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

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Abstract

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

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

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

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

METHODOLOGICAL CONSIDERATIONS

Polydrug Use

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

There are many possible factors which may account for these findings. First, the drugs themselves and/or their adulterants may be directly toxic to the central nervous system. Evidence suggestive of such toxicity has been presented for heroin and opium (Hall and Karp, 1973; Richter and Rosenberg, 1968; Schein, Yessayan, and Mayman, 1971; Thompson and Waldman, 1970), amphetamines (Citron, Halpern, McCarron, Lundberg, McCormick, Pincus, Tatter, and Haverback, 1970; Goodman and Becker, 1970; Kane, Keeler, and Reifler, 1969; Weiss, Raskind, Morganstern, Pytlyk, and Baiz, 1970), and inhalants (Grabski,

1961; Knox and Nelson, 1966; Layzer, Fishman, and Schafer, 1978; Prockop, 1977; Prockop and Couri, 1977; Schaumberg and Spencer, 1976; Valpey, Sumi, Copass, and Goble, 1978). Quinine, a substance used to dilute heroin, has been linked to optic atrophy in at least one case (Richter and Pearson, 1975) and is described as having "well recognized tissue toxic effects" (Pearson & Richter, 1975, p. 316).

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

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

Differential Vulnerability

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

Secondary Effects

There are also a number of secondary factors associated with heavy polydrug use that may increase the likelihood of cerebral impairment. Heavy drug

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

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

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

Degree of Cannabis Use

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

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

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

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

Preexisting Group Differences

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

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

Preexisting group differences are particularly relevant in the cross-cultural studies. Poor nutrition and poor medical care in the cannabis users, and social class differences in the users and nonusers are common. Nonetheless, the cross-

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

Acute and Withdrawal Effects

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

tory screening procedures for drugs other than marijuana, and only one study (Schaeffer, Andrysiak, and Ungerleider, 1981) used such a procedure to screen for the presence of marijuana.

Experimenter Bias

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

Summary on Methodology

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

Table 1

Methodological Issues in the Study of Cannabis Users

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

ASSESSING CEREBRAL DYSFUNCTION

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

Neurological Approach

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

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

Table 2

Neurological Findings Organized by Test

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

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

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

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

The neurological techniques that have been described, with the exception of those that assess behavior (i.e., neurological and mental status examinations),

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

Neuropsychological Approach

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

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

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

Table 3

Psychological and Neuropsychological Findings Organized by Test

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

(continued)

Table 3 (continued)

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

(continued)

Table 3 (continued)

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

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

CHRONIC CEREBRAL EFFECTS OF MARIJUANA USE

Early Research

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

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

The Hemp Drugs Commission was a thorough attempt to study the effects of cannabis, especially considering the lack of auxiliary medical tests available at the time. The commission had no direct contact with the users and conducted very little experimentation. However, its members interviewed 1,193 individuals, including 335 physicians, and reviewed the records of all judicial

proceedings for the previous 20 years in which cannabis had been thought to be a factor in violent crimes. They also reviewed the records of every mental hospital in India and thoroughly studied the files on each of the 222 individuals admitted in 1892 with a possible connection between cannabis use and mental illness.

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

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

The next reported study, also conducted in India, was carried out 45 years later (Chopra and Chopra, 1939). Chopra and Chopra examined 1,238 cannabis smokers using interviews, physical examinations, and in some cases, extended behavioral observations. They concluded that moderate use was not harmful to the central nervous system while excessive use did lead to impairment. In a reanalysis of their data 18 years later (Chopra and Chopra, 1957), they questioned whether even moderate use of marijuana might be harmful. However, several problems plagued this study. These included the likelihood of poor nutrition and infectious disease in the sample (it was noted that 2.5% had a "history" of syphilis), and a probable overrepresentation of social deviates since it was unlikely that productive members of a higher social class would be referred to the investigators by medical and local governmental personnel. In discussing long-term central nervous system changes, they primarily reported symptoms that could as readily have reflected psychopathology, such as lability of affect, impairment of judgment and memory, habitual lying, and insomnia. The authors did report that many subjects demonstrated preexisting "neurotic tendencies" but felt that cannabis had been responsible for enhancing

these tendencies. However, they presented no evidence to show that these individuals demonstrated less psychopathology before the onset of cannabis use.

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

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

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

These early research studies are summarized in Table 4.

Modern Neurological Approaches

Cerebral Atrophy

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

Table 4

A Summary of Early Research on the Effects of Cannabis Use

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

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

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

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

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

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

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

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

Other Neurological Findings

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

Table 5

A Summary of Neurological Studies on the Effects of Cannabis Use

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

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

Summary on Research Findings

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

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