surprising that only a few laboratories have conducted experiments involving repeated dosing and testing for residual effects. Mice injected with 10 mg/kg Δ-9-THC for 20-40 days were found to be persistently impaired in new learning 100 days after the injections stopped (Radouco-Thomas et al., 1976). Similarly, rats given 20 mg/kg of Δ-9-THC orally for 180 days had learning still impaired 2 months after the Δ-9-THC treatment stopped (Fehr et al., 1976). This was confirmed by the same group in two subsequent studies (Fehr et al., 1979; Stiglick and Kalant, in press). Another group of investigators, however, could find no residual learning effects in monkeys 20 days after stopping comparable doses of Δ-9-THC (Ferraro and Grilly, 1974).

Human Studies

Clinical reports of memory impairment, lack of concentration, lethargy, etc., in nonintoxicated chronic users of marijuana have led to studies in which psychological testing was administered to users of marijuana and controls. The results of these studies are inconclusive. Several studies show impaired performance in users as compared to controls (Agarwal et al., 1975; Soueif, 1976; Wig and Varma, 1977; Mendhiratta et al., 1978); others found no significant residual effects in the marijuana users (Bowman and Pihl, 1973; Rubin and Comitas, 1975; Satz et al., 1976; Ray et al., 1978; Schaeffer et al., 1981). All of these studies can be criticized on methodological grounds, and the results have been disputed. This is not surprising, because it is technically very difficult to obtain a sample of chronic marijuana users, get them into a truly drug-free condition, test them, and similarly test an appropriate group of controls.

Several groups of investigators (Dornbush et al., 1972; Frank et al., 1976; Harshman et al., 1976; Rossi et al., 1977) examined

chronic marijuana users before and after 21-94 days of chronic intoxication in a research hospital setting. None of the investigators found any psychological changes during postdrug testing. However, 2 months of use is a relatively short period of time for a change to be detected, and the subjects had already been using marijuana for at least a year prior to entering each study (Fehr et al., 1976).

The available studies of chronic behavioral effects lead to no clear conclusions. Although some animal studies demonstrated a learning deficit that persisted for months after daily marijuana exposure was discontinued, the human studies have such methodological weaknesses that they cannot be interpreted. A prospective concurrent cohort study and a retrospective case-control study of possible outcomes of and risk factors for use of marijuana could add useful information. (See research recommendations at the end of this chapter.)

CLINICAL SYNDROMES

In this section we will discuss both acute and chronic behavioral changes that have been reported in the clinical literature to be associated with the use of marijuana. An association based on case reports does not imply causality. Studies of appropriate control groups are necessary. In general, acute or immediate clinical effects of drugs can be determined scientifically much more readily than chronic or delayed effects. This is as true for marijuana as it is for alcohol and other drugs. Thus, the acute effects of marijuana are based on more solid evidence than are the reported chronic effects.

Acute Effects

The acute clinical effects of marijuana seem to occur on a continuum from mild dysphoria to acute brain syndrome. In the literature, three different syndromes have been described, although there is blurring of the boundaries in this classification and no general agreement as to diagnostic criteria.

Anxiety/Panic Reaction

A major portion of the evidence for this effect comes from reports by marijuana users themselves. Marijuana's popularity notwithstanding, a surprisingly high proportion of users report reactions that they regard as unpleasant or undesirable. For example, 33 percent of regular users reported that while intoxicated they occasionally experienced such symptoms as acute panic, paranoid reaction, hallucinations, and unpleasant distortions in body image (Tart, 1970; Negrete and Kwan, 1972). Another study reported that 16 percent of

regular users reported anxiety, fearfulness, confusion, dependency, or aggressive urges as a "usual occurrence" (Halikas et al., 1971). Similar findings in groups of stable, well-adjusted, moderate users have been found by other investigators (Annis and Smart, 1973; Marcus et al., 1974). First-time users are more likely than are experienced users to report adverse reactions. The frequency of such reactions appears to be higher when the setting for use is not a favorable one; for example, when the user sees the environment as threatening.

These adverse psychological reactions also have been observed in subjects of laboratory experiments with marijuana. Such controlled observations of persons whose immediate prior mental status and whose dosage were known give a basis for concluding that acute adverse psychological reactions can occur under single moderate doses of marijuana. These effects are more likely at higher doses. They usually last no longer than 2 to 4 hours. Acute paranoid reactions under these controlled conditions have been reported (Mendelson and Meyer, 1972; Tassinari et al., 1973; Frank et al., 1976; Melges, 1976). Ingestion, in which titration of dose (dose adjustment as occurs during smoking) is difficult, may be more likely to produce adverse effects than administration by smoking marijuana. However, chronic use and interaction with other psychoactive substances are not required.

As frequently as these adverse reactions are observed and self-reported, medical treatment is rarely sought. For example, a college student health clinic reported only six students per year sought medical treatment for an adverse reaction to marijuana out of a student population of 20,000 (Pillard, 1970). In the general population, a diagnosis of acute cannabis reaction was found in only 10 cases out of 700,000 hospital admissions in the United States (Lundberg et al., 1971). In the U.S. Army, only 18 such cases were treated over a several-year period from a military population of 33,000 (Tennant and Groesbeck, 1972). There are no recent figures showing requests for medical treatment now that the use of marijuana is more intense, widespread, and reaching younger age-groups. However, a unique monitoring of drug causality behavior documenting emergency room encounters conducted by the Drug Enforcement Administration and the National Institute on Drug Abuse (U.S. Department of Health and Human Services, 1979) may in the future provide additional information about the frequency of adverse reactions to use of marijuana.

Dysphoric Reaction

Therapeutic trials have been carried out testing Δ-9-THC as a possible treatment for mood disorders (see Chapter 7). Severe dysphoric reactions characterized by disorientation, catatonialike immobility, acute panic, and heavy sedation have occurred in several patients. The dysphoric symptoms appeared at moderate doses comparable to those used in social settings. They lasted only a few hours and responded to discontinuation of the drug and reassurance of the patients (Kotin et al., 1973; Ablon and Goodwin, 1974).

Similar dysphoric reactions have been reported in cancer patients who were on a therapeutic trial of Δ-9-THC to control the nausea associated with chemotherapy. The symptoms, course, and response to ceasing use of the drug were identical to those described above. Investigators have suggested that the dysphoric response is more likely to occur in older patients not accustomed to drug use for whom the mood-altering effects are unanticipated and unwelcome (Shiling and Stillman, 1980).

Acute Brain Syndrome

Diagnostic criteria for the syndrome now called delirium and previously called acute brain syndrome appear in Diagnostic and Statistical Manual of Mental Disorders, Third Edition, 1980 (DSM III). These include: (a) a clouding of consciousness as manifested by impairment of ability to sustain attention to environmental stimuli, or impairment of ability to sustain goal-directed thinking or goal-directed behavior; (b) a disorder of memory or orientation; (c) perceptual disturbances; and (d) a change in sleep pattern and/or a change in psychomotor activity. The symptoms develop over a short period of time and fluctuate rapidly.

Both the symptom pattern and the course of the acute brain syndrome fit the descriptions of one type of behavior disorder associated with use of marijuana. It has been reported to develop in persons who have a history of prolonged, regular, heavy use of marijuana. It is defined as an "acute" brain syndrome because it comes on during the period of drug use and it gradually disappears after the drug is stopped. The majority of case reports have come from Eastern countries where the cannabis products customarily used have high potency (Spencer, 1970; Chopra and Smith, 1974; Meyer, 1975). It has also been reported in U.S. Army personnel stationed in Viet Nam (Talbott and Teague, 1969) and in Europe (Tennant, 1972), where soldiers had access to very high Δ-9-THC concentrations in cannabis substances. In contrast to the Indian public mental hospital patients who were hospitalized for many weeks, U.S. soldiers recovered in 3 to 11 days and returned to duty. This difference in duration may reflect sociocultural differences in length of in-patient treatment more than a difference in the disorder.

Withdrawal Syndrome

Studies of animals and human subjects given moderate to high doses of marijuana orally or by inhalation several times per day have demonstrated tolerance to many of the effects of marijuana (see Chapter 1). When such use of marijuana is stopped after several days, a withdrawal syndrome occurs. In human subjects, this resembles the typical mild withdrawal symptoms seen after prolonged sedative use (Jones and Benowitz, 1976). Subjects show irritability, agitation, insomnia, and EEG changes (see Chapter 4). These symptoms are self-limiting; they peak at 30 hours and disappear by 90 hours.

There is no clinical evidence that physical dependence plays an important role in persistent use of marijuana. Withdrawal symptoms would not be expected in intermittent users; however, daily round-the-clock users of high-dose marijuana may be expected to show some symptoms of withdrawal soon after stopping regular use.

Chronic Effects

Cannabis Psychosis

Cannabis psychosis refers to a chronic psychotic condition (out of contact with reality) reportedly seen in heavy marijuana users, but extending beyond the period of acute intoxication. Some authors have described a schizophrenialike picture with delusions and hallucinations, and others have stressed the existence of organic mental confusion. Most of the reports have come from observation of hospitalized patients in Asian and African countries (Asuni, 1964; Chopra and Smith, 1974; Thacore and Shukla, 1976). There are no reports in the North American literature. At this time, there is insufficient evidence to say that cannabis psychosis exists as a separate clinical entity (Murphy, 1963; Edwards, 1976).

"Amotivational Syndrome"

Clinicians coined the term "amotivational syndrome" to describe a characteristic set of personality changes seen in some daily users of marijuana (McGlothlin and West, 1968; Smith, 1968). The changes include apathy, loss of ambition, loss of effectiveness, diminished ability to carry out long-term plans, difficulty in concentrating, and a decline in school or work performance. As usually described, these changes are seen in frequent or daily users, and thus they may be considered a form of chronic intoxication. The term "amotivational syndrome" is not an official diagnosis, but there is agreement among many clinicians who treat young people that this constellation of symptoms is common. It may also be seen in nonmarijuana users, and daily use of marijuana is not always associated with loss of motivation.

The evidence presented for the linking of this syndrome with marijuana consists of case reports. For example, Baker and Lucas (1969) described the case of a man whom friends described as previously conscientious, capable, and effective; but after smoking hashish daily for 3 years, he changed into a person for whom use of drugs was a way of life and in whom a serious deterioration of social function was observed. Other reports consist of groups of cases with similar histories (Thurlow, 1971). The symptoms mentioned, in addition to loss of motivation, include falling grades, difficulties in concentration, intermittent confusion, and impaired memory. Some authors report improvement when use of marijuana is stopped (Kolansky and Moore, 1971, 1972).

A variety of other data support such a condition. In a large survey, daily marijuana users were asked about the drug's adverse effects (Johnston et al., 1980). The most common response was "loss of energy" (42 percent). Nearly a third (32 percent) of the daily users thought that marijuana caused them to be less interested in other activities than they had been before, and a third (34 percent) thought that it hurt their school and/or job performance. Another type of evidence comes from comparisons of college students who use marijuana with others who do not. Several such studies (Shean and Fechtmann, 1971; Linn, 1972; Simon, 1974; Finnell and Jones, 1975) found marijuana users had increased levels of psychological disturbance, lower academic performance, and lower performance on scales measuring attitudes toward achievement and purpose in life. But some studies in both the United States and foreign countries have failed to show significant differences between marijuana users and abstainers (Brill and Christie, 1974; Rubin and Comitas, 1975).

Interpretation of the evidence linking marijuana to "amotivational syndrome" is difficult. Such symptoms have been known to occur in the absence of marijuana. Even if there is an association between this syndrome and use of marijuana, that does not prove that marijuana causes the syndrome. Many troubled individuals seek an "escape" into use of drugs; thus, frequent use of marijuana may become one more in a series of counterproductive behaviors for these unhappy people.

The available evidence does not allow a sorting of the various possibilities in the relationship between use of marijuana and the complex of symptoms in the "amotivational syndrome." It appears likely that both self-selection and authentic drug effects contribute to the "motivational" problems seen in some chronic marijuana users (see Chapter 2). Persons who are experiencing loss of motivation, apathy, and the other aforementioned symptoms probably will worsen the situation by taking any sedating drug. They should be warned to avoid frequent use of marijuana, alcohol, and other nonprescribed drugs.

"Flashbacks"

In 1968, Keeler et al. reported four cases of the brief spontaneous recurrence of a mental state similar to that experienced during marijuana intoxication 1 to 21 days after the last drug use. Three of the four subjects complained of hallucinations comparable to flashbacks usually associated with LSD (Horowitz, 1969). Three separate reports of marijuana flashbacks followed (Smith, 1968; Favazza and Domino, 1969; Weil, 1970) and all of these latter subjects had used LSD prior to marijuana. In a survey of 720 servicemen, not a single case of flashback in any subject for whom hashish was the only drug consumed was documented (Tennant and Groesbeck, 1972). But in the same sample, 15 subjects were identified who had LSD flashbacks precipitated by use of marijuana. A larger sample of 2,001 army personnel (Stanton et al., 1976) revealed that use of marijuana had the highest and only statistically

significant association with the precipitation of LSD flashbacks among five classes of abused drugs. Clinical studies also have provided evidence that marijuana precipitates a recurrence of the LSD flashbacks experience (Holsten, 1976; Abraham, 1981).

The existence of flashbacks following use of either LSD or marijuana is entirely based on self-reports, because there are no distinctive physical signs or tests, such as EEG changes, to identify this condition. There is no current pharmacological explanation of the phenomenon, and data regarding dose and time parameters do not exist. Still, the reports by users are reasonably consistent. Thus, there is clinical evidence that use of marijuana by those who have previously used LSD increases the likelihood of recurrence of the LSD experience.

Effects on Preexisting Mental Illness

Only evidence available regarding this issue consists of case [illegible]s of patients who had recovered and apparently were doing well un[illegible] they used marijuana. There is no information on the number of mentally ill patients who have used marijuana without complications.

The available data, therefore, do not prove that marijuana worsens mental illness. Still, there are sufficient numbers of uncontrolled clinical reports showing a temporal association between use of marijuana and return of mental symptoms, so that patients should be warned of this possibility.

Patients with a history of schizophrenia may be particularly sensitive to marijuana's effects. Four schizophrenic patients who were otherwise well controlled with medication suffered serious relapse of their schizophrenic symptoms following use of marijuana (Treffert, 1978). Other cases have been reported (Smith and Mehl, 1970; Weil, 1970; Bernhardson and Gunne, 1972). These all were cases in which marijuana was purchased on the street, so the dose and purity were unknown.

Patients with mood disorders have also been reported to show worsening of mental symptoms after use of marijuana. For example, four cases are known in which marijuana apparently precipitated a relapse of psychotic (hypomanic) behavior (Harding and Knight, 1973). Furthermore, depressed patients treated with Δ-9-THC have been observed to show a high incidence of dysphoric reactions (Ablon and Goodwin, 1974).

Effects Sometimes Reported By Users

Mood Changes

There is a general belief that use of marijuana alters mood. This property is one of the desired effects sought by many users. Investigators have described a number of variables that enter into the mood response to marijuana (Jones, 1971). These include dosage,

past experience, attitude, expectations, and setting. For example, individuals who used marijuana in isolation tended to be relaxed and slightly drowsy; in contrast, when the user was in a group situation, marijuana was associated with euphoria and lack of sedative effect (Jones, 1971). Further evidence that mood changes are not attributable solely to the pharmacological action of marijuana comes from a study that found that elevation in mood occurred immediately before use of marijuana and immediately after, but that mood was not correlated with other indications of the subjective level of intoxication (Rossi et al., 1978). Instead, mood was correlated significantly with the moods of others, whether or not the other persons were intoxicated.

It appears that preexisting mood can influence the decision to use marijuana. High school students who exhibit symptoms of depression are more likely than are others to begin using marijuana as well as other illicit drugs (Paton et al., 1977). There is some evidence that students use the drug as a self-prescribed remedy for their own mood problems, often reporting that they use marijuana as a means of psychological coping (Johnston et al., 1980; Kaplan, 1980).

A belief that marijuana can be used to alleviate clinical depression is not supported by other studies, including one in which Δ-9-THC was carefully tested as an antidepressant. It was given to depressed patients as an experimental treatment without success (Ablon and Goodwin, 1974) (see Chapter 7).

Interpersonal Behavior

Adolescents and young adults often report that they use marijuana to facilitate interaction in new social situations (Mirin and McKenna, 1975). In a survey of 704 midwestern undergraduate students, most reported that marijuana was a meaningful "tool of social bonding" (Linn, 1971). There seems to be a widespread belief that marijuana smoking has several facilitative effects, including enhanced social effectiveness, closer social bonding, heightened interpersonal sensitivity and empathy, and enhanced sexual pleasure. The subcultural lore on one of these measures of interpersonal behavior--sexual effects--has not been studied systematically either in surveys or in experimental studies. The effects on sex hormones are controversial (see Chapter 5). Studies in experimental situations have failed to show any enhancement of social interaction and, in fact, some decrements were noted (Galanter et al., 1974; Clopton et al., 1979; Janowsky et al., 1979). Data from natural settings rather than experimental settings are not available.

Effects on Aggression

Because marijuana users have been involved in delinquent behavior, a number of investigators have questioned whether use of marijuana enhances aggressiveness in human beings. There are specific concerns

about potential links of use of marijuana to aggression. Both retrospective and experimental studies in human beings have failed to yield evidence that marijuana use leads to increased aggression. Most of these studies suggest quite the contrary effect. Marijuana appears to have a sedative effect, and it may reduce somewhat the intensity of angry feelings and the probability of interpersonal aggressive behavior (McGuire and Megaree, 1974; Tinklenberg, 1974; Salzman et al., 1976; Taylor et al., 1976; Tinklenberg et al., 1976b; Hemphill and Fisher, 1980).

SUMMARY

There is experimental evidence that marijuana seriously impairs psychomotor performance. Strong evidence for impairment has been found in:

- coordination as examined by hand steadiness, body sway, and accuracy of execution of movement;
- tracking performance;
- perceptual tasks;
- vigilance;
- performance on automobile driving and flying simulators; and
- operating automobiles on test roadways.

Less reliable evidence of impairment or reliable evidence of a small degree of impairment was found in reaction time, simple sensory functions, and control of eye movements. Although the effects that marijuana produces on psychomotor functions used in driving are clear, studies linking marijuana to auto accidents are inconclusive. The research is impaired by methodological problems related to the pharmacology of marijuana. One recent study reported that marijuana and alcohol had a similar degree of association with fatal accidents, but more investigation is needed.

Studies also have shown acute effects of marijuana on short-term memory. State-dependent learning also has been shown, in that information or problem-solving skills learned in the intoxicated state will be reduced or impaired in the drug-free state. One laboratory has shown tracking impairment to persist for 4 to 8 hours beyond the feeling of intoxication. Some animal studies demonstrate a learning deficit that persists for months after marijuana exposure has been discontinued, but human studies do not permit secure conclusions.

The acute clinical effects of marijuana are fairly well established, although there is no general agreement as to how to classify them. Anxiety and panic reactions have been reported by users and observed in experimental situations. They are not uncommon, but they rarely require medical attention. When marijuana is used to treat nausea and other conditions, mental effects can occur, which some patients, especially older persons, may regard as unpleasant. These mental effects may require cessation of the treatment.

Marijuana also has been found to produce an acute brain syndrome. This is a more severe mental problem consisting of confusion and loss of contact with reality. It lasts from several hours to several days and appears to be more likely to occur with higher doses.

Chronic effects of any drug are more difficult to assess than are immediate effects. The evidence that marijuana produces a chronic psychosis is not convincing. The possible role of marijuana in causing an amotivational syndrome is a matter of great concern. Apathy, poor school work or work performance, and lack of goals characterize a number of long-term marijuana users. But it has not been possible to determine how much is caused by use of marijuana and how much was antecedent; it seems likely that both factors (drug effect and self-selection) contribute to the motivational problems seen in chronic users of marijuana. Existing studies have produced conflicting results. None of the investigators has looked at effects on the very young daily marijuana user, who is regarded as potentially at high risk for damaging effects because of physiological and psychological immaturity.

There is clinical evidence that marijuana use by former LSD users may precipitate a recurrence of LSD-type hallucinations known as a "flashback." Other clinical evidence raises the possibility that marijuana use can worsen preexisting mental illness.

RECOMMENDATIONS FOR RESEARCH

The committee recommends the following types of studies.

- Systematic research on acute behavioral and psychosocial effects of marijuana should be extended to other age groups. There are virtually no data on prepubertal children, young adolescents, older adults, and aging persons.
- Studies of effects of daily use of marijuana on school children are greatly needed. These effects should include the learning of new material, physical, psychological, and social development, acquisition of coping skills, and tools of daily living.
- Systematic studies of long-term effects of marijuana are increasingly possible now that longitudinal studies have identified representative panels of persons known to be chronic heavy users. These studies should cover interactive effects of marijuana and other drugs on behavioral and psychosocial responses, especially interactions of alcohol and marijuana because of their frequency of associated use.
- Dosage effects should be restudied, taking into account the higher potency cannabis that is in current use. Further study is needed of the timing and depth of inhalation of cigarettes with standard doses of marijuana. More animal studies at varying doses are needed. In view of the long-term retention of marijuana in body tissues, further study is needed to see whether or not chronic users may have impairments of function even in the absence of an acute dose

of marijuana. The factors that influence the persistence of effects following an acute dose are not understood.

- The correlation of changes in a physiological marker, such as increased heart rate, with observations of behavioral effects should be encouraged.
- Many of these recommendations, along with those of other chapters, could be consolidated and carried out as part of a study that is both a prospective cohort study and a retrospective case-control study of possible outcomes and risk factors with marijuana use.
- A cohort of drug-naive junior high school students could be assembled and followed over time to see which students become marijuana users and which remain nonusers. Students would be subjected to physical and psychosocial testing at predetermined time intervals. The two groups would be evaluated in terms of the incidence of specific outcomes and the relative risks associated with these outcomes after appropriate follow-up periods.

In order to identify risk factors for marijuana use, individuals who become marijuana users would be compared to individuals who remain nonusers using a case-control methodology. By combining these two epidemiologic research strategies, the etiology and effects of marijuana use may be studied.

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