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Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

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Editor, Robert C. Petersen, Ph.D.

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FOREWORD

This report, like its five predecessors, summarizes our growing, though still limited, knowledge of the health consequences of marihuana use. To the over simplified question, "Is marihuana use safe?", we can offer a simplistic, but unequivocal, "No." There is good evidence that being "high" -- intoxicated by marihuana -- impairs responses ranging from driving to intellectual and interpersonal functioning.

It is hardly surprising that marihuana is not "safe" in any absolute sense for no drug is or can be under all conditions of use. Many substances as diverse as alcohol, tobacco, cyclamates and red dye No. 2, do not harm all users, but may be fraught with adverse health consequences for a significant number of them. Marihuana, too, can be hazardous even when used occasionally.

We now know that marihuana intoxication poses a significant threat to highway safety in much the same way that alcohol does. The exact size of that threat remains a matter for conjecture. Many marihuana users report driving while intoxicated and since we know driving skills are impaired under those circumstances, the problem is real.

A related source of concern is the increasing number of Americans who use marihuana on a daily or near daily basis. Just over 8 percent of the nation's 1976 high school graduates reported virtually daily marihuana use. The number of 1976 graduates using marihuana on that basis was 40 percent greater than the number making equally frequent use of alcohol.

To date, most American marihuana users smoke relatively low potency material and only occasionally. The apparently benign picture presented by that type of use -- aside from possible hazards related to functioning while intoxicated, few other specific health hazards have been definitively identified -- may change if more frequent use of stronger material becomes more common. If laboratory findings of possible effects on the body's immune response, endocrinological functioning and cell metabolism prove to have serious clinical implication, marihuana's persistence in the body may make even episodic use risky.

More realistic than the question of marihuana's absolute safety under all conditions of use are two questions:

1. What is the health risk at present and anticipated levels of use in the United States?

2. What are the specific areas of health hazard and who is at risk?

Neither of these questions can be satisfactorily answered at present. The increasing availability in the United States of large numbers of individuals who have used marihuana over a period of several years makes it increasingly possible to do the type of large

scale study that could previously only be done abroad under quite different cultural conditions. Such studies are being planned. Other, more specific research is planned to resolve the questions raised by the laboratory findings across a broad spectrum.

This report emphasizes the large and apparently growing number of Americans who have used marihuana. While this finding deserves emphasis, it is equally important to recognize that more than half of the Americans who have used marihuana have quit using it. Even larger is the number of people who say that they have not used and have no intention of using marihuana regardless of the legal status of the drug.

In recent years, those who have had to deal with legal substances as diverse as alcohol and red dye No. 2 have had to face the fact that these agents are not "safe" under all circumstances and that whatever social policy is adopted concerning their availability must take this disquieting fact into consideration. Similarly, in the area of illicit drugs, we now recognize that many users suffer no apparent ill effects. The realization that significant numbers of users of legal substances may suffer ill effects at the same time that many users of prohibited substances have no problems with their use, has strained our national capacity to deal rationally with the fundamental social policy issues involved. We hope that this report describing the current state of our knowledge of marihuana's health consequences continues to contribute to a better understanding of the complexity of this important social issue.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

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MARIHUANA RESEARCH FINDINGS: 1976 is the more detailed reference report which provided the basis for the shorter sixth edition of the Marihuana and Health Report. While the latter was intended for a general audience, this more detailed review of each of the areas discussed is more likely to be of interest to the technically trained reader. In order to be of maximum usefulness, this monograph also includes as a summary the text of the sixth report. This volume is provided as part of the Research Monograph series to ensure that the full background reports which formed the basis for the briefer report are available to those with particular need for still more specialized materials.

MARIHUANA RESEARCH FINDINGS: 1976

SUMMARY

Robert C. Petersen Ph.D.

Marihuana use, which first began to involve significant numbers of American youth in the 1960's, continues to increase. Most users reported occasional use of low potency material. However, more regular use of stronger materials has increased. Last year 1 in 12 high school seniors nationwide reported using marihuana 20 or more times per month. In peak using groups, figures are still higher. Among males 20-24 years old, about 1 in 10 uses on a daily basis. If we restrict our analysis to those in this age group who have ever used, nearly one in five (17 percent) does so daily.

The amount of research on chronic use remains modest. This is especially true when considered in the light of the estimated 36 million Americans who have tried the drug and the nearly 15 million who used it within the month preceding the last national survey. While three carefully controlled overseas studies have compared long term user populations to non-using populations, the actual number of matched user/non-user pairs was small (a total of 117 users) due to the complexity of the research design. There is considerable evidence from experience with other drugs that many years of use by substantial numbers is required for the implications

of widespread drug use to surface. Moreover, the small samples studied thus far would probably not have revealed some of the most serious adverse consequences of any habit, as illustrated by cigarette smoking. Laboratory research in the United States has been largely restricted to young males in good health as have larger U.S. studies of psychosocial aspects of use. Marihuana's effects on those in poor health or older people and on females have not been adequately examined. Despite these obvious limitations to our knowledge, many have interpreted the preliminary findings as indicative that "marihuana is safe."

Preliminary marihuana research evidence has been eagerly sought, its limitations too frequently ignored and its implications often overdrawn to provide support for one or another side of the debate on social policy. Changes in social policy dictated by the necessity of finding a wiser, more workable drug policy concerning personal use and possession are in danger of being interpreted as indicating that marihuana is without significant hazard.

While the picture regarding marihuana use is far from complete, it should be emphasized that there is good evidence that use is by no means harmless. Such behaviors as the operation of a motor vehicle or complex psychomotor performance are clearly impaired by marihuana use in a manner somewhat similar to that of alcohol use. A variety of both clinical and experimental observations makes it seem quite likely that heavy use of smoked marihuana will impair lung function and may result in consequences similar to those of cigarette smoking.

Marihuana is most widely used by adolescents and young adults during critical stages in their personality development and while developing intellectual and psychosocial skills. To what extent, if any, chronic intoxication affects development is still unknown. While the percentage of the population which uses heavily on a daily basis is still a small minority even in this group, any serious consequences of use may well be expected to have implications for extended periods of their lives.

The quest for a rational social policy has resulted in a continuing demand for a simple answer to the question, "Is marihuana harmful?" Unfortunately, the apparent simplicity of both the question and the desired answer are deceptive; both are complex.

A series of laboratory findings concerning the possible adverse impact of marihuana on such areas as the body's immune response, basic cell metabolism and other areas of functioning has not yet been adequately explained. Although it is possible that some of them may ultimately prove to be without clinical significance, the possible hazards dictate a degree of caution in prematurely concluding that we now know enough about the dangers of cannabis use. Unlike alcohol in which many of the implications of chronic use are well documented (and from a public health standpoint, serious), similar parameters of risk for cannabis use have not yet been adequately explored.

As marihuana use escalates it is highly probable, for example, that such use will come to include more individuals with already impaired physical or psychological functioning for whom use and particularly regular use may have quite different implications than occasional use by those in optimal health. Evidence on cardiac patients cited over the past two years is one example. Similarly, the implications of use for marginal 'members of the society or for those having greater problems with coping or less skills for doing so, may be quite different from those of the more competent, advantaged student user.

Research over the past several years has markedly expanded our knowledge of many of the effects of marihuana and its patterns of use both here and abroad. Despite this rapid expansion in our knowledge much remains to be learned, especially about the implications of chronic use. Most therapeutic drugs are used in pure forms for a limited duration of time, for a specific purpose, in controlled doses and often under medical direction. Marihuana, by contrast, is quite variable in potency, not uncommonly used regularly over extended periods of time and with no supervision to alert the user to possible adverse effects. Given the widespread patterns of use, it is critical that we continue to define the parameters of risk both when used alone and in combination with other drugs. Now that there are significant numbers of Americans who have been using for periods of several years or more it is desirable that we study use in a manner parallel to the overseas studies which have been conducted, but on a much larger scale. If serious hazards are anticipated, it is essential that they be discovered soon. With the present trend toward increasing use, early detection of more serious health implications may discourage marihuana use before it becomes as firmly entrenched in U.S. social customs as are alcohol and tobacco use.

NATURE AND EXTENT OF MARIHUANA USE IN THE UNITED STATES

Marihuana use among the general U.S. population has not appreciably changed since the issuance of the Fifth Marihuana and Health Report (105). Concentration continues among adolescents and young adults as shown by the most recent national survey (2) which found the largest percentages of those who had "ever used" and now using (defined as use within the month preceding the survey) among the 18-25-year-olds. A majority (53 percent) of this age group has used marihuana at some time; a quarter of the sample within the past month.

Among older age groups (over 25), the percentage of those who have ever used drops precipitously. Similarly, of those adults who have used cannabis, the percentage reporting current use is considerably lower than that of younger groups. For example, approximately one-third (36 percent) of the 26-34-year-olds report having tried marihuana as compared to one-half of the 18-25-year-olds. But less than one-third of the 26-34 age group who have ever used report current use (within the month preceding the survey), while about half of the 18-25 group who have ever used marihuana are current users. In the over 35 age group about 1 in 20 reports having tried the drug; but only 1 in 6 of those who had ever used, reported current use.

Among adolescents questioned in the National Survey, the 12-13-year-olds reported little use: 6 percent of this group report having ever used, half of these within the past month. Among 14-15-year-olds, one in five has used but in the 16-17-year-old group twice as many (two in five) have tried marihuana. For all youth groups (12-17-year-olds) about half of those who have ever used are current users.

When the survey results are analyzed for sex differences, twice as many men as women over 18 (29 percent vs. 14 percent respectively) have had experience with the drug. By contrast, the sex differences are less marked among 12-17-year-olds who have ever used (26 percent of males vs. 19 percent of females). Once again, about half of those who have ever used report that they are currently using.

Tables 1 and 2 provide National Survey data for the years 1971 through 1976 on marihuana use by adults (those over 18) and by youth (the 12-17 age group). When asked about their plans for future use of marihuana, one in five youths (the 12-17 age group) anticipated possible future use. By contrast, one in three of those 18-25 (the peak using age group) anticipated future use, while only one in ten of those over 26 had similar expectations.

When comparisons are made on a national basis between current use of marihuana and use of cigarettes and alcohol, use of the latter drugs is considerably greater than that of marihuana. Among youth, one-third reported having drunk alcohol in the preceding month, one-quarter reported use of tobacco and one-eighth marihuana use. While 60 percent of the adults reported alcohol use in the preceding month

Table 1

MARIHUANA USE AMONG ADULTS, 1971-1976

	% Ever Used				% Current Use**			
	1971	1972	1975	1976	1971	1972	1975	1976
All adults	15	16	19	21	5	8	7	8
Age:								
18-25	39	48	53	53	17	28	25	25
26-34	19	20	29	36	5	9	8	11
35+	7	3	4	6	--*	--*	--*	1
Sex:								
Male	21	22	24	29	7	11	9	11
Female	10	10	14	14	3	5	5	5

*Less than 0.5%
**Used during last month

Table 2

MARIHUANA USE AMONG YOUTH, 1971-1976

	% Ever Used				% Current Use*			
	1971	1972	1975	1976	1971	1972	1975	1976
All youth	14	14	23	22	6	7	12	12
Age:								
12-13	6	4	6	6	2	2	2	3
14-15	10	10	22	21	7	6	12	13
16-17	27	29	39	40	10	16	20	21
Sex:								
Male	14	15	24	26	7	9	12	14
Female	14	13	21	19	5	6	11	11

*Used during last month

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and 40 percent had smoked tobacco during that same period, 10 percent reported current marihuana use.

A continuing concern with respect to cannabis use is a possible shift toward the use of higher potency cannabis. One type, hashish, is widely available in the United States where it, too, has been most widely used by young adults. Nearly one-third (29.2 percent) of the 18-25-year-olds reported ever using hashish, with about one-fifth of these reporting use during the month preceding the survey. Among the 18-25 age group, 19.5 percent reported that he or she "definitely" or "might" use hashish in the future. This contrasts with the less than one in ten for those aged 12-17 and less than 3 percent of adults 26 and over who anticipated future use of hashish. It is not known, however, whether users preferred the hashish to less potent forms of cannabis given a choice. (Hashish, a concentrated resin of cannabis, contains on the order of five to ten times as much of marihuana's principal psychoactive ingredient as marihuana itself. Typical marihuana in the United States contains 1-2 percent THC, as compared with hashish which has as much as 10 percent THC.)

Marihuana Use Among High School Seniors

In addition to the samples of youth mentioned with the National Survey results, an annual national survey of high school seniors on life style and values as related to drugs has been started (40). This study is significant because it represents an attempt to examine the change in attitudes and behavior over time during the critical years of late adolescence and young adulthood. Since this survey taps both drug using behavior and attitudes toward drugs, it will hopefully provide information for predicting future trends. Moreover, the large national, random sample (13,000 representative high school seniors) makes it unusually sensitive to recent trends in drug use among this age group. Although only the classes of 1975 and 1976 have been studied thus far, the results are of considerable interest. The proportions which had ever used marihuana increased from 47 percent in the Class of '75 to 53 percent in the Class of '76. Those who had used within the month preceding the survey had also increased from 27 percent to 32 percent. Because of the large samples involved, it is unlikely that either of these increases is a statistical artifact. Another finding of note was that the percentage of seniors who had used marihuana 20 or more times in the preceding month (8 percent) exceeded the percentage who had used alcohol that many times during the same period (6 percent).

The seniors' attitudes toward marihuana had also shifted. While 55 percent disapproved of occasional marihuana use in the Class of '75, only 48 percent felt that way in the Class of '76. While slightly over one-quarter of 1975 seniors felt "using marihuana should be entirely legal," one-third of the '76 class shared this view (27.4 percent vs. 32.6 percent). An additional quarter (25.5 percent) of the '75 class felt use "should be a minor violation -- like a parking ticket -- but not a crime." This proportion increased to

29.1 percent in the '76 Class. Only a quarter of the seniors surveyed in 1976 felt that marihuana use "should be a crime." On the issue of whether sale of marihuana should also be legal, if use were legalized, nearly two-thirds (63.2 percent) of the '76 class felt it should be as contrasted with 52.3 percent. holding this belief during the Class of '75 survey. Half (49.9 percent) of the seniors would, however, restrict such sales to adults; only 13.3 percent supported the idea of unrestricted sales.

One local survey of junior and senior high school students in San Mateo County is of interest because it has been conducted annually (since 1968) in a county with unusually high rates of drug use (4). As early as 1968 nearly half (48 percent) of this Northern California county's 12th graders had used marihuana 1 or more times in the previous year, over half of these 10 or more times. By 1971, 59 percent of the 12th graders had tried marihuana in the preceding year. Two out of five of this group (43 percent) had used ten or more times that year while one in three (32 percent of 12th graders) had used fifty or more times that year.

Among ninth graders, one in four (27 percent) had used marihuana in the year preceding the 1968 survey. Of those in the ninth grade who were users, half (or 14 percent of the total) had used marihuana 10 or more times that year. By 1971, nearly half (44 percent) of the ninth graders had tried marihuana the previous year, again, about half of the users on 10 or more occasions. Slightly less than one in five ninth graders (17 percent) had used marihuana on fifty or more occasions that year. Since 1971 the figures for use have been fairly consistent for both the younger and older groups at all levels of use. About half of the ninth graders reported some use in the previous year. Of these, approximately 60 percent had used marihuana 10 or more times and approximately 1 in 3 of the user group had used as many as 50 times in the preceding year. The exact figures tracing these trends are to be found in Table 3.

Notably, in this high drug use county, male 12th graders who had used marihuana at least 50 times in the year preceding the Spring, 1976 survey exceeded the number who had made use of tobacco that of ten (30.0 percent had used marihuana 50 or more times compared to 23.5 percent who had used tobacco that frequently). For girls roughly the reverse was true; about one-third had used tobacco fifty or more times versus one in five who had used marihuana that often. Among both boys and girls in the 12th grade, alcohol use on 50 or more occasions only modestly exceeded marihuana use (among boys the figures for 50 or more occasions of alcohol use was 37.6 percent vs. 30.0 percent for marihuana; for girls, comparable figures were 26.2 percent vs. 21.3 percent).

The above figures for San Mateo County are of interest because they provide some, evidence that the use of marihuana in this high use county may have reached a plateau and is even diminishing for some of the other drugs (amphetamines, barbiturates, LSD and tobacco use by males). Since California has elected to decriminalize the personal possession of small quantities of marihuana, subsequent

Table 3

PERCENTAGE OFMARIHUANA USE AMONG MALE SANMATEO COUNTY HIGH SCHOOL STUDENTS

	One or more uses in past year		Ten or more uses in past year		Fifty or more uses in past year	
Grade:	9th	12th	9th	12th	9th	12th
1968	27	45	14	26	NA	NA
1969	35	50	20	34	NA	NA
1970	34	51	20	34	11	22
1971	44	59	26	43	17	32
1972	44	61	27	45	16	32
1973	51	61	32	45	20	32
1974	49	62	30	47	20	34
1975	49	64	30	45	20	31
1976	48	61	27	42	17	30

results from this annual survey may serve as one measure of the impact of this legal change on adolescent use. Thus, this county may provide some indication of future trends in other areas of the U.S. where drug use is still climbing or where laws are being revised.

A study of drug use by young adult males 20-30 years old conducted in late 1974 and early 1975 (reported in the Fifth Marihuana and Health Report, 105) has now become available as a monograph in the National Institute on Drug Abuse's Research Monograph series (73). Findings for this age group are generally quite consistent with data from other studies. Correlates of drug use such as marital status, employment and sizes of community of residence are also reported.

Use Trends -- An Overview

Use of marihuana has markedly increased since the late 1960's when interest in the drug first began to accelerate. Initially, use was confined to a small minority characterized by a counterculture orientation and for whan it was a symbol of opposition to the "establishment." Users now come from a broad cross section of U.S. youth although use, particularly regular use, remains more common among the less conventional. In at least one age group (young adults from 18-25) a majority have at some point tried the drug. Among adolescents and adults under 25 about one-half of those who have ever tried marihuana continue to use it at least occasionally. National statistics regarding marihuana use can, however, be misleading. Average trends can mask significant local and regional differences. Use rates continue to be positively related to sex (male use generally exceeds that of females), age (young adult rates higher than either younger or older age groups), size of community (larger communities report greater use than smaller) and region (higher in West and Northeast than in the South or Midwest). Over the past several years many of these differences have diminished but between 1975 and 1976 there were few changes. In one county of high use in which surveys have been consistently conducted, use by high school students as early as 1968 already exceeded that on most college campuses. Thus, the more modest use picture conveyed by the national data may mask considerably greater use among certain geographic and demographic subgroups.

In spite of the rapid increase in cannabis use over the past decade, its use is still largely confined to the young. Past age 25, experimentation with marihuana and its continuing use becomes increasingly less common. For individuals over 35, marihuana experience and especially continued use are a rarity. These statistics reflect the fact that the members of the first wave of accelerated marihuana interest are only now reaching their early 30's. There is also evidence, however, that increasing age associated with the assumption of adult roles and adult responsibilities makes marihuana use less practical and appealing. Whatever the diminution of use brought about by new role demands, however, it appears quite likely that there will be some increase in continued

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marihuana use among the over-30 group as more of the young adults with histories of cannabis use enter this age group.

While there are areas and groups in which cannabis use may be approaching or has already reached an upper limit, overall use levels may be expected to rise as other groups more recently introduced to marihuana move toward a level of saturated interest. Persistent use for nearly a decade by large numbers, despite significant attempts to discourage marihuana use, suggests that cannabis use is more than a fad and may well prove to be an enduring cultural pattern in the United States.

The amounts and frequency of use in the United States are still quite modest when compared to countries in which cannabis use is more traditional. Use continues to be comparatively infrequent and typically involves relatively low potency material. But there is also evidence that users in significant numbers are beginning to use on a daily basis. For example, among males between 20 and 30, 1 in 6 of those who have ever used marihuana continues to do so on a daily basis. In some locales, as noted in the discussion of the San Mateo County study, regular marihuana use may be nearly as common or even more common than regular cigarette use.

As mentioned earlier, while marihuana use including daily use has decidedly increased in the past decade, the attitudes and behavior of most youth and adults continue to be relatively conservative. Among the high school seniors discussed earlier, nearly three out of four (70 percent) disapproved of regular marihuana use. Half said even were it legal to buy and use, they would not do so. Two out of five high school seniors feel that those who smoke marihuana regularly do so at "great risk of personal harm." With respect to the use of other drugs, a very large majority disapprove of even trying them -- 9 out of 10 disapprove of trying heroin or LSD; 4 out of 5 disapprove of trying uppers or downers.

As was emphasized in earlier reports, many users stop or markedly diminish their use of marihuana as they take on various adult responsibilities such as new marital, parental and work roles (8, 30, 73). Thus, while the future patterns of use of marihuana in our society are in doubt, there is reason for believing that a variety of considerations, including negative attitudes of many potential users toward regular drug use, serve to moderate and discourage more extensive use even when the drug is widely available.

Predicting Marihuana Use

Several studies were published in the past year concerning the prediction of marihuana use based on earlier behavior, personality, belief and attitude indicators. One study (36) found that high school users as compared with non-users placed lower value on achievement and higher value on independence, tended to be more alienated and critical, more tolerant of deviance, less religious, less influenced by parents as compared to friends, and had a lower

grade point average. Moreover, those who initiated marihuana use between their first and second interviews tended to show shifts in the above directions during the interval between contacts.

In a similar study (82), five year longitudinal data were collected for students in grades 4-12. In this study of children and adolescents, rebelliousness was the best predictor of future marihuana use. Non-users tended to describe themselves and to be described by others as obedient, law-abiding, conscientious, trustworthy and hardworking. By contrast, those who became later marihuana users were more likely to be rated as impulsive and less sensitive to the feelings of others; but at the same time, more sociable, talkative and outgoing than non-users. Such ratings were also generally predictive of those more likely to become "early" versus "late" marihuana users.

These high school level studies are reminiscent of college studies reported in previous Marihuana and Health Reports (101, 105) which indicated that college student users tended to be non-conformists when compared to those who did not use. However, as use becomes more typical of the group, the user generally becomes more like his or her peers. It should also be kept in mind that predictors, while useful in anticipating average behavior in a group, are not necessarily usable for individual cases.

Studies of parent-child relationships are of interest in providing some indication of possible influences on use of marihuana and other drugs by children. It has been found that while peer factors are especially important for marihuana initiation, intrapsychic factors and a lack of closeness of family ties are more important in relation to more serious involvement with use of illicit drugs (43).

Given the role that marihuana use has come to play as part of the adolescent and young adult cultures, emergent use often becomes a part of the young person's integration into a social subculture in which drug use is one part.

Many of the factors which have been found to be related to drug use including that of marihuana -- low academic performance, rebelliousness, depression or criminal activity -- appear more often to precede rather than to follow the use of drugs.

CHEMISTRY AND METABOLISM OF CANNABIS

The chemistry and metabolism of cannabis (i.e., the ways in which marihuana is broken down and transformed chemically by the body) are highly technical areas which are of considerable practical importance. Reports in this series have stressed that marihuana is not a single chemical substance. While Δ-9-tetrahydrocannabinol (Δ-9-THC) was identified early as the principal psychoactive ingredient in cannabis, other constituents may be important in modifying the action of THC in addition to having their own physiological implica-

tions. In this respect, marihuana is not like beverage alcohol which is a relatively simple compound.

The detection of marihuana in the human body is an important chemical problem with major legal and research implications. As marihuana comes to be more widely used, it is being used increasingly while driving or under other conditions likely to endanger the user and others. Because Δ-9-THC and other cannabis constituents are rapidly transformed into other chemical substances (metabolites) and because of the very small quantities involved, detection remains a difficult scientific problem.

In 1976, a major monograph on the progress made in developing detection methods was published by the National Institute on Drug Abuse (98). Work is continuing on the development of simple tests, analogous to blood alcohol determinations that might be useful at the site of accidents and in roadside determinations of marihuana intoxication. There are now a variety of techniques suitable for detection by laboratories, although none is reasonably priced or sufficiently simple to be used reliably for this purpose. It still remains to be established, however, that such assays will be useful for law enforcement purposes. To do so will require that there be a demonstrated consistent correlation between the level of intoxification detected and impairment of driving abilities.

Emphasis in chemical research has also been on synthesizing the various naturally occurring cannabis constituents, their biological transformation products or metabolites and related chemical substances. The production of such chemically pure substances provides essential tools for determining possible effects of each constituent alone as well as in combination with other marihuana ingredients.

Availability of these synthetic materials in research quantities can accelerate research on marihuana detection in body fluids as well as other work on the pharmacological effects of marihuana. By radioactively labelling some of the active substances involved, it is possible to trace their passage through the body. Availability of these constituents and related materials also has implications for assessing the possible therapeutic value of cannabis. Since the natural material has some undesirable side effects (e.g., accelerated heart action and an intoxication that is disturbing to some), it would be useful to find related drugs which have the desired therapeutic effect (such as control of nausea for cancer patients or treatment of some forms of glaucoma), but are free from side effects. The synthesis of chemically related substances has the potential of achieving that end.

Some of the metabolites of marihuana are very active in themselves, making an understanding of them important to knowledge of the parent substance. Additionally some constituents can block important drug metabolizing enzymes in the liver (i.e., block natural chemicals which play an essential role in metabolizing drugs or preventing the accumulation of potentially injurious substances). Such blocking

might cause toxic reactions were marihuana to be ingested simultaneously with other drugs normally detoxified in the liver. It is, therefore, important to understand this aspect of marihuana's action.

Tests with dogs (97) and rats (12) revealed that the major marihuana metabolites produced by the lung may be different from those produced by the liver. This suggests that the effects of cannabis may be partly determined by the route of administration (e.g., smoking vs. eating). Similar differences have been reported in humans.

The identification of cannabis metabolites that remain in the body for days following marihuana use (51) was an important development because it paves the way for their synthesis and the careful evaluation of their possible toxic implications.

The finding that there is an interaction between cannabidiol, a major marihuana constituent, and Δ-9-THC, marihuana's principal psychoactive ingredient (53) may ultimately shed light on the common belief among users that different varieties of cannabis with varying composition have different effects only partly related to THC level.

ANIMAL RESEARCH

A considerable amount of animal research on the effects of marihuana continues. Unlike humans, their genetic and learning histories can be accurately specified enabling the researcher to separate the role of marihuana from that of other aspects of life style and development. Their shorter life spans also permit the study of chronic effects over proportionately longer periods of their lives and the use of drug dosages that would not be possible in humans. As in previous years, much of the animal work is primarily of interest to the research specialist; however, some of the behavioral findings are of more general importance.

Marihuana and related drugs have consistently been found to suppress aggression in animals when they are not under stress (1). These findings concur with less systematic human observation which suggests that marihuana is considerably less likely to facilitate the expression of aggression than is alcohol. With animals under stress, however, it has been found that marihuana tended to increase aggression. This suggests that the relationship between marihuana and aggression may be more complex than was earlier supposed. Whether similar results would be obtained with humans in stress situations is not known.

One recent trend in animal behavioral research has been the study of marihuana use in social interaction. In one such experiment reported last year (79, 80) several marihuana-related changes in social behavior of monkeys in three to six member social groups were noted. Given oral doses equivalent to very heavy human cannabis

use, the monkeys responded much like humans. They slept and rested more frequently; active social interaction such as grooming of others was reduced. Over more extended periods of administration, the monkeys gradually showed fewer and fewer of these effects. While aggression was initially reduced, after receiving THC for weeks or months during the year-long study the monkeys became irritable and aggressive (hitting, biting, chasing increased).

Another important area of animal research concerns possible long term, chronic effects of marihuana. Two previously reported studies failed to find any residual effects of Δ-9-THC on learned behavior in rats following discontinuance of the drug after 150 days of use (23) or after seven months of intermittent administration (22). More recently, an impairment in maze learning was found following six months of heavy use (20). Because of the high doses, the relevance of these findings to human experience is questionable. The possibility that heavy doses of cannabis administered during pregnancy might impair learning in the offspring of rats has been raised by one recent study (96). Here, too, the relevance to human use is uncertain. In general, however, it should be emphasized, as in previous editions of this report, that the use of cannabis by pregnant women is especially unwise since the implications of such use in humans have not been adequately explored.

HUMAN EFFECTS

Because many of the effects of marihuana have already been extensively described in previous editions of the Marihuana and Health Report (101, 102, 103, 104, 105) and in other widely available reviews of the literature, this report will be restricted to the developments of the past year. Many of the more recent research publications represent work which has already been discussed in prior years but has only more recently appeared in the scientific literature.

Effects on cardiovascular functioning have been extensively studied. Indeed, tachycardia (an accelerated heart rate) is the most comon and prominent physiological response to marihuana use. Previous editions of the Report have stressed evidence that the effects of marihuana may be dangerous for those with cardiac abnormalities. Evidence that marihuana not only increases heart rate, but may also temporarily weaken heart muscle contractions has led the researchers who originally studied patients with heart disease to express concern about marihuana use among individuals with such problem (74). The research on the effects of marihuana on patients with angina (cardiac related chest pain) illustrates that effects on those with any type of health problem cannot always be predicted from studies of normal volunteers. Studies of normal young men have not revealed any serious effects on heart functioning.

A second area which has received considerable research attention in recent years is that of the effect of marihuana on lung functioning. Because marihuana is characteristically smoked in the United States

and because of the known adverse effects of cigarette smoking, this has been a continuing source of concern. The irritating sensation associated with deep inhalation is well known to users and there have been numerous clinical reports of lung and throat irritation. Although there is now good evidence that marihuana and Δ-9-THC administered acutely produce an increase in the diameter of the air passages of the lung (88, 89, 93, 94), chronic use may have quite different implications. Previously reported research (94) has indicated impairments in pulmonary function in chronic marihuana smokers. More recent work (90) using still more sophisticated measures has demonstrated detectable impairment in lung functioning after six to eight weeks of heavy cannabis smoking. The changes found, while still within normal limits, persisted at least one week after smoking. This suggests that heavy chronic use could well lead to clinically important changes similar to those found in heavy cigarette smokers.

Special Health Problem Areas

Several areas of marihuana research findings which were highlighted in previous years have created considerable concern over the possible biological implications of cannabis use. The possible effects involved are:

a. Impairment of the body's natural defense system against disease -- i.e., interference with or depression of the immune response;
b. Chromosomal alterations -- i.e., increases in the number of abnormal chromosomes and a reduction in the number of chromosomes in some body cells;
c. Basic alterations in cell metabolism;
d. Impairment of endocrine functioning; specifically, a reduction in the male hormone testosterone and in growth hormone levels;
e. Brain damage.

Although evidence is fragmentary and incomplete in all of these areas, the potential seriousness of the possible consequences for the individual and society has resulted in great interest and some controversy over the implications of research. If the immune system is impaired by marihuana use, the clinical consequences might include a seriously heightened susceptibility to a wide range of diseases. Changes in chromosomes, the material of genetic transmission, might have serious implications for both the individual and. conceivably. future generations if abnormalities were genetically transmitted. Changes in cell metabolism, specifically in DNA and RNA production which are basically involved in cell reproduction, might have far-reaching consequences. These include the possibility of a failure in cell reproduction and replacement, erratic cell growth or increased cancer susceptibility. Possible impairment of endocrine functioning is also worrisome because it might result in inadequate or incomplete sex differentiation in the male fetus when a mother uses marihuana heavily while pregnant.

Alterations in testosterone and growth hormone in the developing child or adolescent might adversely affect growth and sexual maturation. Finally, gross damage to the brain might have a wide range of behavioral implications. The present state of the research evidence for each of these consequences is outlined below. It should, however, be re-emphasized that the clinical possibilities outlined in the preceding continue to be speculative. There is as yet no good evidence that marihuana smokers do, in fact, develop clinical abnormalities of the type described.

The immune response: Previous Marihuana and Health Reports (104, 105) have discussed in detail earlier research concerning the question of a possible impairment in this health-sustaining bodily response. Two years ago a report indicated that a marked reduction in the immune response as measured in white blood cell cultures was found in marihuana smokers compared to non-smokers (71). This reduction was reported to be comparable to that of patients with known "T-cell" immunity impairment -- uremia, cancer and transplant patients. Attempts to replicate this finding and to explore its implications by testing for immune response depression by other means have resulted in contradictory reports. To further complicate interpretation, it was found that marihuana smokers off the street (i.e., not specifically part of an on-going study) showed a reduction in the type of immune response involving T-cell or thymus dependent lymphocytes (a type of white blood cell involved in preventing disease). This reduction sometimes found in smokers did not, however, persist in users smoking quality controlled marihuana in a closed ward research setting (75). Thus, the reduction in T-cells observed in some chronic drug users may be the result of some common factor of their life style other than marihuana use. The relationship between a reduced number of T-cells and possible diminished immunologic function is also doubtful because other measures of immunologic functioning (various skin tests used to measure the immune response in those who show clinical evidence of diminished response) have not indicated a reduced functioning in marihuana smokers making use of known amounts of marihuana under controlled conditions. A recently published animal study using high, but still humanly relevant doses of inhaled cannabis smoke, found that it had an immune response suppressing effect in rats that justifies further research (108).

Thus, the issue of possible impaired immune response remains unresolved. There is, as yet, no evidence that users of marihuana are more susceptible to such diseases as viral infections and cancer, which are known to be associated with lowered production of T-cells.

Chromosome abnormalities: There is little new evidence to report in this area. While there have been reports of increases in chromosomal breaks and abnormalities in human cell cultures, the results to date are inconclusive. The three positive studies in humans that have been reported (32, 50, 87) have decided limitations. All were retrospective -- i.e., studies of those who had already used marihuana as ccmpared to non-users. Such variables as differences in life style, exposure to viral infections and possible use of

other drugs, all known to affect chromosome integrity, could not be reliably assessed. In two of the studies, the aberrations observed were found only in a minority of the users.

Three other studies done prospectively (i.e., before and after use) have been reported (55, 56, 72). All were negative although they, too, can be faulted for a variety of reasons: most importantly, the subjects of all three had at least some prior experience with marihuana. It is possible that the baseline levels of chromosome deficits may have been elevated by earlier casual marihuana use, thus masking a drug-related effect.

A team investigating the effect of marihuana smoke on human lung cells in laboratory culture has found an increase in the number of cells containing an abnormal number of chromosomes (52). Another investigator who previously reported a high proportion of cells in marihuana smokers with reduced numbers of chromosomes (63) has more recently reported that the addition of Δ-9-THC (the principal psychoactive ingredient of marihuana) to human white blood cell cultures also resulted in an increased frequency of cells with abnormally low chromosome numbers (64). The implications of these recent findings are uncertain.

Overall, there is no convincing evidence at this time that marihuana use causes clinically significant chromosome damage. However, it should be emphasized that the limitations of the research conducted thus far preclude definitive conclusions.

Alterations in cell metabolism: The implications of laboratory findings on the inhibition of DNA, RNA and protein synthesis (all of which are basically related to cellular reproduction and metabolism) are still unknown. In addition to work previously reported, research last year has found that adding Δ-9-THC to various types of human and animal cell cultures inhibits DNA, RNA and protein synthesis (5). This study detected no effect on DNA repair synthesis or in the uptake of the chemical precursors into the cell although the amount of these precursors within the cells was reduced by half.

The possibility that cannabis, or one or more of its chemical ingredients, differentially affects the cell metabolism and reproduction of cancer cells in animals was raised by research of the last two years. One aspect of the mechanism by which this may occur is an inhibition of DNA metabolism in abnormal cells but not in normal cells.

If this preferential inhibition of DNA synthesis in animal tumors also occurs in humans, the potential value of marihuana as an anticancer drug will be explored. It should, however, again be stressed that there is presently no evidence that cannabis or any of its synthesized or naturally occurring constituents has definite value in inhibiting human cancer growth. There is also the possibility, again related to cell metabolism, that if animal findings of a depressed cell mediated immunity response are substantiated in

humans, cannabis might assist with transplant surgery.

Endocrine functioning: The Fourth and Fifth Marihuana and Health Reports (104, 105) discussed a reported reduction in blood levels of testosterone in smokers and the contradictory findings. Some of the inconsistency in these findings has been explained by the varying time periods over which these levels were assayed. For example, one chronic study under carefully controlled conditions found there was no significant drop in the level of testosterone during the first four weeks of daily use; however, a drop did occur with continued use (48, 49). In most cases, however, the hormone levels tested still remained well within generally accepted normal limits. One recent report (29) indicates a decreased sperm count in otherwise normal young cannabis smokers that may be related to use. Some differences in the cellular characteristics of sperm of chronic hashish users compared to nonusing controls were reported this year, but their functional significance is unclear (107).

The question of the biological significance of the previously reported alterations in testosterone and growth hormone levels remains in doubt. It may well be that these findings will ultimately prove more significant for individuals with already impaired fertility or other evidence of marginal endocrine functioning than for normal individuals.

Recent reports of reduced testosterone levels of heavy alcohol consumers may make the clinical separation of marihuana and alcohol effects more difficult since both drugs are frequently used by the same individuals.

Brain damage research: A British research report, originally appearing in 1971 (9), attributed brain atrophy to cannabis use in a group of young male users. This report is repeatedly cited in popular articles on marihuana use. In the original study 10 patients, all of whom had varying histories of 3-11 years of marihuana use, were examined by a neurological technique (air encephalography) used to detect gross brain changes. The authors concluded that their findings suggested that regular use of cannabis may produce brain atrophy. This research was faulted on several grounds: all of the patients had used other drugs, making the causal connection with marihuana use questionable; and the appropriateness of the comparison group and diagnostic technique were questionable. The potential seriousness of the original observations did, however, lead to several subsequent studies.

In a study of chronic Greek users (86) a different technique (echoencephalography) was employed to determine whether brain atrophy might be present in heavy users. (Air encephalography was not used because the hazards of that technique were not ethically justifiable for purely research purposes.) The findings from the Greek study were negative; that is, users were not found to differ from non-users in evidence of gross brain pathology.

Most recently two studies have been conducted in Missouri (43) and Massachusetts (58), respectively, of two samples of young men with

histories of heavy cannabis smoking using computerized transaxial tomography (CTT), a brain scanning technique for visualizing the anatomy of the brain. In this technique the head is scanned by a narrow beam of X-rays in a series of "slices." Computer processing of the data obtained from a large number of measurements makes it possible to reconstruct the anatomy of the brain in a more detailed manner and with greater precision than pneumoencephalography (the technique used in the original British study of 1971) permits.

In the St. Louis study 12 young male subjects, aged 20-30 (mean age = 24.1) who had smoked at least 5 joints a day (mean # = 9.0/day) for 5 or more years (mean years = 6.6) were compared to 34 neurologically normal young men of similar age who did not indicate drug use. In the Boston study 19 heavily using young male marihuana smokers, whose use was verified on a closed research ward, were matched with a control series of non-using males of similar age.

In both studies, the resulting brain scans were read blindly by experienced neuroradiologists. In neither study was there any evidence of cerebral atrophy. Despite these negative findings, several additional points should be emphasized. Neither study rules out the possibility that more subtle and lasting changes of brain function may occur as a result of heavy and continued marihuana smoking. It is entirely possible to have impairment of brain function from toxic or other causes that is not apparent on gross examination of the brain in the living organism. Nevertheless, virtually all studies completed to date (late 1976) show no evidence of impaired neuropsychologic test performance in humans at dose levels studied so far.

A retrospective study of an Egyptian prison population in which 850 chronic cannabis users were compared to 839 non-cannabis using controls reported slower psychomotor performance, impaired visual coordination and impaired memory for designs in users (83). This investigator reported that such impairment was more commonly found in subjects from urban backgrounds who were younger and more educated than in illiterate, rural and older subjects (84). While this finding suggests the possibility that findings for chronic users may differ depending on their background, the study has obvious deficiencies. Subjects often used other drugs besides cannabis. The study could not specify the actual levels of use, which may have differed in the several groups. In addition, other aspects of the users' life styles or experiences may have affected the outcomes rather than their cannabis use, as such.

As was reported last year, studies of college students which compared users to non-users have not generally found decrements in intellectual performance as measured by the grades achieved by users. The higher levels of motivation possibly involved in students compared to the general user population, the typically modest levels of use (by overseas standards) and the possible elimination of those impaired by marihuana use at an earlier point in their academic careers, are all limitations to a broad interpretation of these findings.

With respect to brain wave tracing (electroencephalography or EEG) in humans, there is ample evidence that cannabis produces reversible and dose-related changes in brain waves as conventionally measured under conditions of acute administration (24, 47). These are not markedly different from those of other psychoactive drugs. In Greece, studies of chronic users which employed advanced computerized EEG; analysis techniques failed to find persistent abnormalities distinguishing a heavy user group from their non-user counterparts (86). However, at least one investigator using deep planted electrodes which measure electrical activity within the brain rather than at its surface has reported persistent changes in monkeys and in a small number of humans (28). Just what, if any, behavioral or functional significance these changes may have is not now known.

Overseas Chronic User Studies

Research on long term, chronic users of cannabis overseas where such use has been characteristic of large numbers for many years continues to be discussed in many contexts without adequate consideration of its many limitations. The older studies of this type suffered from multiple scientific defects making their interpretation difficult. More recently, three studies conducted under Federal aegis in Jamaica (76, 77), Greece (86) and Costa Rica (11) have received considerable publicity. Although they have been discussed in previous years, a review of the findings and their limitations is desirable in order to place them in realistic perspective.

Reports on all three studies have now appeared in the scientific literature (11, 76, 86). In each of the three, considerable effort was made to match chronic users with non-users whose characteristics apart from drug use were quite similar. Such user/non-user matching was rather carefully done in the Jamaican and Costa Rican studies; in the Greek study precise matching was less possible. All subjects were men because male use predominates in the three cultures studied. The elaborate testing procedures limited the total number studied. This is an important limitation since it is possible that the limited sample size may have precluded the detection of rarer consequences of cannabis use. For example, samples of similar sizes of matched cigarette smokers and non-smokers might not have detected some of the known serious consequences of cigarette smoking such as heightened susceptibility to heart disease, lung cancer and emphysema.

A wide range of measures were employed in these studies to detect physical or psychosocial consequences of use. In general, few differences were found that could be directly attributed to cannabis use. In the Greek study, heavy hashish users examined were significantly higher in psychopathology, particularly antisocial personality disorder, but it was not possible to know whether this predisposed them to heavy hashish use or whether use played a role in producing their pathology.

Data on chromosomal assays were collected in Jamaica, and have sometimes been cited as indicating that cannabis use has no chromsomal effects. More accurately, these data must be regarded as inconclusive because of technical deficiencies in the methodology for that phase of the research.

It should again be emphasized that while the results of these studies are somewhat reassuring with regard to grossly adverse consequences of marihuana use, they by no means demonstrate that cannabis use is free of potentially adverse consequences. The small numbers studied, the possibility that cultural differences may have masked drug related performance differences and the differences in the demands of these less industrialized societies from those of our own, all make direct translation of the results to American conditions hazardous. Since adults with long experience in marihuana use were studied, none of the three projects is directly relevant to the implications of marihuana use by American adolescents at an earlier stage of development and under different social conditions.

Psychopathology

Previous editions of the Marihuana and Health Report (102, 103, 104, 105) have discussed at some length the question of possible psychiatric aspects of cannabis use. Probably the most common adverse psychological reaction to marihuana use among American users is the acute panic anxiety reaction (26, 61). It represents an exaggeration of the more usual marihuana response in which the individual loses perspective (i.e., the realization that what she or he is experiencing is a transient drug induced distortion of reality) and becomes acutely anxious. This reaction appears to be more common in relatively inexperienced users although unexpectedly higher doses of the drug can cause such a response in the more experienced as well. Generally the symptoms respond to authoritative assurance and diminish in a few hours as the immediate effects of acute intoxication recede.

Transient mild paranoid feelings are common in users and it has been suggested that those who are characterized by more paranoid defense mechanisms are less likely to experience other acute adverse reactions (68). Earlier it was emphasized that reactions of users are very much influenced by the set and setting of use. Set refers to the pre-existing expectations the individual has regarding use; setting means the physical environment during use. It is generally conceded that anxiety and mild paranoid reactions are more likely if the user is initially anxious about the experience and/or the circumstances of use are anxiety producing. Some additional research support for this clinical impression is found in a field survey which used a questionnaire to measure acute adverse drug reactions (70). Preliminary work has found that, in a college population, those who are more hypochondriacal, and who feel less in control of their own lives and more at the mercy of external events are more likely to have adverse reactions to marihuana and other psychoactive drugs (69).

An acute brain syndrome associated with cannabis intoxication including such features as clouding of mental processes, disorientation, confusion and marked memory impairment has been reported. It is thought to be dose-related (much more likely at unusually high doses) and to be determined more by the size of the dose than by pre-existing personality (61). This set of acute symptoms appears to be rare in the United States, possibly because very strong cannabis materials are less readily available here than in some overseas locations. Acute brain syndrome also diminishes as the toxic effects of the drug wear off.

Descriptions of a specific cannabis psychosis are to be found principally in the Eastern literature (26, 61), from cultures where use is typically more frequent and at higher doses than those generally consumed in the United States. It has been difficult to interpret such reports because diagnosis of mental illness is partly dependent upon socio-cultural factors. In addition, the diagnostic picture is frequently complicated by the use of other drugs and earlier evidence of psychopathology not necessarily associated with drug use. While the recent overseas studies conducted under U.S. auspices in Jamaica, Greece and Costa Rica did not find such adverse consequences, the small size of the user samples studied, together with the probable rarity of the disorder, would have made its detection unlikely.

One recent clinical study in India contrasted the features of a paranoid psychosis arising in the course of long term cannabis use with that of paranoid schizophrenia (91). Twenty-five consecutive patients admitted with each diagnosis were compared. The cannabis users, reportedly, had used the drug for five or more years in amounts up to several grams per day in gradually increasing quantities. Those diagnosed as having a cannabis psychosis were characterized by the authors as showing more bizarre behavior, more violence and panic, an absence of schizophrenic thinking and greater insight into their illness. Patients with the cannabis-related disorder recovered rapidly upon being hospitalized and being treated with a major tranquilizer.

In this and other clinical studies, it is difficult to distinguish the role of cannabis from that of pre-existing psychological problems or other environmental precipitants in marihuana-related psychological difficulties. Frequently, heavy marihuana users are also those who have had emotional problems prior to use.

Marihuana flashbacks -- spontaneous recurrences of feelings and perceptions like those produced by the drug itself -- have been reported (7). A survey of U.S. Army users recently published found that flashbacks occurred in both frequent and infrequent users and were not necessarily related to a history of LSD use (85). Such experiences may range from the quite vivid recreation of a drug related experience to a mild evocation of a previous experience. The origin of such experiences is uncertain but those who have experienced them appear to have required little or no treatment.

One source of information about possible adverse reactions to drugs, including marihuana, is the Federally sponsored Drug Abuse Warning Network (DAWN). This is a nationwide reporting system which provides information about the frequency with which various drugs in-common use are implicated in patient or client contacts with such facilities as hospital emergency rooms and crisis centers. (A crisis center is a facility established to provide "walk in" or "phone in" assistance to those experiencing personal crises, including adverse drug reactions.) Of 118,000 emergency room episodes involving some form of drug abuse between May, 1975 and April, 1976, marihuana ranked 16th among the drugs mentioned. But in crisis center contacts, marihuana ranked second only to heroin as the drug involved. While the interpretation of such figures is made more difficult by ignorance of how the number seeking assistance compares to the total number using a drug during the reference period, it does indicate that marihuana is not an uncommon factor in individuals seeking help.

In the past the Federal Client Oriented Data Acquisition Process (CODAP), a reporting system designed to monitor Federally supported drug treatment programs, found that a significant portion of the effort (more than 10 percent) was being devoted to patients whose primary drug of abuse was marihuana. When it was determined that this was largely an artifact of court and school referrals for administrative convenience, an effort was launched to substantially reduce this inappropriate use of community treatment facilities. As a result of these efforts, between October, 1975 and April, 1976, 3 out of 5 (57 percent) of the inappropriately used treatment slots were freed for patients with more serious problems of drug abuse (this included some slots that were being used for patients reporting alcohol or "no drug" as their basis for referral).

Complex Psychomotor Performance in Driving and Flying

Evidence that marihuana use at typical social levels definitely impairs driving ability and related skills continues to accumulate (17, 33, 65). There are now data indicating impairment from laboratory assessment of driving related skills (19), driver simulator studies (16, 66), test course performance (45), actual street driver performance (46) and, most recently, a study conducted for the National Highway Traffic Safety Administration of drivers involved in fatal accidents (100).

Unfortunately, despite the commonly expressed belief that their driving is impaired by cannabis intoxication, there is reason for believing that more users drive today while intoxicated than was true a few years ago (15, 46, 92). As marihuana use becomes increasingly common and accepted and as the risk of arrest for simple possession decreases, it is likely that more users will risk driving while high. In limited surveys, from 60 percent to 80 percent of marihuana users questioned indicated that they sometimes drive while cannabis intoxicated (45, 46, 81).

Marihuana use in combination with alcohol is also quite common and the risk of the two drugs used in combination my well be greater than that posed by either substance alone.

A recent study of drivers involved in fatal accidents in the greater Boston area was conducted by the Boston University Accident Investigation Team and found that marihuana smokers were over-represented in fatal highway accidents when compared to a control group of non-smokers of similar age and sex (100).

There are, therefore, several converging lines of evidence that driving performance is impaired by marihuana intoxication, viz.: users' subjective assessments of their driving skills while high, measures of driving related perceptual skills, driver simulator and actual driving performance and, finally, a limited study of actual highway fatalities.

The parameters of impairment for the average driver under various dosages of marihuana alone or in combination with alcohol are not yet adequately specified. There is, thus, an obvious need to develop standards in this area for what constitutes driving under the influence of cannabis so as to encourage more responsible use. At present it is clearly desirable to strongly discourage driving while marihuana intoxicated.

As indicated last year, there has been relatively little systematic study of the relationship of marihuana smoking to possible airplane pilot error. Nevertheless, the evidence related to psychomotor skills in driving is partially germane. Such skills as the detection of peripheral visual stimuli and complex psychmotor coordination are at least as important in flying as driving. The inherently greater complexity of flying. suggests that pilot performance is even more likely to be impaired while marihuana intoxicated.

The few studies completed to date have all shown that experienced pilots undergo marked deterioration in performance under flight simulator test conditions while high (34, 35, 57, 99). Although more detailed studies of pilot performance while under the influence of marihuana are desirable, flying an aircraft while marihuana intoxicated is obviously hazardous.

A continuing danger common to both driving and flying is that some of the perceptual or other performance decrements resulting from marihuana use may persist for some time (possibly several hours) beyond the period of subjective intoxication. Under such circumstances, the individual may attempt to fly or drive without realizing that his or her ability to do so is still impaired although he or she no longer feels high.

Tolerance and Dependence

Tolerance to cannabis -- diminished response to a given repeated drug dose -- has been substantiated by research evidence cited in

the Fifth Report (105). Tolerance development was originally suspected because experienced overseas users were able to use large quantities of the drug that would have been toxic to U.S. users accustomed to smaller amounts of the drug. Carefully conducted studies with known doses of marihuana or THC leave little question that tolerance develops with prolonged use (3, 13, 41, 59, 60).

As was pointed out last year, the meaning assigned to cannabis dependence is often vague. If it is defined as a manifestation of physical symptom following discontinuance of the drug, there is experimental evidence that it can occur at least under conditions of extremely heavy research ward administration that would be atypical of U.S. use patterns (3, 21, 41). The changes noted following drug withdrawal under these experimental conditions include: irritability, restlessness, decreased appetite, sleep disturbance, sweating, tremor, nausea, vomiting and diarrhea. Some of these symptoms were experienced in a similar research study by users who selected their own smoked marihuana doses (60). Such a "withdrawal syndrome" is uncommon and has rarely been reported clinically. Only one research report, from Germany, has noted it (106).

THERAPEUTIC ASPECTS

A significant part of the new biology of marihuana research has been the revival of interest in its possible therapeutic value. As earlier editions of these reports have indicated, cannabis has an ancient history of medicinal use which has persisted in the folk medicine of many countries.

While there have been no new therapeutic applications of cannabis or of its synthesized constituents recently, there has been some additional research on earlier cited applications. One of the more promising medicinal uses is based on the observation that in both normals and in patients suffering from glaucoma, marihuana serves to reduce intraocular pressure (31).Δ-9-THC shows definite promise of becoming an effective agent for the management of glaucoma. An eye drop preparation has been developed and is currently undergoing testing in animals preliminary to human trials. Such a preparation has been successfully employed with rabbits (25).

A second area that continues to show promise is the use of Δ-9-THC as a means of reducing or eliminating the nausea, vomiting and loss of appetite in cancer patients following chemotherapy (75). Since present anti-emetics are of ten unsuccessful in controlling such symptoms in these patients, an improved treatment for this purpose would be desirable.

A third area in which marihuana research has shown promise of developing improved treatment methods is in the management of asthmatics. Synthetic Δ-9-THC produces a desirable temporary increase in the size of the air conducting passages. Facilitating breathing in these patients (94, 95). While the natural material

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has a similar effect, it is undesirable because it also has a direct irritant effect on lung tissue. There are some indications that persistent smoking of marihuana itself, like cigarette smoking, may lead to lung pathology (cf., Human Effects).

A book published during 1976 reports on a conference on the therapeutic potential of marihuana and serves as a detailed summary of the work of researchers in this area (14).

Despite the promise that marihuana and/or its synthesized constituents have shown as potential therapeutic agents, it should once again be emphasized that much additional work is necessary before such agents become generally approved as standard medications.

Marihuana and its constituents continue to have adverse side effects. The increase in heart rate produced is obviously undesirable with the elderly or the cardiac impaired. The psychological effects recreationally sought by many are often disturbing and disruptive to patients.

If consistently useful medical applications for marihuana are found, it is quite likely that the product or products resulting will be chemically related but not identical to the natural material's constituents. Cannabis, which was used therapeutically earlier in Western medicine for a variety of reasons, was eventually abandoned because of such problems as variable potency -- it often ranged from being inert to being much more powerful than the prescriber intended -- and undependable shelf life.

Whether or not cannabis, one of its synthesized constituents or a chemically related compound once again finds a place in modern medicine depends on several considerations. One problem is that pharmaceutically desirable effects may not be persistently useful for chronic disorders. Tolerance undoubtedly develops for a number of the effects of the natural material. This may also be true for new chemically related compounds. Like any other new medication, chemically related materials must be carefully tested for toxicity and for therapeutic effectiveness. This process is time consuming and many new pharmaceuticals showing initial promise are ultimately discarded as unanticipated drawbacks and limitations arise.

FUTURE RESEARCH DIRECTIONS

Cannabis research has made impressive progress since the inception of priority emphasis in the late 1960's. We have become increasingly sophisticated in areas as diverse as the chemical characteristics of the material and the psychosocial implications of use. Some of what has been learned has served to allay many of the emotionally based fears of the past. While it now appears that infrequent, experimental use at typical U.S. levels is usually without significant hazard, more frequent, and especially chronic use, may have quite different implications.

Despite some popular assertions to the contrary, much remains to be learned about this drug which has come to play an increasingly important role in the life of American youth. Our studies of chronic use are decidedly limited and are surely insufficient guides to the implications of use by large numbers of Americans. There is an obvious need to study larger samples more carefully to determine the impact of cannabis use on health and the psychosocial functioning of users. Such long-term studies preferably beginning before use and continuing over extended periods are now possible in the United States although the planning and launching of this research is a major undertaking. Because once a large scale longitudinal study is launched, it is often not possible to modify it without compromising the research, planning must be especially painstaking. Such planning is now underway.

Adequately specifying the parameters of risk posed by marihuana is a difficult task. Obviously, it is important to know with some precision what levels of marihuana intoxication pose threats in such areas as highway safety and the operation of potentially hazardous machinery. Since marihuana is often used in conjunction with alcohol and a wide range of less common over-the-counter and prescriptive drugs, it is also important to know under what circumstances significant interactions occur. There has been a range of research concerning biological consequences in such areas as the imune response, endocrine functioning and basic cell metabolism. While there are some who are inclined to dismiss some of the more disquieting results as artifactual and without significant clinical implications, it is important that they be followed up and the issues they raise resolved.

Unlike many other drug substances, marihuana's metabolites tend to be relatively persistent with residuals remaining in the body fat for days or even weeks. This has led to concern that even irregular use might have inadequately foreseen consequences if any of the more serious laboratory findings of possible hazard prove to be clinically significant. Here, too, more must be learned.

Changes in social policy concerning marihuana that have now occurred in eight states provide a kind of natural laboratory for determining some of the impacts of law and social policy on use patterns. A better understanding of use patterns and their implications for functioning may enable us to develop means of discouraging all forms of drug abuse including that of marihuana without resorting to primarily legal measures.

The rise in use among adolescents has generated concern about possible consequences of use in this group especially when such use becomes an escape from the demands of preparing for later life. Some progress has been made in identifying those in this age group who are likely to become more heavily involved with marihuana use. A better understanding of the motivations for heavy use may permit the development of means for early intervention to avert possible life-long patterns of drug dependency.

Although marihuana use does not "cause" other drug use in the way once simplistically believed, it is often associated with other drug use. Exploration of preventive approaches which encourage individuals to avoid patterns of drug dependency (both licit and illicit) is needed.

Progress in the marihuana research program has made us aware that as our knowledge has increased so has our awareness of our need for more subtle understanding of marihuana use and its possible implications.

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Chapter 1
EPIDEMIOLOGY OF MARIHUANA USE

William McGlothlin, Ph.D.

PRESENT PATTERNS AND CHANGES IN USE

National Household Surveys (Adult)

The National Commission on Marihuana and Drug Abuse sponsored national household surveys of marihuana and other drug use in 1971 and 1972 (Abelson et al., 1972, 1973). A third national survey was conducted during late 1974 - early 1975 (Abelson & Atkinson, 1975); and a fourth during late 1975 - early 1976 (Abelson & Fishburne, 1976). Table A-1 provides the trends of use as tabulated by age and sex.

Another national survey conducted for the Drug Abuse Council in 1974 produced very similar results. The percentages of adults (18 and over) reporting ever having used and currently using were 18 and 8 percent respectively (Opinion Research Corporation, 1974). As can be seen in Table A-1, the number of adults currently using marihuana has not changed appreciably in the past four years with usage continuing to be concentrated in the 18-25 age bracket. Use remains about twice as frequent for males as females.

Current usage is similar for white and non-white groups and is positively associated with education -- 12 percent for college graduates versus 4 percent for those not completing high school. It continues to be higher in the West (11 percent) and lowest in the South (6 percent), and higher in large metropolitan areas (9 percent) than in non-metropolitan regions (4 percent). However, all of these racial/ethnic, educational and regional differences have become less pronounced during the past four years.

Because of the relatively small numbers involved, national general population surveys do not provide very accurate estimates of changes in heavy marihuana use. The 1971 Marihuana Commission survey reported daily or more frequent use among adults at 0.5 percent, while the comparable value for 1972 was 1.4 percent. The 1974 Drug Abuse Council national survey found 1.5 percent of the adult sample used marihuana daily or more frequently.

National Household Surveys (Youth)

The results of the Marihuana Commission and subsequent national surveys of youth ages 12-17 are presented in Table A-2. Usage has substantially increased in the last four years, with proportion-

Table A-1

MARIHUANA USE AMONG ADULTS , 1971-1976

	% Ever Used				% Current Use**			
	1971	1972	1975	1976	1971	1972	1975	1976
All adults	15	16	19	21	5	8	7	8
Age:								
18-25	39	48	53	53	17	28	25	25
26-34	19	20	29	36	5	9	8	11
35+	7	3	4	6	--*	--*	--*	1
Sex:								
Male	21	22	24	29	7	11	9	11
Female	10	10	14	14	3	5	5	5

*Less than 0.5%
**Used during last month

Table A-2

MARIHUANA USE AMONG YOUTH, 1971-1976

	% Ever Used				% Current Use*			
	1971	1972	1975	1976	1971	1972	1975	1976
All youth	14	14	23	22	6	7	12	12
Age:								
12-13	6	4	6	6	2	1	2	3
14-15	10	10	22	21	7	6	12	13
16-17	27	29	39	40	10	16	20	21
Sex:								
Male	14	15	24	26	7	9	12	14
Female	14	13	21	19	5	6	11	11

*Used during last month

Table A-3

PERCENTAGE OF MARIHUANA USE
AMONG A NATIONAL SAMPLE OF HIGH SCHOOL MALES

	Senior Year	One Year After Graduation	Five Years After Graduation
	1969	1970	1974
Ever Used	20	35	62
Any use in prior year	20	33	52
Daily or weekly sometime in prior year	6	9	21
Daily use sometime in prior year	1	2	9

Table A-4

PERCENTAGE OF MARIHUANA USE REPORTED IN 22 HIGH SCHOOLS

	Junior H.S.		Senior H.S.	
	1971	1973	1971	1973
Ever used	15	19	38	48
Ever used 60 or more times	2	4	11	17
Used in past two months	11	13	27	36
Used 60 or more times in past two months	1	1	2	4

ately larger gains among the younger age groups. Another set of national household data collected in a Columbia University study produced quite similar results (Josephson, 1974; Elinson, 1975):

	% Ever Used			
	1971	1972	1973	1974-75
Age:				
12-17	15	15	17	22
16-17	28	31	32	40

The Marihuana Commission surveys in 1971 and 1972 reported daily marihuana usage for the 12-17 age group at 0.6 percent and 1.3 percent respectively. The 1974-75 national survey for the Columbia University study found that 2 percent of youth 12-17, and 4 percent of those 16-17 reported using marihuana 60 or more times in the past two months. The percentage of daily use was not recorded for the earlier years. The 1974 Drug Abuse Council survey reported daily or more frequent usage at 1 percent of the 12-17 age group and 3 percent for those 16-17.

Student Surveys

A longitudinal study of high school males followed from the senior year to five years after graduation provides an indication of changes in marihuana usage over time in the same group (Johnston, 1974, 1976). The sample of over 2,000 was selected from 87 public high schools so as to be representative of U.S. males entering high school in 1966. (Data arrayed in Table A-3.)

Another study surveyed drug usage in 22 selected high schools throughout the country in 1971 and 1973 (Josephson, 1974). These data are not necessarily representative of the student population, but do provide an indication of changes in marihuana use over the two-year period (Table A-4).

Surveys of approximately 13,000 male and female high school seniors in 130 schools were conducted in 1975 and again in 1976 (Johnston, 1976). The schools were selected to be representative of public and private high schools throughout the country and the survey is to be repeated annually. The percentage of high school seniors reporting marihuana usage in 1975 and 1976 were:

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	1975	1976
Ever used	47 %	53 %
Used in last 12 months	40	45
Used in last month	27	32
Used 20 or more times in last month	6	8

The only regularly conducted national survey of marihuana use among college students is that prepared by Gallup (Gallup Opinion Index, 1974). The percentages reporting having ever used for the periods 1967-74 are:

Year	% Ever Used
1967	5
1969	22
1970	42
1971	51
1974	55

In one other national student survey conducted in 1974-75 for the Drug Abuse Council, 48 percent of high school and 64 percent of college students reported having used marihuana (Yankelovich, 1975a 1975b). The corresponding percentages for daily use were 6 percent and 8 percent.

One local survey of particular interest is that annually conducted among high school students in San Mateo County, California since 1968 (Blackford, 1976). Table A-5 shows the percentage of 9th and 12th grade male students reporting 1 or more, 10 or more, and 50 or more uses of marihuana during the preceding year. It will be noted that use in this locale has been stable for the past five or six years with some slight decline in 1976. San Mateo County is adjacent to San Francisco, and, thus, had an earlier and more pronounced exposure to the counterculture movement and associated drug use than did most other areas of the U.S. This is particularly evident in the late 1960's. For instance, one year after Gallup found only 5 percent of nationwide college students had used marihuana (1967), the comparable percentage for senior males in San Mateo County high schools was 45 percent. While the percentage of San Mateo seniors (male and female) using marihuana in 1976 (58 percent) is still above the national level (45 percent), the differences are not nearly so large. It is interesting to speculate

Table A-5

PERCENTAGE OF MARIHUANA USE AMONG MALE SAN MATEO COUNTY HIGH SCHOOL STUDENTS

	One or more uses in past year		Ten or more uses in past year		Fifty or more uses in past year	
Grade:	9th	12th	9th	12th	9th	12th
1968	27	45	14	26	NA	NA
1969	35	50	20	34	NA	NA
1970	34	51	20	34	11	22
1971	44	59	26	43	17	32
1972	44	61	27	45	16	32
1973	51	61	32	45	20	32
1974	49	62	30	47	20	34
1975	49	64	30	45	20	31
1976	48	61	27	42	17	30

on the reasons for the narrowing gap. Perhaps the growth of marihuana use in San Mateo schools has reached its limit, and the apparent plateau is actually a ceiling.

In summary, at the national level, marihuana use appears to have significantly increased among youth during the past three to four years, as indicated by the trend in national household surveys as well as surveys of various high school student populations. Similarly, daily marihuana use has apparently increased among youth, although the available data on changes in daily use remain fairly limited.

Marihuana Use Among Males, Aged 20-30

One of the most significant recent epidemiological studies involved the interviewing of 2,500 respondents selected to be representative of the 19,000,000 U.S. males in the 20-30 age group (O'Donnell et al., 1976). This group reports the highest rate of drug use, and the in-depth interviewing of a relatively large representative sample provided more reliable information on marihuana and other drug-using behavior than had previously been available.

The data were collected between October 1974 and May 1975 and showed that 55 percent of those interviewed had used marihuana at some time. Defining as current use any use in the year 1974-1975, the study reported 38 percent current users. Daily or almost daily marihuana use at some time was reported by 15 percent of those interviewed. The proportions of the sample reporting having used marihuana 1,000 or more times, and having used the drug within the past 24 hours were the same, 11 percent. Use of hashish at some time was reported by 29 percent and the use of hashish oil by 11 percent. Surprisingly, 11 percent of the total sample and 41 percent of those described as heavy users reported growing marihuana for their own use.

When particular age categories within this group are examined, the data show that 37 percent of the men who were 29-30 at the time of the interview had used marihuana in comparison to 63 percent of the 20-24 age group. When those described as light or experimental marihuana users are excluded, the differences are even more striking: 12 percent of those 29-30 reported use in comparison to 37 percent of those 20-24. These results indicate that males now in their late 20's are less likely to have tried marihuana than men 5-10 years younger, and are considerably less likely to adopt marihuana use as a frequent behavior. Similar or more pronounced differences probably exist for those over 30. For instance, the 1974 follow-on to the Marihuana Commission Survey found 7 percent of males and females aged 34-49 reported having used marihuana, but only 1 percent had done so within the past month.

The peak year of first marihuana use for the sample of males between 20 and 30 was 1969; however, the peak year for any use during any one calendar year was 1974 when the rate for this group reached 37

percent. The authors concluded that the data were clearly consistent with an upward trend in marihuana use.

This study also revealed that the differences in marihuana use as a function of various demographic characteristics were not as pronounced in the group sampled as those reported in the general population. In the male 20-30 age group, 70 percent of those living in cities of over 1,000,000 population had used marihuana in comparison to 43 percent of those in communities of fewer than 2,500. In terms of education, the percentage reporting some use of marihuana was almost identical for those with less than high school education, high school graduates and college graduates. This contrasts sharply with the positive correlation between marihuana use and educational level reported for the general adult population. Those who had attended college without graduating showed a higher rate. For those aged 20-23 at the time of the interview, the percent having used marihuana was virtually the same for those still in school and those not. A higher percentage of blacks (65 percent) than whites (54 percent) reported some use, but the inverse relation of marihuana use to age was not as apparent in the black group. Blacks and other ethnic minorities showed a higher prevalence of marihuana use prior to the late 1960's, but minority youth were less influenced by the recent epidemic (Bloom et al., 1974).

A Synthesis

The overall survey results indicate that marihuana use has not significantly penetrated the portion of the adult population over 30 years of age. Where use has occurred in this group, the frequency has bean mostly of an experimental nature. However, the plateau in current marihuana use among adults found in national survey results may be deceptive in predicting future usage. As the more frequently using younger groups enter the adult age range, the overall rates are likely to increase.

Results from both household surveys and student studies indicate that marihuana use is still increasing among youth at the national level, although usage appears to have stabilized in certain areas which reached a relatively high level in the early 1970's. Most of the data on youth also indicate that daily or near-daily usage has increased in the past two to four years.

If recent marihuana usage in the United States is compared with usage patterns prior to the "epidemic" which began in the late 1960's and with patterns of use in countries where cannabis use has been indigenous for many years, some useful perspectives emerge. Much of the recent American usage is comparatively minimal, both in terms of frequency of use and amount consumed (McGlothlin, 1975; Rubin & Comitas, 1975). The recent American patterns of use often seem to be based more on the adoption of a fad or life style than on an attraction to the pharmacological properties of the drug. However, once introduced as a fad, it is quite possible that marihuana use will be sustained because of its pharmacological effects.

Based on currently available survey data, it appears that around 2 percent of youth, aged 12-17, or about 8 percent of those who have tried marihuana, are currently using the drug daily. For those 17-year-olds, around 4-5 percent are probably daily users. For males of this same age group, the percentage using marihuana daily is approximately 6-7 percent, or about 13 percent of those having tried it.

For adults, the overall daily use is probably only 1 or 2 percent, but a more meaningful percentage is that for the age groups primarily involved. As described earlier, the percentage of daily use among males 20-30 years old is around 8-9 percent, or 15 percent of those who have tried marihuana. For males 20-24 years of age, current daily use is around 10 or 11 percent, or about 17 percent of those having ever used the drug.

SOCIAL AND PSYCHOLOGICAL CORRELATES

Antecedents of Marihuana Use

Numerous researchers have compared personality and behavioral traits of students using and not using marihuana. Most studies have been cross-sectional (data collected at one point in time); however, several longitudinal studies have investigated the phenomenon over two or more points in time. The latter approach has the advantage of examining individuals prior to marihuana use and determining those variables which predict subsequent initiation. In one such study of high school students, Jessor (1976) has shown that those individuals who initiate marihuana use can be predicted from various personality, belief and attitude measures. When compared with non-users, those beginning use demonstrated generally less conventional attributes prior to onset. They showed lower values on achievement and higher values on independence, were more alienated and more socially critical, more tolerant of deviance, less religious, less influenced by parents than by friends, more deviant with respect to other behavior, and had a lower grade point average. Furthermore, the group initiating marihuana use between the first and second data collection periods showed some significant changes in the above directions during the same period. Jessor interprets such changes as increasing Transition proneness," and has found similar results with regard to the initiation of alcohol drinking and sexual behavior.

Smith and Fogg (1975, 1976) collected longitudinal data over a 5-year period for students in grades 4-12. Measures of personality and behavior were based on both self-report and peer ratings. In both instances, the best predictor of future involvement in marihuana use was rebelliousness -- those who did not initiate use were described as obedient, law-abiding, conscientious, trustworthy and hardworking. Non-users also received higher grades in school (Smith, 1973). Future marihuana users were rated by their peers as being more impulsive and less sensitive to the feelings of others;

but, at the same time, more sociable, talkative and outgoing. In general, the scales which differentiated users and non-users were also predictive of early versus late use. The authors interpret the results in terms of degree of socialization -- early users being at the low end of the scale, late users at the intermediate range and non-users at the high end.

Haagen (1970) conducted an early study of male college students with extensive data collected at the time of admission (1965), when virtually none had used marihuana, and three years later, when 59 percent reported some use. At the time of admission, the group that subsequently used marihuana scored slightly higher than the non-user group on a series of aptitude and achievement tests. On the other hand, the group that later became frequent marihuana users had poorer study habits in high school, were less likely to describe themselves as hard workers, were more dissatisfied with school, and made lower grades than did the non-user group. At the time they entered college, 56 percent of the subsequent frequent users were undecided as to their intended major study as compared to 7 percent of the non-users. Users were initially more accepting of a non-conformist philosophy and moved further in this direction during college. Psychological tests administered at the time of college admission showed distinctly different patterns among the subsequent frequent , infrequent and non-users. Non-users were more optimistic, self-confident and disciplined, emphasizing rationality and suppressing emotional impulses in favor of regularity and responsibility. In contrast, students who subsequently became frequent users described themselves as more pessimistic and insecure with behavior and mood states and were more restless, erratic and unpredictable. They found routine especially distasteful. The characteristics of the infrequent users were intermediate between the two other groups; they were flexible, confident and interested in trying new experiences.

The above studies are quite consistent in showing potential marihuana users to be low in what Kandel et al. (1976) term an index of conformity to adult expectations.[2] However, in assessing these results, it is important to keep in mind the changing context in which the behavior occurs. A few years ago marihuana use was much more indicative of social deviance and general lack of conformity than is presently the case. As seen in the tables in the previous

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[1]Two other recent studies have employed psychological tests to measure personality differences between marihuana users and non-users. Segal (1975) confirmed earlier findings that marihuana users score higher on sensation-seeking scales. Naditch (1975) found users more open to experience and more prone to use regression as an ego defense.

[2]A number of other studies have reported findings generally consistent with the three studies outlined above (Brill & Christie, 1974; Gulas & King, 1976; Johnston, 1974; Kandel et al., 1976; O'Malley, 1975).

section, use at some time is currently the statistical norm for certain age groups. In some groups, the fact that an individual has never tried marihuana may be more predictive of other traits than is the opposite behavior. In this connection, it is interesting to note that the measures Jessor found to predict the onset of marihuana in high school students were not predictive of use among a college sample conducted in 1970 and 1971 (Jessor et al., 1973). He interprets this as being due to marihuana becoming the norm in the college environment, with initiation being due more to accidental associations than to a systematic set of personality and belief variables. However, as he points out, behavioral norms are related to age, and the initiation of marihuana use during early adolescence is likely to continue to be related to a larger pattern of nonconformity. The same is true for early initiation of drinking or sexual behavior.

Factors Influencing Transition from Non-Use to Use

Several studies have investigated the role of child-rearing practices and parents' drug-using behavior in the initiation of adolescent drug use. Kandel et al. (1976) found that parents' use of alcohol was related to adolescent use of alcohol but not marihuana. Other studies have found weak relations between the parents' use of prescription drugs such as tranquilizers, stimulants and sedatives and the child's use of marihuana (Kandel, 1974; Prendergast, 1974; Smart & Fejer, 1971).

One study found perceived laissez-faire parent-child relationships led to high marihuana usage among the offspring; an autocratic relationship led to medium usage; and quasi-democratic or democratic relationships led to low usage (Hunt, 1974). Others have found lower adolescent usage with strong parental disapproval compared to a tolerant attitude (Kandel et al., 1976; Prendergast, 1974). Lack of closeness with parents was found to be somewhat predictive of marihuana use, but more strongly related to serious involvement with other illicit drugs (Kandel et al., 1976).

Whatever the influence of child-rearing practices, they are generally minor in comparison to peer influences. This emphasis on peer influence is in accord with the thesis of Suchman and others that student marihuana and other drug use is largely determined by the integration into a social subculture in which drug use is a part (Suchman, 1968; Thomas et al., 1975).

As would be expected, the initiation of marihuana use tends to be preceded by increasingly favorable attitudes toward the behavior

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[1]Elinson, 1976; Jessor & Jessor, 1976; Johnston, 1973; Kandel, 1974; Kandel et al., 1976; Lucas et al., 1975.

and beliefs as to the lack of associated harm.[1]

One social environment, the military, has apparently proved to have less influence on marihuana and other drug use than was initially believed. O'Donnell et al. (1976) in their study of 20-30-year-old males found that neither domestic nor overseas service had any effect on marihuana use. Robins (1975) has also found that Vietnam veterans' marihuana use after return was not significantly increased over that for a comparison group who did not enter the military.

Since marihuana use is known to generally precede other illicit drug usage, the question is often raised as to the role of marihuana in facilitating the transition or progression to more dangerous drugs. While not specifically answering this question, Kandel and associates have determined that the temporal sequence along the legal-illegal drug continuum is consistent (Kandel & Faust, 1975; Single et al., 1974). By conducting longitudinal studies of two large samples of high school students, they were able to determine the order in which the various drugs were used. Only 1 percent of the sample began using illicit drugs without first using a legal drug. Beer and wine collectively constituted by far the most common "entry drug" (28 percent) with cigarettes accounting for 6 percent and hard liquor 3 percent. In addition to the fact that legal drug use virtually always preceded illicit use, heavy use of both liquor (weekly) and cigarettes (over a pack a day) resulted in a high percentage (40 percent) moving from non-use to use of illicit drugs in a five month period. Only 2-3 percent of adolescent legal drug users progressed to other illicit drugs without first trying marihuana. If the individual progressed beyond marihuana, the next step was generally pills. Subsequent steps were psychedelics, cocaine and heroin, in that order; but, of course, only a small percentage progressed to the higher levels of the sequence. Heavy use of marihuana or other drugs along the sequence was more often followed by progression to the next step, and also by a higher probability of moving two or more steps during a single time period.

Correlates of Marihuana Use

The two previous subsections have dealt primarily with the antecedents of marihuana use. Obviously, since they precede the behavior of interest, there is no possibility of their being caused by marihuana usage. Research which simply shows a correlation between marihuana use and other behavior leaves the question of causality unresolved. It should be stressed that, while research on social and psychological correlates can sometimes rule out causality between two variables that are statistically correlated, it can rarely, if ever, establish that one is the consequence of the other.

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[1]Elinson, 1976; Jessor, 1976; Kandel et al., 1976; Lucas et al., 1975; Smith & Fogg, 1976; Sadava, 1973.

Current living arrangement is one correlate of marihuana use that is apparently related to the general pattern of unconventionality described earlier. In their national study of males, ages 20-30, O'Donnell et al. (1976) found that the proportions currently using marihuana were as follows: married, 25 percent; living with parents, 38 percent; living independently, 56 percent; consensual union (living with a woman but not married), 68 percent.

The same study (O'Donnell et al., 1976) found 72 percent of those unemployed at the time of the interview had used marihuana in comparison to 52 percent of those employed. In another study of Air Force personnel, those reporting marihuana use showed somewhat poorer work performance than a comparison group of non-users (Mullins et al., 1975).

Several studies have found a positive relation between marihuana use and self-reported criminal acts and/or contacts with the criminal justice system. However, the one longitudinal study which has extensively examined the association found no evidence that non-addictive drug use causes crime (Johnston et al., 1976). The study involved a representative sample of 2,200 10th grade males first contacted in 1966, when very few had used illicit drugs. There were four subsequent follow-ups through 1974. The study found a static relationship between drug use and crime; i.e., drug users reported more crime than non-users at each data collection point, although those using only marihuana were less delinquent than other drug-using groups. The longitudinal data showed that "the preponderance of the delinquency differences among the non-users and various drug-user groups existed before drug usage." Other analyses showed that groups that increased drug use over the period did not show a parallel increase in criminal behavior.

Similar results have been found with respect to drug use and dropping out of high school and college (Carlin & Post, 1974; Johnston, 1973; Mellinger et al., 1976a), and career indecision (Brill & Christie, 1974; Haagen, 1970; Mellinger et al., 1976b). Drug users show a higher drop-out rate and more career indecision. However, the differences generally disappear when pre-use factors such as academic motivation and family background are controlled (Mellinger et al., 1976a, 1976b). This is especially true for those students using only marihuana.

In summary, it is clear that marihuana usage is frequently part of a larger pattern of non-conformity, but where longitudinal data have permitted adequate multivariate analyses, the results have generally suggested the lack of any causal effects.

William McGlothlin, Ph.D.
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[1]Brill and Christie, 1974; Jessor & Jessor, 1976; Johnston et al., 1976; Kandel et al., 1976; O'Donnell et al., 1976.

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Chapter 2
CHEMISTRY AND METABOLISM

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SUMMARY

The continuing research into the chemistry of marihuana has focused on two approaches -- chemical analysis and synthesis -- aimed at some fundamental problems. There are, first, the analytical problems which exist because marihuana is a complex mixture of substances present in variable amounts, and the constituents must be defined so that their individual properties may be related to those of marihuana itself; in addition, such definition may provide, for forensic purposes, a means of identifying the origin of marihuana samples. Secondly, the analysis of marihuana must be extended beyond the mere identification of its constituents to the experimental situation in which the drug's metabolic products are described in body tissues and fluids. The goal of such studies is, obviously, to relate the fate of the drugs in the body to their effects. The techniques generally used to solve these problems have been chromatography, mass spectrometry and radiolabelled drugs.

The objective of the synthesis research is to produce naturally occurring cannabinoids as well as their metabolites and synthetic congeners or surrogates. This ongoing synthesis provides pharmacologists with adequate supplies of pure drugs whose properties can then be evaluated relative to marihuana; additionally, such syntheses produce a variety of congeners to be screened for their pharmacological properties so that the therapeutic potential of the cannabinoids may be assessed with some degree of reliability. Indeed, the synthesis of many of the human metabolites of Δ-9-THC -- the major psychotoxic constituent of marihuana -- has now been achieved, and the consequently greater availability of these drugs will enable pharmacologists to study the role of the metabolites in the pharmacology and toxicology of marihuana on a much broader scale. For example, a simplified, but small-scale, synthesis of several cannabinoids was described within the past year. An increased availability of pure -- although very small -- metabolite samples can bridge a serious prevailing analytical gap vis-a-vis the experimental situations that require a positive identification of the substances in order to determine their fate in the body.

Moreover, synthetic cannabinoids were the subject of numerous publications whose main thrust was the development of marihuana surrogates with greater pharmacological selectivity. Most potential therapeutic uses of marihuana can be realized only if concomitant toxic manifestations can be eliminated, or at least minimized, by molecular modifications of the naturally occurring cannabinoids.

To this end, many new derivatives must be synthesized and then screened using the pharmacological criteria customarily applied to any new class of drugs. Clearly, the large numbers of synthesis studies cited in the present report attempt to fulfill this purpose.

The chemical analysis of marihuana continued to define some toxicological problems. The recognition that cannabichromene (CBC) is a major constituent of most samples of marihuana is a case in point, for, although it has been identified, certain questions must now be posed: What are CBC's properties and does its presence contribute to the effects characteristically produced by marihuana? In fact, there is at present very little known about the pharmacology of CBC.

The continuing refinement of established analytical techniques for cannabinoids has been most noteworthy in gas and thin-layer chromatography. However, two relatively new techniques have received some attention: plasma chromatography and high-pressure liquid chromatography. The former method offers a new and very sensitive approach to the analysis of cannabinoids. High-pressure liquid chromatography holds great promise because of its potential for physically separating closely related cannabinoids and because the method is inherently simpler than gas chromatography in that it obviates the need for derivatization prior to analysis.

The ongoing metabolic studies are significant primarily for two reasons: First, some of the metabolites of these drugs are extremely active pharmacologically; thus, their identification and subsequent investigation are necessary for an understanding of the pharmacology of marihuana. Secondly, some of the constituents of marihuana can block the important drug metabolizing enzymes in the liver, which creates the possibility of toxic interaction with other drugs (including other marihuana constituents) by altering their normal rate of hepatic metabolism or inactivation. Numerous contributions to the elucidation of cannabinoid metabolism have been made in the past year. The finding that in both dogs and rats the major metabolites produced by the lung are different from those produced by the liver is noteworthy because it implies that the effects of marihuana may, in part, be determined by its route of administration. It is now important to determine in humans whether there are corresponding differences in tissue metabolism, or whether the route of administration affects the nature of the elicited pharmacological reactions.

A report also appeared on the identification of cannabis metabolites that persist in tissues for many days after drug exposure, a characteristic of great potential toxicological significance. The identification of these metabolites leads the way to their synthesis and subsequent evaluation for toxicity.

Finally, a kinetic interaction was reported between cannabinol and Δ-9-THC which may account for previous descriptions of a cannabinol antagonism of some effects of Δ-9-THC. This finding lends some credence to the suggestion that the cannabinoids in marihuana can interact with one another; therefore, their relative concentrations

may be critical in the pharmacological manifestations of any given marihuana preparation.

DRUG SOURCES

A new procedure for the determination of the source or origin of illicit marihuana samples has been devised by Novotny et al. (1976b) who used a combination of gas chromatography and mass spectrometry to isolate and identify 38 non-polar constituents of marihuana, thereby providing a "fingerprint" of the composition of any given sample of cannabis. This detailed analysis of marihuana may be superior to the more conventional procedure of limiting such measurements to the relative concentrations of the so-called "main cannabinoids": cannabidiol (CBD), Δ-9-tetrahydrocannabinol (Δ-9-THC) and cannabinol (CBN). The technique reported in the Fifth Marihuana and Health Report (1975) for the quantification of the CBD and CBC content of marihuana has now been extended to the analysis of numerous cannabis samples of known geographical origin (Halley et al., 1975). The results indicate that for most variants of cannabis, CBC is present in greater amounts than is CBD. Consistent with these data is the finding that a potent Mexican variant contains much more CBC than CBD (Turner et al., 1975). Whether the presence of CBC influences the pharmacological activity of Δ-9-THC, as has been reported for CBD and CBN, remains to be determined.

The continuing chemical elucidation of the constituents of cannabis has produced several results: Two new neutral cannabinoids, cannabichromevarin and cannabigerovarin -- propyl homologues of CBD and cannabigerol -- have been found (Shoyama et al., 1975); the butyl homologues of Δ-9-THC, CBN and CBD have also been identified in cannabis (Harvey, 1976), as well as the mono- and sesqui-terpene constituents (Hendriks et al., 1975); the chemistry of both the terpene substances of cannabis and the nitrogen-containing compounds has been reviewed by Hanus (1975a, 1975b); meanwhile, Novotny et al. (1976a) have undertaken additional work on marihuana sterol constituents which are of particular interest because they may act as precursors of carcinogenic hydrocarbons.

The stability of cannabis preparations, including pure cannabinoids, under various conditions has been described by Fairbairn et al. (1976) who report that exposure to light is the greatest single factor in the loss of cannabinoids: The decomposition of Δ-9-THC by light does not yield CBN, but air oxidation does. The results demonstrate that cannabinoids stored in solution in the dark at room temperature are reasonably stable for one to two years.

More new cannabinoids have been synthesized and studied for pharmacological activity. Another report describes the rapid synthesis

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[1]Kraatz & Korte, 1976a, 1976b; Kurth et al., 1976a, 1976b; Lemberger & Rowe, 1975; Pars et al., 1976; Razdan & Dalzell, 1976; Razdan et al., 1976a, 1976b, 1976c, 1976d; Weiner & Zilkha, 1975; Winn et al.; 1976.

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of small quantities of 32 different cannabinoids, including the major naturally occurring agents (Crombie & Crombie, 1975). Such small quantities can be useful as reference standards for the qualitative analysis of unknown samples of cannabinoids. The synthesis of human metabolites continues to be important because of the demonstrated activity of some of these substances. New syntheses of the 11-hydroxy-, 8-α-, and 8-ß-hydroxy metabolites of Δ-9-THC have been reported as well as the first synthesis of the 8α, ll-, the 8-ß,11-dihydroxy and the 11-norΔ-9-THC-9-carboxylic acid metabolites (Pitt et al., 1975). Additionally, Lander et al. (1976) described another synthesis of CBD and the first syntheses of some of its metabolites.

The pharmacological properties of the various types of marihuana preparation are not known, but numerous reports have suggested some differences. For example, marihuana prepared by a boiling water treatment was found to be significantly enriched in cannabinoids, including Δ-9-THC (Segelman et al. , 1975), which may account for the apparent increased activity of such preparations. The residual marihuana "teas" (boiled-water extracts) may also exhibit some pharmacological activity; however, a water-soluble fraction obtained by smoking cannabis through a water pipe was found to be inactive in a variety of pharmacological tests (Savaki et al., 1976).

ANALYTICAL TECHNIQUES: DETECTION

Various techniques continue to be developed for the analysis of cannabinoids in cannabis preparations and in experimental animal tissues. Gas-liquid chromatography with a solid injection procedure (Rasmussen, 1975a) has been combined with an on-column silylation of cannabinoids (Rasmussen, 1975b) in order to obviate the need for extraction. Thus, the volatile constituents released from the injected material are cold trapped and the derivatives of the trapped compounds are formed directly on the column.

A combination of liquid, thin-layer and gas chromatography has been used to separate synthetic mixtures of the major naturally occurring cannabinoids and their mono-oxygenated metabolites (Fonseka & Widman, 1976). In a similar study, the mono- and dihydroxy cannabinoids were determined by combined gas chromatography and mass spectrometry (Harvey & Paton, 1975), and good chromatographic separations of the hydroxylated derivatives were obtained with the formation of homologous trialkylsilyl derivatives. In another report, the first mass fragmentographic assay for 11-hydroxy-Δ-9-THC was based on the derivatization of the phenol moiety by extractive alkylation (Rosenfeld & Taguchi, 1976).

High-pressure liquid chromatography has been used for the comparative analysis of cannabis samples (Smith, 1975; Wheals & Smith, 1975; Wheals, 1976) and the investigators maintain that this technique is superior to gas-liquid chromatography because both acid

and neutral cannabinoids can be quantitated without prior derivatization. A relatively simple thin-layer chromatographic technique using silica gel plates impregnated with a tertiary amine, triethylamine, yielded good resolution of the major cannabinoids (Vinson & Hooyman, 1975), and the plates were shown to be little affected by storage for 10 weeks. In addition, a new and potentially very sensitive chromatographic technique, plasma chromatography, has been used to measure Δ-9-THC (Karasek et al., 1975).

The Rutgers Identification for Marihuana test appears to be relatively specific, since a total of 526 non-marihuana plant samples representing 427 different plant species failed to yield any false positive results (Segelman & Segelman, 1976). Fluorescent techniques for cannabinoid analyses also continue to be developed. Simple heating can convert the major naturally occurring cannabinoids into fluorescent products (Dionyssion-Asterion & Miras, 1975) and the test is sensitive enough to detect cannabinoid substances in the urine of marihuana users. Bourdon (1976) has used another fluorometric method to determine Δ-9-THC and its metabolites in urine.

It should also be noted that two major reviews in this area have appeared this year: Mechoulam et al. (1976) and Nahas et al. (1976).

METABOLISM

Investigations of the biological disposition of the cannabinoids continue to yield a greater understanding of factors affecting their metabolism, the nature of the metabolites, their distribution in the body and, finally, the routes of their excretion.

The in‘ vitro metabolism studies of the cannabinoids have been pursued because adequate cannabinoid concentrations can be recovered from such reaction systems, thereby facilitating the identification of some cannabinoid matabolites, which are of interest because of their potential pharmacological activity. The metabolism of Δ-9-THC has been compared in the isolated, perfused dog lung with that in a dog liver microsomal preparation (Widman et al., 1975). The major metabolites produced by the liver microsomes were 8-α- and 8-ß-hydroxy-Δ-9-THC; in contrast, the major metabolites recovered in the dog lung experiments were 3"- and 4"-hydroxy-Δ-9-THC. This is the first report of the formation of these side-chain hydroxylated compounds. The differential results of these experiments may provide an explanation of the impression that the route of administration can influence some pharmacological and toxicological effects of marihuana. The potential role of the pulmonary metabolism of cannabinoids in their pharmacology and toxicology is also emphasized by the report that rat lung homogenates metabolize Δ-9-THC differently than does rat liver; hence, the characteristic activity of the drug may depend on the mute of administration (Cohen, 1975).

The in vitro metabolism of CBN has been compared in rat and in rabbit liver preparations (Widman, 1975). In both of these species, the 11-hydroxy derivative is a major metabolite and side-chain hydroxylated compounds also form; the latter are minor in the rat, but in the rabbit 4"-hydroxy-CBN is a major product. In general, the metabolism of CBN resembles that of Δ-9-THC because hydroxylations occur in the C-11 position and in various positions in the pentyl side chain. In a similar study of the in vitro metabolism of CBD by rat liver microsomes, eight monohydroxylated metabolites were isolated (Martin et al., 1976). As reported previously, the major metabolite was 11-hydroxy-CBD, and the second most important was 8-α-hydroxy-CBD. Hydroxylations also occurred in all positions of the pentyl side chain.

Some in vivo and in vitro effects of Δ-9-THC have been reported on drug metabolism by rat liver microsomes (Mitra et al., 1976). In doses of 50 mg/kg, six hours after intraperitoneal administration, Δ-9-THC inhibited microsomal metabolism, as measured by the activity of two demethylases and aniline hydroxylase. Repeated treatment (21 days) with a daily dose of 10 mg/kg resulted in complete inhibition of the two demethylases without any effect on the hydroxylase. In vitro, 2, 4, and 8 mcg drug/mg protein inhibited both demethylases and the hydroxylase. In vivo and acutely, the inhibition was of the mixed type for the two demethylases but only non-competitive for the hydroxylase. With repeated treatment, the inhibition of the demethylases was only of the competitive type, which is similar to the results obtained in vitro. In the latter instance, however, the inhibition of aniline hydmxylase activity was of the mixed type.

Previous investigators have demonstrated the long persistence of cannabinoids in tissues after their administration and the nature of the long-retained metabolites has now been defined (Leighty et al., 1976): They are 11-acyloxy derivatives, primarily conjugates of palmitic and stearic acids, which accounts for their decreased polarity relative to the parent drugs. The long retention of these metabolites implies kinetically that they will accumulate with repeated drug exposure; however, because the pharmacological properties of these metabolites are unknown, the biological significance of such an accumulation is difficult to determine.

Using a method combining gas chromatography and mass spectrometry for measuring cannabis metabolites in urine, Kelley and Arnold (1976) were able to identify both CBN and 11-hydroxy-Δ-9-THC samples obtained from marihuana users. This identification required the use of hydrolized urine samples and selected ion monitoring. The limit of detection of the cannabinoids was about 1 mcg/ml urine. The general problems associated with the detection of cannabinoids in body fluids have been summarized by Lemberger (1976).

The kinetic interaction between Δ-9-THC and CBD and Δ-9-THC and CBN has also been described. The simultaneous intravenous administration of CBD and Δ-9-THC does not affect the elimination rate of either of the individual cannabinoids; in contrast, in the presence

of CBN the rate of clearance of Δ-9-THC was greatly enhanced, although that of CBN remained unchanged (Levy & McCallum, 1975). This kinetic interaction may account for the previously reported antagonism between CBN and Δ-9-THC.

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Chapter 3

TOXICOLOGICAL AND PHARMACOLOGICAL EFFECTS

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The toxicological research reviewed in the present Marihuana and Health Report generally represents extensions of some previous lines of investigation. For example, the toxicity of the cannabinoids has been determined with high and low doses, by different routes of administration, under both acute and chronic conditions. The conclusions from these studies are consistent with those drawn from other experiments; that is, marihuana or its principal psychoactive constituent, Δ-9-THC, produces a variety of reversible effects, but they do not cause any irreversible pathological changes. These observations do not preclude the possibility that marihuana may produce some irreversible functional changes, although no such evidence has yet been presented.

The toxicological assessment of marihuana must, by necessity, consider the known adverse effects of tobacco smoke on the lung and on the cardiovascular system. Experimentally discernible effects on the lung were reportedly produced by chronic exposure of both rats and dogs to marihuana smoke. In fact, the lung is the only organ to display pathological changes as a consequence of chronic exposure to marihuana smoke. Chronic administration of the drug by other routes of administration does not produce any demonstrable pathology, emphasizing that the direct effects of marihuana smoke on the lung represent a potential toxic factor in humans. The problem is that the toxic effects of marihuana, like those of tobacco, cannot be completely evaluated in animal studies because they, too, may require many years of exposure to manifest themselves. On the basis of the human experience with chronic exposure to tobacco smoke, however, similar toxic effects can be expected in response to marihuana smoke. Whether these toxic effects will be more or less prominent with marihuana use than they are with tobacco is not known. Of immediate interest in this regard is the report that the carcinogenic hydrocarbon content of marihuana smoke is greater than that of tobacco smoke. This observation suggests the possibility that chronic, long-term use of marihuana carries as great, or greater, carcinogenic liability than does the use of tobacco.

The current Report cites numerous publications dealing with the teratogenic potential of Δ-9-THC. Despite some earlier claims to the contrary, there is general agreement that the drug is not teratogenic, except possibly in high doses. There is, however, a growing body of evidence from a wide variety of experimental situations that Δ-9-THC has the potential, especially in high doses, for the disruption of cellular processes involved in growth and development. Whether this is a unique property of marihuana or whether it is an effect that is characteristic of high doses of any

cellular depressant is not known.

The results described below from the studies of the influence of Δ-9-THC on the activity of the adrenal cortex are of special interest because of the species differences observed. In rats the drug produced a marked increase in the activity of the adrenal cortex, but no such effect occurred in the rabbit. The difference in response between species emphasizes that results obtained in animal studies are at best only suggestive of potential effects in humans. The complexity of the effects of Δ-9-THC on an endocrine function is further illustrated by the reports of antiestrogenic activity on the uterus of normal rats but estrogenic activity on the uterus of ovariectomized animals. The apparent contradiction remains to be resolved.

Various aspects of the pharmacology of marihuana and its constituents continued to be examined in detail; and during the past year some important contributions were made to our understanding of: 1) factors that affect the fate of the drugs in the body; 2) the interactions of marihuana constituents with the effects of other drugs; and 3) the pharmacological effects of the constituents. A study of the nature of the binding of Δ-9-THC to plasma proteins indicated that the drug is bound by lipoproteins and by albumin. The binding to lipoproteins does not appear to be related to the drug's lipid solubility because other lipid soluble drugs are not necessarily bound to this plasma protein fraction. The influence of some experimental variables on the fate of Δ-9-THC in the body was also studied. The vehicle and the route of administration affected absorption, tissue distribution and excretion; the vehicle alone even influenced tissue distribution following intravenous administration, as did repeated daily treatment. These results, like those of earlier similar studies, emphasize the importance of these variables in determining the fate of cannabinoids in the body. In turn, their fate may influence their pharmacological and toxicological manifestations.

Little attention has been given in the past to the means by which cannabinoids are removed from the brain. The report described below on the ability of the choroid plexus to actively accumulate Δ-9-THC suggests that this organ may transport the cannabinoids from the brain into the cerebral spinal fluid. Whether this is, in fact, a fate of the cannabinoids in the brain remains to be shown.

The Report contains additional descriptions of the central nervous system effects. The anticonvulsant activity and its therapeutic potential continue to be examined in different antiseizure tests involving a variety of species. The results presented are generally consistent with those of previous studies: The cannabinoids are effective anticonvulsants in some seizure test systems but not in others, and Δ-9-THC exhibits excitatory properties, which distinguish it from cannabidiol (CBD). The results of these investigations again emphasize the similarities between CBD and diphenylhydantoin-like drugs, suggesting that the cannabinoids may be effective clinically against grand mal but not absence seizures.

The cannabinoids' effects on a variety of neurochemical factors are also noted. The basic assumption of such studies is that the central nervous system effects of marihuana must have some neurochemical correlates. Chronic exposure of animals to marihuana smoke produced changes in brain RNA and acetylcholinesterase activity, both of which coincided with behavioral changes. These results are also significant because they essentially duplicate those previously obtained following oral administration of the drug. More data are also presented to support previous contentions that some of Δ-9-THC's effects are mediated by an anticholinergic mechanism. Physostigmine reversed some effects of Δ-9-THC on the EEG; and Δ-9-THC inhibited acetylcholine synthesis, which may be associated with a decreased turnover of acetylcholine. The effects of cannabinoids on other putative transmitter systems, such as gamma-aminobutyric acid, 5-hydroxytryptamine, norepinephrine, dopamine and monoamine oxidase activity were also investigated in various experimental situations; however, in most, but not all, instances, changes in these neurotransmitter systems could not be related to central effects.

In the cardiovascular studies, tolerance to the effect on cardiac rate and on blood pressure continues to be reported; tolerance developed to the hypotensive activity in hypertensive animals. The results of a brain-blood flow study suggest that Δ-9-THC can significantly reduce blood flow to certain areas of the brain; such alterations in flow may reflect regional functional changes. The constriction of cranial blood vessels by Δ-9-THC raises the possibility that there may be a pharmacological basis for the suggested use of marihuana in the treatment of migraine.

A structure-activity study of the analgesic properties of cannabinoids has revealed that the 11-hydroxy metabolite of Δ-9-THC is many times more potent than is the parent compound; the activity of the metabolite in a hot-plate test approaches that of morphine. Naloxone, an opiate antagonist, also antagonizes this effect of the cannabinoids. Another pharmacological relationship between the cannabinoids and the opiates appears to exist: Δ-9-THC attenuates the naloxone-precipitated morphine-abstinence syndrome, an effect noted in the 1975 Marihuana and Health Report, and confirmed by the two investigations described in the current Report. CBD alone was found to be ineffective in this test, but in combination with Δ-9-THC, it enhanced the abstinence-attenuation properties of Δ-9-THC. The effect of Δ-9-THC on the abstinence syndrome may be selective for the opiates because the drug was shown to exacerbate the ethanol-abstinence reactions.

In addition to the drug interactions described above, Δ-9-THC was also observed to prolong ether anesthesia, which is antagonized by CBD. Many cannabinoid-drug interactions probably result from the ability of the cannabinoids to interfere with hepatic drug metabolism; however, since the duration of action of ether is not limited by drug metabolism, the cannabinoid effects on ether anesthesia suggest a central nervous system locus of interaction. In

general, the cannabinoids are not anesthetics, but a potential for. this effect is demonstrated by dimethylheptylpyran, which is an anesthetic in dogs. This potential may account for the observed cannabinoid interaction with ether.

TOXICOLOGICAL EFFECTS

Investigators have continued to evaluate the toxicity associated with repeated exposure to high and low doses of cannabinoids administered to different species by different routes of administration. One such study, which is similar to another report (Thompson et al., 1975), was designed to determine systemic toxicity of Δ-9-THC (dosages: 3-100 mg/kg/day) administered subcutaneously for 13 days to female rabbits (Banerjee et al., 1976). Some metabolic effects were noted at both high and low doses; but, except for anorexia and some local dermal irritation, Δ-9-THC did not produce any significant toxicity.

A previous study of marihuana inhalation toxicity in rats (Rosenkrantz & Braude, 1974) has been extended from 23 days of exposure to 87 days (Fleischman et al., 1975a). This is the first report on the chronic effect of marihuana under conditions comparable to human use. Animals were exposed to daily doses of either 0.7, 2.0, or 4.0 mg/kg. The results demonstrated that rats exposed daily to relatively low doses of Δ-9-THC display a cumulative lethal toxicity and that lethality was sex-linked to males. Cumulative drug-related morphological changes were observed only in the lungs; these changes included focal pneumonitis with the accmulation of alveolar macrophages, polymorphonuclear leukocytes, and lymphocytes. Similar results were obtained in female dogs chronically exposed (over 900 days) to inhalation of marihuana and tobacco smoke (Roy et al., 1976). The ability of marihuana to affect adversely pulmonary and peritoneal macrophages has also been studied (Huber et al., 1975; Raz & Goldman, 1976).

As a means of facilitating the investigation of the carcinogenic potential of marihuana smoke, a technique for the preparation of marihuana cigarettes and for monitoring marihuana smoke condensate samples has been reported by Patel and Gori (1975). An extensive comparative analysis of the polynuclear hydrocarbon fractions of marihuana smoke condensates indicates that there are more than 150 different such compounds present in marihuana smoke (Lee et al., 1976). Similar results were obtained from the analysis of tobacco smoke; marihuana smoke, however, contains higher amounts of the carcinogenic hydrocarbons (Novotny et al., 1976) and evidence is presented to show that the greater hydrocarbon content of marihuana smoke may be due to the pyrolysis of cannabinoids.

Numerous reports concerning the teratogenic potential of Δ-9-THC have been published and three of these involve non-mammalian models -- the zebra fish embryo (Thomas, 1975), chick embryo (Jakubovic et al., 1976), and Tetrahymena pyriformis (McClean & Zimmerman, 1976).

In the zebra fish study, Δ-9-THC produced morphological alterations in the concentration range of 2.0 ppm, but in the chick embryo the drug, in combination with ethanol, was non-teratogenic. Δ-9-THC did, however, depress growth or cell division and the synthesis of protein and nucleic acids in both the chick embryo and in Tetrahymena. The relationship of these effects in non-mammalian systems to teratogenicity in humans is not certain; however, it appears that Δ-9-THC has a potential for disruption of the cellular processes involved in normal growth and development.

In past mammalian studies of marihuana teratogenicity, some conflicting results have been reported, probably because of species differences, of differences in marihuana preparations, in dose, route and time of administration during embryogenesis. Generally speaking, however, Δ-9-THC does not appear to be teratogenic in mammals, except in high doses, These conclusions have been borne out by several recent studies. The early reports of teratogenicity in animals may have been related to impurities in marihuana preparations rather than to the use of high doses of Δ-9-THC. The subject of teratogenicity is reviewed by Fleischman et al. (1975b) and by Joneja (1976).

In studies on the hypothalamic-pituitary-gonadal and -adrenal systems, Δ-9-THC, both acutely and chronically, stimulates the adrenal cortex in rats (Biswas et al., 1976); in the chronic experiments, the stimulation of adrenocortical function is manifested by increased functional properties in the fasciculata-reticularis regions, as well as marked hypertrophy of the adrenals. These findings are consistent with previous reports that Δ-9-THC acutely increases ACTH and corticosterone secretions in the rat. In another study, the adrenal stimulatory effect of the cannabinoids in rats was confirmed, and the effect abolished by hypophysectomy, implicating ACTH release as the mediator of the response (Maier & Maitre, 1975). The cannabinoids, however, did not affect adrenal function in the rabbit.

In studies of the mode of the endocrine actions of Δ-9-THC, microgram quantities of the drug were injected daily for one week into the lateral ventricle of the brains of two groups of rats, prepuberal and mature males (Collu, 1976). The main purpose of the investigation was to determine whether endocrine effects produced by Δ-9-THC are central in origin or are direct effects on target organs. In prepuberal animals, prostate weights were reduced and plasma and pituitary amounts of growth hormone were increased. Pituitary concentrations of prolactin were increased in both groups of rats, whereas adrenal weights and plasma corticosterone levels were increased only in adults. The results demonstrate that Δ-9-THC can affect some endocrine functions by a central mechanism of action. Furthermore, young and adult animals may respond differ-

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[1]Banerjee et al., 1975a; Fleischman et al., 1975b; Joneja, 1976; Mantilla-Plata et al., 1975.

ently to repeated drug exposure.

In order to elucidate the antiovulatory and decreased lactation effects of Δ-9-THC and their relationship to serum concentrations of luteinizing hormone and of prolactin, rat experiments were undertaken in which the drug was administered acutely in a high dose (50 mg/kg) at the beginning of estrus (Chakravarty, 1975b). Under these conditions, Δ-9-THC produced a drastic reduction in serum concentration of both hormones, which may account for the previously noted effects on ovulation and lactation.

Several studies have focused on cannabis effects on the uterus. The acute and chronic administration of a cannabis extract to female rats and mice (Chakravarty et al., 1975a; Dixit et al., 1975) and to female gerbils (Dixit et al., 1976) results in antiestrogenic effects on the uterus. The antiestrogen activity of cannabis was also manifested on the monoamine oxidase activity in the rat uterus. Estradiol decreases the activity, whereas cannabis extract increases it in both control and estradiol-treated animals (Chakravarty et al., 1976). In direct contrast to these antiestrogen observations, Δ-9-THC (1-10 mg/day for 14 days) was shown to have estrogen-like activity on the uterus of ovariectomized rats (Solomon et al., 1976).

Effects on bone marrow activity have previously been noted, but generally these effects have been observed in high-dose studies; Δ-9-THC (1 mg/kg/day) given to rats from the 2nd-30th day of life, however, produced a significant myeloid hyperplasia with an accompanying blood granulocytosis, and, in the growing animal, it was found that this effect persisted for up to four months after the end of treatment (Giusti & Carnevale, 1975).

PHARMACOLOGICAL EFFECTS

The tissue distribution of Δ-9-THC has been the general subject of various investigations: Thus, the binding of Δ-9-THC to rat and human plasma proteins has been studied with the use of zonal ultracentrifugation (Klausner et al., 1975). About 60 percent of the drug in plasma was found to be associated with the lipoproteins, the remaining 40 percent is bound to albumin; in addition to Δ-9-THC, several other lipid soluble drugs were bound by plasma proteins, but these drugs, unlike Δ-9-THC, did not associate with the lipoproteins. Therefore, the lipoprotein-Δ-9-THC interaction is not related simply to the drug's lipid solubility, and the nature of the interaction remains to be determined.

In another study, the investigators evaluated the influence of vehicle, route of administration and duration of treatment on the tissue distribution and excretion of ^{14}C-Δ-9-THC (Mantilla-Plata & Harbison, 1975). The vehicles were either saline with Tween 80, bovine serum albumin, propylene glycol, or corn oil. Total ^{14}C content was measured in plasma, liver, brain, lung and fat. Both vehicle and route of administration affected absorption and distri-

bution of the drug; furthermore, the results of intravenous administration showed that the vehicle alone influenced tissue distribution. Daily intravenous administration, compared with a single such administration, resulted in relatively high concentrations of ^{14}C in some tissues, but lower in others; such results emphasize that valid comparisons of pharmacological and toxicological data can only be made if the vehicle, route of administration, and treatment schedules are the same.

Brain concentrations of many drugs are known to be regulated, in part, by active transport processes in the choroid plexus; such may also be the case for Δ-9-THC, which has been shown to be actively accumulated by this organ (Agnew et al., 1976). The uptake of Δ-9-THC is notable because it is much greater than for many other drugs actively transported by the choroid plexus.

The subcellular tissue distribution of Δ-9-THC and its metabolites has been studied in relation to the effect of the drug on motor activity (Malor et al., 1976) and in relation to the development of tolerance (Martin et al., 1976). The results of the correlation with motor activity indicate that there is no preferential intracellular site of accumulation and that there is, as a function of time, a decrease in the relative specific activities of Δ-9-THC and its 11-hydroxy metabolite, with a concomitant increase in the quantity of polar metabolites in all subcellular fractions. The data suggest that the termination of the depressant effect on motor activity is a consequence of the metabolism of Δ-9-THC to pharmacologically inactive metabolites. The tolerance study revealed that, in the dog, tolerance is not generally associated with any significant changes in the rate of metabolism, in peripheral tissue distribution, in distribution between different areas of the brain, or in intracellular distribution. The only impressive change in intracellular distribution was found in the synaptic vesicle fraction, which contained 40 percent less radioactivity than did the corresponding fraction from non-tolerant dogs. How this change relates, if at all, to the mechanism of tolerance is not immediately obvious.

The anticonvulsant properties of the cannabinoids continue to be investigated in a variety of seizure models. Δ-9-THC is effective against photically induced seizures in acutely treated epileptic chickens (Johnson et al., 1975). Dose-response data, however, indicate that the drug has limited efficacy in this test. Against pentylenetetrazol-induced seizures, Δ-9-THC was ineffective in both normal and epileptic chickens. The anticonvulsant effect of Δ-9-THC in gerbils that exhibit spontaneous seizures was also studied (Ten Ham et al., 1975), and it was found that, acutely, these seizures were abolished by Δ-9-THC: however, there was a rapid development of tolerance to the effect but not to the motor toxicity, which was exacerbated by repeated daily administration.

Another seizure model, the baboon, has been used to assess the anticonvulsant properties of Δ-8- and Δ-9-THC against two different types of seizure -- photogenic and kindled amygdaloid seizures

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(Wada et al., 1975). The results show a differential effect: The cannabinoids suppressed the kindled convulsions but had no effect on susceptibility to photogenic seizures. In still another study, this time in the rat, the effect of anticonvulsant doses of Δ-9-THC and CBD on the after-discharge potentials of the visually evoked response was determined (Turkanis et al., in press). These potentials, like some of those associated with epileptic activity, are known to be differentially sensitive to the major types of antiepileptics. In this test system, the potentials were suppressed only by trimethadione-like drugs; they were unaffected by CBD and diphenylhydantoin, but they were markedly augmented by either Δ-9-THC or pentylenetetrazol. The similarity in action between CBD and diphenylhydantoin was described in other tests, as was the CNS excitatory activity of anticonvulsant doses of Δ-9-THC (Karler & Turkanis, 1976a).

Finally, there is a report on an anticonvulsant benefit derived from smoking marihuana (Consroe et al., 1975). This is a case history of a 24-year-old with grand mal epilepsy who empirically determined that he could control his seizures by combining marihuana use with his therapeutic doses of phenobarbital and diphenylhydantoin. Karler and Turkanis (1976b) have reviewed the antiepileptic potential of the cannabinoids.

In the area of cannabinoid effects on EEG; and other electrophysiological parameters, the role of cholinergic mechanisms in the actions of Δ-9-THC was tested by measuring the influence of physostigmine on the EEG response to Δ-9-THC and on behavior in the rabbit (Jones et al., 1975). Δ-9-THC increased the mean cortical voltage output, an effect reversed by physostigmine. Furthermore, physostigmine restored the Δ-9-THC-induced disruption of hippocampal theta rhythm, and antagonized the behavioral effects produced by Δ-9-THC. In another study, Δ-9-THC and pentobarbital were shown to exert opposite effects on the activity of neurons in the post-arcuate cortex (Boyd et al., 1975). Pentobarbital depressed the activity, whereas Δ-9-THC augmented it. These data are consistent with the authors' previous suggestion that the marihuana-caused distortions in sensory perception are related to the effects of Δ-9-THC on the polysensory area of the cortex. Transmission at the neuromuscular junction is also affected by Δ-9-THC: Both frequency and amplitude of miniature end-plate potentials are increased, as is the duration of end-plate potentials; there is no effect on the resting membrane potential of muscle fibers (Hoekman et al., 1976). These findings suggest that the drug acts presynaptically in the manner of a local anesthetic. The work on Δ-9-THC's effects on nerve action potentials of single cells in Aplysia has shown that the drug causes a depression in nerve cell excitability, as measured by a reduction in the amplitude of action potentials and an increase in the lability of spike conduction (Acosta-Urquidi & Chase, 1975). These results are at variance with the previously published negative effects of Δ-9-THC on squid axons (Brady & Carbone, 1973), but they are in agreement with the effect on rabbit nonmyelinated peripheral nerve (Byck & Ritchie, 1973).

Among the numerous neurochemical studies which have been reported is an investigation of the role of the gamma-aminobutyric acid (GABA) system in rat cerebellum in relation to cannabinoid-induced catalepsy (Edery & Gottesfeld, 1975). It was determined that the GABA system was only affected by repeated drug administration; therefore, the motor impairment produced by the cannabinoids is not associated with changes in this transmitter system in the cerebellum. Other investigators studying the effect of Δ-9-THC on monoamine oxidase activity of rat tissues (Banerjee et al., 1975b) have found that in both acute and chronic treatment experiments the enzyme activity of whole brain and hypothalamus was markedly increased. Because of the effect on the hypothalamus, which is rich in adrenergic neurons, the authors hypothesize that these neurons may be an important site of action of Δ-9-THC. Such a conclusion, however, is not supported by another report of the failure of relatively large doses of Δ-9-THC to alter either rat brain concentrations of 5-HT, noradrenaline or dopamine, or the turnover of the latter two amines (Bracs et al., 1975). A peripheral interaction between Δ-9-THC and adrenergic neurons, nevertheless, may occur. Previous studies of the influence of cannabinoids on the uptake and release of norepinephrine by isolated tissues have been extended to a description of the mechanism of Δ-9-THC accumulation by tissues (Egan et al., 1976). In this work, the amount of Δ-9-THC accumulated by the vas deferens was not affected in vitro by desmethylimipramine but was affected by the pretreatment of the animal with 6-hydroxydopamine. These results suggest that the tissue uptake involves, at least in part, functionally competent adrenergic neurons, but that different mechanisms exist for the neuronal uptake of Δ-9-THC and norepinephrine.

The influence of subchronic and chronic exposure to marihuana smoke on some cerebral and cerebellar neurochemical parameters has been compared with earlier results obtained from the oral administration of the drug (Luthra et al., 1976). The report shows that there are changes in brain RNA and in acetylcholinesterase activity which coincide with behavioral changes and that some of the effects extended into the recovery period. In general, these results are similar to those previously noted with oral administration of the drug.

The effect of cannabinoids on the cholinergic system has been examined in another study (Friedman et al., 1976) in which both Δ-8- and Δ-9-THC were shown to inhibit acetylcholine synthesis in cortical, hypothalamic and striatal rat brain slices from animals pretreated with the drugs. The effect generally persisted after repeated daily drug administration (five days). CBD, on the other hand, did not affect acetylcholine synthesis. The mechanism of the depression produced by Δ-8- and Δ-9-THC was unrelated to either changes in choline acetyltransferase activity or the high-affinity uptake system for choline, but the effect was antagonized by K+. In contrast to an earlier report, these authors found that Δ-8- and Δ-9-THC did not change the acetylcholine content of the brain; therefore, they concluded that these cannabinoids depress the turnover of brain acetylcholine, which supports the proposal of various

investigators that the actions of Δ-9-THC are, in part, anticholinergic.

The effect of Δ-9-THC and 18 of its analogues on the high-affinity uptake of serotonin into synaptosomes was investigated (Johnson et al., 1976) and it was found that the cannabinoids in general inhibited the serotonin uptake, but that the activity varied with the different compounds. This action, however, was not restricted only to those drugs that produce typical marihuana-like effects. The authors concluded that the diverse pharmacological properties of the cannabinoids may be a manifestation of composite effects on many neurochemical systems, only one of which is the synaptic uptake of serotonin.

The continuing interest in the cardiovascular effects of the cannabinoids has yielded one study of dogs in which Δ-9-THC failed to produce bradycardia in conscious animals after repeated administration (twice daily for seven days) (Jandhyala et al., 1976); although the drug induced bradycardia in these animals under pentobarbital anesthesia. The investigators propose that so-caused bradycardia may be due to a Δ-9-THC antagonism of the inhibitory action of pentobarbital on central vagal centers. In another study, the influence of 28 days of pretreatment with Δ-9-THC (10 mg/kg i.p./day) on body weight, body temperature, spontaneous motor activity and cardiovascular responses in rats was measured (Adams et al., 1976a). Tolerance developed to the effects on body weight and temperature; however, the suppression of spontaneous motor activity persisted. With respect to the cardiovascular effects, tolerance developed to the hypotensive response and the bradycardia normally elicited by Δ-9-THC given intravenously to urethane-anesthetized rats. Nevertheless, tolerance did not develop to the transient pressor response to intravenous Δ-9-THC in these animals.

A study of the effects of cannabinoids on the isolated perfused rat heart indicated that Δ-8- and Δ-9-THC, CBD and CBN, in bath concentrations of 10-30 mcm, all depressed myocardial contractility (Smiley et al., 1976). Their effects on rate were variable: Δ-8-THC produced arrhythmias; Δ-9-THC and CBN caused tachycardia; CBD caused bradycardia, arrhythmias and asystole. The drugs accumulated in the heart; consequently, relatively high tissue concentrations were associated with the direct cardiac effects. The effects of chronic Δ-9-THC treatment on the blood pressure of metacorticoid and renal hypertensive rats have also been described (Varma & Goldbaum, 1975). Acutely, Δ-9-THC produced a significant decrease in systolic pressure and heart rate, whereas in chronically treated animals (1-2 mg/kg s.c./day for 3-5 weeks) tolerance developed to both of these effects.

Other studies of the effects of Δ-9-THC on the vascular system have also been reported. Blood flow to various areas of the brain was measured in conscious, unrestrained rats (Goldman et al., 1975). After Δ-9-THC (1 mg/kg i.v.), animals displayed cataleptoid behavior; blood flow during this response was reduced significantly to the dorsal hippocampus, hypothalamus, cerebellum and basal ganglia

but was unaffected to cortical areas. The authors suggest that the observed blood flow changes reflect changes in functional and, therefore, metabolic activity. Adams et al. (1976b) examined the relationship of the vasoconstrictor effect of cannabinoids to the peripheral sympathetic nervous system. Intravenously, Δ-8- and Δ-9-THC produce, in the urethane-anesthetized rat, a transient pressor response followed by a prolonged hypotension; but intra-arterially, the drugs produce vasoconstriction in perfused hindquarters. The pharmacological evidence presented suggests that this latter response may be mediated by a release of norepinephrine from adrenergic nerve terminals.

The past year has seen the appearance of another study on cannabis's respiratory effects. In anesthetized dogs, Δ-9-THC caused a marked decrease in ventilatory response to carbon dioxide (Moss & Friedman, 1976). Such a depression of respiratory function raises the question of a possible toxic consequence of the use of marihuana in combination with other respiratory depressants, such as ethanol.

Two reports have appeared on the antineoplastic activity of the cannabinoids. Δ-9- and Δ-8-THC and CBN, but not CBD, retard the growth of the Lewis lung adenocarcinoma in a dose-dependent fashion (Munson et al. , 1975). Δ-9-THC was ineffective against L1210 murine leukemia, but was effective against Friend leukemia. It should be noted that these tests involved the use of very high doses of the cannabinoids (e.g., 200 mg/kg). In another study the mechanism of the antitumor activity was investigated (White et al., 1976) and the drug was shown to inhibit growth in tissue-cultured Lewis lung adenocarcinoma cells and to decrease, in a dose-dependent manner, DNA synthesis in the cultured cells. The inhibition occurs at some point beyond the uptake of 3-H-thymidine.

Cur understanding of the analgesic property of the cannabinoids has been extended with the results of a structure-activity analysis by Wilson and May (1975). They evaluated the activity of a variety of cannabinoids, including Δ-8- and Δ-9-THC and some of their metabolites with the hot-plate test. Their findings establish the fact that the 11-hydroxy metabolites are many times more potent than the parent compounds, and imply that the metabolites are responsible for most, if not all, of the analgesic activity of Δ-8- and Δ-9-THC. The potency of the metabolites in this test is nearly equal to that of morphine. A mechanistic relationship to morphine may even exist because the cannabinoid-caused analgesia is antagonized by naloxone.

A relationship between the cannabinoids, morphine and naloxone was noted in the Fifth Marihuana and Health Report (1975). Δ-9-THC was shown to attenuate the naloxone-precipitated morphine abstinence syndrome. This property has now been confirmed in mice (Bhargava, 1976). Hine et al. (1975) have extended their original investigation of the effect to a study of the influence of CBD pretreatment on Δ-9-THC antagonism of the abstinence syndrome. CBD alone had little effect on the abstinence reactions, but it significantly increased the abstinence-attenuation properties of Δ-9-THC. The

effect of the cannabinoids on the abstinence syndrome may be selective for the opiates because Δ-9-THC has been shown to exacerbate abstinence reactions associated with withdrawal from ethanol (Kralik et al., 1976).

In another cannabinoid-drug interaction study, pretreatment of mice with either CBD or Δ-9-THC prolonged methaqualone-induced sleep time (Stone et al., 1976); the Δ-9-THC effect was significantly greater than that of CBD. Ether anesthesia is also prolonged by Δ-9-THC and to a more limited degree by CBN, but appears to be antagonized by CBD (Malor et al., 1975).

The cannabinoids have been linked to a diversity of other pharmacological effects, including antitussive activity (Gordon et al., 1976), antihistaminic activity (Turker et al., 1975), antibacterial activity (Van Klingeren & Ten Ham, 1976), and a reduction in platelet count (Levy & Livne, 1976) and in twitch tension of the isolated guinea pig ileum (Rosell & Agurell, 1975).

A variety of subcellular effects have been investigated in relation to the mechanisms of action of the cannabinoids. The psychoactive cannabinoids exert an effect on spin-labelled liposomes similar to that produced by subanesthetic doses of general anesthetics (Lawrence & Gill, 1975). The cannabinoids have also been shown to produce a transient decrease in the electrical resistance of black lipid membranes generated from lecithin but not from a negatively charged phospholipid membrane of phosphatidyl serine (Bach et al., 1976). Δ-9-THC in vitro causes a marked inhibition of monoamine oxidase activity (MAO) in porcine brain mitochondria (Schurr & Livne, 1976). Equal concentrations of CBD are inactive in this test system, although when a combination of the two cannabinoids was tested, CBD blocked the Δ-9-THC effect. The individual cannabinoids were ineffective against MAO activity in liver mitochondria. These differential effects illustrate at a biochemical level both drug and tissue selectivity of action. Δ-9-THC administered to rats both acutely and daily (10 mg/kg/day for 21 days) inhibited liver microsomal lipid peroxidation (Mitra et al., 1975). The effect was also obtained in vitro in control microsomes, as well as in carbon tetrachloride-induced microsomes. Δ-9-THC also elevates plasma concentrations of non-esterified fatty acids in the mouse (Malor et al., 1976). Unlike the response to epinephrine, the mobilization of fat by Δ-9-THC was not blocked by propranolol. Several cannabinoids were previously shown to inhibit prostaglandin synthesis in vitro, and this effect can also be caused by essential oil components of marihuana (Burstein et al., 1975).

During the past year, two books on marihuana were published. They both contain chapters specifically relevant to the pharmacology and toxicology of marihuana (Braude & Szara, 1976; Nahas et al., 1976).

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Chapter 4

PRECLINICAL EFFECTS: UNLEARNED BEHAVIOR

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The cannabinoids produce a variety of effects on unlearned behavior in different animal species. The voluminous literature pertaining to cannabis and unlearned behavior has been reviewed in the five previous Marihuana and Health Reports (1971 through 1975). The present chapter relies heavily on these previous reports for background and focuses primarily on the relevant literature which has appeared during the past two years, although a continuing attempt is made to consider the more recent literature in the context of previous findings. As in the 1975 Marihuana and Health Report, the present chapter is organized for expository purposes around four categories of unlearned behavior: gross behavior; activity and exploration; consummatory behavior; and aggressive behavior.

GROSS BEHAVIOR

The bulk of the early preclinical research with cannabinoids investigated the effects of these drugs on the gross behavior of a wide range of animal species. As has been discussed in previous Marihuana and Health Reports and recent reviews of the animal literature (Miller & Drew, 1974), a variety of gross behavioral changes are induced in animals by the cannabinoids. Included among these effects are: catalepsy, ataxia, tonic immobility, abnormal body postures, hypersensitivity and hyperactivity (e.g., Goldman et al., 1975; Maser et al., 1975). Subsequent to this earlier work on gross behavioral changes, much of the preclinical work with cannabinoids pertained to learned rather than unlearned behavior. Most recently, however, there has been a renewed interest in the gross behavioral changes induced in animals by cannabinoids. One primary reason for this has been the recognition that complex pharmacological interactions may occur among the cannabinoids.

The majority of cannabinoid research on unlearned behavior has used Δ-9-THC or Δ-8-THC since these particular cannabinoids have been established as the major active components of cannabis samples (Mechoulam, 1970). However, several researchers reported that the pharmacological activity of cannabis samples is not always entirely explained by the tetrahydrocannabinol content of the samples (Borgen et al., 1973b; Karniol & Carlini, 1972; Poddar & Ghosh, 1972). These reports have led to several suggestions: 1) that non-cannabinoid behaviorally active components occur in marihuana (Truitt et al., 1975); and 2) that interactions between THC and other cannabinoid constituents of cannabis -- namely cannabidiol (CBD), cannabinol (CBN), and cannabichromene (CBC) -- may be impor-

tant in animals as well as in humans (e.g., Dalton et al., 1976; Hollister & Gillespie, 1975). The latter suggestion is buttressed by previous findings that CBD inhibits the metabolism of Δ-9-THC (Fernandes et al., 1973; Jones & Pertwee, 1972; Kupfer et al., 1973).

Experiments dealing with interactions of cannabinoids on gross unlearned behavior are still few in number. Furthermore, those interactions which have been observed appear, at this time, to be complex and not always consistent. For example, in testing the effects of cannabinoids on catalepsy in rodents, investigators have found CBD or CBN administered alone to be either active (Karniol & Carlini, 1973; Takahashi & Karniol, 1975) or inactive (Fernandes et al., 1974). Savaki et al. (1975) suggest that the CBN/CBD ratio in cannabis samples can be an important determinant of cannabis induced catatonia. However, when administered in combination with Δ-9-THC, CBN has been reported either to have no effect on catalepsy (Fernandes et al., 1974) or to potentiate Δ-9-THC-induced catalepsy (Takahashi & Karniol, 1975). Furthermore, CBD in combination with Δ-9-THC has been reported to prolong (Fernandes et al., 1974) or to enhance (Karniol & Carlini, 1973) catalepsy induced by Δ-9-THC.

The interactions between the cannabinoids on drug-induced loss of the righting reflex (anesthesia, sleeping-time) seem to be particularly complex. For example, CBN antagonizes Δ-9-THC effects on pentobarbitone- (Krantz et al., 1971) and hexobarbitone- (Fernandes et al., 1973) induced loss of the righting reflex but potentiates Δ-9-THC-ether effects on the same unlearned response system in the same animal species (Malor et al., 1975). The complexity of these and other interactions (Chesher et al., 1975) will most likely be better understood with additional research. In particular, research to distinguish between drug interactions involving CNS activity and those involving cannabinoid-induced changes in tetrahydrocannabinol metabolism is needed.

As would be expected, THC interacts with drugs other than the cannabinoids to affect unlearned gross behavior. Recent experiments have shown that Δ-8-THC potentiates the loss of righting reflex induced in rats by alcohol (Friedman & Gershon, 1974) while Δ-9-THC potentiates some, and antagonizes other, amphetamine-induced postural and activity behaviors in rats (Gough & Olley, 1975) and rabbits (Consroe et al., 1975a). Alternatively, caffeine and methamphetamine reverse, whereas cocaine and apomorphine enhance, Δ-9-THC-induced sprawling behavior in rabbits (Laird et al., 1975). Physostigmine also antagonizes Δ-9-THC-induced alterations of postural and activity behaviors in rabbits (Jones et al., 1975).

A second major reason for the renewed interest in the effects of cannabinoids on unlearned behavior is the recent derivation of drugs from cannabinoids (e.g., Pars et al., 1976; Razdan et al.,

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[1]Chesher et al., 1974, 1975; Fernandes et al., 1973; Karniol & Carlini, 1973; Krantz et al., 1971; Malor et al., 1975; Takahashi & Karniol, 1975.

1976b) and tne need for a preclinical test to determine the activity of these derivatives. For example, Razdan et al. (1976a) found an ataxia test in dogs to be very useful for establishing marihuana-like activity of a novel analog of Δ-9-THC, namely (-)-8ß-hydroxy-methyl-Δ-9-tetrahydrocannabinol. Similarly, Martin et al. (1975) used an ataxia test in dogs to establish cannabinoid activity for 11-methyl-Δ-8-, 9-nor-Δ-8-, and 9-nor-Δ-9-THC.

It has been suggested that the 1 I-hydroxy metabolites of Δ-8- and Δ-9-THC largely account for the pharmacological activity of the Δ-8- and Δ-9-THC constituents of marihuana. The findings that 11-methyl-Δ-8-, 9-nor-Δ-8- and 9-nor-Δ-9-THC have marihuana-like activity (Ford & Balster, 1975; Martin et al., 1975) are relevant to this suggestion since these latter compounds are not 11-hydroxylated in vivo. Indeed, the findings suggest that the 11-hydroxy metabolites of Δ-8- and Δ-9-THC do not solely account for the activity of tetrahydrocannabiols.

ACTIVITY AND EXPLORATION

The literature reviewed in past Marihuana and Health Reports has supported the conclusion that cannabinoids generally suppress the spontaneous motor activity and exploration of animals, although findings regarding these effects must be qualified, as always, by drug route, time-effect and dose-response considerations. The suppression effect of Δ-9-THC on spontaneous motor activity is as apparent in recent experiments (e.g., Adams et al., 1976; Anderson et al., 1975; Fried, 1976; Pryor & Braude, 1975) as it was in earlier experiments (e.g., Drew et al., 1973; Fried & Nieman, 1973).

In one of these recent studies (Anderson et al., 1975), oral doses of Δ-9-THC ranging from 1.25 mg/kg to 40.0 mg/kg were administered acutely to mice. The lowest drug dose produced a significant increase in activity while the remaining drug doses produced a dose-dependent suppression of activity. Other mice were used to investigate tolerance to the suppressive effects of 40 mg/kg of Δ-9-THC (p.o.) on spontaneous activity. Complete tolerance developed after one dose and had a duration of less than four days.

Another aspect of this latter study (Anderson et al., 1975) deserves mention. Specifically, the activity of mice that had been previously habituated to the experimental apparatus was not suppressed by a 40 mg/kg dose of Δ-9-THC. This finding is in accord with other research (Consroe et al., 1975b; Drew & Miller, 1973) which shows that prior habituation to an experimental situation can alter the effects of THC on motor activity in animals. Further, Adams et al. (1976) found that tolerance failed to develop to the suppression of spontaneous motor activity produced by 10 mg/kg administered i.p. for 28 days to rats that had not been previously habituated to the apparatus used to measure activity. Alternatively, Fried (1976) obtained tolerance to cannabis smoke-induced decrements in activity after his rats had received 13 exposures to the cannabis smoke.

Interestingly, in the latter (Fried, 1976) experiment, when the cannabis-smoke tolerant rats were given an i.p. injection of 4 mg/kg Δ-9-THC, male rats significantly increased their activity whereas the females did not alter their activity relative to the last exposure to cannabis smoke. Importantly, cross-tolerance was demonstrated for activity effects between inhaled cannabis and i.p. injections of Δ-9-THC. In contrast to the above effects, rats that had previously been exposed only to placebo smoke significantly decreased their activity after receiving the i.p. injection of Δ-9-THC.

Several novel analogs of Δ-8- and Δ-9-THC have been shown to produce marihuana-like reductions in spontaneous motor activity in mice (Martin et al., 1975; Razdan et al., 1976a). Indeed, 11-methyl-Δ-8-THC is more effective, and 9-nor-Δ-8-THC is as effective, as Δ-8-THC in decreasing spontaneous motor activity in mice (Martin et al., 1975).

The spontaneous activity of rats has been used to study the drug interaction between Δ-9-THC and phencyclidine (Pryor & Braude, 1975). It was found that an increase in activity produced by 5 mg/kg intraperitoneal injections of phencyclidine was antagonized by oral doses of Δ-9-THC, ranging from 2.5 to 10.0 mg/kg, in a dose-related manner. The drug interactions between Δ-9-THC and other cannabinoids have not been studied using the spontaneous activity of animals as the referent response. However, exploratory behavior and performance on simple unlearned motor tasks have been subjected to the drug interactions of Δ-9-THC with other cannabinoids. Primarily, it has been reported that CBD and cannabichromene (CBC), in inhaled doses from 1-2 mg/kg, decrease exploratory behavior of rats in a dose-related manner (Rosenkrantz & Braude, 1975; Rosenkrantz et al., 1976) while CBN (10 mg/kg i.p. injection) significantly increased exploration-ambulation in rats (Takahashi & Karniol, 1975). However, CBD did not affect the motor coordination of mice over a wide range of i.p. doses (Ten Ham & DeJong, 1975). In combination with Δ-9-THC, both CBD (Karniol & Carlini, 1973) and CBN (Takahaski & Karniol, 1975) produce a pharmacological interaction on exploratory behavior in rats, although Δ-9-THC and CBD do not seem to interact to affect motor coordination in mice (Ten Ham & DeJong, 1975).

Cannabinoids are known to transfer the placental barrier (e.g., Borgen et al., 1973; Vardaris et al., 1976). Consequently, the existence of any effects on unlearned behaviors in offspring caused by placentally-transferred cannabis has been investigated. The data available to date are somewhat mixed on this topic. For example, Uyeno (1975) administered subcutaneous Δ-9-THC doses of 30, 60 and 120 mg/kg to pregnant rats on the fourth day of gestation. He found that Δ-9-THC produced an increase in abnormal pregnancies, but that it had no significant effect on the locomotor activity or on the maze learning of the offspring. These latter findings are at odds with two previous experiments (Borgen et al., 1973a; Gianutsos & Abbatiello, 1972). In the first of these, disruptive effects were observed on the unlearned behavior of

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offspring from pregnant rats that had been administered Δ-9-THC subcutaneously during the 10th-12th days of gestation. In the Gianutsos and Abbatiello (1972) experiment, female rats were injected subcutaneously with 250 mg of a cannabis resin extract during the 8th-11th days of gestation. The offspring of these cannabis-injected rats showed little evidence of stunting but did exhibit an impairment in maze learning. In a more recent experiment, Vardaris et al. (1976) orally administered pregnant rats 2 mg/kg/day of tritiated Δ-9-THC throughout pregnancy. No teratogenicity was observed nor was any consistent effect observed in the exploratory behavior of the rat pup offspring of the drugged mothers. However, the pups did show a deficit in learning a passive avoidance response at 21 days of age. This deficit apparently was transient since it was not evident when the pups were retested at 90 days of age.

It was suggested in the Fifth Marihuana and Health Report (1975) that "additional research is needed to determine whether Δ-9-THC has a direct action on the developing fetus which becomes manifest in the unlearned behavior of offspring." This same suggestion remains appropriate this year. The behavioral manifestations of cannabinoid action, in terms of unlearned gross responses and activity and exploration, are sufficiently well established now so as to be useful in investigating the as yet relatively unknown effects of cannabinoids.

CONSUMMATORY BEHAVIOR

A review of the previous Marihuana and Health Reports as well as other summaries of the relevant literature (e.g., Abel, 1975b) leaves little doubt that the vast majority of preclinical animal studies have demonstrated that Δ-8-THC, Δ-9-THC, hashish resin and pyrahexyl produce reductions in food and water intake, with a consequent loss in weight when administered acutely. Under continued administration of these cannabinoids, some tolerance to the drug-induced effects on consummatory behavior is usually observed, although there are clear cut exceptions where no tolerance has been observed (e.g., Sofia & Barry, 1974). At any rate, studies published this year using an oral or intraperitoneal route of administration in rats (e.g., Ferraro et al., 1976; Sofia & Knobloch, 1976) have generally supported the earlier findings of Δ-9-THC-induced decrements in food and water consumption.

The data pertaining to the effects of other cannabinoid constituents of marihuana such as CBN, CBD and CBC are quite mixed in comparison to the data for Δ-8- and Δ-9-THC. For example, inhaled doses of CBD and CBC have been shown both to decrease (Rosenkrantz & Braude, 1975) and to increase (Rosenkrantz et al., 1976) food and water consumption in a dose related manner. On the other hand, Fernandes et al. (1974) did not obtain any CBN or CBD produced effects on food and water consumption in the rat over a range of i.p. doses up to 80 mg/kg, although CBD -- but not CBN -- enhanced the suppressive effects on consummatory behavior produced by Δ-9-

THC. Beyond this, Sofia & Knobloch (1976) produced consistent decrements in food, sucrose, and water consumption in rats given 50 mg/kg i.p. doses of CBN and CBD or 2.5 and 5.0 mg/kg doses of Δ-9-THC. Quite interestingly in the Sofia and Knobloch (1976) experiment, sucrose intake was less affected by each cannabinoid than was food and water intake. These data indicate that the rats had a preference for sweet calories; a preference reported in humans following the use of cannabis.

Actually, the general finding of a cannabinoid-induced suppression of consummatory behavior stands in stark contrast to the findings that marihuana or hashish will increase the human appetite for food (Abel, 1971; Hollister, 1971; Greenberg et al., 1976). Several possible explanations have been offered to account for the discrepancy between the effects of cannabis on animal and human consummatory behavior (cf., Abel, 1975b). To briefly. summarize some of these here, Sofia and Barry (1974) have suggested that since pure Δ-9-THC has not typically been used with humans, the appetite-stimulant effect of marihuana might be due to a marihuana constituent other than THC. The recent findings regarding the effects on consummatory behavior of CBN, CBD and CBC reported above (e.g. , Rosenkrantz et al., 1976; Sofia & Knobloch, 1976) are sufficiently mixed to hold this suggestion in abeyance. It has also been suggested that, since most animal studies have not taken continuous measurements of consummatory behavior, increases in consumption may have been overlooked. However, in a recent experiment with rats where such continuous measures were taken (Ferraro et al., 1976), dose-related Δ-9-THC decreases in consummatory behavior were confirmed. There is some evidence (Glick & Milloy, 1972) to support the contention (Elsmore & Fletcher, 1972) that the discrepancy between animal and human consummatory behavior is due to the higher cannabinoid doses, relative to body weight, administered to animals than to humans. Furthermore, the possibility that the discrepancy is related to humans' adaptation to a long-term deprivation regimen (most experimental animals are either non-deprived or acutely deprived) has also received empirical support (Gluck & Ferraro, 1974). Finally, there is the suggestion that route of drug administration may play an important role in determining the direction of the drug effects on consummatory behavior in animals. At least three recent studies have shown that when cannabinoids are administered to animals by the inhalation route, increases in consummatory behavior result (Huy & Roy, 1976; Rosenkrantz & Braude, 1974; Rosenkrantz et al., 1976). Neverthelsss, the discrepancy between animal and human experiments is still inadequately explained. There is, of course, the possibility that the differences are due solely to between-species differences. If so, consummatory behavior will stand as a rare instance in which preclinical animal research with cannabinoids has not served reliably as a predictor of cannabinoid effects in humans.

If aggression is taken as a uniform behavior of threatening or attacking another animal, then conflicting findings regarding the effects of cannabinoids on aggressive behavior exist in the literature. However, a variety of procedures has been used to study the aggressive interactions between animals under the influence of cannabinoids, each of which tends to involve a different kind of aggressive behavior. In fact, when separated by aggression paradigms, the literature regarding cannabinoid effects on aggressive behavior is quite consistent. In general, the conclusion from both the recent Marihuana and Health Reports (1974, 1975) and an extensive review of the cannabis and aggression literature in animals (Abel, 1975a) is that cannabinoids suppress aggressiveness in non-stressed animals but increase stress-induced aggression. This conclusion applied to acute cannabinoid experiments but may not hold true for chronic experiments. At least three recent studies (Luthra et al., 1976; Matte, 1975; Miczek, 1976) have demonstrated an induction in aggression following long-term administration of THC to rats that were not apparently otherwise stressed. Of course, if long-term drug administration is viewed as being in itself stressful, then the conclusion that cannabinoids increase aggression in stressed animals becomes more general. Be that as it may, the effects of cannabinoids on aggressive behavior will be discussed under the categories of stress-induced and non-stress-induced aggression, with the latter category being subdivided into isolation-induced aggression, competitive aggression and predatory aggression.

AGGRESSIVE BEHAVIOR

As indicated, when stressed animals are put under the influence of cannabinoids the usual outcome is an increase in aggressiveness. This outcome seems to be independent of the nature of the stressor used. Increased aggression under cannabinoids has been reported for such stressors as: starvation (Carlini & Masur, 1970), low temperature (Carlini & Masur, 1969), REM sleep deprivation (Carlini & Lindsey, 1974; Carlini et al., 1976; Monti & Carlini, 1975), withdrawal from morphine (Carlini & Gonzalez, 1972), septal lesions (Dubinsky et al., 1973), electric shock (Carder & Olson, 1972) and ovariectomy (Palermo-Neto et al., 1975).

Takahashi and Karniol (1975) have investigated the interaction between CBN and Δ-9-THC with respect to stress-induced aggression. Generally, this experiment produced results comparable to a similar previous investigation of the interactive effects of CBD and Δ-9-THC on aggression induced by REM sleep deprivation (Karniol & Carlini, 1973). Intraperitoneal injections of 20 mg/kg Δ-9-THC and 80 mg/kg CBN induced aggressiveness in the stressed rats. Interestingly, however, when the same doses of CBN and Δ-9-THC were concurrently administered, the amount of aggressiveness was less than that produced by Δ-9-THC alone (Takahashi & Karniol, 1975).

Isolation-Induced Aggression

Several experiments have shown that Δ-9-THC and cannabis extract will suppress isolation-induced aggression in rats which have not also been subjected to stress (Dubinsky et al., 1973; Santos et al., 1966). Other studies have shown that this cannabinoid-induced suppression of aggression is not a result of motor impairment (Kilbey, 1971) nor does it exhibit tolerance (Ten Ham & van Noordwijk, 1973).

The interaction between Δ-9-THC and CBD on isolation-induced aggression was investigated last year in mice (Ten Ham & DeJong, 1975). Intraperitoneal doses of 2.5 mg/kg Δ-9-THC and 40.0 mg/kg CBD individually suppressed aggressiveness although the interaction between these two cannabinoids was not significant.

Competitive Aggression

Most recent findings are in accord with previous results (Jones et al., 1974; Miczek & Barry, 1974; Uyeno, 1973, 1974) showing that Δ-9-THC reduced dominance and social competition in animals. Cutler and her associates have run a series of experiments relating cannabinoids to the social behavior of animals (Cutler & Mackintosh, 1975; Cutler et al., 1975a, 1975b, 1975c). In two of these experiments (Cutler & Mackintosh, 1975; Cutler et al., 1975c) male mice and rats received i.p. injections of either a cannabis resin or Δ-9-THC and then were placed with unfamiliar and undrugged male partners. The drug did not affect non-social behavior or social investigaton but it did produce dose-related increases in immobility and flight relative to aggression. A similar finding was recently obtained by Dorr and Steinberg (1976). Cutler et al. (1975b) further found that drugged male mice placed with unfamiliar and undrugged female partners reduced the number of mounts and attempts to mount the female and also exhibited a concomitant increase in immobility.

Ely et al. (1975) demonstrated the importance of the existing social structure in their examinations of cannabinoid effects on animal aggression. Doses of 0.5, 2.0 and 20.0 mg/kg of Δ-9-THC were intravenously injected into mice whose dominant or subordinate status in their colonies was either relatively stable or whose dominance was threatened either by a rival or an intruder. In the stable colonies the only behavioral change noted was a limited period of reduced activity by the dominant males. Dominant mice confronted with a rival exhibited a reduction of activity and a consequent loss of their daninant status. Dominant mice confronted with an intruder made fewer attacks on the intruder than non-drugged dominant mice, but their aggressiveness returned to the predrug baseline level after 24 hours.

Dose effects of Δ-9-THC on aggressive behaviors of resident and intruder rats were examined by Miczek (1976). This investigator varied i.p. dose level from 0.125 to 4.0 mg/kg and found that as the

dose was increased, attack and threat behaviors of the dominant resident rat decreased. Only at the highest dose level of 4.0 mg/kg did Δ-9-THC interfere with the defensive and submissive behaviors of the intruder.

Cutler et al. (1975a) fed cannabis in the diet of either dominant or subordinate male mice. Dominant males reduced non-social activity and increased flight behavior while subordinate males were not markedly affected by the cannabis diet. After withdrawal of cannabis, the dominant males showed an increase in aggressiveness.

A long-term increase in aggressiveness in social situations has also been observed by Sassenrath and Chapman (1975, 1976). These researchers drugged monkeys living in group situations with oral doses of 2.4 mg/kg/day of Δ-9-THC. Initially under the influence of the drug, daninant monkeys displayed less aggression and less non-social behavior. Subsequently, a tolerance to the suppressive effects of Δ-9-THC developed and an increase in aggressiveness was observed. This later increase in aggressiveness was sometimes accompanied by an increase in dominance ranking within the group.

Predatory Aggression

Most research supports the conclusion that cannabinoids reduce predatory aggression in non-stressed animals (Abel, 1975a). Although one study (Alves & Carlini, 1973) indicated that THC could produce muricidal behavior in rats which did not previously display such behavior, it was not possible to conclusively determine whether stress induced by food deprivation or the administration of the cannabinoid over a 40-day period was responsible for this result. However, a recent study by Miczek (1976) indicates that the long-term administration period may have been the crucial factor. This investigator found that during an administration period of 60 days, previously non-muricidal rats given sufficient food and water so as not to lose weight and an intraperitoneal Δ-9-THC dose of 10 or 20 mg/kg/day developed mouse-killing behavior.

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Chapter 5

PRECLINICAL EFFECTS: LEARNED BEHAVIOR

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A review of the previous Marihuana and Health Reports (1971-1975) reveals that an extensive array of experimental procedures and contexts have been used to study the effects of cannabinoids on the performance of learned behavior in animals. These preclinical behavioral experiments have provided a framework for, and guided the design of, subsequent human experimentation. Compared to previous years, only a few experiments pertaining to cannabinoids and learned behavior have appeared during the past two years. By and large these more recent experiments confirm previous findings; no particularly novel procedures have been explored nor have there been dramatically unpredictable results. In part, the decrease in activity in cannabinoid preclinical animal research on learned behavior indicates an increase in human cannabinoid-learning investigations.

Several detailed taxonomies of learned behavior are possible. However, for the purposes of the present report, learned behaviors will be categorized into those involving: avoidance learning and aversive control; reinforcement schedules and maze learning; and discrimination learning.

AVOIDANCE LEARNING AND AVERSIVE CONTROL

Previous research has shown that cannabinoids can enhance, depress, or fail to affect the acquisition of avoidance behavior depending upon the cannabinoid time-course of action (Miller & Drew, 1974) and dose (Goldberg et al., 1973) as well as on the particular cannabinoid (Izquierdo and Nasselo, 1973) and type of avoidance task used (Robichaud et al., 1973). More recent research has tended to confirm the previous findings by demonstrating further that the effects of cannabinoids, particularly Δ-9-THC, on avoidance acquisition are dependent upon drug and task parameters. For example, Weisz and Vardaris (1976) obtained no effect on shuttle box avoidance acquisition in rats by administering oral Δ-9-THC doses of 2, 4, or 6 mg/kg. On the other hand, Waser et al. (1976) produced an increase in avoidance learning in a Y maze by injecting rats i.p. with 3 and 9 mg/kg Δ-9-THC, and Pandina and Musty (1975) increased rats' acquisition of a 2-way active avoidance task by giving i.v. injections of 0.75, 1.5, and 3.0 mg/kg of Δ-9-THC.

In contrast to the variable outcomes obtained when the acquisition of avoidance learning is studied, cannabinoids have been found to have consistent disruptive effects when the behavior investigated

is the maintained performance of an already learned avoidance task (Davis et al., 1973; Houser, 1975; Newman et al., 1974). Additional reports of cannabinoid-induced impairment of established avoidance behavior have cane from Tayal et al. (1974) and Pryor and Braude (1975). In the latter study, it was further reported that Δ-9-THC had a more than additive interaction with phencyclidine, over a wide range of doses for both drugs, in impairing conditioned avoidance behavior. The Tayal et al. (1974) experiment also found that tolerance develops to the disruption in avoidance performance induced by an alcoholic extract of cannabis. This finding of tolerance confirms and extends previous reports of cannabinoid tolerance development under learned avoidance tasks (Houser, 1975; Manning, 1974b). No new research has appeared to add to the finding (Newman et al., 1974) that Δ-9-THC is cross-tolerant with ethyl alcohol but not with morphine or chlorpromazine in a shuttle box avoidance task. However, Δ-9-THC does exhibit cross tolerance to a reserpine congener in a swimming escape task (Carder & Deikel, 1976).

With respect to aversive control situations other than avoidance or escape learning, Δ-9-THC does not seem to affect the suppressive effect produced on licking behavior in the rat by electric shock punishment (Schoenfeld, 1976). There have been several reports that cannabinoids reduce the conditioned emotional response of animals to a stimulus previously associated with an unavoidable electric shock, regardless of whether an appetitive or aversive situation is used to maintain baseline responding (e.g., Gonzalez et al., 1972; Houser, 1975). The usual interpretation of this finding is that cannabinoids act to reduce fear or anxiety. However, a fear-reduction interpretation is not always supported by human research (Pillard et al., 1974). Moreover, it has been shown (Ferraro & Bruce, 1975) that a reduction in the conditioned emotional response under Δ-9-THC can be, in part, confounded by drug-state changes which occur between the training and testing phase of experiments. Indeed, when the conditioned emotional responses of rats who had received all of their training and testing under 2 mg/kg Δ-9-THC (i.p.) was studied, it was found that Δ-9-THC produced an increase in the conditioned emotional response (Ferraro & Bruce, 1975). This latter finding suggests that Δ-9-THC does not reduce fear. A similar interpretation can be provided for the finding that hashish resin can increase the resistance to extinction of rats in a shock avoidance situation (Jaffe & Baum, 1971).

Another factor which may be considered to temper the interpretation that cannabinoids reduce fear in aversive control situations is that Δ-9-THC has been found to have an analgesic effect in animals (Kaymakcalan et al., 1974) and humans (Noyes et al., 1975a, 1975b). This was demonstrated by Dykstra and McMillan (1974) who used a titration procedure to determine the intensity at which monkeys would maintain a continuously applied electric shock. It was found that an injection of 15 mg/kg Δ-8-THC caused the monkeys to adjust the shock to a higher intensity than they had in the absence of the drug.

With respect to cannabinoids other than Δ-9-THC, CBN has been found

to increase the reaction time of mice in a hot-plate test (Takahashi & Karniol, 1975) and to raise the pain threshold of the inflamed hind paw of the rat (Sofia et al., 1975). Furthermore, CBN produces additive effects with Δ-9-THC in suppressing the abdominal constriction response of mice to formic acid (Welburn et al., 1976). However, CBN appears to be devoid of antitussive activity in anesthetized cats (Gordon et al., 1976). More generally, it has been concluded the CBN has non-narcotic type analgesic activity like that of aspirin, while Δ-9-THC has narcotic-like analgesic activity similar to morphine or codeine (Cordon et al., 1976; Sofia et al., 1975). In contrast, CBD does not appear to display any analgesic, antitussive, or abdominal constriction effects (Gordon et al., 1976; Sofia et al., 1975; Welburn et al., 1976), although CBD does antagonize the antinociceptive effects of both Δ-9-THC and CBN in a dose-dependent manner (Welburn et al., 1976).

In still another aversive control context, Corcoran et al. (1974) have extended previous findings that Δ-9-THC (Elsmore & Fletcher, 1972) and hashish extract (Corcoran, 1973) produce "bait shyness" in rats when paired with novel tastes. In the Corcoran et al. (1974) study, Δ-8-THC, CBD, and cannabigerol (CBS) all produced bait shyness. However, cannabichromene (CBC) did not produce a conditioned taste aversion in this aversive control situation. More recently, Kay (1975) has extended the finding of "bait shyness" to situations involving repeated injections of Δ-9-THC.

REINFORCEMENT SCHEDULES AND MAZE LEARNING

Both operant and instrumental conditioning paradigms have been used to study the effects of cannabinoids on appetitively reinforced learned behavior in animals. In the operant conditioning context, schedules of reinforcement have received the most study. In the instrumental conditioning context, maze or alley learning has been the usual baseline for determining cannabinoid effects.

Following the outline established in the Fourth and Fifth Marihuana and Health Reports, experiments dealing with cannabinoid-reinforcement schedule interactions will be categorized into two major types: Type I experiments which focus on changes in schedule controlled responses, and Type II experiments in which responses merely provide a baseline for the study of drug-related parameters.

The bulk of the earlier cannabinoid research with reinforcement schedules was of Type I. What little research of this type there has been in the past few years (Davis et al., 1973; Frankenheim, 1974; Wagner et al., 1973) has mainly tended to replicate and confirm the findings from the earlier research even where more canplicated reinforcement schedules have been used (Adams & Barratt, 1974). Taken together, the research demonstrates that behavior under reinforcement schedule control is reactive to Δ-9-THC and Δ-8-THC as well as to other constituents of cannabis (Davis & Borgen, 1974; Frankenheim et al., 1971). In general, such

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behavior is depressed in a dose-related manner by cannabinoids, although under schedules which tend to generate low response rates, a bi-phasic dose-response function or an alternation between periods of no responding and increased rates of responding are sometimes observed (e.g., Boyd et al., 1976). Recently, Type I experiments with schedules of reinforcement have been shown to be useful in preclinical marihuana studies in humans (Mendelson et al., 1976).

Although only limited attention has been given to the effects of cannabinoids on the acquisition and extinction of operant behaviors (Ferraro et al., 1974a; Drewnowski & Gray, 1975), the now extensive literature on the relationship between cannabinoids and performance of schedule controlled responses has stimulated the use of such responses as baselines in Type II studies of drug-related parameters.

Among other things, reinforcement schedule baselines have been used in the past two years to study: between-cannabinoid comparisons (Kosersky et al., 1974); the effects of inter-injection interval on the development of tolerance to Δ-9-THC (Davis & Borgen, 1975); cross tolerance between cannabinoids and other drugs (Newman et al., 1974); and differences between drug vehicles and routes of cannabinoid administration (Abel et al., 1974; Elsmore & Manning, 1974; Ferraro & Gluck, 1974). An operant paradigm has also been used to investigate the interaction between Δ-9-THC and cannabidiol. Davis and Borgen (1974) found that intraperitoneal injections of 3 mg/kg Δ-9-THC suppressed schedule controlled responding in rats while 25 mg/kg CBD did not. Similarly, intramuscular injections of 1 mg/kg Δ-9-THC suppressed responding in pigeons while 50 mg/kg CBD did not. However, when animals were pretreated with their respective CBD doses, the THC-induced suppression of responding was reduced.

A further instance of the Type II reinforcement schedule experiment was performed by Dykstra et al. (1975). These researchers injected pigeons responding under variable interval, fixed ratio and fixed interval schedules with a range of Δ-9-THC and SP-III doses (0.3 to 18.0 mg/kg intramuscular injection administered either one or two hours before the start of the experimental session). SP-III is a water soluble ester of Δ-9-THC which bears a basic amino function (Zitko et al., 1972). Both drugs produced a dose-related suppression of reinforcement schedule responding although Δ-9-THC was three to six times more potent than SP-III and had a faster time of onset. A still more recent study (Ford et al., 1976) has investigated the effects of acute and chronic i.p. injections of 0.1 to 10.0 mg/kg Δ-9-THC and its 11-OH metabolite on rats responding under fixed interval and differential reinforcement of low rate schedules of reinforcement. 11-OH-Δ-9-THC was about three times as potent as Δ-9-THC and had a faster time of onset and a shorter duration of effects than Δ-9-THC. However, tolerance and cross-tolerance developed at the same rate to equipotent doses of the two drugs. Ford et al. (1976) viewed their results as being consistent with the hypothesis that 11-OH-Δ-9-THC is responsible for the behavioral effects of Δ-9-THC.

A large number of both types of reinforcement schedule experiments have investigated the development of tolerance under the cannabinoids. These experiments have uniformly shown that tolerance readily develops in animals to cannabinoid-induced suppressant effects on operant responding. However, two studies have shown that, in this situation, tolerance development to Δ-9-THC is due to the animals responding under the influence of the drug rather than to the mere exposure of the animals to Δ-9-THC (Bruce & Ferraro, 1975; Manning, 1974a). Moreover, Frankenheim (1974) observed that repeated i.p. injections of Δ-8-THC (13.0 and 17.8 mg/kg) tended to increase the sensitivity of rats to a response rate-increasing effect of the drug under a differential reinforcement of low rate schedule of reinforcement. This increased sensitivity was likened by Frankenheim (1974) to the reverse tolerance sometimes reported for marihuana effects in humans.

Compared to operant reinforcement schedule research, the effects of cannabinoids on the acquisition and performance of instrumental maze or alley-way responding have not received extensive study. Based on previously published literature, it may be concluded that the cannabinoids impair reinforced and latent learning in a variety of instrumental conditioning situations including the Y maze, Lashley III maze and straight alley.[2]

The straight alley has also been used to investigate the influence of i.p. injections of 0.5 mg/kg of Δ-9-THC on partial reinforcement effects in rats (Drewnowski & Gray, 1975). Both the partial reinforcement acquisition effect (i.e., the higher running speed reached by animals trained on partial reinforcement as compared to continuous reinforcement) and the partial reinforcement extinction effect (i.e., the greater resistance to extinction of animals trained on partial reinforcement) were abolished by Δ-9-THC. These data suggest that cannabinoids may have antifrustrational properties (Drewnowski & Gray, 1975).

Residual learning deficits in a Hebb-Williams maze were investigated in rats following chronic exposure to cannabis extract by Fehr et al. (1976). Initially, these investigators established that an oral dose of 10 mg/kg of THC acutely impaired maze learning. Following a chronic dose regimen in which the same dose was administered for up to three months, no residual learning impairment was found after a 25-day drug-free period. However, significant residual impairment of maze learning was produced two months or more after a six-month period of daily oral administration of 20 mg/kg THC.

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[1]Abel et al., 1974; Adams & Barratt, 1974; Davis & Borgen, 1975; Ford et al., 1976; Frankenheim, 1974; Kosersky et al., 1974; Manning, 1974a; Newman et al., 1974.

[2]Drew et al., 1973; Jarbe & Henriksson, 1973; Miller & Drew, 1973; Miller et al., 1973; Uyeno, 1973.

DISCRIMINATION LEARNING

The effects of cannabinoids on discrimination learning may be conveniently discussed under two subtopics: 1) the effects of cannabinoids on the performance of discriminations based on exteroceptive stimuli, and 2) the acquisition of stimulus control of behavior based on the presence or absence of cannabinoids. Since only a few recent experiments describing the effects of cannabinoids on discrimination learning with extercoeptive stimuli have been published, this subtopic will be treated only briefly.

In general, the effects of cannabinoids on established stimulus discriminations are influenced by the same variables as determine the effects of other psychotropic drugs on discrimination performance. More specifically, disruption of discrimination performance by cannabinoids is more likely if the discrimination is complex rather than simple and if the discrimination is successive rather than simultaneous. The typical cannabinoid-induced disruption of discrimination performance is the result of dose-related decreases in responses to the stimulus associated with reinforcement and corresponding increases in responses to the stimulus associated with non-reinforcement (cf., Marihuana and Health, 1974). Quite recently, Miller and Deets (1976) have shown that Δ-9-THC can enhance the discriminative ability of rhesus monkeys in a social learning context. Alternatively, Adams and Barratt (1976) have shown that a low dose of orally administered marihuana extract will impair color and form discriminations in monkeys, and that no tolerance develops to the accuracy impairment effects of the drug although response time impairments do exhibit tolerance. Lewis et al. (1976) reported that altitudes of 8,000 and 12,000 feet do not potentiate the effects of Δ-9-THC, based on the accuracy of a complex discrimination, but do markedly reduce response speeds under the influence of the drug as compared to drugged performance at ground level. Apparently, some behavioral impairments produced by marihuana can be potentiated by hypoxia.

In a similar context -- and in accord with the effects of most psychotropic drugs -- during generalization testing, Δ-9-THC usually reduces total response output but does not typically alter the slope of the generalization gradient. An exception to this was reported by Weisz and Vardaris (1975) who investigated auditory generalization in rats performing under a shuttle box avoidance task. It was found that oral doses of 4 and 6 mg/kg Δ-9-THC affected the slope of the auditory generalization gradient which was obtained in extinction.

Research prior to 1975 established that animals can learn to discriminate between the presence of cannabinoids and a vehicle control solution.[1] Still more recent research has served to confirm

[1]Barry & Kubena, 1972; Ferraro et al., 1974b; Henriksson & Jarbe, 1972; Jarbe & Henriksson, 1973c, 1974; Kubena & Barry, 1972.

and to extend this earlier work.[1] Jarbe et al. (1975) used an experimental procedure which is prototypic of research on this topic. Gerbils trained in a T maze were required to make discriminative choices based on whether Δ-9-THC or drug vehicle alone had been injected prior to the training session. As is the usual outcome in cannabinoid stimlus studies of this sort, it was found that the Δ-9-THC discrimination was acquired in a dose-related manner (from 0.5 to 16.0 mg/kg, i.p.). Furthermore, decreasing the dose or increasing the injection-test interval from that used in training led to a decrease in Δ-9-THC associated choices. One unique aspect of this study is that pentobarbital (20 mg/kg) interacted in a more than additive fashion with Δ-9-THC to determine drug versus control solution choice responses.

The Δ-9-THC discrimination paradigm has been used to compare the potency of different routes of drug administration (Barry & Krimmer, 1975, 1976; Jarbe & Henriksson, 1974). As compared to intraperitoneal administration, Δ-9-THC administered orally or by inhalation has stronger stimulus properties while lesser stimulus properties are manifest after intravenous administration of Δ-9-THC.

Although sane quantitative differences exist, it now appears that the stimulus properties of Δ-9-THC are interchangeable with Δ-8-THC, cannabis extract and hashish smoke (Barry & Krimmer, 1975; Jarbe & Henriksson, 1974) as well as with the metabolites 11-OH-Δ-8- and 11-OH-Δ-9-THC (Barry & Krimmer, 1976; Ford & Balster, 1975) and with the analog 9-nor-9ß-OH-hexahydrocannabinol. On the other hand, CBN and CBD do not seem to produce THC-like stimulus properties (Barry & Kubena, 1972; Henriksson et al., 1975; Jarbe & Henriksson, 1974), although Bueno et al. (1976) recently reported that CBN -- but not CBD -- induces Δ-9-THC-like responses in a drug discriminative stimulus-generalization test. Further, a wide range of drugs fran several pharmacological classes have been shown not to be interchangeable, in terms of stimulus properties, with Δ-9-THC (e.g., Greenberg et al., 1975). Thus, there is support for a hypothesis that the active cannabinoids may have a unique mode of pharmacological action.

One final aspect of the cannabinoid-stimulus discrimination paradigm merits further study: whether or not tolerance develops to the drug-stimulus properties of Δ-9-THC. There have been four studies which address this concern. One study supports the development of tolerance (Hirschhorn & Rosencrans, 1974), another provides indirect evidence supporting tolerance development (Jarbe & Henriksson, 1973b), while the other two provide data indirectly supporting a lack of tolerance development (Bueno & Carlini, 1972; Bueno et al., 1976). Until additional experiments are performed, one can tenta-

[1]Barry & Krimmer, 1975, 1976; Bueno et al., 1976; Ford & Balster, 1975; Greenberg et al., 1975; Henriksson et al., 1975; Jarbe et al., 1975, 1976.

tively conclude that a slow, and perhaps partial, tolerance develops to the stimulus properties of Δ-9-THC.

State-dependent learning refers to the phenanenon that animals perform better if trained and tested under the influence of a drug than if a drug-state change occurs between the training and testing phases of an experiment. State-dependent learning has been shown for Δ-8-THC and Δ-9-THC (e.g., Waser et al., 1976). However, it is not clear from the THC literature whether or not symmetric disruptive effects are obtained between a change from a drugged to a non-drugged state (D-ND) and a change from a non-drugged to a drugged state (ND-D). Both symmetric and asymmetric state-dependent effects have been reported for THC (Henriksson & Jarbe, 1971). In the case of asymmetric effects, a change from the D to ND state produces greater impairment of responding than does a change from the ND to D state (Goldberg et al., 1973). Johansson et al. (1974) have shown that Δ-8-THC will reliably induce asymmetric state dependency of this latter type if animals are first made tolerant to the acute disruptive effects of the drug.

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Chapter 6

PRECLINICAL CHRONIC EFFECTS: UNLEARNED AND LEARNED BEHAVIOR

Douglas Peter Ferraro, Ph.D.

Whether or not tolerance develops to cannabinoid-induced effects on unlearned and learned behavior cannot be answered unequivocally. In certain response systems, tolerance clearly develops and is characterized by its rapid development and extended length. Indeed, in the past few years tolerance has been demonstrated for both unlearned and learned responses in a range of animal species under a variety of drug conditions in studies examining: unlearned motor responses in rats (Barnes & Fried, 1974); spontaneous activity in rats and mice (Anderson et al., 1975; Fried, 1976); conditioned avoidance performance in rodents and monkeys (Houser, 1975; Manning, 1976; Waser et al., 1976); dominance status in monkeys (Sassenrath & Chapman, 1975); analgesia in dogs (Kaymakcalan et al., 1974); discrimination performance in monkeys (Adams & Barratt, 1976); and reinforcement schedule performance in pigeons, monkeys and rats.

In addition to demonstrations that tolerance to the cannabinoids can develop in unlearned and learned behavioral situations, several experiments have elucidated some of the determinants -- both pharmacological and extrapharmacological -- of cannabinoid tolerance development. These latter experiments encanpass a wide variety of situations and parameters and, in some instances, suggest constraints on the generality or pervasiveness of tolerance. The studies described below are representative of these experiments.

Abel et al. (1974) have shown that tolerance to the effects of Δ-9-THC on reinforcement schedule responding develops in pigeons at about the same rate after intramuscular, intravenous or peroral administration. Cross-tolerance between inhaled cannabis and intraperitoneal injections of Δ-9-THC was obtained for the spontaneous motor activity of rats by Fried (1976). Tolerance to the depressant effects of Δ-9-THC on reinforcement schedule performance was directly related to the number of administrations of the drug, but was inversely related to the tneatment interval, i.e., the amount of time separating successive drug administration (Davis & Borgen, 1975). Tolerance follows a similar course for Δ-9-THC and its metabolite 11-OH-Δ-9-THC (Kosersky et al., 1974). Additionally, Fernandes et al. (1974) have suggested that CBD interacts with THC to enhance the tolerance development to THC.

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[1]Adams & Barratt, 1974; Bruce & Ferraro, 1975; Davis & Borgen, 1975; Frankenheim, 1974.

Barnes and Fried (1974) have shown that the age of the subject at the time of first exposure to Δ-9-THC is a factor in later tolerance development. Rats who first received Δ-9-THC when immature developed tolerance more rapidly as adults than did rats who were adults when first drugged.

Rate of tolerance appears to depend as well on: the amount of prior training on a learning task (Olson & Carder, 1974); and the type (Adams & Barratt, 1976; Bueno et al., 1976; Newman et al., 1974), parameter values (Ferraro et al., 1374; Houser, 1975; Manning, 1976) and canplexity of the learned task (Ferraro & Grilly, 1973a; Snyder et al., 1975). In general, as the amount of prior training is decreased and the difficulty of the learned task is increased, tolerance develops more slowly or does not develop at all. Another behavioral variable that seems to determine the rate of tolerance development is the behavioral consequences produced by Δ-9-THC (Ferraro, 1972; Manning, 1974b). For example, in one recent experiment (Manning, 1976), tolerance developed to Δ-9-THC much more rapidly if Δ-9-THC acted to increase the number of shocks received by rats working under a conditioned avoidance task. In this same learning context, it appears that the development of Δ-9-THC tolerance in appetitive reinforcement situations is facilitated if animals are given the opportunity to respond under the influence of the drug rather than merely exposing them to the drug. This latter finding has been reported for rats (Carder & Olson, 1973), pigeons (Bruce & Ferraro, 1975), monkeys (Manning, 1974a) and chimpanzees (Ferraro & Grilly, 1974).

On the basis of findings such as those above, Ferraro (1976) has followed the lead of others (Elsmore, 1972; Harris et al., 1972) in proposing a behavioral model of marihuana tolerance. The essence of this position is that learning or drug-behavior interactions account, in part, for sane of the characteristics of tolerance development to Δ-9-THC. The pharmacological mechanism underlying tolerance development to the cannabinoids is not definitively known (cf., McMillan et al., 1971). However, there is evidence suggesting that the development of tolerance to Δ-9-THC may proceed by more than one pharmacodynamic mechanism of action. For example, Anderson et al. (1975) found that both the time of onset and the duration of tolerance to Δ-9-THC differed in mice with respect to drug effects on intestinal motility, temperature and locomotor activity. As these researchers concluded, it seems unlikely that any one mechanism, such as metabolic tolerance, could account for the obtained differences in tolerance development over so wide a range of response systems. However, Davis and Borgen (1975) have obtained data which suggest a metabolic mechanism of tolerance development. Still other experimenters (Dewey et al., 1973; McMillan et al., 1973; Martin et al., 1976) have argued that Δ-9-THC tolerance is not solely metabolic or drug distributional. Another recent hypothesis regarding toleranoe development to Δ-9-THC-produced behavioral effects has been offered by Deikel and Carder (1976). These workers suggest that stress augments tolerance development in such a way that the rate and extent of tolerance development to Δ-9-THC is directly related to the amount of stress

present in the drug situation. Obviously , additional research is still necessary in order to specify definitively just what pharmacodynamic and learning factors are important in determining the development of tolerance to marihuana.

Admittedly, it is not possible to make direct comparisons among different cannabinoid tolerance experiments since they often differ in non-systematic ways with respect to such variables as number, level and distribution of drug doses, behavioral task and species of subject. Nevertheless, it must be noted that the literature contains a fair number of experiments where a lack of tolerance development to the cannabinoids has been reported. This has been found for rodents and monkeys in a wide variety of situations such as: open-field behavior (Sjoden et al., 1973); isolation-induced aggression (Dubinsky et al 1973); food and water consumption (Gluck & Ferraro, 1974; Sofia & Barry, 1974); free-operant shook avoidance (Manning, 1976); performance under a schedule of positive reinforcement (Snyder et al., 1975); and discrimination learning based on exteroceptive (Adams & Barratt, 1976; Fetterolf & Ferraro, 1975) or drug-produced stimuli (Bueno et al., 1976). By contrast, Frankenheim (1974) has reported that repeated injections of Δ-8-THC produce an increased sensitivity to some of the effects produced by this drug on reinforcement schedule-controlled responding in rats. This increased sensitivity was likened by the investigator to a reverse tolerance effect.

With respect to other chronic effects of the cannabinoids, two experiments have failed to find any residual effects on learned behavior following discontinuance of Δ-9-THC previously administered for 150 consecutive days (Ferraro & Grilly, 1974) or aperiodically for seven months (Ferraro & Grilly, 1973b). More recently, residual learning deficits have been reported in rats after heavy exposure to a cannabis extract. Fehr et al. (1976) observed a significant residual impairment of maze learning two months following a six month long drug regimen in which rats were administered a THC oral dose of 20 mg/kg daily. In the context of behavioral teratogenesis (Coyle et al., 1976), a learning deficit has been reported in the offspring of rats whose mothers were orally administered 2 mg/kg/day of tritiated Δ-9-THC throughout pregnancy (Vardaris et al., 1976). The learning deficit was in the acquisition of an avoidance response and occurred when the offspring were 21 days of age, but not 90 days of age. More permanent effects were observed in a competitive-aggression situation where it was found that rats whose mothers had received the drug were more aggressive than control rats across the 90-day testing period. Further, with respect to aggressiveness, Luthra et al. (1976) found a return to normal aggressiveness in rats following cessation of treatment with marihuana smoke under a chronic drug treatment of up to 87 days at inhaled Δ-9-THC doses of 4 mg/kg. In contrast, post-Δ-9-THC treatment increases in aggressiveness have been observed in mice (Cutler et al., 1975) and in monkeys (Sassenrath & Chapman, 1975), although no other behavioral manifestations of abstinence from the drug were apparent in these experiments.

With the exception of two experiments (Deneau & Kaymakcalan, 1971; Pickens et al., 1972), animals have not been observed to self-administer cannabinoids. More specifically, monkeys do not self-administer Δ-9-THC after receiving the drug for a month or when offered it as a substitute for cocaine (Harris et al., 1974). Rats forced to drink cannabis extract or hashish suspensions for long periods of time (up to 126 days) reject the drug in favor of a control solution (Corcoran & Amit, 1974; Leite & Carlini, 1974). Finally, mice are reluctant to consume food pellets containing Δ-9-THC even after subsisting on the pellets for over two months (Maker et al., 1974; Cutler et al., 1975). It is noteworthy that no behavioral symptoms of abstinence or withdrawal were reported in the above experiments at the termination of the forced drug regimens used. One further experiment by Chesher and Jackson (1974) reported the absence of an abstinence syndrome after withdrawal of cannabis extract administered in oral doses equivalent to up to 80 mg/kg Δ-9-THC for 11, 13 and 28 days. In this study, mice were tested for their convulsive thresholds to pentylenetetrazol between six hours and six days following termination of the cannabis drug regimen. No differences were found between drug and control animals.

Despite the above evidence to the contrary, two reports in the literature suggest Δ-9-THC produced dependence and abstinence symptans (Hirschhorn & Rosencrans, 1974; Stadnicki et al., 1974). In the better controlled of these experiments (Stadnicki et al., 1974) rats were administered naloxone hydrochloride after a five-week pretreatment period with Δ-9-THC (8 to 32 mg/kg, i.p.). The rats exhibited narcotic-like withdrawal symptoms including diarrhea, teeth chattering and "wet dog" shakes.

Three experiments have demonstrated that Δ-9-THC, Δ-8-THC and its metabolite 11-OH-Δ-8-THC reduce the abstinence symptoms precipitated by naloxone hydrochloride in morphine-dependent rats (Bhargava, 1976; Hine et al., 1975a, 1975b). In one of these (Hine et al., 1975a), Δ-9-THC doses of 5 and 10 mg/kg administered by the intraperitoneal route one hour before naloxone administration significantly reduced the frequency of wet shakes and diarrhea in the morphine treated rats. Other research (Bhargava, 1976) has shown that CBD and CBN can also inhibit naloxone-precipitated morphine withdrawal symptoms and that CBN and CBD interact with Δ-9-THC to further attenuate these withdrawal symptoms (Hine et al. , 1975b). Data such as these have led to the conclusion that tetrahydrocannabinols may have sane therapeutic utility in clinical narcotic detoxification programs. The same conclusion may not be appropriate for alcohol withdrawal situations. Kralik et al. (1976) have reported that 10 mg/kg Δ-9-THC administered i.p. to mice immediately after withdrawal from a 3-day exposure to ethanol vapor intensifies the alcohol-withdrawal syndrome.

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Chapter 7
HUMAN EFFECTS

Reese Jones, M.D.

ACUTE EFFECTS

A person ingesting or smoking cannabis experiences a fairly predictable sequence of physiologic and psychologic changes which last a few hours and then gradually disappear. Although dose administered and individual differences in personality, expectations, setting and past drug experience all contribute to varied consequences from a given dose of cannabis, the variability in acute effects from cannabis seems no greater than with any other psychoactive drug. Recently, a number of reviews and collections of papers have appeared which attempt to cover the vast amount of information accumulating about the acute and chronic effects of cannabis. Some authors have attempted to consider the research findings in the context of political-social decisions (Edwards, 1974; Pillard, 1974) and point out the lacunae in the data as well as the well established facts (Edwards, 1974). Other reviews tend to emphasize possible adverse effects (Nahas, 1975a, 1975b; Kaymakcalan, 1975), legal vs. health issues (Brecher, 1975) or the chemistry of cannabis (Lemberger & Rubin, 1975; Mechoulam et al., 1976). The continuing research efforts this past year have attempted to fill some of the gaps. Research papers on cannabis are appearing at an average rate of more than one per day and about a third of them deal with effects in humans. Thus, a single detailed review of the literature is becoming an almost impossible task.

Activity of Natural and Synthetic Cannabinoids

Detailed pharmacokinetic studies of Δ-8-THC in man using mass fragmentographic techniques indicate a similar time course and clearance pattern to that seen with Δ-9-THC (Agurell et al., 1976). A very rapid a phase was followed by a slower phase. While blood levels did not always predict physiological and psychological effects, they paralleled heart rate changes well.

DMHP, a synthetic cannabinoid, differs from Δ-9-THC by having a double bond in the 6a, 10a positions. Intravenous administration in

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[1]Beth et al., 1974; Brecher, 1975; Committee on Drugs, 1975; Edwards, 1974; Hollister, 1974a;. Kalant & Kalant, 1974; Kaymakcalan, 1975; Lemberger & Rubin, 1975; McGlothlin, 1975; Mechoulam et al., 1976; Miller, 1974; Nahas, 1975a, 1975b.

man produced profound cardiovascular effects but only minimal psychological effects (Lemberger et al., 1976). As is the case with natural cannabinoids, hydroxylation seemed to be the major metabolic pathway.

A report of an early phase I clinical trial of Nabilone, a synthetic cannabinoid-like compound, is probably one of the first of many investigations with drugs of novel chemical structures that resemble cannabinoids (Lemberger & Rowe, 1975). Nabilone and other synthetics, such as a series of benzopyrans (Mechoulam et al., 1976), have many advantages over natural cannabinoids in terms of stability, water solubility, etc. Most important, they have more specific pharmacologic actions. That is, it seems possible to develop compounds with more cardiovascular effects and less central nervous system effects or vice versa. Compounds with analgesic, sedative, hypnotic, and anticonvulsant activity are undergoing preclinical and early clinical trials. Some of these are discussed in the chapter on Therapeutic Aspects (cf. Chapter 9). If there is any clinical application of cannabinoid-like drugs, it is likely they will come from these newer synthetics rather than from the administration of cannabis sativa to people.

Metabolism of Cannabinoids and Biochemistry

Metabolites. Although studies of a major metabolite of Δ-9-THC, 11-hydroxy-THC, indicate it is pharmacologically active, some question remains whether it is the only metabolite or whether Δ-9-THC needs to be hydroxylated to 11-hydroxy-THC before the THC is active (Hollister & Gillespie, 1975a; Lemberger & Rubin, 1975; Mechoulam et al., 1976). In an attempt to clarify these issues, Hollister and Gillespie sorted people into fast and slow hydroxylators on the basis of antipyrine and phenylbutazone plasma disappearance rates. THC and these drugs are metabolized by the same liver microsomal enzyme system (Wall et al., 1976). There was no difference in speed of onset, intensity or duration of effects after intravenous injection of Δ-9-THC when the two groups were compared. Such results suggest 11-hydroxy-THC may not be the sole source of Δ-9-THC effects. Another group of investigators found 11-hydroxy-THC to leave the plasma more rapidly than THC, suggesting THC may, in fact, be more potent (Perez-Reyes et al., 1976).

A number of additional marihuana metabolites have been reported in a series of studies (Kanter et al., 1974a, 1974b, 1975) and for the first time, unchanged Δ-9-THC was identified in the urine using conventional thin layer chromatographic techniques in amounts estimated at 0.01-0.005 percent of the dose (Hollister et al., 1974). New extraction procedures revealed a previously ignored fraction containing abundant metabolites (Kanter et al., 1974b) including many polar metabolites (Kanter et al., 1974a). The exact identity and activity has yet to be determined. In a review of structure activity relationships of cannabinoids in humans, Hollister (1974b) concluded that the potency of the THC molecule is altered by changing length of side chains, or by metabolic hydroxylations. No

material has yet been formed in nature, in cannabis itself or in THC metabolites which differs qualitatively from THC. There is now evidence indicating the human small intestinal mucosa, as well as the liver, can hydroxylate THC (Greene & Saunders, 1974).

Cannabinoid Interactions. Studies of the possible interaction between Δ-9-THC and the other two major cannabinoids of marihuana -- cannabinol (CBN) and cannabidiol(CBD) -- are not completely consistent in their conclusions. Hollister and Gillespie (1975a) found only slight interaction between THC and CBD. After administration of CBD, there was a delayed onset and prolonged effects of THC that were slightly more intense. The magnitude of the interactions was so small as to be clinically insignificant. A similar study using smoked plant material found diminished euphoria when CBD was mixed with THC, as well as a trend toward decreased THC effects on psychomotor impairments (Dalton et al., 1976). CBD smoked alone was inactive. Other experiments in man with samples of marihuana plant material containing varied amounts of CBN and CBD found differences in effects possibly due to differing proportions of CBN, CBD and THC (Carlini et al., 1974). In subsequent studies by the same group, large doses of CBD blocked many of the effects of THC (Karniol et al., 1974) and oral doses of CBN slightly increased THC effects on some physiological and psychological processes (Karniol et al., 1975). One possible complicating factor in cannabinoid interaction studies is the question of relative stability of various synthetic and naturally occurring cannabinoids (Turner & Henry, 1975). Some are more stable than others. There is little question that interactions occur, although at this point they seem to be inconsistent and of limited magnitude.

Interactions with Other Drugs. Besides CBD and CBN, other drug interactions with THC have been investigated in man. Secobarbital and smoked marihuana had additive effects on subjective responses and psychomotor impairment (Dalton et al., 1975). Subjects had difficulty distinguishing 150 mg of secobarbital from 25 micrograms of THC/kg. When the effects of amphetamine and smoked marihuana were combined, additive effects of heart rate and blood pressure and subjective symptoms were observed, but no interaction effect on psychomotor performance was found (Evans et al., 1974). Based on the assumption that THC interferes with cholinergic brain mechanisms, physostigmine was administered after THC and decreased the tachycardia and conjunctival injection, but had little effect on psychological changes (Freemon et al., 1975). Little potentiation of narcotic drug effects was noted in a study evaluating THC as a pre-anesthetic agent (Johnstone et al., 1974). Animal studies indicate that whatever the drug combination, the depressant effects of THC tend to predominate (Pryor, 1976). Effects of alcohol and cannabis were similar in their impairment of a divided attention performance task (MacAvoy & Marks, 1975). When combined the drugs had synergistic effects in non-users users, at least at lower doses of alcohol.

Assay Techniques. A great deal of effort has gone into the development of practical assays of cannabinoid levels in man. Such

measures are needed not only for research purposes, but would be useful clinically and in law enforcement (particularly in cases where intoxication while driving an automobile is an issue). A number of techniques using saliva and THC with mass spectrometry (Just et al., 1974), radioimmunoassay of blood and urine (Marks et al., 1975; Teale et al., 1974), and gas chromatography of blood McCallum, 1974) have been developed. The problems regarding sensitivity, specificity and reliability of assays have been partially solved and some methods can now be employed in a routine manner. The tight binding of THC to plasma protein (Widman et al., 1974) is only one of the many problems in the development of sensitive, reliable tissue level assays (cf. Analytical Techniques: Detection, in Chapter 2, Chemistry and Metabolism).

A report "Cannabinoid Assays in Humans" from a recent conference sponsored by the National Institute on Drug Abuse describes the tremendous progress in assay techniques made over the past few years (Willette, 1976). Investigators from ten different laboratories in the United States and abroad reported on the results of a variety of analytic techniques -- radioimmunoassays, high-pressure gas chromatography, thin-layer chromatography and gas chromatographic/mass spectrometry. No single technique is the best, with each having advantages or disadvantages depending on the purpose of the analysis, the type of body fluid or tissue, the drug levels of interest, etc. The monograph describes many of the characteristics of cannabinoids that make sensitive, specific and reliable assays difficult. Cannabinoids are lipophilic drugs, tightly bound to lipoproteins; selected antibodies for the various cannabinoids are difficult to obtain as are radioligands with high specificity. Unidentified factors in human plasma appear to interfere with assays even though animal studies are satisfactory. Interlaboratory comparisons are risky since sensitivity to test conditions is great and standardized test procedures are just developing. The most precise and sensitive techniques still require cumbersome and expensive equipment. The radioimmunoassays may ultimately be ideal for routine clinical tests but they still have not lived up to their potential. However, the monograph, written for those with highly specialized backgrounds, reports a number of optimistic studies indicating that practical and sensitive assays will soon be available for routine application in clinical, research and medical-legal situations.

Cardiovascular Effects

Cannabis has long been known to have marked cardiovascular effects (Clark? 1975; Savary et al., 1974). Previous reports reviewed preliminary data which resulted in some expressed concern about electrocardiographic changes during acute intoxication. The subsequent publication of a number of studies where cardiovascular dynamics were studied some time after administration of large doses of THC indicates that cannabis produces only minimal EKG changes in young healthy subjects (Benowitz & Jones, 1975; Clark et al., 1974; Johnstone et al., 1974; Malit et al., 1975). Nonspecific P or T

changes are most commonly noted. Occasional premature beats also occur. Tachycardia continues to be the most common and prominent physiological response to acute doses (Schaefer et al., 1975b). In a study of prolonged administration of oral doses of 30 mg Δ-9-THC given every four hours, heart rate slowing and blood pressure drops developed (Benowitz & Jones, 1975). Blunting of peripheral vascular reflexes developed along with plasma volume expansion. Although tolerance developed to the orthostatic hypotension, the supine hypotensive effects persisted throughout the period of drug administration. These changes commonly seen in laboratory animals but not previously noted in man suggest a biphasic action of THC in humans with an increase in sympathetic activity involving the heart and peripheral blood vessels at low doses and a centrally mediated sympathetic inhibition at higher doses (Hardman & Hosko, 1976). Similar biphasic cardiovascular effects were noted after intravenous THC was given as a premeditation for oral surgery (Gregg et al., 1976a). The slightly increased supine blood pressure following drug administration would be consistent with this mechanism (Clark et al., 1974; Johnstone et al., 1974; Malit et al., 1975). Forearm blood flow increases and total peripheral resistance decreases slightly with acute doses (Malit et al., 1975; Johnstone et al., 1974) consistent with ß-adrenergic stimulation. The great individual variability in response to large intravenous doses has, however, led one group to suggest an indirect episodic activation of the sympathetic system secondary to psychological arousal in addition to the ß-adrenergic stimulation (Malit et al., 1975). Cardiovascular and psychological mechanisms of action may be independent as is suggested by the observation that DMHP, a synthetic cannabinoid, produces profound cardiovascular but few psychological effects (Lemberger et al., 1976).

A study with hospitalized volunteers investigated cardiovascular responses to isoproterenol, phenylephrine, atropine and propranolol before and after 14 days of chronic cannabis intoxication (Benowitz & Jones, in press). There was no significant change in response to isoproterenol or phenylephrine. Heart rate and blood pressure increase after atropine was greater during THC ingestion. The pattern of changes suggested enhanced parasympathetic activity along with sympathetic insufficiency. The interaction with atropine may represent a clinically significant event in chronic high dose cannabis users presenting as patients. Such an interaction might explain the prolonged postoperative tachycardia in marihuana smokers given atropine prior to general anesthesia (Gregg et al., 1976a).

A series of reports on the cardiovascular effects of cannabis smoking in persons with coronary disease are consistent with the preliminary report cited several years ago (Angelico & Brown, 1974; Aronow & Cassidy, 1975; Prakash et al., 1975). Smoking either marihuana or high nicotine cigarettes decreased exercise performance prior to the onset of angina by increasing myocardial oxygen demand and decreasing myocardial oxygen delivery (Aronow & Cassidy, 1975). Cardiovascular hemodynamics were evaluated by echocardiography (Prakash et al., 1975). After marihuana, stroke index and

ejection fraction decreased. Elevated carboxyhemoglobin levels probably produced some changes after both smoked marihuana and placebo. There was some disagreement between experts as to the explanation for the observed cannabis effects. One group favored an explanation in which the diminished cardiac performance was secondary to THC-induced increase in heart rate and afterload rather than a direct negative inotropic effect of THC (Kanakis, 1976) and cited data from cannabis studies with normal people suggesting enhanced cardiac performance and an increase in cardiac index (Kanakis et al., 1976a, 1976b; Malit et al., 1975). The group who did the original study with coronary diseased patients remains concerned about negative inotropic effects of THC (Prakash & Aronow, 1976). Whatever the mechanism, these studies demonstrate that marihuana effects may differ in individuals with pre-existing disease from those in normals. Most cannabis research thus far has, of course, been done on youthful, carefully selected, normal volunteers. Effects in various disease states cannot always be predicted from studies in healthy populations of research subjects.

Pulmonary Effects

Because smoking is the most common means of cannabis consumption in this country, the effects of cannabinoids and marihuana smoke on pulmonary function have been of continuing interest. The Fifth Marihuana and Health Report described bronchodilating effects with possible therapeutic implications after marihuana smoking. Previous reports have described mainly adverse findings in frequent and chronic cannabis smokers including bronchitis, obstructive pulmonary defects, and chronic cough (Abramson, 1974).

Two groups have published reports of cannabis' effects in people with asthma (Shapiro & Tashkin, 1976; Tashkin et al., 1974, 1976a; Vachon et al., 1976). In these studies, acute administration of either smoked marihuana or oral doses of THC produced statistically significant increases in bronchodilation and reversed experimentally induced bronchospasm in young adults with bronchial asthma (Tashkin et al., 1974, 1976a; Vachon et al., 1976). Indications are that the mechanism is independent of ß-adrenergic or antimuscarinic effects (Shapiro & Tashkin, 1976). In contrast to these promising reports, a British group (Davies et al., 1975; Graham et al., 1976) found that measures of forced vital capacity, peak expiratory flow rate and other clinically useful measures of pulmonary function did not improve in a group of patients with reversible airway obstruction given 10 mg doses of oral THC. One possible reason for these discrepant findings may be that the groups reporting cannabis-induced bronchodilation (Shapiro & Tashkin, 1976; Tashkin et al., 1974) used whole body plethysmography, an exceedingly sensitive measure that will detect very small changes in pulmonary function, whereas the less optimistic reports came from a group using less sensitive, although clinically relevant, measurement techniques.

Chronic smoking may produce different and less useful effects than acute administration, as indicated by pulmonary function changes

during periods of chronic administration. Mendelson et al. (1974b) found significant impairments in pulmonary function tests (vital capacity, or FEV 1.0) in a group of chronic marihuana smokers. Further reduction in pulmonary function test performance developed during this study in which the volunteers smoked 3-10 marihuana cigarettes daily for 21 days. Using more sophisticated measures, another group found decreases in maximal mid-expiratory flow rates and specific airway conductance after six to eight weeks of heavy cannabis smoking (Tashkin et al., 1975, 1976b). Although still within the limits of normality, the changes persisted at least one week after smoking and suggest that a longer period of smoking could lead to clinically important changes. An outpatient study of young adults with varying tobacco cigarette habits found more improvement in pulmonary function during an eight-week period of no smoking in the cannabis smoker subgroup (Backhouse, 1975). An in vitro study suggests that the water soluble components of marihuana smoke may contain substances toxic to the defense network of the lung other than Δ-9-THC or other cannabinoids (Cutting et al., 1974). Studies using high doses of THC given intravenously noted only modest changes in minute ventilation and the ventilatory response to CO_2 equivalent to that produced by 5 mg doses of morphine (Johnstone et al., 1974; Malit et al., 1975). However, a more sensitive technique produced evidence of a small degree of respiratory depression (Wiberg et al., 1975).

Another study of the respiratory effects of smoked marihuana and orally ingested Δ-9-THC has examined the effects of the drugs on the respiratory response curve. Both the synthetic and natural material produced a respiratory depression in a group of previously chronic users. Although the effect was found to be slight, the authors recommended further study because of the possible relevance of this effect to patients with chronic lung disease or central nervous system impairment of respiratory regulation (Bellville et al., 1975b).

A clinical study of patients with pneumomediastinum identified a small group of patients who had a common history of repeated and sustained Valsalva'a maneuvers during marihuana smoking or heroin injection and no other obvious explanation for the mediastinal or cervical emphysema (Mattox, 1976). The author suggested that the forceful Valsalva's maneuver used during marihuana smoking may have been an etiologic factor.

Endocrine and Metabolic Effects

The report of depressed plasma testosterone levels in chronic marihuana smokers (Kolodny et al., 1974a) and the report of a failure to find such a change in marihuana smokers receiving the drug daily over a 21-day period (Mendelson et al., 1974a) or in a sample of college student smokers (Cushman, 1975) have led to

further studies and discussion.[1] Kolodny (1975a) reviewed the numerous problems confounding the study of drug effects on the hypothalamic-pituitary-testicular axis in man and discussed possible biologic implications of lowered testosterone levels. He presented data (Kolodny, 1975b; Kolodny et al., 1976) showing significant drops in plasma testosterone levels and luteinizing hormone levels two and three hours after smoking a single marihuana cigarette. In a chronic administration study, subjects showed no significant drop in levels after the first four weeks of daily marihuana smoking; but with continued smoking they had significant drops in luteinizing hormone, followed by falling testosterone levels and follicle stimulating hormone levels. Thus, the data from research finding no marihuana-related hormone changes[2] are quite consistent with studies that do (Kolodny, 1975b; Kolodny et al., 1974a, 1976) if the different time periods of marihuana use are taken into account. The biological significance of these changes is unclear and Kolodny (1975a) is appropriately cautious in his interpretation of their importance. In most cases the plasma hormone levels remain well within the usually accepted normal limits. However, a recent study (Hembree et al., 1976) confirmed a decreased sperm count in otherwise normal marihuana smokers. Such hormone alterations might be expected to be more important for prepubertal or pubertal males or males with already impaired sexual functioning. Corresponding endocrine changes in females have not been studied. There might also be adverse effects on sexual differentiation of the fetus of expectant mothers using cannabis. In the absence of clinical evidence for these consequences, such concern is at present only speculative. Since recent reports (Gordon et al., 1976; Stitmmel, 1975) suggest alcohol may have similar effects, interpretation of many clinical findings will be complicated, since cannabis and alcohol are usually both used by cannabis users.

One surgeon has attempted to link such hormonal changes to the development of gynecomastia in male marihuana users (Harmon & Aliapoulios, 1974; Hill, 1975). He was able to stimulate the development of rat breast tissue by Δ-9-THC administration (Harmon & Aliapoulios, 1974). Other investigators (Lemberger et al., 1975) have not found changes in serum prolactin levels in men given THC experimentally. The absence of prolactin changes is surprising since many centrally acting drugs alter prolactin levels. The reported gynecomastia was postulated to result from a prolactin dependent mechanism.

In a previous Marihuana and Health Report, a study by Hollister and Reaven (1974) was mentioned which described glucose intolerance in a small group of subjects given intravenous doses of Δ-9-THC. A

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[1]Friedman, 1975; Koff, 1974; Kolodny, 1975a; Kolodny, 1975b; Kolodny et al., 1974b, 1976; Lemberger et al., 1975.

[2]Cushman, 1975; Hembree et al., 1976; Koff, 1974; Mendelson et al., 1974a; Schaefer et al., 1975a.

lower dose of THC given as smoked hashish had no effect on blood glucose though blood lactic acid decreased (Papadakis et al., 1974). Glucose efflux from human erythrocytes was inhibited by THC and cannabidiol, suggesting some drug effects on glucose transport mechanisms (Schurr et al., 1974). It would, however, be quite speculative to try to relate these changes to the craving for sweets often reported by cannabis users. A more recent study (Permutt et al., 1976) found no changes in carbohydrate metabolism in marihuana users.

A depressed growth hormone and cortisol response to insulin hypoglycemia was found after a period of prolonged THC ingestion in hospitalized volunteers (Benowitz et al., 1976). As was the case with the testosterone changes described above, the decreased growth hormone levels were still within acceptable limits of normality. The findings are consistent with others suggesting suppression of the hypothalamic-pituitary axis after prolonged THC administration.

Sexual Functioning

Reports discussed in the above section entitled "Endocrine and Metabolic Effects" describe sex hormone changes related to cannabis use. Although anecdotal accounts describe cases of sexual dysfunction possibly associated with such changes, properly controlled studies are needed to confirm them (Kolodny, 1975a; Kolodny et al., 1976). A number of accounts report enhanced sexual activity associated with cannabis use.[1] However, the psychological, social and pharmacologic factors associated with sexual activity probably interact in complicated ways as is true with most other drug effects on sexual behavior (Chausow & Saper, 1974; Ellinwood & Rockwell, 1975; Hollister, 1976; Koff, 1974). For example, with cannabis, as with alcohol, dose is important. Small to moderate doses appear to be most effective as releasers of inhibitions (Koff, 1974). Larger doses and/or chronic use of marihuana may actually diminish sexual interest and potency in males. Adequate data elucidating the effect of marihuana use on sexual functioning are not yet available.

Neurological Effects

Perceptual, cognitive and mood changes are presumably reflected in changes in nervous system activity. Thus there is no question as to the presence of neurological effects. As with any psychoactive drug, however, simple one-to-one correlations between behavioral changes and brain activity are rare (Jones, 1973). The most important questions have to do with how long the effects persist: for hours, days, weeks or are they permanent?

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[1]Brill & Christie, 1974; Chausow & Saper, 1974; Fisher & Steckler, 1974; Hager, 1975; Koff, 1974.

Most recently two studies have been conducted in Missouri (Co et al., in press) and Massachusetts (Kuehnle et al., in press), respectively, of two samples of young men with histories of heavy cannabis smoking using computerized transaxial tomography (CTT), a brain scanning technique for visualizing the anatomy of the brain. In this technique the head is scanned by a narrow beam of X-rays in a series of "slices." Computer processing of the data obtained from a large number of measurements makes it possible to reconstruct the anatomy of the brain in a more detailed manner and with greater precision than pneumoencephalography.

In the St. Louis study 12 young male subjects, aged 20-30 (mean age = 24.1) who had smoked at least 5 joints a day (mean # = 9.0/day) for 5 or more years (mean years = 6.6) were compared to 34 neurologitally normal young men of similar age who did not indicate drug use. In the Cambridge study 19 heavily using young male marihuana smokers, whose use was verified on a closed research ward, were matched with a control series of non-using males of similar age.

In both studies, the resulting brain scans were read blindly by experienced neuroradiologists. In neither study was there any evidence of cerebral atrophy. Despite these negative findings, several additional points should be emphasized. Neither study rules out the possibility that more subtle changes of brain function may occur as a result of heavy and continued marihuana smoking. It is entirely possible to have impairment of brain function from toxic or other causes that is not apparent on gross examination of the brain in the living organism. Nevertheless, virtually all studies completed to date (late 1976) show no evidence of impaired neuropsychologic test performance in humans at dose levels studied so far.

Other recent studies are extensions of or attempts to replicate findings reported previously. Smoked cannabis produces acute, reversible, dose-related changes in brain waves as measured by computer-analyzed EEG (Fink et al., 1976; Klonoff & Low, 1974). Following ordinarily used doses, the changes are modest, consisting mostly of α wave slowing and are not indicative of any particular pathology. Cannabis does not appear to have unique qualities among CNS active drugs as measured by scalp EEGs. Changes in EEG recorded from deep brain structures, consisting of slow wave and spiking activity, have not, however, been seen with any other drug (Heath, 1976). These changes have been well-described in monkeys. Similar changes have been reported in a small number of humans (Heath, 1976). The behavioral significance of these lasting neurological changes is yet to be determined (Jones, 1973). Drew and Miller (1974), in a review of possible neural mechanisms of cannabis, suggest the hippocampus and other deep structures may be important sites of action, at least in animals.

Scalp EEG and evoked potentials showed marked changes in subjects given very large smoked doses of THC or marihuana (Tassinari et al., 1974, 1976). α abundance increased with posterior slow wave activity becoming prominent. Ataxia, hypersomnia, increased deep

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tendon reflexes, tremor, tonic muscle contractions and myoclonus followed these 1 mg/kg doses of THC. In contrast, Seyf eddininpur (1975) administered 2 gm of hashish to subjects and found no pathological changes in scalp EEG; even though the dose produced profound hypotension, anxiety and ataxia.

Loss of REM sleep appears to be a predictable effect of cannabis (Tassinari et al., 1974, 1976). Total sleep time increases, while stage 4 or slow wave sleep is relatively unaffected. In this respect cannabis is unlike any sedative-hypnotic drug studied thus far (Feinberg et al., 1975). When the drug is stopped after a period of prolonged administration, REM sleep stage and eye movement show a rebound above baseline levels. In contrast to the relatively small changes in waking EEGs after the drug is given, sleep EEG changes are very dramatic and large -- both when the drug is acutely or chronically administered (Feinberg et al., 1975, 1976).

Changes in the slow cortical potentials recorded from the scalp (contingent negative variation or CNV) after cannabis are of particular interest since this measure is said to be sensitive to changes in motivation and attention deployment, among other factors . A recent study of the CNV (Braden et al., 1974) obtained somewhat different results from those reported earlier. Like many neurophysiologic measures, it appears the CNV is far more complicated than was originally assumed. It appears the CNV may get larger or smaller after cannabis or it may not change at all (Roth et al., in press), depending on the level of intoxication, the task demands, the motivation of the subject and changes in attention; The group originally reporting CNV changes associated with cannabis intoxication now reports another EEG evoked potential component, P300 or the positive going wave at about 300 milliseconds after the stimulus, as being the component most sensitive to cannabis and ethanol (Roth et al., in press). The researchers suggest that P300 is sensitive to both subjective probability judgments and response set attention. Both cannabis and alcohol intoxication were associated with decreased P300 waves. However, their own work as well as other reports suggests that to view the cannabis-induced CNV or P300 changes as any direct measure of attention deployment or motivation is probably an oversimplication (Braden et al., 1974).

Coleman et al. (1976) reported cranial nerve damage; specifically, a paresis of the fourth cranial nerve leading to superior oblique muscle weakness, headache and hyperphoria. The only common denominator of the 83 percent of drug treatment clinic patients showing this somewhat unusual condition was heavy cannabis use. The investigator thought the trochlear nerve may be more sensitive to toxic drug effects because of its anatomy. A study of peripheral nerve function using electrostimulation produced no evidence of conduction defects in marihuana smokers (DiBenedetto, 1976).

Effects on Cell-Mediated Immunity

Conflicting opinions as to the possible effects of cannabis on the cell-mediated immune response continue to appear (Segelman et al., 1974). (These are reviewed more fully in the section on Genetic and Immune Systems, Chapter 8.) In the previous Marihuana and Health Reports, the observation that chronic marihuana users had decreased in vitro lymphocyte response to allogeneic cells and to a mitogen was described (Nahas et al., 1976). This original observation led to extensive in vitro and animal studies described elsewhere in this report. Related studies in humans published in the past few years provide partial support for the notion of an immune system or thymus-derived cell alteration in people who smoke marihuana.[1] However, Silverstein and Lessin (1976), using an in vivo skin testing procedure, found no evidence of impairment of cell-mediated immunity in chronic marihuana users. Petersen et al. (1974) found that marihuana smokers had less T cell response to phytohemagglutin stimulation and decreased PMH phagocytic capacity; however, they caution that the clinical significance of these findings is uncertain. In possibly related in vivo studies, the white blood cells from both cannabis users and non-users showed similar dose-related inhibition of migration when exposed to THC and extracts of cannabis (Schwartzfarb et al., 1974). However, substances other than THC in the crude extract may have effects on this test system.

Administration of THC or cannabis to controlled populations, with before and after testing, is underway and may provide useful information in clarifying the etiology of the cell-mediated immune effects (Nichols et al., 1974) as was the case with the supposed chromosome breakage, One such controlled study with hospitalized volunteers found no alterations in lymphocyte responses to phytohemagglutinin after subjects received a substantial oral dose of THC for 18 days (Lau et al., 1976).

The problem of interpreting data from groups of cannabis users indicating high rates of infection arises from the possibility that uncontrolled factors such as living habits and shared drugs may contribute to such events rather than some defect in the immune system (Drachler, 1975).

Other Physiologic Effects

Cannabis has many effects on the eye and on visual functioning (Dawson, 1976). Previous findings associated cannabis intoxication with decreases in intraocular pressure. The possible therapeutic implication of this unexpected effect is discussed in the chapter on therapeutic applications (Chapter 9). More extensive studies in normal volunteer subjects indicate a non-dose-related pressure drop

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[1]Cushman et al., 1974; Cushman & Khurana, 1975; Nahas et al., 1976; Petersen et al., 1974, 1975a, 1975b.

from four to five hours (Hepler et al., 1976; Purnell & Gregg, 1975). The magnitude of the eye pressure decrease (about 30 percent) was the same whether the person smoked 1 or 22 marihuana cigarettes. Effects on other aspects of eye physiology (acuity, refractive error, biomicroscopy, fundus changes, visual fields, ophthalmodynamometry, electroretinography and orthoptic evaluation) were minimal or absent. Other investigators concluded that the observed eye pressure decreases were more likely a consequence of drug-induced relaxation and sedation rather than specific cannabis effects on the eye, since other sedative drugs produced similar changes in eye pressure (Flom et al., 1975). Results of studies of the effects of smoked marihuana on galvanic skin response are consistent with drug-induced reduction in level of autonomic nervous system arousal (Cohen et al., 1975). However, recent findings seem to contradict this interpretation (cf. Therapeutic Aspects).

Intravenous administration of water infusions of cannabis plant material fortunately seems to be rarely used (Farber & Huertas, 1976; Payne & Brand, 1975). In the few cases reported, gastroenteritis, hypoalbuminemia, hepatitis and many cardiovascular changes secondary to hypovolemia or renal insufficiency, thrombocytopenia and rhabdomyolysis are severe and require vigorous treatment (Payne & Brand, 1975). The syndrome is quite different from that following intravenous administration of medically pure and sterile cannabis components mentioned elsewhere in this report. Many of the consequences of injections of crude extracts seem to be more the effect of injected foreign plant material, particulate matter and bacteremia.

Given the probable potency of marihuana plant material as allergins there are surprisingly few reports of allergic reactions associated with the handling of the substance (Shapiro et al., 1975; Lewis & Slavin, 1975).

Acute Effects on Mental and Psychomotor Performance

As in previous years a host of studies have reported impaired functioning on a variety of cognitive and performance tasks while marihuana intoxicated. For the most part, impairments were dose-related. As research designs become more sophisticated, evidence is accumulating that interactions between dose and task difficulty are such that performance on some cognitive tasks might even improve when low doses are used (Weckowicz et al., 1975). This study also looked for selective brain laterality effects and surprisingly found more impairment on non-dominant hemisphere related tasks.

Greater appreciation has developed for the need to study a range of doses on a variety of cognitive tasks before trying to describe the effect of cannabis. There are apt to be multiple cannabis effects depending on dose and the exact demands of the task. Prior practice on a task (Beautrais & Marks, 1976; Peeke et al., 1976) may or may not alter the effects of a given dose of cannabis depending on the type of task. Incentives to perform well (more money for correct

responses) can decrease some marihuana effects (Casswell, 1975).

In general, investigators using the smallest doses of marihuana have reported the fewest effects. Impaired memory[1] , altered time sense (Borg & Gershon, 1975; Vachon et al., 1974) and decrements in performance on a number of tasks -- such as those involving reaction time, concept formation, learning, perceptual motor coordination, attention and signal detection -- are commonly described in the literature.[2]

A number of discussions of the locus of the memory impairment are available (Darley et al., 1974; Dornbush, 1974; Tinklenberg & Darley, 1976). There is a growing consensus that the memory defect is due to an alteration in storage rather than acquisition or retrieval. In most laboratory studies, the duration of measurable memory alterations is a few hours after a smoked marihuana cigarette. However, preliminary study by Gianutsos and Litwack (1976) suggests lasting problems with transfer of new information into long term memory storage for some marihuana smokers.

There has been concern that cannabis may increase the suggestibility of those using it. In laboratory studies marihuana smoking had no effect on hypnotic susceptibility (Beahrs et al., 1974).

Effects on Sensory Function

One of the more commonly reported effects of cannabis is a subjective change in sensation, often a feeling of enhanced sensations. A number of groups investigated drug effects on various aspects of sensory functioning. None has reported improved or enhanced sensitivity. Although subjective impressions of changes in skin sensitivity are commonly associated with cannabis intoxication, no objective or measurable change in cutaneous sensitivity using a number of measures was noted (Milstein et al., 1974). The decrease in auditory signal detection while intoxicated appeared to be due to a decrease in sensitivity rather than a change in criteria (Moskowitz & McGlothlin, 1974). This finding contrasts with the usual subjective reports of enhanced auditory sensitivity. The characteristics of preferred tone frequency were shifted while intoxicated (DeSouza et al., 1974).

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[1]Borg & Gershon, 1975; Darley et al., 1974; Domino et al., 1976; Dornbush, 1974; Vachon et al., 1974.

[2]Borg & Gershon, 1975; Cohen & Rickles, 1974; Cohen et al., 1975; Dalton et al., 1975; DeSouza et al., 1974; Dittrich et al., 1975; Linton et al., 1975; Milstein et al., 1974, 1975b; Moskowitz & McGlothlin, 1974; Moskowitz et al., 1973, 1974; Roth et al,, 1975; Salvendy & McCabe, 1975; Sharma & Moskowitz, 1974; Steadward & Singh, 1975; Stoller et al., 1976; Thoden et al., 1974.

A number of aspects of visual functioning seem to be altered by cannabis. Visual acuity for detection of a small moving target was decreased by smoked marihuana (Brown et al., 1975). Alcohol had an even greater effect, however. Reduced dynamic acuity may be a factor in traffic accidents. Static visual acuity, an easier task, was not altered by alcohol or cannabis (Adams et al., 1975). Significant dose related impairments in color discrimination were produced by both alcohol and smoked cannabis (Adams et al., 1976). The transient changes were similar to those seen in retinal disease and were of a magnitude such that tasks where stable color perception is important could be affected by the drugs.

THC given to patients suffering from pain demonstrated mild analgesic effects but 20 mg doses administered orally produced many unpleasant side effects -- somnolence, dizziness, ataxia, blurred vision, etc. (Noyes et al., 1975a, 1975b). The experience of experimentally induced pain in normal subjects was also diminished by smoked marihuana (Milstein et al., 1975a; Payer, 1974). Pain secondary to spinal cord injury was decreased by cannabis use (Dunn & Davis, 1974).

Automobile Driving Performance

More evidence has accumulated indicating that driving ability and related skills are impaired by cannabis at doses likely to be commonly used in the United States.[1] Despite their commonly expressed belief that their driving ability is impaired when intoxicated (Dalton et al., 1975; Klonoff, 1974b; Thompson, 1975), more cannabis users appear to drive today while intoxicated than was the case a few years ago. In limited surveys 60-80 percent of the users questioned reported driving soon after marihuana use (Klonoff, 1974b; Smart, 1974). The use of alcohol in combination with marihuana before driving was reported by 64 percent of one sample and during driving by 20 percent of the sample (Klonoff, 1974b). As the risks of arrest for possession decrease, one might expect more users will take the chance of being caught while intoxicated and driving (Smart, 1974).

A recent study of drivers involved in fatal accidents in the greater Boston area was conducted by the Boston University Accident Investigation Team for the National Highway Traffic Safety Administration (NHTSA). The study found that marihuana smokers were overrepresented in fatal highway accidents when compared to a control group of non-smokers of similar age and sex (Sterling-Smith, 1976).

A more detailed report of a Canadian driving study (Klonoff, 1974a, 1974b) revealed data that clearly demonstrated that marihuana, in relatively low doses (cigarettes containing approximately 5 and 8

[1]Ehrlich, 1974; Isrealstam & Lambert, 1974; Klonoff, 1974a, 1974b; Moskowitz, 1976; Moskowitz et al., 1973.

mg of THC), typically had a detrimental effect on driving skills and performance not only on a test course but also under more usual city driving conditions. However, as is true with alcohol, effects were not uniform with all drivers. Some, particularly at the lower dose, actually improved their performance. Thus, the problem of individual differences that has complicated developing and enforcing "drunk driving" laws will probably recur when medical and legal discussions of the minimal allowable dose or blood level of cannabinoids begin.

Compared to most of the behavioral tasks studied in the laboratory, automobile driving is more complex. The relative importance of the various perceptual, cognitive and psychomotor functions in determining driving ability is not completely understood. For example, in some situations the cognitive impairment produced by cannabis may have only limited impact on actual driving performance due to concomitant drug-induced changes in risk acceptance or feelings of aggression. In a laboratory simulation of driving, cannabis-intoxicated subjects took longer to decide whether to pass another car, seemed less likely to accept the risks of passing and seemed less aggressive than alcohol-intoxicated subjects (Dott, 1974; Ellingstad et al., 1973). Other laboratory simulator studies have found that, while some driving skills are relatively unaffected by marihuana, there is a dose-related impairment in the ability to attend to peripheral stimuli while driving (Moskowitz et al., 1973, 1976). Such an impairment might interfere with such things as a driver's, response to a car suddenly emerging from a side street even though tracking and car control are not impaired.

Because of the many inherent inadequacies' of laboratory driving simulator studies (Klonoff, 1974b), cannabis-related driving risks will ultimately have to be assessed on the basis of studies of actual accident rates for users compared to non-users. This has been difficult in the study of alcohol. It promises to be still more difficult with cannabis because of the problems of measuring tissue levels of the cannabinoids, the longer excretion times, the more complicated metabolism and the often combined use of cannabis and alcohol while driving, making the relative contribution of either drug uncertain (Garriott & Latman, 1976; Klonoff, 1974b; Smart, 1974). Blood and urine analysis for cannabinoids revealed extremely high levels in an automobile driver killed in a head-on collision (Teale & Marks, 1976). Cannabis leaf and a pipe were found in the car. No alcohol was found in the blood, nor were other explanations found for the erratic driving prior to the accident. How common this pattern of events is can only be determined when practical assays for cannabinoids in body fluids become available.

Flying an airplane demands still more complex skills than does driving. There is little information concerning possible pilot error or impairment in performance as a result of having used marihuana (Zeller, 1975). Several studies have shown that under flight simulator test conditions experienced pilots showed marked deterioration in performance following smoking marihuana containing 6 mg of THC (Meacham et al., 1974), 0.9 mg/kg Δ-9-tetrahydrocanna-

binol (Janowsky et al., 1976a), and 2.1 percent Δ-9-tetrahydrocannabinol in 0.09 mg/kg (Janowsky et al., 1976b). More detailed studies are planned to follow up these initial observations.

Non-Pharmacologic Determinants of Subjective Response

Sociocultural factors (Adamec et al., 1976; Klonoff & Clark, 1976; Orcutt & Biggs, 1975) appear to interact with such pharmacologic aspects as dose and route of administration so as to modify marihuana's subjective effects. To some extent what happens during cannabis intoxication is determined by the individual's expectations, as is the case with most psychoactive drugs. Sometimes even students in a professional health field are misinformed as to what can happen (Seiden et al., 1975). Some of these factors were explored in previous studies.

Laboratory studies are often criticized because a sterile, scientific laboratory setting may alter the response to the drug so that findings have little relevance to more typical conditions of use. This does not necessarily seem to be the case. Hollister et al. (1975) randomly assigned a group of subjects to smoke marihuana (16 mg THC) either in a typical medical research laboratory or a private living room designed to facilitate a pleasurable drug experience. Although there were great differences between subjects in their subjective responses to the smoked marihuana, the effect of the very different settings was negligible. A similar study using only a subjective level of intoxication as an index of drug effects found a psychedelic environment was associated with greater intoxication at intermediate dose levels, but not at the highest (16 mg THC) dose employed (Cappell & Kuchar, 1974). Another attribute of the setting in which cannabis is often used is the possible effect other intoxicated friends have on a person's "high." However, in a study testing the effect of modeling, subjects smoking marihuana for the first time were relatively unaffected by the presence of an actor modeling a marihuana high (Carlin et al., 1974). The results of this study suggest that previous experience with cannabis is a complicated socialization process in which individuals learn from friends and others to discriminate and label various aspects of the drug state (Carlin et al., 1974).

The mood one is in before smoking is sometimes thought to interact with the drug effects to produce varied outcomes. A laboratory study found no difference in subjective response to low doses of smoked marihuana and no difference in level of anxiety in groups of subjects made anxious by exposure to laboratory stresses (Pillard et al., 1974). Finally, Cappell and Pliner (1974) found that the dose of cannabis consumed in an experimental laboratory setting was determined by many factors (size of cigarettes, past drug experience) other than pharmacologic potency of the drug. A similar study by the same group (Cappell & Kuchar, 1974) found that controlling the amount of drug consumed in accord with its varying strength was difficult for subjects, again suggesting that non-pharmacologic considerations are important in affecting the amounts consumed.

CANNABIS AND PSYCHOPATHOLOGY

The association of cannabis use with psychiatric illness raises complex questions for which no completely satisfactory answers are yet available. Two reviews of past research point out the many methodological and theoretical shortcomings of existing work (Halikas, 1974; Meyer, 1975). A variety of psychiatric disorders are clearly associated with the use of cannabis; however, whether the psychopathology is an antecedent to use, a consequence or a mere coincidence is still very much open to question. There are some hints that those using cannabis with therapeutic intent experience more adverse reactions (Naditch, 1974). A "best guess" is that cannabis use, like that of many other psychoactive drugs, will sometimes be an antecedent, a consequence or a coincidence psychopathology, depending on the person and many other variables.[1]

As is often true in medicine, the ambiguity in diagnostic classification and definitions adds to the confusion concerning adverse psychological reactions associated with cannabis use. The classification of the subsections below has been adopted to impose some order on the literature (Halikas, 1974; Meyer, 1975).

Acute Panic Anxiety Reactions

The acute panic anxiety reaction has been noted by many reviewers to be the most common adverse reaction to cannabis use (Halikas, 1974; Meyer, 1975). The symptoms and signs are usually exaggerations of normal cannabis effects more generally described by users. Anxiety is often focused on fears of "going crazy." This reaction appears most likely to occur in novices and after consuming more potent materials. Personality variables that make for poorer coping skills play a role. The symptoms diminish with authoritative reassurance or in a few hours when the immediate drug effects have worn off . A number of reports illustrate these considerations.[2]

Patients with chronic pain (Noyes et al., 1975a) and depression (Ablon & Goodwin, 1974; Regelson et al., 1976) given low doses of THC in therapeutic trials had far more dysphoric and acute panic episodes than would be expected if the same doses were given to typically youthful cannabis users. These older people presumably found it difficult to accept the drug-induced mental changes as desirable. Younger, but equally inexperienced, "cannabis experi-

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[1]Abruzzi, 1975; El Guebaly, 1975; Kroll, 1975; Meyer, 1975; Segal & Merenda, 1975; Stefanis et al., 1976b; Tennant et al., 1975; Westermeyer & Walzer, 1975.

[2]Ablon & Goodwin, 1974; Keeler & Moore, 1974; Mirin & McKenna, 1975; Naditch, 1974; Noyes et al., 1975a; Tinklenberg & Darley, 1976; Tylden, 1974.

menters" often react similarly (Mirin & McKenna, 1975; Tinklenberg & Darley, 1976) as do people under stress (Bridger, 1975; Gregg et al., 1976b).

Cannabis-induced mild paranoid feelings in student and "counter culture" users of marihuana are common and usually not a source of undue concern to them (Keeler & Moore, 1974). About two-thirds of a student group and 95 percent of a counterculture group studied described suspicion of being subjected to a police raid or having friends tricking them while intoxicated. Inability to test reality concerning these suspicions was reported by over half of the subjects. Another field survey found that individuals with a tendency to use paranoid defense mechanisms experienced fewer acute anxiety reactions after cannabis (Naditch, 1974). The authors thought that the more sophisticated defenses represented in paranoid functioning may be effective in preventing acute adverse reactions. The same study found that persons with high scores on the schizophrenia subscale of the MMPI tended to have more problems with adverse psychological reactions indicating (as have a host of previous studies) that pre-existing psychopathology is an important factor in such reactions. The same survey (Naditch et al., 1975) suggested that the setting in which the drug is consumed may be a less important determinant of adverse reactions.

Cannabis-Induced Acute-Brain Syndrome or Toxic Delirium

The clinical features of the acute brain syndrome associated with cannabis intoxication -- such as clouding of mental processes, disorientation, confusion and marked memory impairment -- are similar to those produced by other exogenous toxins (Halikas, 1974; Meyer, 1975). The syndrome is most likely to occur at high doses and to be dose-related, whereas the panic reactions may occur at any dose unfamiliar to the user (Halikas, 1974; Jones, 1975; Meyer, 1975). The toxic delirium is likely to follow the time course of other drug effects. This syndrome appears to be relatively rare in the United States.

A four-year-old child presumably ate some cannabis resin (up to 1.5 g) and was found thereafter alternately stuporous and excited with inappropriate laughing and ataxia. Body temperature was markedly lowered and respiration rate decreased. Residue on the child's teeth was identified as cannabis material. All symptoms and signs cleared in about a day (Bro et al., 1975). Two cases from Nigeria involved children given smoked cannabis (Binitie, 1975). One child was perspiring and restless and didn't sleep. Hyperactive and destructive behavior continued for four months. The second child manifested more of a toxic psychosis with hyperactivity lasting for some weeks. One must assume that a large dose was involved in these latter cases in addition to preexisting problems given the duration of symptoms. Such case reports are rarely definitive, but can point the way for more controlled surveys and clinical studies.

In clinical studies where patients were given substantial intra-

venous doses of THC prior to surgery, many experienced dysphoria and psychotic-like shifts from euphoria to dysphoria, panic and paranoid thinking (Gregg et al., 1976b). The stress of surgery was, of course, a factor as was the large dose of intravenous THC, but the study does point out that such reactions are possible and even common under certain conditions even with healthy, relatively well-adjusted people.

Prolonged Reactions

Possible prolonged psychological effects of cannabis use are an area of serious concern and much controversy. These include not only psychotic reactions but also personality change, change in life style, a possible "amotivational syndrome," "flashbacks" and a possible causal relationship between marihuana use and use of other drugs. Here it is even more difficult to establish precise cause and effect because the close temporal relationship between ingestion of the drug and acute effects is lacking.

Descriptions of a specific long lasting cannabis psychosis appear largely in the Eastern literature, and, thus, are largely drawn from a culture where use is generally more frequent, and at higher dose levels, than is typical for the United States. This acute "cannabis psychosis" is generally associated with very frequent use and reportedly lasts one to six weeks or longer (Halikas, 1974; Meyer, 1975). Recent studies abroad, in Jamaica (Rubin & Comitas, 1975), Greece (Stefanis et al., 1976a) and Costa Rica (Coggins, 1976) where frequent users of high potency cannabis were examined failed to document the existence of a specific cannabis psychosis. However, small sample sizes were involved and a relatively rare occurrence could well have been missed.

In contrast, a clinical study done in India contrasted the features of a paranoid psychosis arising in the course of long term cannabis use with paranoid schizophrenia (Thacore & Shukla, 1976). The study compared 25 consecutive admissions for each diagnosis. The majority of cannabis users had used bhang daily for five or more years in doses up to several grams, gradually increasing dose. The cannabis psychosis, in contrast to the paranoid schizophrenia, was characterized by more bizarre behavior, more violence and panic, an absence of schizophrenic thought disorder and more insight. The cannabis psychosis cleared rapidly after hospitalization and phenothiazine treatment. Patients relapsed only when cannabis administration was reinitiated.

A few years ago a clinical report by Kolansky and Moore (1971) described 8 psychotic reactions in a group of 39 marihuana smokers in this country and attempted to demonstrate a cause-and-effect relationship to their marihuana use. A more recent clinical study demonstrates how correlations between various behaviors and subsequent psychiatric disorders can be misleading (Altman & Evenson, 1973). Consecutive first admissions to a psychiatric hospital were evaluated. Thirty-eight patients who had used marihuana prior to

the onset of psychiatric problems were studied. Indeed, apathy, poor judgment, confusion and depression followed marihuana smoking, but the correlations between marihuana use and subsequent illness was less than with such presumably causally unrelated variables as having masturbated, having experienced sex education, and having drunk beer. In this clinical study marihuana use could not be singled out as a prime factor leading to psychiatric illness.

Marihuana flashbacks -- spontaneous recurrences of feelings and perceptions similar to those produced by the drug -- continue to be reported (Brown & Stickgold, 1974). Data from a survey of drug users in the Army indicate flashbacks attributed to marihuana occur in infrequent as well as frequent users and are experienced by people who have never had LSD (Stanton et al., 1976). The etiology of such flashbacks remains obscure, but most of those who experience them seem to require minimal treatment if any.

Non-Psychotic Prolonged Adverse Reactions

Surveys of user and non-user populations provide some information as to neuropsychological changes, changes in life style and the so-called amotivational syndrome associated by some with cannabis use. As was pointed out in Chapter 1, when discussing issues related to marihuana use it is difficult to distinguish between antecedents and consequences of cannabis use. Therefore, the question of causality remains unresolved in many studies. In an all too rare prospective study, Culver and King (1974) compared groups of LSD-mescaline users with marihuana, hashish users and non-drug using controls. The investigators used a sophisticated psychological test battery including the Halsted-Reitan tests, the Wechsler Adult Intelligence Scale and tests of spatial perceptual abilities. When tested a year later, the LSD-mescaline group scored least well on the trail making test but the performance of all three groups fell within normal limits. No evidence could be found for the existence of a neuropsychological deficit with either light or frequent cannabis use. Another study of heavy drug users using a similar test battery arrived at similar conclusions (Bruhn & Maage, 1975). However, the authors of the study remind their readers that one should not conclude that no organic changes occurred since psychological test data are inferential and definitive statements as to organic changes can only be based on radiological or pathological evidence. One study of multiple drug users in the Navy (Gunderson et al., 1975) found a large number of psychiatric symptoms reported by them on the Cornell Medical Index; but because of the variety of drugs habitually used, it was impossible to single out marihuana use as an important factor.

The possible effects of cannabis on student performance have been a major concern because of the extensive use by that group. A longitudinal study of a sample of 1,970 college students examined the relationship between cannabis use and psychosocial adaptation and academic performance (Brill & Christie, 1974). Users and non-users did not differ in grade point average or in educational

achievement, but the marihuana users seemed to have more difficulty in deciding on career goals and dropped out of college more often to reassess goals. A smaller percentage of regular users planned to seek advanced or professional degrees. There was, in the opinion of the users themselves, a poorer academic adjustment among the most frequent users than among infrequent or non-users. Only 6 percent of non-users reported a worsening of their emotional state since beginning college but 20 percent of the long duration users reported negative changes in emotional state. A problem with the study was that a significant percentage of the initial sample was lost over the three year period. If the loss was from the group who failed out or dropped cut, those most likely to show loss of motivation or intellectual functions may have been automatically excluded from the study. Also, the study merely reported the students' own assessment of their adaptation since no interviews were attempted.

Investigations of why people stop using marihuana can give hints as to possible adverse effects. In a follow-up on the longitudinal survey of marihuana quitters described above, continuing users and never users were compared (Pack et al., 1976). The quitters had used marihuana less frequently than the continuing users. It was used more often as a mild intoxicant than a consciousness alterer. More had experienced adverse effects. Fear of punishment was not a reason for quitting. Quitters had more experience with psychotherapy. For one group of quitters, cannabis use was mostly a social accident; they were in the right place at the right time to obtain the drug. A second type was the ex-rebel who changed identity and quit. The third group seemed to be emotionally fragile people who were psychologically threatened by the drug.

Other questionnaire surveys reported differences between users and non-users but the question of causation remains and the mental health significance of some of the findings is unclear. In a study of high school students marihuana users were intermediate between non-users and hard drug users on grades, absenteeism, suspensions and likelihood of graduation (Smith & Fogg, 1976). Another study found little difference between marihuana users and non-users in terms of their responses on personality inventories although users of other drugs differed from non-users (Richek et al., 1975). Simon (1974) found that non-users scored higher on need for achievement and order and, thus, not surprisingly, had higher grades. Other surveys found marihuana users to be more dissatisfied, disillusioned and alienated (Cunningham et al., 1974), more oriented towards the past (King & Manaster, 1975); but, also, to be more creative and adventuresome (Grossman et al., 1974). They also had lower levels of achievement (Carlin & Post, 1974), and heavy users dropped out of school more often (Kahn & Kulick, 1975).

A comparison of 850 chronic cannabis users and 839 non-cannabis using controls recruited from Egyptian prisons revealed slower psychomotor performance, defective visual-motor coordination and impaired memory for designs in the cannabis users (Soueif, 1975). Most were presumably not using the drug at the time of testing. When literate and illiterate and urban and rural users and non-users

were compared, Soueif (1976) found more evidence of drug induced impairment in the subjects with literate and urban backgrounds. He presents a working hypothesis and some data suggesting that there is less functional impairment after cannabis use in the illiterate, rural and older subjects. Of course, if such a hypothesis proves true, then the results of studies of chronic users in less sophisticated and more rural countries (Rubin & Comitas, 1975) may not apply to other populations -- particularly in highly literate, urban and young populations.

The ability of cannabis users to work in non-academic contexts has been examined in attempts to see if a measurable "amotivational syndrome" exists (Mendelson et al., 1976a, 1976b; Miles et al., 1974). In a study of frequent and infrequent users smoking cannabis while living on a research ward, work output decreased as marihuana consumption increased (Mendelson et al., 1976a, 1976b). However, the investigators noted that "motivation" is a function of situational variables as well as drug factors. These authors reasoned that to term the decrement in work output "amotivational" would imply that the users in the experiment had lost interest in working for money. However, if the work decrement resulted from a drug-induced impairment of performance, it would not be proper to term it a motivational effect. They found the change in work output to be due more to the latter than the former drug effects. In a similar Canadian study (Miles et al., 1974), a decrease in productivity (making stools) followed the smoking of cannabis. The decreased productivity appeared to be due to less time spent working rather than to reduced efficiency. The authors interpret this as indicative of an "amotivational syndrome," present at least during the period of drug use. To the extent that these types of studies involve artificial work conditions and tasks dissimilar to more usual employment, it is hazardous to draw more general conclusions regarding the role of cannabis in a more generalized amotivational picture. Moreover, these studies involved intensive daily use. The relationship of their findings to episodic or less frequent use in altering motivation is unknown. However, uncontrolled clinical reports from countries where cannabis is readily available continue to report decreased work output and initiative in chronic cannabis users (Sharma, 1975). Thus, further studies are important.

An assumed relationship between cannabis use and the use of other drugs (mainly opiates) has been a source of concern. The best predictor of marihuana and other illicit drug use may be early (before age 12) tobacco and alcohol use (Tennant & Detels, 1976). The progression hypothesis is a good example of a theoretical construct repeated so many times by so many people that it has become verified by repetition rather than by facts (Tee, 1974). The patterns of the shifts from one drug to another seem to be changing with more of a "progression" to "polydrugs," excluding heroin (Could & Kleber, 1974). In both military and civilian populations, the pattern of drug use and selection of drugs were determined more by availability, peer pressure and drug use fads than by pharmacologic or personality variables (Nace et al., 1975; Tzeng & Skafidas, 1975). Cannabis users are, however, very likely to use other licit

and illicit drugs with a positive correlation between level of cannabis use and the variety of drugs used (Mullins et al., 1975).

Criminal and Aggressive Behavior

The often discussed possible link between cannabis use and crime or aggressive behavior has been the topic of reviews (Goode, 1974; Knudten & Meade, 1974) and experimental studies (Colaiuta & Breed, 1974; McGuire & Megargee, 1974; Salzman et al., 1975). Both reviews concluded that evidence showing marihuana to cause crime is virtually nonexistent. McGuire and Megargee (1974) compared young prisoners who varied in their degree of marihuana use on a number of personality measures (e.g., MMPI, CPI). Non-users and occasional users had typical criminal profiles. Regular users of only marihuana were better socialized and adjusted, though more deviant than collegiate marihuana users. Prisoners who used marihuana plus other drugs were the most deviant.

In addition to concern about marihuana use and criminality, the association between marihuana intoxication and hostile human behavior has been a topic of great interest and discussion. Surveys of California adolescents noted that aggressive and sexually assaultive behavior was more commonly associated with ethanol intoxication even though the adolescents used marihuana almost as frequently (Tinklenberg, 1974). The results of observation and self reports of hostile, aggressive feelings from subjects acutely or chronically intoxicated with cannabis in laboratory experiments suggest the usual effects are to decrease expressed and experienced hostility (Jones & Benowitz, 1976; Mendelson et al., 1974b; Salzman et al., 1975). In one laboratory study, college undergraduates were placed in a situation in which they could aggressively interact with another person. Those intoxicated with alcohol instigated more intense aggression than similar students intoxicated with THC (Taylor et al., 1976). Yet, in other cultures, for example, in India, violent behavior is commonly associated with cannabis psychosis (Thacore & Shukla, 1976).

CHRONIC EFFECTS

Tolerance

Marked tolerance to the effects of cannabis doses commonly consumed in this country is not usually evident, presumably because of relatively infrequent use and the generally low doses of active material. However, as data accumulate from countries where more frequent use of high doses is common,[1] it is apparent that tolerance

[1]Coggins, 1976; Fink et al., 1976; Rubin & Comitas, 1975; Stefanis et al., 1976a.

must develop to many of the psychological and physiological effects. In controlled experimental situations where prolonged administration of THC or marihuana to volunteer subjects has been undertaken what appears to be dose-related tolerance develops rapidly,[1] as judged by behavioral, psychologic and physiologic measures. At lower doses (one cigarette per day) a longer period of administration (27 days) is necessary for clear cut tolerance to develop (Gibbins et al., 1976).

In outpatient studies where frequent and infrequent users or other populations with differing drug histories are compared in their response to a given dose of cannabis, the results are less consistent. Marked tolerance to measured effects is rarely obvious, if evident at all.[2] However, when sensitive and reliable measures are used, even infrequent use may produce evidence of some degree of tolerance on outpatient laboratory tests (Borg & Gershon, 1975; Cohen & Rickles, 1974). Tolerance in humans is apparently a dose-related effect as it is in animals (Dewey et al., 1976). Although tolerance regularly develops when cannabis is given experimentally for periods of time, changes in drug seeking behavior do not seem to be clearly related to degree of tolerance (Babor et al., 1975). The determinants of just how many cigarettes per day are smoked appear to be altered by many factors besides the presence or absence of drug tolerance.

Dependence

When volunteers were given 30 mg doses of THC orally every 4 hours for 10-20 days, sudden cessation of the drug was associated with the appearance of irritability, restlessness, decreased appetite, marked sleep disturbance (including sleep EEG; alterations), sweating, salivation, tremor, weight loss, nausea and vomiting, diarrhea and, in general, a clinical picture similar to that following chronic administration at moderate doses of many sedative-hypnotic drugs (Benowitz & Jones, 1975; Feinberg et al., 1975; Jones & Benowitz, 1976). Such psychologic and physiologic changes have not been ccmmonly observed in other chronic administration studies in this country, although it has been reported once in a German paper (Kielholz & Ladewig, 1970). Restlessness, anorexia and a sudden 12 lb. weight loss were reported by one group in an inpatient volunteer study at the end of a 21-day smoking period (Mendelson et al., 1974b; Greenberg et al., 1976). Drug-seeking behavior has not been associated with the withdrawal syndrome, but the presence or absence of such behavior is difficult to assess in the laboratory. A withdrawal syndrome has not been described in recent investigations

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[1]Benowitz & Jones, 1975; Cohen et al., 1976; Jones & Benowitz, 1976; Mendelson et al., 1974b, 1976b.

[2]Dornbush & Kokkevi , 1976; Perez-Reyes et al., 1974; Renault et al., 1974; Stefanis et al., 1976a.

of chronic users abroad (Coggins, 1976; Fink et al., 1976; Rubin & Comitas, 1975).

Field Studies of Chronic Users

Several field studies of populations of frequent long-term users have searched for possible adverse or other effects associated with chronic use.[1] These were all concerned with users in countries in which high potency cannabis is more readily available than in the United States.

The results of a chronic user study discussed in two previous reports were recently published in book form (Rubin & Comitas, 1975). The 30 experimental subjects had been smoking high potency cannabis almost daily for 10 years or more. Many of the non-cannabis smokers in the control groups did use cannabis tea. This type of drug use was not controlled for; thus, both cannabis smokers and many non-smokers were cannabis users. Few psychological or physiological differences between the cannabis smokers and non-smokers were evident. There was no evidence for liver, kidney or cardiovascular malfunction. While no differences in chromosomal abnormalities were found, the results must be regarded as inconclusive because of various technical deficiencies of the study. Modest decreases in pulmonary function and altered hemoglobin levels were the only physiologic differences evident. The impact of tobacco use by the subjects on these findings is uncertain. After smoking cannabis, a small group of workers produced less work (weeding, hoeing, digging) with more movements, but otherwise showed no evidence of "amotivation." The importance of cultural differences in the interpretation of drug effects is evident in that people in Jamaica did not find their appetite increased by cannabis and, in fact, seemed often to use it to decrease appetite. This is, of course, not the expected effect in the United States (Abel, 1975). They did not think their hearing was enhanced nor their time sense altered, and, in fact, said they used cannabis to work better. Although reassuring, the findings should also be judged in perspective. They were derived from a small group of selected users, so that rare consequences (if they did occur) such as brain atrophy or psychosis might not have been detected. The subjects were laborers and farmers in a very different culture, so that intellectual impairment may have been relatively difficult to detect. Soueif (1976) has argued that such subjects may show fewer cannabis effects than urban and literate subjects.

A similar although larger and more complex study is underway in Costa Rica. Coggins (1976) presented a preliminary report. Eighty daily marihuana users and matched non-cannabis-using controls were evaluated with extensive medical examinations, laboratory studies,

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[1]Coggins, 1976; Fink et al., 1976; Dornbush & Kokkevi, 1976; Rubin & Comitas, 1975.

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X-rays, EEG, EKG and neuropsychological testing. Although the study is still in progress, no evidence for a greater incidence of disease or deterioration among the cannabis users has yet been found.

In studies of Greek and chronic hashish users approximately 47 chronic users were compared with 40 control non-users on a variety of EEG, echoencephalographic, neuropsychologic and experimental laboratory tests (Fink et al., 1976; Dornbush & Kokkevi, 1976; Stefanis et al., 1976a). Conventional clinical measures of brain damage (EEG, echo-EEG;) showed no evidence of abnormality in the chronic users. Tolerance to administered doses rapidly developed on the EEG indices. No evidence of withdrawal symptoms after three days of chronic administration was evident. When given high doses of THC, some of these very experienced subjects developed unpleasant psychological symptoms when their tolerance level was exceeded. These were all outpatients so no precise control over drug use outside of the laboratory was possible. A slightly higher incidence of personality disorders in the hashish-using group was better explained by psychosocial variables than by marihuana use.

Thus, these three field studies of users abroad do not report brain damage, psychosis or an "amotivational syndrome." However, the cultures are different, and the sample populations are relatively small so such drug effects cannot be ruled out. Such adverse effects may be simply uncommon or difficult to measure, should they exist.

Chronic Effects -- Laboratory Studies

A number of groups have studied the effects of daily cannabis use in paid volunteer subjects consuming cannabis for up to 72-day periods while hospitalized.[1] Although even 72 days is not really chronic use, such studies complement the more commonly performed acute outpatient studies. In general, in all these chronic or subchronic studies, subjects have tolerated the drug treatment phase well and very few dropouts, psychoses, or other blatant manifestations of distress were revealed. Except for the pulmonary function impairment noted in two studies (Mendelson et al., 1974b; Tashkin et al., 1975, 1976b), drug effects on mental, behavioral and physiologic functions seem to disappear rapidly on cessation of drug administration and have been, in general, similar to those seen in acute studies. Tolerance is evident at lower doses[2] and obvious at higher doses (Jones & Benowitz, 1976).

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[1]Benowitz & Jones, 1975; Feinberg et al., 1975; Cohen et al., 1976; Jones & Benowitz, 1976; Mendelson et al., 1974b, 1976b; Miles et al., 1974.

[2]Babor et al., 1975; Bellville et al., 1975a; Cohen et al., 1976; Mendelson et al., 1974b.

Adverse Physiologic Effects Associated with Chronic Use

Mention has already been made of the endocrine and immunologic changes reported in some populations of users. Mutagenesis and teratogenesis are discussed elsewhere in this report.

A discussion of the report of brain ventricle changes was presented in a previous report. A paper describing the same group of subjects appeared subsequently (Evans, 1974), but no similar reports have followed. The difficulty of performing pneumoencephalograms in neurologically normal volunteers makes survey studies impossible. A number of groups are testing cannabis users with non-invasive techniques for measuring brain ventricle size (computerized tomography) and preliminary results should be available soon. An investigator who reported the electrical changes in the deep brain structures of a human smoking marihuana has now completed chronic studies in monkeys, finding similar electrical changes. The slow wave activity persists for months after the cessation of a chronic period of smoking. The behavioral and biological significance of the changes in humans is uncertain.

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Chapter 8

EFFECTS OF MARIHUANA ON THE GENETIC AND IMMUNE SYSTEMS

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With the continued widespread abuse of marihuana and the potential use of marihuana as a therapeutic agent being widely discussed, it becomes important to assess the effects of marihuana and other cannabis preparations on the immune mechanisms and the genetic material. This chapter integrates recent findings with those in the Fifth Marihuana and Health Report (1975) to provide a wider data base from which conclusions may be drawn. Animal studies and human studies are considered separately because it is not known to what extent, if at all, results from animal studies can be directly extrapolated to man.

ANIMAL STUDIES

Chromosome Analyses

Of the two reports of chromosome studies in animals, one in rats and one in hamsters, both have been negative (Martin, 1969; Pace et al., 1971). However, cytological examinations of hamster lung cultures (Leuchtenberger & Leuchtenberger, 1976) exposed to smoke from marihuana and tobacco cigarettes were reported to show multiple effects (i.e., inhibition of DNA synthesis and cell division, abnormalities in mitosis, and variable DNA content of chromosomes).

Immune Responses

The effect of marihuana on various aspects of the host defense system of animals has been intensively investigated. In an in vitro bioassay system, fresh marihuana smoke was found to impair in a dose-related manner the antibactericidal activity of pulmonary alveolar macrophages obtained from rats (Huber et al., 1975; McCarthy et al., 1976). However, smoke from tobacco cigarettes and placebo marihuana cigarettes (all tetrahydrocannabinols removed) also impaired macrophage function. By contrast, purified tetrahydrocannabinol introduced directly to the bioassay system did not affect the macrophage bactericidal activity. Thus, it appears that the psychoactive agent in marihuana is not the agent that impairs alveolar macrophage function. In another study, in vitro exposure of mouse peritoneal macrophages to Δ-9-THC and cannabidiol resulted in cell death (Raz & Goldman, 1976). This finding is consistent with Mann et al. (1971), who noted a decrease in alveolar macrophages in marihuana smokers compared to non-smokers. Gaul and Mellors (1975) reported that intraperitoneal injection of Δ-9-THC

to immunized rats suppressed the macrophage migration inhibition factor (MIF) activity. (MIF is a lymphokine released by sensitized T lymphocytes and is a measure of cell-mediated immunity.)

In a prospective study, Daul and Heath (1975) evaluated the immunological competence of rhesus monkeys prior to and following six months of chronic marihuana usage (at three different dosages) and detected reduced immunoglobulin levels as well as decreased in vitro lymphocyte responsiveness. Their report, however, must be viewed with caution because of the small number of animals studied: one each in the high and medium dose groups, three in the low dose group and one in the control group, totalling only six monkeys. Lefkowitz and Chiang (1975) administered Δ-9-THC to mice and found that it reduced the number of splenic lymphocytes and leukocytes and inhibited the hemolytic plaque forming cell response (a measure of antibody producing cells). In another study by Johnson and Wiersema (1974), an increase in lymphocytes in rat bone marrow accompanied the inhibition of myelopoiesis following Δ-9-THC administration.

Other reports (Carchman et al., 1976; Harris et al., 1974; Munson et al., 1975) noted that Δ-9-THC administered orally to mice retarded tumor growth and increased survival 36 percent. These studies have found that Δ-9-THC, Δ-8-THC and cannabinol inhibited growth of Lewis lung adenocarcinoma both in vivo and in vitro. More importantly, differential sensitivity was reported with Δ-9-THC decreasing 3H-thymidine uptake into the DNA of tumor cells but not into the DNA of bone marrow, spleen, testes or brain cells. This was not the case for Δ-8-THC and cannabinol. It was also reported that Δ-9-THC inhibited Friend leukemia virus (FLV), induced splenomegaly, but did not have an effect against mice hosting L1210 murine luekemia (Munson, et al., 1975).

If the acute administration of Δ-9-THC preferentially inhibits DNA synthesis in tumor cells in humans as well as in mice, the potential usefulness of marihuana as an antineoplastic agent will have to be evaluated. There is, however, a problem of increasing tumor insensitivity over time, the reasons for which are unclear at this time. Marihuana may also have potential therapeutic use an an immunosuppressant in transplantation surgery if the findings that it depresses cell-mediated immunity in rodents[1] are substantiated in human studies.

Early studies of marihuana indicated teratogenic activity in rats, rabbits, mice and hamsters.[2] Recently, Mantilla-Plats et al. (1973) and Fournier et al. (1976) confirmed the findings in mice and

[1]Levy et al. , 1974; Munson et al., 1976; Nahas et al., 1973; Rosenkrantz, 1976.

[2]Geber & Schramm, 1969a, 1969b; Persaud & Ellington, 1967, 1968.

rabbits, respectively. A significant teratogenic effect was reported in mice following intragastric (but not intravenous or subcutaneous) administration of large doses of Δ-9-THC on a specific gestational day (Joneja, 1976). Another team of investigators (Mantilla-Plats et al., *1973;* Mantilla-Plata & Harbison, 1976) reported that the teratogenicity of Δ-9-THC in mice could be modified by pretreatment with phenobarbital and SKF525 A. Phenobarbital partially antagonized THC-induced reduction of fetal body weight while SKF525 A either antagonized or potentiated reduction of fetal body weight depending on the gestational age at which it was administered. In addition, SKF525 A significantly increased the incidence of THC-induced fetal resorptions. By contrast, the studies conducted on rats, mice, rabbits and chimpanzees by the National Institute on Drug Abuse[1] did not show deleterious effects of marihuana on either the pregnant mother or the fetus. Another negative finding was reported by Banerjee et al. (1975), who found that Δ-9-THC produced a dose related increase in the incidence of spongy spinal cords and a decrease in maternal weight gain but was not considered to have a teratogenic effect. Jakubovic et al. (1976) failed to find visible teratogenic effects following Δ-9-THC administration to developing chick embryos. Finally, there is the negative report by Legator et al. (1976). A battery of tests (including the host-mediated assay, microsomal activation, blood and urine studies, dominant lethal and cytogenetic -- micronucleus -- examinations) failed to detect any effect of Δ-9-THC administered orally in the one mouse strain used in all of these studies. By contrast, Uyeno (1973) reported increasing complications associated with Δ-9-THC administration to pregnant rats. Unfortunately, results of a later study (Uyeno, 1975) are not interpretable for lack of controls.

The conflicting reports on teratogenic effects may be due to a number of variables including dosage, route and time of administration as well as the specific strain used. Well-designed research projects are needed to determine under what circumstances marihuana acts as a teratogen in animals and how these findings may be applied to humans. To date, aside from occasional case reports, no systematic human studies on the teratogenic effect of marihuana have been carried out.

HUMAN STUDIES

Chromosome Analyses

The assessment of genetic effects in man has been exclusively based on cytogenetic analysis; specifically, the examination of human chromosomes. In vitro cytogenetic studies did not show an increase

[1]Fleischman et al., 1976; Grilly et al., 1973; Haley et al., 1973; Keplinger et al., 1973; Marihuana and Health, 1973.

in the frequency of chromosome breaks following the addition of Δ-8-THC (Neu et al., 1970), Δ-9-THC (Stenchever & Allen, 1972) and cannabis resin (Martin et al., 1973) to lymphocyte cultures, but did show dose dependent mitotic inhibition. Cytogenetic analyses of lymphocyte cultures from chronic marihuana smokers have been contradictory. The majority of these studies have been retrospective with comparisons made between marihuana smokers and controls. Seven studies of this type have been published. Negative findings were reported by Martin et al. (1973) on a Jamaican population and by Dorrance et al. (1970) on light marihuana users. Gilmour et al. (1971) also reported that light marihuana users did not show an increased frequency of cells with aberrations but that polydrug users, all of whom used marihuana heavily, did show a significant increase in abnormal cells. However, the use of other drugs makes it impossible to interpret this increase as due specifically to marihuana. Nahas et al. (1974) mentioned increased chromosome damage in chronic marihuana smokers but did not provide further information. According to Morishima (1975), this increase was not statistically significant.

The three positive studies of marihuana effects on chromosomes should be interpreted with caution. Stenchever et al. (1974) reported a significant increase in the number of cells with breaks in marihuana users as compared to controls (3.4 percent vs. 1.2 percent). However as stated in the Fourth Marihuana and Health Report (1974), "the biological significance of the findings remained unclear because of several methodological and sampling questions raised by the authors themselves." Herha and Obe (1974) reported increased exchange-type aberrations (dicentrics and translocations) in chronic cannabis users. Close inspection of their data shows that 5 of the 9 aberrations they observed occurred in only 1 of the 11 subjects. Further, chromatid and chromosome breaks, the most commonly reported type of aberrations, were not included in their analysis; when these are considered, there is no longer any difference between users and controls. In the third study (Kumar & Kunwar, 1972) -- the only one to examine chromosomes from direct bone marrow preparations -- the authors reported a statistically significant increase in the frequency of breaks. Again, the increase was accounted for by two of the seven heavy cannabis users; the others showed no breaks. In addition, the total number of cells examined was small, 157 cells for all of the 7 subjects. (In drug studies, 50-100 cells per subject are customarily considered minimal.) Since information on the number of cells analyzed for each subject was not provided, it cannot be determined whether the number was evenly distributed among all subjects.

Retrospective studies such as those cited above, with their many uncontrolled variables, make definitive interpretations and conclusions difficult, if not impossible. To resolve the controversy, prospective studies are needed.

So far, the results of three prospective studies with subjects serving as their own controls have become available, and all have been essentially negative. Nichols et al. (1974) did not detect an

increase in the percentage of cells with breaks following the oral administration of hashish extract (containing THC, CBN and CBD), marihuana extract (Δ-9-THC alone) and synthetic Δ-9-THC to 30 subjects following a variety of schedules. The second study (a 94-day study with 72 days of unlimited smoking of marihuana cigarettes containing approximately 2.2 percent Δ-9-THC) found no increase in the break frequency when baseline and post-exposure values were compared (Matsuyama et al., 1976). In the third study, three groups of volunteers smoked placebo (1 percent or 2 percent natural blend marihuana cigarettes, 1 per day, for 28 days). A temporal sequential design for chromosome analyses was utilized with blood samples taken before, during and after the 28-day smoking schedule (Matsuyama et al., in press). This study is of further interest since it compared the results of independent cultures and analyses by two cytogenetic laboratories which analyzed blood samples from a single venipuncture drawn from a limited number of subjects with a subsequent exchange of slides for reanalysis. Although striking differences in break frequencies between laboratories were observed and differences were demonstrated for both techniques of cell culture and metaphase analysis neither laboratory detected a significant increase in chromosome aberrations with marihuana smoking. However, subjects in these three studies were all marihuana users and their baseline values may already have been elevated above those of non-drug using controls. Thus, even these prospective findings are not definitive.

Effects on chromosome complements have also been published. Leuchtenberger and associates (Leuchtenberger & Leuchtenberger, 1976; Leuchtenberger et al., 1973), using an in vitro exposure of human lung cells, reported a relative increase in aneuploid cells. Even more strikingly, Morishima (1974) reported that in marihuana smokers, a high proportion of cells (30.6 percent) contained from 5-30 chromosomes instead of the normal 46. In a subsequent study (Morishima et al., 1976), the in vitro addition of Δ-9-THC to leukocyte cultures was found to increase the frequency of cells with abnormally low chromosome numbers. The possibility that these types of cells have been overlooked by other investigators as technical artifacts, or that these cells may indeed be technical artifacts, is not settled. Since it markedly reduces the potential for technical artifacts, use of the flow microfluorometry technique to measure DNA content in intact lymphocytes from marihuana smokers and to compare it with DNA content of nonusers may resolve this question.

At this time, there is no conclusive evidence that the consumption of marihuana causes chromosome damage. Indeed, the three prospective studies carried out as part of large biobehavioral investigations on the effects of marihuana did not show increased break frequencies with marihuana consumption. There are no data available, however, on the long-term consequences of marihuana use.

Immune Responses

The immune system of man is compartmentalized into two parts: cell-mediated immunity and humoral- or antibody-mediated immunity. Each is dependent upon a major subpopulation of lymphocytes, the T- or thymus dependent cells and the B- or thymus independent cells, respectively. The initial publication in this area was that of Nahas and associates (1974) reporting that in vitro cell-mediated immunity, as assessed by mitogenic (phytohemagglutinin) and allogeneic cell stimulation, was significantly depressed in 51 chronic marihuana users compared to 81 controls. Indeed, it was depressed to a level similar to that seen in patients with known T-cell immunity impairment (uremia, cancer and transplant patients).

Investigations attempting to replicate this finding have led to contradictory reports. Gupta et al. (1974) compared, by rosette formation, the circulating populations of T- and B-cells in 23 healthy chronic marihuana smokers and 23 normal controls. They found that the mean percentage of T-cells forming rosettes was significantly lower in the marihuana smokers while the percentage of B-cells forming rosettes was similar in both populations. One might conclude, therefore, that smoking impaired T-cell function. Intradermal testing, however, on a limited subsample of marihuana smokers (including those with low or normal percentages of rosette forming T-cells) revealed no correlation with the presence or absence of a positive reaction to one or more antigens tested. Therefore, the results of this study concerning T-cell function are equivocal: When measured by rosette-formation, T-cell function was impaired; when measured by intradermal challenge, it was not. In a follow-up study, the in vitro addition of Δ-9-THC, cannabinol and cannabidiol to control lymphocytes gave a dose related reduction in T-cell rosettes (Cushman, 1976; Cushman & Khurana, 1975). Petersen et al. (1975) also reported significantly lower percentages of rosette-forming T-cells in marihuana smokers, while B-cells remained normal. Although the responsiveness to phytohemagglutinin was not significantly different from that of controls, in that same study the cells from smokers did tend to be less responsive suggesting possible impairment of T-cell function. Serum levels of immunoglobulins G, A and M (a measure of B-cell function) were similar in marihuana smokers and non-smokers. Further, the capability of polymorphonuclear leukocytes to phagocytize killed yeast cells was reduced in smokers (phagocytic activity of polymorphonuclear leukocytes is a necessary prerequisite for the transformation of lymphocytes into macrophages which process antigens in the immune system).

The effects on macromolecular synthesis (i.e., DNA, RNA and protein synthesis) in lymphocyte cultures from normal controls exposed in vitro to many of the natural cannabinoids have been investigated. DeSoize et al. (1975) reported that in vitro addition of the natural cannabinoids (Δ-9-THC, Δ-8-THC, cannabinol, cannabidiol, cannabichromene, and cannabicyclol) to human lymphocyte cultures all affected DNA, RNA and protein synthesis as measured by uptake of 3H-thymidine, 3H-uridine, and 3H-leucine, respectively. Results

obtained by Blevins and Regan (1976) confirmed inhibition of DNA, RNA and protein synthesis following the in vitro addition of Δ-9-THC to human diploid fibroblast, neuroblastoma cells and mouse neuroblastoma cells in culture. Further analysis detected no effect on either DNA repair synthesis or uptake of radioactively labelled precursors into the cell, but did demonstrate that the intracellular pool sizes of these precursors were depressed 50 percent. This last finding could account for the reduced synthesis reported by others.

All of the studies discussed so far point to impairment of cell-mediated immunity in marihuana users. There are others, however, which failed to confirm such impairment. Silverstein and Lessin (1974) in an in vivo study evaluated the immunocompetence of 22 chronic marihuana smokers compared to 60 controls by the gross criterion of ability to be sensitized to DNCB (2,4-dinitrochlorobenzene) and found no differences. White et al. (1975) using both PHA and pokeweed mitogens in an in vitro study, also reported no impairment of mitogen-induced blastogenic response in 12 chronic marihuana users as compared to 12 matched controls. Lau et al. (1975, 1976), in a prospective study, could detect no differences in either peak level of response to PHA or concentration of PHA at which the maximal blastogenic response occurred. However, they did find that in cultures without PHA, the level of 3H-thymidine incorporation was higher in marihuana smokers than in controls. These investigators carried out assessments before and after 14 days of oral doses of 210 mg/day Δ-9-THC and at a one-week follow-up. Rachelefsky et al. (1975) in a prospective study evaluated the immune system of 12 chronic marihuana smokers before and after 64 consecutive days of smoking unlimited quantities of marihuana cigarettes containing approximately 2.2 percent Δ-9-THC. They found that baseline total T-cells and B-cells were significantly lower than controls but increased to normal by the 63rd day, suggesting that factors other than marihuana smoking may have caused the depression seen at baseline. Response to PHA and allogeneic cells was normal and did not change over time; serum levels of immunoglobulins G, A and M were also within normal limits in their study.

Some progress toward reconciling these contradictory findings will be possible when the impact of certain subtle procedural variations becomes known. For example, Nahas et al. (1976b) found that the cytotoxic effect of Δ-9-THC added to 72-hour lymphocyte cultures for the initial 24 hours could be reversed by prolonged washing of the cells with the nutrient medium RPMI. That is, the level of incorporation of tritiated thymidine at 72 hours was the same in treated and non-treated cultures. They surmised that the negative findings by White et al. (1975) may have been the result of the washing procedure used in the isolation of lymphocytes; the cell-bound THC may have been washed away. Nahas et al. (1976b) also found that THC-induced inhibition of thymidine incorporation increased as the serum concentration of the culture medium decreased. This, they suggested, could help resolve an apparent inconsistency between two earlier findings: the Nahas et al. results summarized above (1974), which showed marked inhibition of

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DNA synthesis in a medium with a serum concentration of 10 percent, and a later study (Nahas et al., 1976a) which examined the effect of THC on healthy blood in vitro and found the inhibition to be considerably less with a serum concentration of 20 percent. However, even this may not be an adequate explanation since in the first study fetal calf serum was used and in the second, pooled human serum.

There is general agreement among investigators that marihuana smokers taken off the street and tested have a reduced number of T-cells as measured by rosette formation. In light of the report by Rachelef sky et al. (1975) that the initially low level of T-cells returned to normal while subjects were confined on a ward smoking quality controlled marihuana cigarettes, it may be concluded that some as yet unidentified variable, and not marihuana, may be the cause of the reduced number of T-cells seen in chronic drug users. The relationship between reduced T-cell rosette formation and immunologic function, as assessed by mitogen and/or allogeneic cell stimulation, is not clear since Petersen et al. (1975) reported a significantly lower mean percentage of T-cells in marihuana smokers than controls, but no statistically significant differences in PHA responsiveness. There is as yet no evidence that marihuana smokers are more susceptible to diseases known to be associated with lower percentages of T-cells (e.g., cancer, viral infections) and/or reduced responsivity to mitogens. Also, skin testing of chronic marihuana smokers indicates intact and normal T-cell functions. B-cell function, too, appears to be normal regardless of how assessed.

SUMMARY AND CONCLUSION

The retrospective design and other methodological imperfections of most human studies, whether chromosomal or immune, leave much to be desired and preclude definitive conclusions concerning the effects of marihuana on the genetic and immune systems. For example, information on nutrition, health care, recent radiation exposure and drug use pattern -- all of which are variables known to affect both the genetic and immune systems -- is generally obtained retrospectively from the participating subjects and is, therefore, of dubious validity. The potential inaccuracy of such information may doom any attempt to identify a deleterious effect of a specific drug, like marihuana, even were the composition of illicitly obtained marihuana known. Many of the other methodological questions now plaguing researchers could be settled by the collaboration of several laboratories, particularly those reporting contradictory findings, in a single prospective double-blind research design with appropriate control groups.

There is no information on the teratogenic effects in humans and it may take several generations to detect them. The reports on teratogenic effects in animals are contradictory and further rigidly designed experimental studies are needed to supplement the few done so far.

Bearing in mind the limitations of the studies discussed in this report, there is at this time no conclusive evidence that the consumption of marihuana causes chromosome damage. The studies which have been most carefully controlled have failed to show such damage, but insufficient research has been conducted to allow any definitive conclusions.

A number of investigators have reported results indicating that marihuana may interfere with cell-mediated immunity, but until the inconsistencies between these findings and the negative results which have also been reported are resolved, and until the implications of particular procedural variations are more clearly understood, the question of whether or not THC impairs cell-mediated immunity in humans remains a moot one. There is preliminary evidence, however, that in certain rodents Δ-9-THC depresses cell-mediated immunity and preferentially inhibits DNA synthesis in tumor cells as compared to cells of normal tissue. It is important, therefore, to verify the antiimmune and antitumor activity of Δ-9-THC in animals since, if these findings are confirmed and found to hold true for humans, Δ-9-THC may have potential as an immunosuppressing and antineoplastic agent.

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Chapter 9
THERAPEUTIC ASPECTS

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While cannabis is one of the most ancient of drugs used for medicinal purposes, this is no reason to expect that it would pass today's stringent tests of efficacy and toxicity. Nor should one summarily dismiss the possibility that cannabis may have some therapeutic utility simply because the plant is currently the subject of socio-political controversy. The controversy makes its impartial evaluation more difficult, but its potential benefits should be studied with the same careful pre-marketing procedures used for other investigational drugs.

Furthermore, if some substantial utility is found, marihuana itself will not be the marketed product; it is a complex mixture of over a dozen cannabinoids, about 30 terpenes, assorted sterols and other substances, most of which do not contribute to a desired therapeutic effect. Even its active cannabinoids can be improved upon for specific indications by synthetic chemists. The benzopyran structure is an unique one, and it can be modified at many positions on the molecule: if the psychological effects are not desired, they can be eliminated; if water solubility or a longer shelf life is preferred, that can be achieved. Although much more testing is needed, there is promise that certain of the pharmacologic actions of cannabis and its derivatives can be helpful for specific conditions.

As we survey those specific indications for which cannabis may be useful, some appear more promising than others. It is now reasonable to believe that intraocular pressure is reduced by cannabis in both normal subjects and in glaucoma patients with ocular hypertension. Δ-9-THC is the most potent agent for this purpose, and when a safe, topically-instilled ophthalmic preparation is developed, it may come to be a helpful medication in the management of some wide-angle glaucoma patients. Although satisfactory antiglaucoma preparations are now available, there is a suggestion that an occasional patient responds better to Δ-9-THC than to those drugs currently in use.

Both asthmatics and normal subjects respond with bronchodilation to aerosolized, smoked or oral Δ-9-THC as well as they do to the conventional antiasthmatic medications. A next logical step will be the development of a non-intoxicating pharmaceutical preparation such as an aerosol or a non-intoxicating congener with bronchodilating properties. Marihuana itself, although a bronchodilator, is unsatisfactory because of its direct irritant effect upon pulmonary tissues.

Further studies will determine whether Δ-9-THC is sufficiently useful clinically in ameliorating the anorexia, nausea and vomiting of cancer chemotherapy patients. In such patients, the standard antiemetics are only partially effective, and a superior, new compound would be quite desirable. Patients in such investigations could also be studied to evaluate the appetite enhancing and antianxiety effects of Δ-9-THC.

Except for isolated case reports, no recent work has been reported in which a cannabinoid was employed for the treatment of epilepsy in humans. The animal data are encouraging, but the finding that Δ-9-THC is also a convulsant in certain animal strains requires caution. Cannabidiol or one of the synthetics may turn out to be the preferred agent in certain convulsive disorders if the animal work can be extrapolated to the convulsant syndromes in humans.

In a number of conditions, the evidence of the clinical effectiveness of the cannabinoids remains either preliminary or ambiguous. These include the utility of Δ-9-THC as an hypnotic, as a treatment for depression and as an antitumor agent. It appears to offer no advantage over existing pre-anesthetic agents. On the basis of available studies, its analgesic efficacy remains in doubt, despite its widespread use in folk medicine for this purpose. In addition, it would have to compete in the marketplace with existing effective and stable analgesic compounds. No evidence exists that the cannabinoids are superior to available preparations now in use in the detoxification of drug or alcohol dependent persons. The possibility that hemp may have topical antibiotic activity should be pursued.

In addition to the possibility that therapeutic benefits may, one day, accrue, another reason for studying the potential medicinal value of the cannabinoids is the possibility that their mechanisms of action may be different from the currently available medicaments. In this case, the elucidation of these mechanisms would be even more significant than the mere discovery of another therapeutic agent. A possible explanation for cannabis' precise mode of action is its inhibitory action on prostaglandin synthetase. Adrenergic stimulation has also been noted at certain end organs, a finding which has led to the investigation of the influence of the cannabinoids on various neurotransmitters; no definitive findings have been reported, however.

Recently, a large series of synthetic benzopyrans have been produced by modifying the cannabinoid structure. These or related analogues may come to be the preferred therapeutic substances. They have been designed to provide a selective action either with or without the psychic effects of cannabis. Some of the synthetic benzopyrans are water soluble, permitting more reliable gastrointestinal absorption and making parenteral administration less difficult.

A promising start has been made in the scientific exploration of the therapeutic potential of the cannabinoids although much more work

is needed before any compound will be approved for general medical use for any indication.

A noteworthy effort in assessing the therapeutic potential of marihuana and its constituents was made at the first conference assembled for that purpose during November, 1975 at the Asilomar Conference Center, Monterey, California. Sponsored by the National Institute on Drug Abuse (NIDA), the conference included 28 papers related to preclinical or clinical therapeutics (Cohen & Stillman, 1976).

THE ANCIENT LORE

The use of cannabis for purposes of healing predates recorded history. The earliest written reference is found in the 15th century B.C. Chinese Pharmacopeia, the Rh-Ya (Emboden, 1972). Cannabis had many uses as a medicinal herb in China; these are mentioned in the first or second century A.D. Pen Ts'oo Ching (Rubin, 1976) and are based upon traditions passed down from prehistoric times. In this ancient pharmacopeia, a boiled hemp compound given to surgical patients as an anesthetic is described. From the Chinese plateau, the use of hemp as a folk medicine, ritual potion, condiment and intoxicating agent spread to India, the Middle East and beyond.

Rubin has reviewed the cross-cultural uses of cannabis, some of which are repetitive, but others are unusual. In Viet Nam, for example, cannabis was used to prevent memory loss and mental confusion, to eliminate blood wastes and to treat gynecological and obstetrical problems, such as dysmenorrhea. Allergies and rheumatism were treated by a preparation made by pulverizing roasted cannabis kernels (seeds?) in baby's urine and taking a small glass of the extract three times a day. It was also employed as a cure for falling hair and tapeworm.

In Cambodia, ganja was used for other purposes, such as restoring appetite. Hemp cigarettes, smoked daily, were also supposed to reduce polyps of the nose and relieve asthma. The Cambodians also administered hemp preparations to facilitate contractions during difficult childbirth.

An examination of the multiple, diverse claims made for the therapeutic benefits of cannabis during earlier epochs reveals that many cannot be justified from our current knowledge of its pharmacologic activity. For example, it had a purported effectiveness in cases of leprosy, gonorrhea and arsenic poisoning. The smoke was tried as an enema for strangulated hernia and juice of the leaves was recommended for dandruff, vermin infestation and for a variety of other skin conditions, usually as a lotion or poultice.

On the other hand, some justification can be found for certain of the ancient medical applications. Cannabis was frequently used for

painful conditions like neuralgia, dysmenorrhea and toothache. Because of its analgesic effect, only partially supported by recent research findings, it also found service in minor operations like circumcision and boil lancing. Its relaxant and euphoriant properties may have been exploited in the management of psychological problems, such as melancholia and hysteria.

A number of therapeutic references can be found involving the seeds of Cannabis sativa L. (Grinspoon, 1971). For example, seventh century Scythians inhaled and bathed in the vapors of hemp seeds thrown on hot coals, and "they howled with joy." This apparently euphoriant effect is doubtful, however, since the seeds contain essentially no Δ-9-THC, and are usually discarded when marihuana is "manicured." Whatever joy the Scythians experienced must have been due to the effects of the sauna. Interestingly, the inhalation of hemp vapors remains a popular form of administering cannabis for toothache in parts of the Ukraine, the same region where Scythians once lived.

Earlier and more recent reports about an aphrodisiac property are not as easily evaluated. Much seems to depend upon the mental set of the consumer. If it is taken for that purpose, sexual interest, activity and enjoyment are likely to be enhanced. However, cannabis was also utilized by sexually abstinent Buddhist monks to diminish sex drives and aid in meditation. While marihuana may enhance sensory perception, prolong the subjective experience of time and reduce inhibitions, thus intensifying the sexual experience, it appears to have no direct effect upon sexual drive states (Cohen, 1975). In fact, in view of reports of lowered plasma testosterone levels after chronic, heavy smoking, there remains the possibility that potency could actually be reduced (Kolodny et al., 1976).

One interesting effect of bhang and ganja mentioned in the Report of the Indian Hemp Drugs Commission (1969) and, more recently, in the Jamaican (Rubin & Comitas, 1975) and Colombian field studies (Rubin, 1976), is the assertion that it is a "creator of energy," that it increases staying power, relieves fatigue and acts as a stimulant. The Jamaican report tells of its use as an energizer and motivator to work. Ganja breaks in the Jamaican hinterland seem to be the equivalent of North American coffee breaks. Employers have been known to supply their employees with ganja to get more work out of them. In Colombia, marihuana is smoked by day-laborers and peasants to reduce fatigue and to give "spirit for working." This energizing effect is the principal motivation for use reported by Jamaican working class males and is in sharp contrast to American concerns about the marihuana-induced "amotivational syndrome." These conflicting effects are probably reflections of the importance of expectations in determining which pharmacologic effects will become manifest.

Rubin (1976) also points out another facet of the preponderant impact of psychophysiologic set over pharmacologic action of a drug like cannabis when taken in moderate dosages. As mentioned above, it is used as a stimulant during the day among unskilled laborers in

Jamaica, but is also taken for its sedative effect at night to promote sleep. We should not be confused about this apparent paradox, since we do the same with our most popular intoxicant, alcohol. Americans drink at social gatherings to achieve a stimulating effect and take a nightcap a few hours later to produce drowsiness. This practice is our contribution to the power of expectation in determining drug action.

Cannabis was one of the more important drugs in the Indian Materia Medica at the turn of the century. It was, and still is, widely used in rural areas of the Indian subcontinent for asthma, bronchitis and loss of appetite. Although a bronchodilator action has recently been quite well established (Tashkin et al., 1974; Vachon et al., 1976b), cannabis is likely to be a cause of, rather than a cure for, bronchitis. Its appetite-stimulating activity is confirmed in numerous subjective reports, although no precise mode of action for this effect is known.

THE MIDDLE PERIOD

During the latter half of the 19th century, a resurgent interest in the medical usefulness of the hemp plant developed. Over 100 papers appeared on the subject in the medical journals of the day, some of which are worth citing briefly.

In Calcutta, O'Shaughnessy (1842) administered cannabis to patients with a variety of ailments, including tetanus, rabies, epilepsy and rheumatism. He reported favorably on its anticonvulsant, analgesic and muscle-relaxing properties. His article sparked a flurry of clinical studies, including those of M'Meens (1860), who considered the drug to be a sedative-hypnotic and of value in such diverse disorders as neuralgia, dysmenorrhea, asthma and sciatica. Other favorable papers appeared, including those of Birch (1889) and Mattison (1891) who recommended cannabis enthusiastically for the treatment of morphinism, alcoholism and other addictions. Reynolds (1890) wrote of its value in senile insomnia and in tic doloureux (trigeminal neuralgia). During this same period, Moreau de Tours (1857) used cannabis successfully to treat a variety of psychiatric syndromes, including melancholia and obsessive-compulsive neurosis. His positive findings in managing mental disorders were confirmed by some investigators, and challenged by others.

Despite these encouraging testimonials, cannabis began to slip into disuse. By the beginning of the 20th century, several factors had combined to account for its neglect by Western medicine:

1) A standardized preparation was not available. Different batches of the plant had widely varying potencies, from essentially inactive to much stronger than the prescriber anticipated.

2) The drug had an unsatisfactory shelf life. Some of the

extracts and fluid extracts were practically inert if they were dispensed a few years after they were obtained from the pharmaceutical firm. Δ-9-THC gradually breaks down into inert cannabinol when stored at room temperature and exposed to light and air. The dried leaves of Cannabis sativa L. and its pharmaceutical preparations were quite unreliable after storage, and some of the contradictory clinical results might be explained on this basis.

3) Δ-9-THC is completely insoluble in water and is absorbed across the gastrointestinal mucosa with some difficulty. Therefore, the oral route of administration is not completely reliable. This may be the reason that swallowed Δ-9-THC is two to three times less effective by weight than the smoked drug.

4) By the early 1900's, a series of synthetic, water soluble analgesics and sedatives with a much more stable and predictable pharmacologic action had begun to appear. This resulted in a diminished need for and use of cannabis and other botanicals.

5) The final blow to interest in marihuana as a therapeutic agent was the Marijuana Tax Act of 1937 which classified the drug as a narcotic. By that year, however, it was essentially no longer prescribed in the United States.

Even after the first synthetic tetrahydrocannabinol, pyrahexyl (Synhexyl), was produced in 1940, it was not widely employed, although it was tried in the treatment of the depressions, the epilepsies and the addictive states. Some work was done with this synthetic by Thompson and Proctor (1967), who treated certain drug withdrawal syndromes with some success. In what may have been the first double blind study with a cannabinoid, Parker and Wrigley (1950) gave pyrahexyl or a placebo to 57 depressed patients, but were unable to demonstrate a significant difference between the experimental and control groups. Later this study was criticized by Grinspoon (1971) for having used an inadequate dosage level. At any rate, both favorable and unfavorable reports with pyrahexyl are to be found in the literature.

The value of these earlier reports is questionable, except perhaps as preliminary clinical explorations. They were usually uncontrolled and impressionistic, and were not carefully designed. Still, they did provide certain clues that were helpful to subsequent investigators.

Between 1950 and 1965, a series of 30 papers on cannabis were published by Czechoslovakian scientists, principally from the Medical Faculty of the Palacky University of Olomouc. Eighteen of the reports[1] dealt with the use of cannabis as a topical antibiotic.

[1]Hubacek, 1955; Kabelik, 1955, 1957; Kabelik et al., 1960; Krejci 1950, 1952, 1955, 1958, 1961a, 1961b; Krejci & Heczko, 1958; Krejci et al., 1959; Krejci & Vybiral, 1962; Navratil, 1955; Procek, 1955; Simek, 1955; Sirek, 1955; Soldan, 1955.

Kabelik et al. (1960) surveyed thousands of plant varieties for their antibiotic activity and reported that more than 500 cases of herpes labialis and ulcerous gingivitis were successfully treated with a hemp salve or spray. Hubacek (1955) used cannabis in otorhinolaryngological conditions including otitis media, chronic sinusitis and tonsilopharyngitis with good results. The Czechoslovakian orthopedists injected cannabis solutions into a few osteomyelitic fistulas with healing results in some cases. An analgesic effect is often mentioned in these papers, as in two cases of second degree burns. The reports are not widely known, nor have they been confirmed, partly due to their publication in journals that are not widely circulated outside of Czechoslovakia.

THE CURRENT PERIOD

The systematic study of the clinical pharmacology of cannabis did not evolve until the last decade. A number of scientific accomplishments and administrative decisions were required before a modern scientific program could develop. These events included:

1) The total synthesis of Δ-9-THC by Mechoulam and Gaoni (1965), permitting the manufacture of sufficient supplies of pure material for investigators.

2) The elucidation of the relationship between the pharmacology of cannabis and Δ-9-THC indicating that the latter was responsible for most of the activity of the whole plant (Mechoulam et al., 1970).

3) The development of a reliable source of uniform, assayed marihuana grown at the University of Mississippi (Quimby et al., 1973) under contract to NIDA.

4) The availability of a reliable quantitative procedure for Δ-9-THC and other cannabinoids.

5) The development of satisfactory controls for obtaining cannabis or a variety of cannabinoids from NIDA for research purposes.

6) A forward plan designed to fund grants and contracts that would clarify the physiologic, pharmacologic and psychologic properties of cannabis.

7) The recent development of assay procedures for the qualitative analysis of cannabinoids in biological fluids (Agurell et al., 1973).

In the overall pharmacological assessment of cannabis, the drug was found to have effects that were potentially therapeutic. The areas of possible therapeutic application can be placed into two general groups: those that utilize the psychologic changes induced by the

drug, and those that do not. In the latter instance, the well-known subjective symptoms are often considered undesired side effects by the patient.

The therapeutic uses that do not utilize the mental effects of the drug include intraocular pressure reduction, bronchodilation, anticonvulsant action and tumor growth retardation. Those therapeutic trials that rely on the mental changes include the evaluation of marihuana's effectiveness as a sedative-hypnotic, analgesic, antidepressant, tranquilizer, pre-anesthetic, antinauseant, antiemetic, antianorexiant as well as its utility in the areas of drug and alcohol dependence.

Intraocular Pressure (IOP) Reduction

Hepler and Frank (1971) studied the spectrum of physiologic ocular changes produced by smoking marihuana. Among their early findings was a consistent, dose-related, clinically significant reduction of intraocular pressure (IOP) in normal subjects. The IOP was also reduced with doses of oral Δ-9-THC, Δ-8-THC and, to a much lesser degree, with cannabinol and cannabidiol. Publications by Shapiro (1974), Purnell and Gregg (1975), and Green and Podos (1974) have confirmed the IOP-reducing effect of marihuana and the tetrahydrocannabinols. Flom et al. (1975) suggested that the lowering of IOP was apparently secondary to a relaxing and euphoriant effect. However, when Hepler gave subjects full doses of diazepam (Valium) blind, he found that the IOP reduction was not significantly different from the effect of a placebo.

Twelve open angle glaucoma patients were studied by the UCLA group (Hepler et al., 1976). In 10 of the 12, impressive reductions in ocular hypertension were achieved. The reduction averaged 30 percent and lasted 4-5 hours. In two instances, however, the smoked marihuana or ingested Δ-9-THC failed to induce a pressure reduction. The IOP-reducing effects of cannabis appear to be additive to the conventional glaucoma medications. In a preliminary study of a topically applied eye drop preparation of Δ-9-THC in sesame oil, 12 rabbits showed a 40 percent IOP reduction when compared to those treated with sesame oil alone.

Green (1975) and his associates (Green & Kim, 1976, 1973; Green et al., 1976) demonstrated a decrease in the IOP of rabbits given intravenous Δ-9-THC. They postulated that Δ-9-THC interacts with the adrenergic innervation system of the eye; in other words, that α-adrenergic blockade would dampen the Δ-9-THC effect. Apparently, ß-adrenergic blockade also partly inhibits the Δ-9-THC effect. The end result of the adrenergic stimulation by Δ-9-THC appears to be a dilation of the efferent blood vessels, modulated by an inhibition of prostaglandin synthetase. Green and Kim (1973) have concluded that the outflow facility may be regulated by adrenergic receptors with Δ-9-THC acting as a vasodilator of the outflow blood vessels of the anterior uvea. There is also the possibility that cannabis acts to constrict afferent episcleral plexus vessels.

In further studies in rabbits, Green et al. (1976) found that Δ-9-THC dissolved in light or heavy mineral oil penetrates ocular tissues better than Tween 80 or sesame oil. A 0.1 percent solution of Δ-9-THC produced an IOP reduction approximately equal to one marihuana cigarette. When the ophthalmic solution was applied to one eye, Green et al. found that the second eye had a lesser pressure reduction with a later onset, indicating systemic absorption of the drug.

Cooler and Gregg (1976) compared intravenous doses of 1.5 mg and 3 mg of Δ-9-THC, 10 mg diazepam and a placebo in 10 normal volunteers. IOP was diminished 29 percent with the low and 37 percent with the high dosages of Δ-9-THC. Diazepam lowered pressures 10 percent and the placebo 2 percent. These investigators also measured analgesia and noted no cutaneous or periosteal analgesic effects. The anxiety and dysphoria levels increased at both strengths of Δ-9-THC, but not with diazepam or the placebo. Intravenous Δ-9-THC appears to evoke anxiety much more often than when administered by the smoked or oral route.

Mechoulam et al. (1976) produced ocular hypertension in rabbits by means of α-chymotrypsin injections into the eyeball. They tested a series of compounds and observed that 2 percent pilocarpine and 0.001 percent Δ-9-THC were comparably potent while cannabidiol and cannabinol showed practically no effects.

As a matter of interest, the Food and Drug Administration (FDA), with the cooperation of NIDA and the Drug Enforcement Administration (DEA), has recently granted permission for a patient with glaucoma to be treated with marihuana cigarettes under an Investigational New Drug application from an ophthalmologist at Howard University. The subject was one of the patients in the previously cited study of Hepler et al. (1976), and was found to respond better to Δ-9-THC than to the traditional antiglaucoma medications.

Bronchodilation

Two lines of research, that of the Vachon group and the work of Tashkin and his collaborators, have clarified a number of questions about the effects of cannabis upon bronchial diameter. Vachon et al. (1973) observed the effects of a single administration of smoked marihuana on normal subjects and on asthmatic patients. They found that airway resistance decreased significantly in the normal group, permitting specific airway conductance and mean expiratory flow rates to increase. In the asthmatics bronchoconstriction was reversed for hours. From subsequent animal work, Vachon et al. (1976a) assume that the bronchodilation that follows Δ-9-THC administration involves the adrenergic system. Recently, Vachon et al. (1976b, 1976c) used a microaerosolized Δ-9-THC spray in 10 asthma This aerosol was found to decrease airway resistance by an average of 16 percent at 90 minutes and increase flow rates without any significant tachycardia or high.

Tashkin et al. (1973) conducted a double blind study of 32 non-naive male subjects randomly assigned to groups smoking a placebo, using 1 percent Δ-9-THC and 2 percent Δ-9-THC. They found that both experimental dosages decreased airway resistance with a peak occurring 15 minutes after administration. Activity was still present after an hour. In a later study (1974), they examined dose-response curves with oral placebo, 10, 15 and 20 mg of Δ-9-THC. Peak effects for the active drug were obtained at three hours with persisting effects for six hours.

Tashkin et al. (1975) also induced bronchospasm in asthmatics with either methacholine or exercise. Utilizing a single blind method, 10 mg of smoked Δ-9-THC was compared with 1.25 mg of inhaled isoproterenol (Isuprel), both drugs having appropriate placebo controls. Bronchospasm was promptly relieved by both active drugs and not by their placebos. The isoproterenol had a quicker and higher peak effect, while Δ-9-THC had a longer duration of action.

Tashkin et al. (1976b) also tried to clarify the mechanism of marihuana's bronchodilator action. In one set of experiments, 16 normal young males were either injected with atropine or smoked a cigarette containing 10 mg of Δ-9-THC, and then received a methacholine challenge. In contrast to atropine, the Δ-9-THC-induced increase in specific airway conductance was not blocked by methacholine.

In succeeding experiments, combinations of propanolol and Δ-9-THC induced increases in specific airway conductance. This bronchodilator effect of cannabis may be independent of ß-adrenergic or antimuscarinic mechanisms.

In a recent article, Abboud and Sanders (1976) report on a double blind study involving six asthmatics and six control patients who were given oral Δ-9-THC in 10 mg doses. They concluded that oral administration of Δ-9-THC is unlikely to be of therapeutic value in asthma since its bronchodilator action is mild and inconstant. In addition, it is associated with significant CNS effects (mild depression and hangover). Moreover, one asthmatic patient in the study developed severe bronchoconstriction following the ingestion of Δ-9-THC.

Tashkin et al. (1976b) and Olsen et al. (1975) have attempted to improve the delivery of Δ-9-THC to the bronchioles by using an inhalation aerosol, since the use of marihuana cigarettes for this purpose is considered undesirable because of irritants, and possibly even carcinogens, in the smoke. Furthermore, the tachycardia end the psychic effects may not be desirable in asthmatics. A dose of 10 mg of Δ-9-THC in a specially prepared aerosol produced substantial therapeutic levels of bronchodilation with lesser degrees of tachycardia and high than with a comparable oral amount. Unfortunately, the aerosol has a localized irritant effect that makes use in its current form undersirable.

Despite its bronchodilating effect, marihuana smoke is an irritant

and, thus, interferes with other aspects of bronchial dynamics (Tashkin et al., 1976a). In addition, Huber et al. (1975) noted that alveolar macrophages harvested from rats by lavage, later incubated with Staphylococcus albus and graded amounts of marihuana smoke, caused a sustained dose-related depression of bactericidal activity. The reduction in bacterial macrophage activity was present in the gas phase and was water soluble. Further studies with purified Δ-9-THC indicated that the impairment in alveolar macrophage function was not related to either the psychic or the bronchodilating components of marihuana.

Anticonvulsant

Most of the work investigating the anticonvulsant properties of cannabis has been preclinical. The effects of cannabinoids on animal seizures induced by pentylentetrazol (Metrazol), audiogenic or electrical stimulation have been recently examined. Consroe and his associates (Consroe et al., 1973, 1975b; Consroe & Man, 1973) found that Δ-8- and Δ-9-THC blocked all three types of seizures in a dose-related manner. These drugs were qualitatively comparable to diphenylhydantoin (Dilantin). Boggan et al. (1973) also confirmed the effect of Δ-9-THC in mice with induced audiogenic seizures.

Dwivedi and Harbison (1975) found that Δ-8- and Δ-9-THC, marihuana extract and uridine protected against pentylentetrazol-induced convulsions in mice. None of these drugs protected against maximal electroshock-induced convulsions. The authors found that their anticonvulsant effects were not additive to diphenylhydantoin, but were additive to phenobarbital. Therefore, their mechanism of action may be similar to that of diphenylhydantoin but different from that of phenobarbital.

Sofia et al. (1976) determined that both Δ-9-THC and diphenylhydantoin decrease polysynaptic transmission and post-tetanic potentiation. They concluded from their experiments on mice that there may be a clinical usefulness for a compound such as Δ-9-THC which combines some degree of the anticonvulsant specificity of diphenylhydantoin with the general sedative effects of phenobarbital and chlordiazepoxide.

Rat hippocampal seizures precipitated by afferent electrical stimulation were studied by Feeney et al. (1973) to determine whether a series of cannabinoids would be effective. The cannabinoids were found to be more effective than diphenylhydantoin in diminishing the seizure discharges. Cannabidiol was the most potent, followed in order of effectiveness by cannabinol, Δ-9-THC and Δ-8-THC. In this study, the psychologically inactive cannabinoids outperformed the active ones.

Karler et al. (1973, 1974a, 1974b) demonstrated that tolerance developed to the antiseizure property in the maximal electroshock test. Their subjects were rats treated with Δ-9-THC and mice treated with Δ-9-THC, cannabidiol, diphenylhydantoin and pheno-

barbital. In other electrical seizure models, tolerance was variable and specific for each model. Karler et al. considered it possible that cannabidiol, which has no psychotoxicity or cardiotoxicity, has the further advantage of being a better anticonvulsant than Δ-9-THC. Turkanis and Karler (1975) investigated the post-tetanic potentiation of bullfrog paravertebral ganglia in vitro using 7-hydroxy-THC, 6α-7-dihydroxy-THC, Δ-9-THC, cannabidiol, diphenylhydantoin and phenobarbital. Both hydroxy-THC metabolites and cannabidiol markedly depressed the post-tetanic potential at 30 to 90 minutes. Diphenylhydantoin depressed it moderately and Δ-9-THC and phenobarbital had no effect. In this instance, the hydroxylated metabolites showed activity different from that of the parent compound.

Carlini et al. (1975) confirmed that cannabidiol may be the best cannabinoid anticonvulsant. Albino mice were administered transcorneal electroshocks and treated with either cannabidiol, cannabidiol-aldehyde acetate, 6-oxo-cannabidiol acetate, 6-hydroxy-cannabidiol triacetate or 9-hydroxy-cannabidiol triacetate. Cannabidiol and 6-oxo-cannabidiol acetate had the best anticonvulsant effect and therefore merit further study.

Johnson et al. (1975) determined the anticonvulsant activity of intravenous Δ-9-THC in epileptic chickens by intermittent photic stimulation and pentylentetrazol. Cannabis reduced the severity and incidence of seizures produced by intermittent photic stimulation. A reduction in frequency of inter-ictal, slow-wave, high voltage EEG; activity and an absence of spiking was also noted. Δ-9-THC had no effect on the incidence of pentylentetrazol-induced seizures.

Ten Ham et al. (1975) gave 20 mg/kg of Δ-9-THC for six days to gerbils with spontaneous epileptiform seizures. No effect was seen on the latency, duration or severity of the seizures. At a 50 mg/kg dose level, seizures were completely abolished after a single injection, but tolerance developed within six days. Severe toxicity occurred at the 50 mg/kg dosage level.

Wada et al. (1975) reported that Δ-8-THC and Δ-9-THC failed to affect the myoclonic response to photic stimulation in the Senegalese baboon. However, both drugs exerted dose-related antiepileptic effects upon established kindled convulsions provoked by electrical stimulation of the amygdala. The antiepileptic action of the two THC isomers appears to be caused by a suppression of propagation of the induced afterdischarge to distant cerebral structures, although high doses also suppress the afterdischarge at the site of stimulation. In previous investigations, Wada et al. (1974) and Corcoran et al. (1973) had reported that Δ-9-THC transiently suppresses the clinical and EEG seizure manifestations caused by subcortical stimulation in rats and cats.

Convulsant as well as anticonvulsant activity can be demonstrated with cannabinoids. The former is usually noted when toxic or high, chronic doses are used. However, Consroe et al. (1976) have bred a

strain of New Zealand rabbit that is quite susceptible to Δ-9-THC seizures. Doses of 0.1-0.8 mg/kg i.v. produced behavioral seizures regularly in these animals. In addition, spontaneously epileptic beagles were given varying doses of Δ-9-THC, cannabidiol or a placebo for 20 days. Myoclonic jerks and generalized seizures were observed in those dogs receiving 3-5 mg/kg of Δ-9-THC orally (Feeney et al. 1976).

Little work has been done in humans with cerebral dysrhythmias. The Davis and Ramsey (1949) study was a pilot effort that examined the effect of tetrahydrocannabinols in epileptic, hospitalized children who had been receiving diphenylhydantoin or mephenytoin (Mesantoin). Two children showed improvement on one cannabinoid, but transfer to a second cannabinoid gave mixed results. Perez-Reyes and Wingf ield (1974), in a case report, mentioned that intravenously infused cannabidiol did not reduce, and may have increased, the abnormal EEG; activity of a 24-year-old man with centricephalic epilepsy. In this case, symmetrical spike and wave activity appeared only during light sleep. The 40 mg cannabidiol injection may have increased the dysrhythmia even though it produced a diminution in its intensity after awakening. Another case report (Consroe et al., 1975b) suggests that smoked marihuana may have a beneficial action in some types of human epilepsy. On the other hand, Keeler and Reifler (1967) suggest that marihuana may be detrimental in epileptics with grand mal convulsions. Feeney (1976) surveyed epileptics concerning illegal drug use. Practically none over 30 years of age reported illicit drug use, but 29 percent under 30 mentioned marihuana smoking. Only 4 percent had discussed the matter with their physicians. Most reported that it had no effect; one stated that it decreased epileptic seizures and another said that it caused his seizures.

The problems encountered with Δ-9-THC (insolubility, variable oral absorption, psychotoxicity, tachycardia and the possibility of a convulsant capability) have resulted in the production of a series of synthesized benzopyrans. In particular, three analogues of dimethylheptylpyran (DMHP) were found to exhibit significant anticonvulsant activity against audiogenic, supramaximal electroshock and maximal pentylentetrazol-induced seizures in mice (Plotnikoff, 1976). In rats, these compounds were found to be more active than diphenylhydantoin in the supramaximal electroshock test. One of them, SP-175, showed a different profile of anticonvulsant activity than DMHP or Δ-9-THC. On the basis of five-day studies of diphenylhydantoin, phenobarbital, DMHP and SP-175 in mice, tolerance was not found to develop.

Retardation of Tumor Growth

Harris et al. (1976) have reported that mice innoculated with Lewis lung adenocarcinoma showed tumor size reductions ranging from 25-82 percent depending on the dose and duration of treatment with oral Δ-8-THC, Δ-9-THC and cannabinol. No reductions were found with cannabidiol. The effective cannabinoids increased survival time

from one-quarter to one-third compared to a 50 percent increase with cyclophosphamide. Friend leukemia virus growth was inhibited by Δ-9-THC, but L1210 murine leukemia was not. In vitro experiments confirmed the inhibition of neoplastic growth in mice, leading the authors to conclude that certain cannabinoids possess antineoplastic properties by virtue of their interference with RNA and DNA synthesis. In a later study (Harris, 1976), other tumor systems and other cannabinoids were tested. He found that cannabidiol seems to have a growth-enhancing, rather than reducing, effect on the Lewis lung tumor.

White et al. (1976), working with Lewis lung cell cultures exposed to Δ-9-THC concluded that at non-toxic doses, the drug inhibits replication after thymidine uptake. This cytotoxicity may be related to Δ-9-THC's extreme lipophilia, and, therefore, the results are related to effects on membrane function.

Antibacterial Activity

In an effort to replicate the work of Kabelik (1957) and Krejci (1958) mentioned earlier, van Klingeren and ten Ham (1976) tested the antibacterial activity of Δ-9-THC and cannabidiol. Broth cultures of staphylococci and streptococci were innoculated with varying concentrations of Δ-9-THC and cannabidiol. They found that both substances were bacteriostatic and bactericidal, but were ineffective against gram negative bacilli. When horse serum was incorporated, the antibacterial effect was greatly reduced, presumably due to protein binding. The utility of these cannabinoids as a topical antibacterial, as suggested by Krejci, seems to have been confirmed on an in vitro basis.

Those therapeutic studies that utilize the psychologic effects of marihuana follow.

Sedative-Hypnotic Action

Sofia and Knobloch (1973) demonstrated that pretreatment of laboratory animals with Δ-9-THC reduces the dose of barbiturates needed for hypnosis and increases total sleep time. Freemon (1974) confirmed the observation of other investigators that Δ-9-THC, like most hypnosedatives, reduces REM time. However, in contrast to other hypnotics, the abrupt withdrawal of Δ-9-THC after six consecutive nights of usage failed to produce a REM rebound, although mild insomnia was observed.

Feinberg et al. (1976), using both marihuana extract and Δ-9-THC, found that both drugs reduced REM activity and increased Stage IV sleep. Abrupt withdrawal led to considerably increased amounts of REM sleep and a transient decrease in Stage IV sleep. The difference in these findings from those of Freemon and others may be due to the large amounts of Δ-9-THC given the subjects. Feinberg's subjects received from 70-210 mg per day.

In an attempt to exploit the well known relaxing and sedating effects of cannabis, two studies were performed by Neu et al. (1976). In the first study, nine subjects with sleep difficulties were given 10, 20 or 30 mg. of Δ-9-THC or a placebo at weekly intervals using a double blind method. The drug, as compared to the placebo, significantly reduced sleep latency. Furthermore, sleep was less interrupted during the drug nights. Side effects were mild, but they increased with increasing dosage. The chief complaint was a hangover the next day. In the second study, the Δ-9-THC doses were reduced to 5, 10 and 15 mg in order to avoid side effects. These were compared to a placebo and to 500 mg of chloral hydrate, a well-established hypnotic. Surprisingly, neither the chloral hydrate nor the Δ-9-THC facilitated sleep induction or extended the duration of sleep as compared to the placebo. At the 15 mg dose level, a few complaints of hangover were noted. The authors suggested that difficulties in controlling the room temperature during the winter may have sufficiently interfered with sleep to negate any possible hypnotic effects of the active substances.

Tassinari et al. (1976) reported increases in total sleep time in eight volunteer subjects. Stage II sleep was increased while REM sleep was reduced. The dosages used were rather large (0.7- 1.0 mg/kg of Δ-9-THC), however.

Analgesia

One of the earliest folk uses for cannabis was for pain relief. A series of preclinical investigations by Kaymakcalan et al. (1974) tended to confirm this analgesic effect. After having received intravenous administrations of 1 mg/kg Δ-9-THC, dogs received electric stimulation through an implanted dental electrode. The cannabinoid produced a definite analgesic effect, as shown by a fourfold increase in pain thresholds. Tolerance to analgesia, sedation and ataxia occurred in eight days.

In another study, Δ-9-THC produced pain reduction in mice and rats as measured by tail flick and writhing tests, and in rabbits receiving sciatic nerve stimulation. The analgesia produced with the doses used was equivalent to morphine analgesia -- in fact, in rats, a cross tolerance between Δ-9-THC and morphine was found. An earlier study (Parker & Dubas, 1973) measured the effect of Δ-9-THC on rats with electrodes implanted in aversive brain sites. A non-dose related elevation of the pain threshold and an attenuation of the escape response were also recorded.

Sofia et al. (1975) tested the analgesic effectiveness of Δ-9-THC, crude marihuana extract, cannabinol, cannabidiol, morphine and aspirin orally in mice using the acetic-induced writhing and the hot plate tests. They also exposed rats to the Randall-Selito paw pressure test. Δ-9-THC and morphine were equipotent except in the paw pressure test in which morphine exceeded Δ-9-THC in elevating the pain threshhold. The crude marihuana extract was as effective in all tests except in the acetic writhing test where it was three

times more potent. Cannabinol resembled aspirin in that it was only efficacious in the writhing test.

A double blind Canadian study by Milstein et al. (1975) revealed a significant increase in pain tolerance among those who had smoked marihuana. Using a pressure algometer, the experimenter found that experienced subjects obtained greater analgesia than non-experienced subjects, although the increased pain tolerance was found only in the preferred hand. No effects on sensitivity to pain sensation were noted.

In another human study, Hill et al. (1974) recorded opposite results. Here, 26 subjects received blind, either marihuana smoke containing 12 mg of Δ-9-THC from a spirometer or a marihuana placebo. They were then given electrical skin stimulation. The THC was found to decrease tolerance and heighten sensitivity to pain.

In an impressionistic report, Dunn and Davis (1974) questioned 10 paraplegics hospitalized in a V.A. hospital, all of whom had admitted using marihuana in the past. Four reported that it produced a decrease in phantom pain sensations, five mentioned a decrease in spasticity and five noted a decrease in headache pain and an increase in pleasant sensations.

Cancer patients in pain were studied by Noyes et al. (1975). Patients were given either Δ-9-THC in 5, 10, 15 or 20 mg doses or a placebo. Pain reduction was greater at all Δ-9-THC levels than in the placebo condition. Significant pain reduction was noted at the 15 and 20 mg THC levels. These researchers felt that the pain relief was not due to the sedative or euphoriant effects; and, therefore, attempted to compare the analgesic effect of 10 and 20 mg of Δ-9-THC with 60 and 120 mg of codeine in a group of cancer patients with moderate pain. At the higher doses of both drugs, significant levels of analgesia were reported. The 20 mg dose of Δ-9-THC produced marked sedation, and even the 10 mg dose was associated with considerable drowsiness. The sedation and mental effects of 20 mg of Δ-9-THC preclude its therapeutic usefulness, but the investigators concluded that Δ-9-THC has mild analgesic activity.

In a letter to the editor (Neiburg et al., 1976) in response to the Sallan et al. (1975) article on amelioration of nausea and vomiting by Δ-9-THC in cancer chemotherapy patients, the writers tell of two patients with malignancies who had to stop smoking marihuana because of increased bone pain.

Wilson and May (1974) postulated 'that the analgesic activity of -8- and Δ-9-THC resides primarily in their 11-hydroxy metabolites, the latter being three times more potent than the former. They based this assumption on the observation that 9-nor derivatives (which cannot be transformed into 11-hydroxy metabolites) lacked significant analgesic activity. These do exhibit dog ataxia and cardiovascular profiles nearly identical to Δ-8- and Δ-9-THC. This finding led to the preparation of 9-nor-9-ß-hydroxyhexahydrocanna-

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binol which proved to be an analgesic in the mouse hot plate test nearly equal to morphine. Whether or not the analgesia occurs over an opiate receptor site is unresolved.

Harris (1976) was not able to confirm the analgesic effect of Δ-9-THC using the standard analgesic test procedures. He did find the 9-nor-9-ßhydroxyhexahydrocannabinol to be a potent antinocioceptive agent, confirming Wilson and May's work.

Pre-Anesthetic

A number of studies have examined the role that Δ-9-THC can play as a pre-anesthetic agent, with mixed results. When it was given prior to inhalation anesthesia, the requirement for cyclopropane and halothane was decreased (Paton & Temple, 1973; Stoelting et al., 1973). Smith (1976) found that normal volunteers given 200 mcg/kg THC intravenously experienced marked sedation with minimal respiratory depression. Also salivation was diminished, bronchodilation occurred and cardiac output increased on the basis of the expected tachycardia. Although the author cautioned that some of the observed effects may have been due to the alcohol in which the Δ-9-THC was dissolved, the amount of the drug given intravenously could easily have provided the manifestations recorded. Whether Δ-9-THC has a potential usefulness in anesthesiology will depend on findings from additional studies.

Having searched for suitable pre-anesthetic combinations, Smith reported that 5 mg of Δ-9-THC intravenously produced fear in a number of patients. In combination with an opioid it provided useful sedation, but with a marked decrease in carbon dioxide sensitivity. When combined with a barbiturate, the CNS depression was unpleasant and associated with some restlessness, but the response to carbon dioxide was unchanged. With diazepam, definite drowsiness and other depressive effects were notable, and the ventilatory response to carbon dioxide was decreased. The investigator suggested that the combination of marihuana with pre-anesthetic or anesthetic medications could lead to undesirable results.

Gregg and Small (1974) found two dosage levels of intravenous Δ-9-THC ineffective in controlling anxiety in oral surgery patients. In fact, in low doses it elevated anxiety, sometimes to a marked degree. Intravenous diazepam out-performed the drug under investigation.

In an expansion of this study, Gregg et al. (1976b) found that the combination of presurgical stress and intravenous Δ-9-THC produced dysphoria and a tendency to syncopal hypotension. No measurable effect on pain tolerance could be detected. The investigators concluded that surgical stress plus marihuana use immediately prior to the surgery might lead to psychophysiologic reactions.

Johnstone et al. (1975) also examined Δ-9-THC in combination with other drugs. It was administered intravenously after subjects had

been pretreated with oxymorphone (OXM) or pentobarbital (PBL). The sedative effects of OXM were increased by Δ-9-THC, but the cannabinoid also increased respiratory depression. The combination of PBL and Δ-9-THC did not cause respiratory depression but produced such intense anxiety and psychotomimetic reactions that four of the seven subjects receiving this combination were not given the full course of five doses. The investigators concluded that neither combination was a desirable anesthetic premeditation. They also expressed reservations about the value of Δ-9-THC alone for such a purpose.

A number of reports in this area mention the cardio-accelerating effect of Δ-9-THC as an undesirable feature of its activity. When it is combined with other drugs like atropine, and with the stress of pending surgery, syncopal hypotension can result. From a different perspective, Gregg and associates (1976a) mention that patients given general anesthesia within 72 hours of smoking marihuana sustained abnormal heart rate increases when compared with control non-smokers. They speculate that it could have resulted from an interaction between the stored cannabinoid metabolites and the various other elements of the surgical state that are conducive to tachycardia.

Antidepressant

Since marihuana tends to elevate mood, it follows that an evaluation of its antidepressant potential would be sought. Kotin et al. (1973) administered 0.3 mg/kg of Δ-9-THC or a matching placebo twice daily to eight patients who required hospitalization for their affective disorder. The patients were all considered moderately or severely depressed. Treatment lasted a week, with placebos substituted for the active drug thereafter. No evidence of a significant affectual change could be demonstrated. In chronic depressive states, a longer duration of drug administration is sometimes needed before improvement is noted.

A group at the Medical College of Virginia (Regelson et al., 1976) performed a double blind study with cancer patients receiving chemotherapy. An initial starting dose of 0.1 mg/kg t.i.d. was used. The dosage was raised only if previous doses were well-tolerated. On a battery of personality tests and mood scales, the Δ-9-THC acted as a mood elevator and tranquilizer producing significant improvement on two of three Zung depression scales. Cognitive functioning was unimpaired and appetite enhancement and retardation of weight loss were noted from clinical records. The need for narcotics was decreased, and patients had the impression that some pain relief resulted.

Antinauseant, Antiemetic and Appetite Enhancer

The double blind Regelson study at the Medical College of Virginia is mentioned above in the section on antidepressant effects, but the

researchers believed that the principal benefits seen in their cancer chemotherapy patients were the improvement of appetite and lack of the expected weight loss. Increased sociability and tranquilization were achieved by many patients according to the check lists used. Sedation, which could be desirable in this group of patients, was a frequent side effect. Nausea and vomiting were brought under control significantly more often by Δ-9-THC than with the placebo.

Sallan et al. (1975) gave either oral Δ-9-THC in 10 mg/sq. meter body surface or a placebo to 20 patients with each serving as his own control. An antiemetic effect was observed in 14 of the 20 drug courses, but not in the placebo courses. The antiemetic effect paralleled the subjective high. Studies comparing Δ-9-THC with a standard antiemetic, prochlorperazine (Compazine), are underway at a few centers.

Treatment of Alcohol and Drug Dependence

Rosenberg (1976) has studied the response of a group of alcoholics and normal volunteers to marihuana cigarettes (0.4 gm/50 lb. body weight) and to alcohol (2 ml vodka/kg.). This investigator found that sober alcoholics tended to be less responsive to stresses (mental arithmetic and talking to a videocamera) and were more likely to withdraw from a stress situation than the normals. Alcoholics became more angry and depressed after alcohol ingestion as measured by mood scales. Marihuana produced a more positive mood state and did not interfere with the arousal reaction, although it greatly increased heart rate and produced an acute paranoid or confusional state in 3 of the 27 subjects. This investigator also found that disulfiram (Antabuse) and marihuana could be given safely together in the treatment of alcoholism. The study is continuing, but the early findings indicate that marihuana may be a suitable therapeutic adjunct for some alcoholics as a reward to encourage them to take disulfiram.

Hine and colleagues (1975a) implanted morphine pellets in rats. Δ-9-THC in 1, 2, 5 and 10 mg/kg doses were injected intraperitoneally 71 hours later. An hour afterwards, 4 mg/kg of naloxone (Narcan) was delivered into the same site. Attenuation of abstinence was achieved with a dose of 2 mg/kg and higher. Cannabidiol significantly potentiated the Δ-9-THC effect on diarrhea and wet shakes. In a letter, Carder (1975) criticized the paper by Hine on suppression of naloxone-precipitated morphine abstinence. He pointed out that only two of nine symptoms were reduced (wet shakes and defecations). It was suggested that this could simply be a non-specific depressant effect . In reply, Hine et al. (1975b) stated that the decrease in wet shakes, diarrhea and bolus counts was dose related. The relative importance of one abstinence symptom over another is difficult to evaluate. Hine et al. retain the belief that a clinical trial of Δ-9-THC in opiate detoxification is justified.

Bhargava (1976) has performed a similar study in mice. The naloxone

precipitated jumping response was inhibited, and two other signs of morphine withdrawal (defecation and rearing behavior) were also suppressed by Δ-9-THC. The author considers the jumping response to be a major sign of withdrawal.

The Synthetics

A long series of synthetic compounds has been developed over the past few years. They represent attempts to intensify certain desired activities of the tetrahydrocannabinols while avoiding the unwanted effects. Pars and Razdan (1976) have described. a series of nitrogen and sulfur substituted benzopyrans. Dren (1976) has studied the neuropharmacology of three nitrogen-containing heterocyclic benzopyrans and reported tranquilizing, analgesic, sedative-hypnotic and intraocular pressure lowering activity. Plotnikoff et al. (1975) states that these nitrogen analogues have anticonvulsant properties in mice and rats. Nabilone, which has a ketone instead of a methyl on the 9 position of Δ-9-THC, was investigated by Lemberger and Rowe (1976). It produced relaxation and sedative effects in humans. Little euphoria or tachycardia occurred, but in high doses postural hypotension developed. Tolerance to the euphoria and postural hypotension took place rapidly.

Mechanism of Therapeutic Action

The precise mechanism by which cannabis exerts its pharmacologic effects remains unknown. Burstein and Raz (1972) and Burstein et al. (1973) have gathered a considerable amount of indirect evidence that some of the actions are mediated via a prostaglandin-cyclic AMP system. He found that Δ-9-THC reduced prostaglandin formation by inhibiting prostaglandin synthetase. Other cannabinoids have this effect as does olivetol from which Δ-9-THC is synthesized. PGE2 and PGE1 are two of the prostaglandins affected. Prostaglandin inhibition could account for the intraocular pressure reducing and the bronchodilating actions.

The influence of cannabinoids upon neurotransmitters has been examined, but the results are inconsistent. Banerjee et al. (1975) have shown in vitro that Δ-8- and Δ-9-THC and their hydroxylated metabolites inhibit the uptake of norepinephrine and serotonin in hypothalamic synaptosome preparations and of dopamine in the corpus striatum. Gamma-aminobutyric acid uptake in cerebral cortical preparations is also inhibited. The latter may explain the anticonvulsant properties of some of the cannabinoids. Drew and Miller (1974) believe that cholinergic dominance best explains the mental effects. The adrenergic activity of cannabis mentioned earlier (Green & Kim, 1976) is not inconsistent with the prostaglandin-cyclic AMP hypothesis; rather, it may be an antecedent reaction to the release of adrenergic amines. Selective monoamine oxidase inhibitory activity is also a possible feature of some activity of the cannabinoids (Schurr and Livne, 1975).

CONCLUSION

The further study of the cannabinoids for various therapeutic applications seems worthwhile. A large number of synthetic cannabinoids have begun to appear which do not have some of the disadvantages intrinsic in the naturally occurring ones. Therapeutic efficacy could be enhanced by certain molecular manipulations. Thus, it is likely that if any cannabinoid ever achieves clinical acceptance, it will be a synthetic.

The cannabinoid configuration would be important to human therapeutics because: 1) there is a wide safety margin between effective and lethal doses, and 2) in certain instances, the mechanism of action appears to differ from the standard medications now employed.

It should be noted that successful clinical trials of cannabis or its constituents do not provide sufficient justification for removal of the drug from Schedule I (no medical usefulness, high abuse potential) to a less restricted scheduled. Only when the substance has gone through the entire investigational process of testing, and the FDA has approved its New Drug Application, would its rescheduling be considered by the regulatory agencies.

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