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Marijuana Research Findings: 1980

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

Marijuana
Research Findings: 1980

Editor:

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Foreword

1980 marks the 10th anniversary of the Marijuana and Health Reporting Act, which called for annual reports to the Congress on the health consequences of marijuana use. The letter of transmittal accompanying the first Marihuana and Health report expressed the conviction that the reports would "prove to be valuable tools in the public education and debate concerning the health impact of this widely discussed drug" and that they would "stimulate additional research concerning marihuana in those areas which need further attention." The widespread use of the reports which have been issued in succeeding years suggests that they have fulfilled these expectations.

In 1976, in addition to the mandated report for Congress and the public, the National Institute on Drug Abuse published a monograph intended for readers who wanted to pursue the subject in greater depth. NIDA Research Monograph 14, Marihuana Research Findings: 1976, presented the scientific background papers upon which that year's Marihuana and Health report was based. More recent developments now call for the publication of another monograph, to bring the record up to date for those with a serious interest in discovering the present extent and limits of knowledge of marijuana chemistry and metabolism and its effects on human health. Now, as then, extensive reference listings make the original sources accessible to the reader.

For Marijuana Research Findings: 1980, research reports through late 1979 reviewed by eight scientists/authors, and care has been taken that the reporting and interpretation of data are balanced and unbiased. The new monograph appears at a time when major changes in marijuana use have been occurring. Today, street marijuana is used by larger numbers of young people, beginning at earlier ages, more frequently, and often in much higher potency than it was 10 or even 5 years ago. There is widespread and justified concern over the effects of this use

and a desire for authoritative answers to questions about it. The pendulum of public opinion, which in the early and mid seventies appeared to swing in favor of reducing penalties for possession and use of marijuana, has reversed its direction. Cne sign of this is the growing numbers of parents who are banding together to find ways of discouraging marijuana use by their children.

We hope that the findings presented in this monograph, while intended primarily for those with a scientific interest, will also benefit legislators, judges, health professionals, educators, parents, and others who are often asked to make decisions or give advice based on the most reliable information available.

Despite advances in research, our knowledge of the acute and long term effects of marijuana is still limited, and much as we may wish for quick, definitive answers to our questions, the accumulation of solid facts can occur only gradually. The full picture may become clear only after many more years of study--and, unfortunately, of continuing marijuana use. To that end, however, the National Institute on Drug Abuse will continue to support investigations that promise to broaden our understanding of the implications of marijuana use for the health of our citizens.

William Pollin, M.D.
Director
National Institute on Drug Abuse

Contents

Marijuana and Health: 1980

The first chapter of this volume, with the exception of the addendum on pages 10-11, is a reprint of the text of the eighth Marijuana and Health report, which was presented to the U. S. Congress in February 1980. Its annual publication provides to political decisionmakers and others a summary of current marijuana research. The more general distribution of this report has served a further function as a source of information on marijuana's effects for an interested and concerned public.

Preparation of the eighth Marijuana and Health report was made possible by contribution of preliminary project reports and other data from members of the scientific community. The report is based on the technical reviews of various aspects of these findings, which follow the first chapter. Dr. Robert C. Petersen, Assistant Director of the Division of Research, National Institute on Drug Abuse, wrote the report and had primary responsibility for its overall preparation. In addition, members of the Division of Research staff offered many helpful suggestions.

EXECUTIVE SUMMARY

In this eighth edition of the Marijuana and Health Report several areas of recent developments in marijuana research are highlighted together with a summary of the scientific research accumulated through the end of 1979 concerning the drug's possible health implications.

Nature and Extent of Use

By contrast with a decade ago, marijuana use now often begins at a much earlier age and is more likely to be frequent rather than experimental use. The most significant increases noted in the 1977 National Survey of drug use were in marijuana use by 12-to 17-year-olds. Other, more recent sources of data are generally consistent. Among high school seniors, for example, daily use nearly doubled from the Class of 1975 to those of 1978 and 1979 (from 5.8 percent to 10.7 and 10.3 percent for each of these classes). Moreover the percentage of each of these senior classes which began use in the ninth grade or earlier has also nearly doubled (from 16.9 percent of the Class of 1975 to 30.4 percent of the 1979 class). Despite these increases in use, most members of all age groups surveyed continue to disapprove of regular marijuana use and to advocate continued prohibition.

Chemistry

"Street" marijuana has increased markedly in potency over the past five years. Confiscated materials in 1975 rarely exceeded one percent THC content. By 1979 samples as high as five percent THC content were common. "Hash oil," a marijuana extract unavailable a decade ago, has been found to have a THC content as high as 28 percent, with more typical samples analyzed by University of Mississippi chemists ranging from fifteen to twenty percent THC.

Considerable progress has been made in developing simpler laboratory techniques for detecting marijuana use by examining body fluids. Methods are now being field tested which will probably be commercially available by mid 1980 which can be used for such purposes as detection of driving under the influence of marijuana.

Acute Effects

A review of marijuana's acute effects on intellectual functioning done for this year's report indicates the data is generally consistent: marijuana intoxication interferes with immediate memory

and a wide range of intellectual tasks in a manner that might be expected to impair classroom learning among student users. There is also good evidence that marijuana interferes with driving skills and is a significant factor in erratic driving.

Long Term Effects

While much remains to be learned about the chronic effects of marijuana, there are converging lines of evidence with respect to its pulmonary effects. Both animal and human experiments suggest that marijuana impairs lung function to a greater extent than tobacco cigarettes do. While there is as yet no direct evidence that it can play a causal role in lung cancer, it is known that, like tobacco smoke residuals, the "tar" from marijuana is tumor-producing when applied to the skin of test animals. One known cancer-producing chemical, benzopyrene, has been reported to be 70 percent more abundant in marijuana smoke than in tobacco smoke. Following exposure to marijuana smoke the lung's defense systems against bacterial invasion have been shown to be impaired.

Although the evidence is by no means definitive, several kinds of animal and human research have suggested that heavy marijuana use may impair reproductive functioning. Such impairment may include diminished sperm count and motility in males and possible interference with fertility in females. Such preliminary findings may have greater significance for the marginally fertile. Given the many unknowns concerning the effects of marijuana on fetal development, the use of marijuana during pregnancy should continue to be strongly discouraged.

Other questions of possible marijuana effects continue to be unresolved. Evidence concerning an effect on the body's principal defense against disease, the immune response, remains contradictory. While some human studies have found laboratory evidence of impairment, others have not, and the clinical significance of such findings is still in doubt. There have been no large-scale epidemiological studies to determine whether or not chronic marijuana users suffer from infections and other diseases to a greater extent than do nonusers of similar life style. Evidence concerning possible effects on chromosomes is also contradictory and its clinical significance questionable.

Psychopathological Effects

There have been few new developments in this area. An acute panic anxiety reaction is the most common adverse psychological reaction to use, especially when unexpectedly strong material is consumed. A number of clinicians have cautioned against use of marijuana by those with a history of serious psychological problems or who have previously had drug-precipitated emotional disturbances (so-called "bad trips"). While more serious psychiatric problems such as a cannabis-related psychosis have been reported in countries with a long tradition of use, such reactions

do not appear common here. Concern has been expressed that availability of much stronger varieties of cannabis may result in more serious problems than in the past.

While there have been a number of overseas studies of the impact. of chronic marijuana use on intellectual functioning, most of which have reported some impairment, the quality of such studies is highly variable and the question also remains in doubt. Studies of American users have not generally reported such impairment, although the American experience has been limited to relatively highly motivated college populations using smaller amounts of cannabis for shorter periods of time. Since user populations in the United States are generally younger than those overseas, the question of possible impact on younger users is an important one which remains to be studied.

Therapeutic Uses

Overall, marijuana, THC and related drugs have shown definite promise in treating the nausea and vomiting which often accompany cancer chemotherapy. While thus far they have not proven to be invariably superior to other medication, they may be enduringly useful with patients for whom other drugs are relatively ineffective.

A second therapeutic application which has received wide publicity is the use of THC or marijuana in reducing the vision-destroying intraocular pressure in open-angle glaucoma. Initial trials with oral THC found the drug to be of variable success, although when used with other standard drugs better results were achieved. An eye drop preparation has been developed which in initial human trials produced eye irritation and was not consistently effective. Additional studies are in progress.

It should once again be emphasized that although marijuana, THC and related drugs have shown some therapeutic promise, much work remains to be done and that any pharmaceuticals developed will be chemically related but not identical to the constituents of the natural material. Such compounds would be chosen to minimize undesirable side effects and to provide a better-focused therapeutic effect. Like any other new medication, chemically related materials must be carefully tested for toxicity and for therapeutic effectiveness.

INTRODUCTION

This edition of Marijuana and Health represents the eighth in a series of annual reports from the Secretary of Health, Education, and Welfare to the Congress and the American people as required by Title V of Public Law 91-296. The seventh edition dated 1977, which included research findings available to the end of 1977, was released last year. This edition has been dated 1980 so as to reduce the confusion concerning the date of actual release. In order to make it as current as possible, research reports have been included virtually to the end of 1979. Although it is not yet possible to be definitive in our answers to many of the health questions that marijuana use raises, the report once again tries to answer the central question as it can best be answered at this time: "What are the health implications of marijuana use for Americans?"

While all of us would wish for greater certainty in this area, such certainty is not yet possible. The American marijuana experience has been of brief duration. It is comparatively recently that significant numbers of individuals have been using the more potent cannabis now available on a daily basis. As our experience with tobacco and alcohol demonstrates, it frequently requires many years of use by large numbers for long range effects of a drug to become apparent. While there are cultures in which cannabis use has been traditional for many years, the drug is often used differently, and traditional users rarely include women or the very young. Perhaps the most disquieting development in our society has been the rapid increase in younger users, under age eighteen. Use is beginning earlier and earlier and is often on a daily basis. Even those who regard occasional use by well integrated, healthy adults as unlikely to pose serious public health problems agree that use, especially frequent use, by children and adolescents can be seriously disruptive,

Research developments since issuance of the seventh report last year include additional information on the possible effects on reproduction and pulmonary function. Despite our increasing knowledge, much remains to be learned about the effects of chronic use. Unfortunately, our present limited knowledge is often interpreted as indicating that marijuana is "safe." More accurately, there are many areas in which we simply do not know the parameters of risk. We do know that even acute use poses hazards in driving and other complex behavior and definitely interferes with memory and intellectual functioning while "high." As use comes to involve both younger and older persons it becomes increasingly important that we be able to specify more precisely the kinds and degree of public health risk which present and anticipated levels of cannabis use pose. This report summarizing our present knowledge is another step in achieving a better understanding of marijuana's public health implications.

NATURE AND EXTENT OF MARIJUANA USE IN THE UNITED STATES

Although a comprehensive updated picture of national trends in marijuana use since the last 1977 National Survey on Drug Abuse will not be available until the 1979 Survev results have been tabulated and analyzed in mid-1980, a review of previous years and of more limited recent findings indicates a generally consistent upward trend in use.* There are indicators that the increase is greatest among younger users (under 18). For example, the most notable changes in the 1977 National Survey from its predecessor in 1976 were a 25 percent increase in the total of those between ages 12 and 17 who had ever used marijuana and a nearly 30 percent increase in the number of that age group who were currently using marijuana (i.e., who had used it in the month preceding the Survey). By contrast, current use in the over-18 population did not increase significantly. Nearly three out of ten (28.2 percent) of 12-to 17-year-olds in 1977 reported having tried marijuana at some point in their lives; nearly one in six (16.1 percent) were current users (1).

Young adulthood--from age 18 to 25--represents the peak period for marijuana use. Three out of five in that age group reported having ever used marijuana in the most recent National Survey; over one in four (27.7 percent) 18-to 25-year-olds was currently using in 1977. Use continues to be correlated with age. This is true whether we are talking about those who have ever used the drug or about current use. For example, among children between ages 12 and 13, eight percent have had some experience with marijuana, a figure which climbs to 29 percent for 14-and 15-year-olds and to 47 percent for those ages 16 and 17. The 22-to 25-year-old group reports the peak level of use--with 62 percent indicating ever having done so. The percentage who have used is 44 percent in the 26-34-year-old group and only 7 percent of those over 35 report any past use. Similar trends are to be found in current use (i.e., use in the month preceding the Survey). While 4 percent of the 12-and 13-year-olds report current use, the peak years for such use are between 18 and 21. Three out of ten (31 percent) of those between 18 and 2l were current users in the 1977 Survey (I).

Although the percentages of females who had either tried marijuana or were currently using it have generally increased in the course of the five national surveys to date, female use has tended to lag behind that of males. Interestingly enough, among 12-to 17-year-olds, the percentage of girls and boys who had ever used remained nearly equal in the three Surveys conducted in 1971, 1972, and 1974. However, by 1976 the percentage of males who had used in this age group was significantly greater than that of females (26 percent for males and 19 percent for females). In 1977, a still greater difference in cannabis use by the two sexes developed in the 12 to 17 age group (33 percent of males had used at some point compared with 23 percent for females). While boys' use in the 12 to 17 group increased significantly between 1976 and 1977, use by girls did not. Among those over 18, by contrast, prevalence of male use

*see ADDENDUM, pages 10-11

in all five survey years has been consistently higher, about twice that of females up until the 1977 survey in which the gap narrowed. This survey indicates 30 percent of males over 18 had ever used marijuana as compared with 19 percent of females. However, the percentage of females over 18 who had ever used increased statistically significantly between 1976 and 1977 while that of males did not. When one examines current use, generally similar trends are present--male use predominates by a ratio of about two to one among those over 18, while in the 12 to 17 age group the difference is smaller. Half again more boys than girls ages 12 to 17 were currently using in 1977, unchanged from the 1976 findings (1).

Racial differences are of some interest although the broad statistical breakdown into "white" and "other races" categories precludes more detailed analysis. Among the 12 to 17 age group, white use for most survey years has slightly exceeded that of other races whether we are talking about those who have ever used or about those currently using. In 1977, use by whites 12 to 17 significantly increased both in the "ever used" and "current use" categories (from 22 percent to 29 percent ever having used and from 12 percent to 17 percent for current use). Among those over 18 the percentages of whites and of other races who have ever tried marijuana were nearly equal in 1977 (24 percent of whites had used compared to 27 percent of other races) in contrast to previous years in which "other races" use by the over-18 group tended to be greater than that of whites. Among current users in the 12-to 17-year age group, whites consistently predominate over "other races" for all survey years. Among those over 18, current use by whites and other races was approximately equal for all survey years including that of 1977 (eight percent of each group in the current survey).

In earlier national surveys adults with college training were considerably more likely to have used marijuana than were adults who had not gone beyond high school graduation. These differences have narrowed in recent years. For example, the percentage of college graduates who had ever used marijuana at the time of the 1977 Survey was 28 percent, compared to 26 percent of the high school graduates.

In terms of the four geographical regions into which the National Survey results are divided (Northeast, Northcentral, South, and West), the only area to note a statistically significant increase in marijuana use between 1976 and 1977 was the Northeast. There a significant increase was found in the number of 12- to 17-year-olds who reported having used marijuana. By contrast with previous survey years, marijuana use in 1977 in the Northeast approximately equalled that in the West. This was true both for lifetime prevalence and for current use. Other areas of the country had lower levels of use.

If one takes the percentages of cannabis users noted in the 1977 Survey and extrapolates to the general population, 43 million

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Americans had tried marijuana as of spring 1977, and about 16 million were currently using the drug (i.e., had smoked it in the month previous to the 1977 Survey).

Although more recent national statistics for the general population are not yet available, there are some additional data on the drug attitudes and behavior of American youth who are at a pivotal point of transition to adult life--their senior year in high school. Since 1975, a representative nationwide sample of high school seniors has been queried. Because of the large sample involved, this survey is a particularly reliable source of information on drug using trends, sensitive to even small changes. It is also a source of information on student attitudes and beliefs about drugs, which may be useful in anticipating future drug trends. While statistically significant increases (i.e., increases likely to reflect actual behavior changes rather than survey artifacts) in marijuana use were noted in each of the years through 1978, data for the senior class of 1979 indicate a leveling off of marijuana use, although at fairly high levels. The percentage of each of the five senior classes from 1975 to 1979 who had tried marijuana steadily increased from 47.3 percent in 1975 to 60.4 percent of the Class of 1979. Indeed, the percentage of 1979 high school seniors with marijuana experience is equal to that of the National Survey's peak-using group, the 18- to 25-year-olds. The increase in use between the classes of 1978 and 1979 was the smallest annual increment to date, less than one percent (2,3).

Daily use rates which rose from six percent in 1975 to 9.1 percent in 1977, reaching a peak level of 10.7 percent in the Class of 1978, were 10.3 percent in 1979. While use within the 30 days prior to each of the surveys rose from a little over a quarter of the seniors of the Class of 1975 to 37.1 percent of the Class of 1978, it leveled off at 36.5 percent in the 1979 senior class. Thus, this study suggests that the proportion of high school seniors using marijuana has remained stable for the past two years (2,3).

A disturbing trend continues to be the tendency toward initial marijuana use at younger ages. For example, 16.9 percent of the Class of 1975 had used the drug prior to the tenth grade, but the corresponding percentages in the 1976, 1977, and 1978 classes were 22.3, 25.2, and 28.2 percent. In the most recent senior high school class studied, the 1979 group, 30.4 percent had used prior to the tenth grade. Thus, the percentage of seniors who first used in the ninth grade or earlier has nearly doubled over the past five years (2,3).

Although overall the use of alcohol and tobacco continues to exceed that of marijuana, <u>daily</u> use of marijuana among high school seniors in the Class of 1978, for example, (10.7 percent) was nearly double that for alcohol (5.7 percent daily use) and exceeded only by daily cigarette smoking (27.5 percent). Daily use of marijuana has been about twice as frequent among males as females. However, at less

frequent levels of marijuana use, the sexes do not differ markedly in the percentages using (2,3).

Nationwide statistics may obscure considerable local variation. For example, in Maryland and Maine, where druq surveys were conducted in 1978, higher levels of daily or nearly daily use of marijuana were found than among high school seniors nationwide (10.7 percent of seniors nationally). In Maryland, use "daily or several times a week" was reported by a quarter (25.3 percent) of the twelfth graders (4). In Maine, nearly one in six high school students reported daily marijuana use, four times as many as used alcohol daily (four percent) (5).

Summary--Nature and Extent of Marijuana Use

Although national data representative of the general population subsequent to 1977 are not available at this time, several trends are noteworthy. Among high school seniors use may be plateauing, although at fairly high levels--over a third of the seniors in recent years--report use in the month preceding the surveys. About one in ten reported daily use in the 1979 senior class. The percentages of seniors using marijuana prior to the tenth grade has steadily increased since 1975, nearly doubling in that five year period.

Current Attitudes and Beliefs About Marijuana

Both the National Survey and the high school senior survey include questions dealing with respondents' attitudes and beliefs about drugs in addition to asking about actual behavior. Such attitudes and beliefs are, of course, subject to change in response to new information and do not necessarily reflect objective reality. Nevertheless, they are of considerable interest in enabling us to better understand user assumptions and present behavior, and they may be to some extent predictive of future behavior.

Despite the general assumption of widespread acceptance of marijuana in our society it is noteworthy that youth (12-17), young adults (18-25), and older adult groups (26+) all contain substantial proportions advocating either that marijuana continue to be illegal or our present laws be made still stricter. Seventy-four percent of youth and 79 percent of older adults take this tack. Even among the peak-using 18-25 year-old group, 40 percent support in about equal proportions the position that marijuana continue to be illegal (20 percent) or that ideally the laws be made still stricter (also 20 percent of the group). Similarly two-thirds of high school seniors disapprove of regular use.

Respondents in the National Survey were also asked to indicate which of a list of drugs each regarded as "addictive," ("that is, anybody who uses it regularly becomes physically and psychologically dependent on it and can't get along without it"). Alcohol and heroin were classified as "addictive" by four out of five or more respondents

in the 12- to 17-, the 18- to 25-, and the over-26 age groups, Tobacco was also typically classified as "addictive," with the percentage so designating it increasing with age (youth: 62.4 percent; young adults: 78.6 percent, and older adults: 83.1 percent). Marijuana, by contrast, was seen as "addictive" by less than half of youth and young adults (47.3 percent and 43.7 percent respectively), but was so classified by over three out of five (63.6 percent) older (26+) adults.

The percentage of high school seniors who disapprove of regular marijuana use has remained fairly constant at just over two-thirds in senior classes from 1975 to 1978 (1975 = 71.9 percent; 1976 = 69.5 percent; 1977 = 65.5 percent; and 1978 = 67.5 percent). A similar percentage to those disapproving of regular marijuana use objects to taking one or two alcoholic drinks each day and to smoking one or more packs of cigarettes daily. A little less than half of the classes of 1976 to 1978 disapproved of occasional marijuana use; about a third objected to even trying it. Although nearly half (or more) of the seniors disapproved of even occasional marijuana use, they did not associate "great risk" with use. The percentage who believe there is great risk of some form of harm even from regular use of marijuana has steadily decreased. While 43.3 percent of the Class of 1975 placed regular use in the "great risk" category, the percentage of those in the 1978 Class who so described it had decreased to 34.9 percent. Only 15 percent in the Class of 1975 saw "great risk" in trying marijuana once or twice, and that has decreased to nearly half (8.1 percent) in the Class of 1978. While three out of five seniors in the Classes from 1975 to 1978 continued to feel people should be legally prohibited from smoking marijuana in public, the percentage who believe that use in private should be legally prohibited has steadily decreased (from a third of the Class of 1975 to a quarter of the Class of 1978). While two out of five 1977 and 1978 seniors believe that cigarette smoking should be legally prohibited in public, only a quarter believe that marijuana smoking should be illegal in private.

ADDENDUM

The 1979 National Survey--A Marijuana Use Update

At the time of completion of the Eighth Marijuana and Health Report (late 1979), the 1979 National Household Survey has not yet been completed. The following addendum is a brief summary of this most recent National Survey, which was released on June 20, 1980.

As has been consistently true since the National Survey was first conducted in 1972, marijuana use is highly correlated with age. This past year (1979), 8 percent of 12- and 13-year-olds reported some experience with the drug, but by ages 14 and 15 the percentage who had used it increased to 32 percent. A simple majority--51

percent--had used it by ages 16 and 17. Peak use was found among 18- to 25-year-olds, a group in which over two-thirds (68 percent) had tried the drug at some time in their lives. Taking the 12- to 17-year-old group as a whole, the percentage that had ever used marijuana had more than doubled since 1972--from 14 percent to 31 percent. Among young adults (18- to 25-year-olds) the increase was smaller--from 48 percent in 1972 to 68 percent in 1979 (a significant increase from 60 percent in 1977).

Current use--defined as use within the month preceding the survey--is also markedly age related. For youth (12 to 17) and young adults (18 to 25), about half as many currently use marijuana as have ever used. Thus 16.7 percent of youth currently use marijuana, a figure unchanged from the 1977 survey, but also more than double the 7 percent of this age group that reported then current use in 1972. Thirty-five percent of young adults were currently using by late 1979, a figure nearly a third larger than that of 1977. Until this past year's survey, current use was consistently between 25 and 28 percent for all survey years from 1972 to 1977.

For older age groups, that is, those over 26, both lifetime prevalence and current use are markedly lower than for younger persons. Nearly 20 percent (19.6 percent) of older adults had ever used marijuana by 1979, compared to the 7.4 percent who had had marijuana experience in 1972. Current use by this age group has risen from 2.5 percent in 1972 to 6.0 percent this past year (1979). The percentage of older adults reporting current use has nearly doubled since 1977 (from 3.3 to 6 percent).

As the figures indicate, while there have been marked changes in all age groups since 1972, statistically significant changes (i.e., changes not likely to be the result of chance) between 1977 and 1979 were confined to the young adult and older age groups. Youthful use was unchanged from 1977.

This year's survey, for the first time, included questions about perceived hazards of marijuana use. It is noteworthy that only 5 percent of the peak-using 18- to 25-year-old group saw the drug as having "no bad effects." Perceived adverse consequences range from performance and health impairment to possible psychological effects and the increased likelihood of using stronger drugs, Nearly three quarters (72.2 percent) of young adults believed that being high causes impaired driving performance. One in eight young adults felt it would not. These observations on perceived hazards should serve as a useful baseline for future comparisons.

HUMAN EFFECTS

Chemistry and Metabolism of Cannabis

Although the chemistry and metabolism of marijuana (i.e., the ways in which the drug is broken down and chemically transformed in the body) are technical topics not easily translated into everyday language, they are important. For example, contrary to popular belief, the plant material is quite complex, containing at least 421 individual compounds. Sixty-one of the chemicals which have been identified in the plant--the cannabinoids--are specific to cannabis. Ten are now routinely quantified in identifying cannabis samples. When smoked, some of the chemicals contained are further transformed by burning (pyrolysis) into still other compounds (6).

Plant material differs widely in the amount of the principal psychoactive ingredient--delta-9-tetrahydrocannabinol (THC, for short)--contained, as well as in the proportions of other chemicals. Although the effects of cannabinoids other than delta-9-THC have been studied, much remains to be learned about their effects, both singly and in interaction with one another. While, for many practical purposes, the percentage of delta-9-THC is a useful guide to the psychoactivity of a drug sample, other chemical ingredients may ultimately prove to be-important in modifying THC's effects as well as because of their own impact on the body. A good deal of valuable basic research has been done on THC, but it should be emphasized that it is only one ingredient of the natural material: Thus, some of the research on THC may be only partially relevant to the effects of the plant material itself. In addition, the ratios of the different cannabinoids found in cannabis change in response to the passage of time and storage conditions. Plants which have been specifically cultivated for their psychoactivity contain much more delta-9-THC than do those grown for fiber. Most of the cannabis qrowing wild in the United States derives from plants which were originally cultivated for their fiber, rather than drug content, so that they could be used in making rope and other nondrug products. Thus the THC content of this wild cannabis in the United States rarely exceeds one percent THC.

Although there has been no representative random sampling of illicit marijuana that can provide an accurate indication of changes over time, there is evidence that material now sold is significantly higher in THC content than was true only a few years ago. Chemists at the University of Mississippi who have been analyzing confiscated samples of cannabis for several years have found increases on the order of ten times in potency since 1974. Mexican "brick" (i.e., compressed kilogram quantities of marijuana) samples studied in 1974 averaged about a fifth of one percent delta-9-THC. Mexican samples analyzed thus far in 1979 have averaged nearly two percent. Other cannabis samples, probably of Colombian origin, which were analyzed in 1979 have averaged over four percent THC content. Hash oil, a concentrated liquid marijuana extract not available on the street up until a few years ago has been found to have THC levels

ranging from nearly eleven percent to twenty-eight percent. Such stronger materials are more likely to lead to higher levels of intoxication and to possibly adverse consequences.

As knowledge of cannabis chemistry and metabolism has increased and the role of various metabolites becomes more important, there has been a corresponding need to synthesize supplies of these substances. Research availability of these materials enables us to tease out their effects from those of other constituents. In the past year several improved methods for synthesizing metabolites have been developed. The ability to synthesize marijuana components and metabolites in research quantities has accelerated work on the detection of marijuana in body fluids, as well as permitted studying the drug's metabolism. By radioactively labelling the substances involved, it is possible to trace their passage through the body.

The chemistry of marijuana smoke has commanded considerable attention in recent years. Some 150 compounds have been identified in the smoke itself (7). One of them, benzopyrene, known to be carcinogenic, is 70 percent more abundant in marijuana smoke than in tobacco smoke (7). There is also evidence that more "tar" is found in marijuana cigarettes than in high tar tobacco cigarettes (8).

The metabolism of marijuana is only partially understood. Over 35 metabolites of delta-9-THC have thus far been identified along with several dozen metabolites of other marijuana constituents. Ability to identify and trace the pathways of these chemicals in the body provides vital information concerning how they are stored and eventually eliminated. Such information is useful in helping determine the possible sites of action for long term effects of marijuana.

Detection and quantification of cannabinoids and their metabolites in body fluids continues to be an important problem. Sophisticated laboratory techniques are available for the precise measurement of cannabinoid levels in blood and other biological samples. More routine and simpler techniques have also been developed recently and are currently undergoing field testing. When this is completed and the techniques become generally available (probably by mid 1980), they will be useful for such purposes as the routine laboratory detection of marijuana-intoxicated automobile drivers, screening individuals for current marijuana use in treatment programs, etc. The earlier, more elaborate techniques have been important for research purposes as well as to provide the necessary standards by which the results of more rapid and convenient techniques can be evaluated.

A good beginning has been made in understanding marijuana chemistry and metabolism. It has enabled researchers to demonstrate that marijuana constituents cross the placental barrier and as a result may affect fetal development (9). The presence of cannabinoids in mother's milk also raises the question of possible impact on the

infant of the marijuana-using mother (10). Greater understanding of the chemistry of marijuana has also raised the possibility (cf., Therapeutic Aspects) that one or more of the synthesized components of cannabis in its original or chemically modified form may come to have therapeutic usefulness. Finally, our increased awareness of marijuana's chemical complexity and the ways in which components other than delta-9-THC modify the drug's effects may shed light on the common street belief that different types of marijuana have different effects not wholly related to their THC content.

Acute Effects of Marijuana

Although much recent interest has been focused on the possible long term, chronic effects of marijuana, it is important to recognize that some of the drug's acute effects on intellectual and psychomotor performance have definite practical significance. This includes the likelihood of impaired learning ability when marijuana is used by students during the school day, as well as adverse effects on driving and other complex psychomotor performance.

Effects of the marijuana "high" on various aspects of psychological performance were systematically observed as early as the 1930s and, of course, more subjective accounts of marijuana's effects exist that long antedate scientific description (11, 12). These earlier clinical descriptions have generally been verified by more systematic research investigation.

A wide range of impairment of intellectual performance was initially found. It included such tasks as digit symbol substitution (a timed task in which the individual substitutes a series of symbols for numbers) (13),choice-reaction time (a reaction-time task in which the response depends on rapidly discriminating between choices) (14), the ability to repeat in forward and backward order a succession of digits (15), and to mentally make a succession of repeated subtractions (16). Many other task performances, including concept formation (17), reading comprehension (18), and speech have also been found to be impaired to a greater or lesser extent (19).

Generally, such impairment has been found to be related to several kinds of variables, including the dose of drug, the level of motivation, the individual's tolerance to marijuana, and the complexity and familiarity of the task being performed. More familiar, less demanding tasks are less interfered with than those involving new material and more difficult task requirements. A common denominator to impairment of functioning is the effects of marijuana on short term memory. Marijuana appears to interfere with the transfer of material from immediate to longer term memory storage. (20)

When marijuana is smoked, the ability to recall material learned while "high" is typically impaired. This impairment occurs with a wide variety of verbal, as well as graphic, material. The body of research evidence accumulated to date indicates that marijuana intoxication has a detrimental effect on memory functioning, in that material learned while "high" is significantly less well recalled than that learned in a nondrugged state. This is especially true when the task involves recalling the learned material rather than simply its recognition.

There are now dozens of experimental studies which have been conducted, all of which are generally consistent. While marijuana's acute effects on memory and cognition vary with the task and amounts used, they are almost invariably detrimental.

Although there have been no studies directly assessing the impact of marijuana intoxication on classroom learning the similarities with laboratory experiments which have been done make it virtually certain that the drug interferes with classroom performance as well. Since there is now evidence that substantial numbers of high school students are using marijuana during the course of the school day, it is likely that its use is having a detrimental effect on their classroom functioning and knowledge acquisition.

Acute Marijuana Intoxication and Complex Psychomotor Performance in Driving and Flying

There is good evidence that marijuana use at typical social levels definitely impairs driving ability and related skills. Studies indicating impairment of driving skills include: laboratory assessment of driving-related skills (22), driver-simulator studies (23), test-course performance (24), actual street-driver performance (25) and, as previously reported, a study conducted for the National Highway Traffic Safety Administration of drivers involved in fatal accidents (26).

As use becomes increasingly common and socially acceptable and as the risk of arrest for simple possession decreases, more users are likely to risk driving while high. In limited surveys, from 60 percent to 80 percent of marijuana users questioned indicated that they sometimes drive while high.

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

A study of drivers involved in fatal accidents in the greater Boston area was conducted by the Boston University Accident Investigation Team. They found that marijuana smokers were overrepresented in fatal highway accidents as compared to a control group of nonusers of similar age and sex (26).

A more recent study, conducted by the California State Department of Justice, found that of nearly 1,800 blood samples taken from drivers arrested for driving while intoxicated, sixteen percent were positive for marijuana. Where no alcohol was present in the blood sample (about ten percent of the samples) the incidence of marijuana detected rose to twenty-four percent (27). Additional studies of motorist impairment related to marijuana use are being conducted.

There are, therefore, several converging lines of evidence that driving performance is impaired when under the influence of marijuana, viz.: users' subjective assessments of their driving skills while high, measures of driving-related performance, a limited study of actual highway fatalities and a study of individuals arrested for driving while intoxicated.

The parameters of impairment for the average driver under various dosages of marijuana cannot yet be adequately specified. It is important to develop reliable standards for what constitutes driving under the influence of cannabis so as to discourage potentially dangerous driving. At present it is clearly desirable to discourage driving while "high" and to make drivers aware that it is a significant risk.

While there have been no recent studies, previous research findings indicate that experienced pilots undergo marked deterioration in performance under flight simulator test conditions while "high"(28). Thus, flying while marijuana-intoxicated is clearly dangerous.

A continuing danger common to both driving and flying is that some of the perceptual or other performance decrements resulting from marijuana 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."

Pulmonary Effects

Because marijuana is typically smoked, its possible adverse effects on the lung and pulmonary function have long been of concern both here and abroad. It is noteworthy that one of the earliest attempts to assess the health and social implications of cannabis use, the Report of the Indian Hemp Drugs Commission of 1893-94, includes observations about its pulmonary effects that are surprisingly similar to more contemporary observations. For example, this report mentions a possible value in the treatment of asthma because of the drug's "pulmonary sedative" qualities. However, it goes on to say that "long continued smoking...doubtless results in the deposition of finely divided carbonaceous matter in the lung tissues, and the presence of other irritating substances in the smoke ultimately causes local irritation of the bronchial mucous membrane, leading to increased secretion, and resulting in the condition which is described as chronic bronchitis in ganja smokers." ("Ganja" is the Indian term for a type of smoked cannabis preparation intermediate in potency between that of marijuana and hashish.) The report makes still another observation strikingly descriptive of present day marijuana use, viz.: “In ganja smoking...the

inspiratory act is far greater and more prolonged, a larger volume of smoke entering the lungs than in cigarette smoking" (29). Such deep inhalation of marijuana may well offset the typically smaller amounts smoked as compared to cigarette smoking. One indication of this is to be found in a study comparing marijuana and cigarette smokers which found that smoking less than one "joint" per day decreases vital capacity--the amount of air the lungs can expel following a deep breath--as much as smoking sixteen cigarettes per day (30). Although the ratio found needs to be confirmed by more extensive research, it suggests that the mode of marijuana inhalation and the way in which it is consumed may result in disproportionately adverse pulmonary effects as compared to modern cigarettes. Part of this difference may be accounted for by the fact that present day cigarettes are filtered and have significantly lower levels of "tar" than was true in the past. Marijuana "joints" are unfiltered and virtually entirely consumed. Moreover, under conditions of ready availability there is some evidence that the number of "joints" consumed may approach that of tobacco cigarettes (as high as ten per day) (31).

Thus far there is no direct evidence that smoking marijuana is correlated with lung cancer. The American experience has been too brief for this to be a likely outcome. Nevertheless, there is good reason for concern about the possibility of pulmonary cancer resulting from extended use over several decades. Like tobacco smoke residuals--so-called "tar"--cannabis residuals when applied to the skin of experimental animals have been shown to be tumor-producing (32). Analysis of marijuana smoke has also found evidence that it contains larger amounts of cancer-producing hydrocarbons. For example, benzopyrene, a known cancer-producing chemical found in tobacco smoke, has been reported to be 70 percent more abundant in marijuana smoke (33).

Cilia which assist in moving inhaled dust and other small foreign particles from the lungs have been found to be adversely affected by marijuana smoke. Following exposure to marijuana smoke, anti-bacterial defense systems in the lung have been shown to be less effective against staphylococcus aureus, a bacterium causing a serious form of pneumonia (34).

While similar effects have not yet been demonstrated in humans, it would be surprising if they did not occur and they may be expected to be dose related. The greater the amount and frequency of use, the greater the likelihood of adverse pulmonary (and other) consequences.

Serious effects on the lungs have been found in rats exposed to marijuana smoke in quantities producing blood cannabinoid levels similar to those of human daily users. The animals were made to inhale smoke in a specially constructed apparatus at daily

intervals for periods corresponding to an eighth to one-half their normal life span. Extensive lung inflammation and degenerative changes were found, similar to but more severe than those produced by exposure to tobacco smoke. The authors conclude that in addition to the irritating effects of smoke, the cannabinoids, chemicals specific to marijuana, "may have a direct undesirable effect on pulmonary function" (35).

There have been several clinical studies of human users which have reported such symptoms as laryngitis, cough, hoarseness, bronchitis, and cellular change in chronic marijuana and hashish smokers which resemble those of heavy tobacco smokers (36,37,38). In one of these, a study of American soldiers stationed in Europe, these symptoms were serious enough for the chronic hashish users involved to seek medical treatment (38). While studies of small numbers of chronic cannabis users in Jamaica, Greece, and Costa Rica did not find evidence of lung pathology, this may have been because traditional users in those countries do not inhale cannabis smoke as deeply and retain it in their lungs as do American users (39,40,41).

From the total body of clinical and experimental evidence accumulated to date, it appears likely that daily use of marijuana leads to lung damage similar to that resulting from heavy cigarette smoking. Since marijuana users often smoke both tobacco and marijuana, the effects of the combination require additional study.

Reproductive Effects of Marijuana

Effects on reproduction have been attributed to marijuana as far back as the earliest cannabis commission's scientific report, that of the Indian Hemp Drugs Commission of 1894. While commenting on a sexual "stimulant" effect similar to that of alcohol, the Report also describes cannabis as "used by ascetics in this country (i.e., India) with the ostensible object of destroying sexual appetite" (42). Quite apart from the drug's psychologically related reproductive effects, there have been numerous experiments with animals detailing effects on organs, processes, and hormone levels related to reproduction. At doses generally much higher than those used by humans, the evidence is consistent--cannabis causes decreases in the weight of organs such as testes and ovaries, as well as altering various hormone levels that are involved in reproduction and lactation. Some more recent studies have examined the effects in animals of drug doses more clearly comparable to heavy use in humans. There have also been a few experiments in which researchers have attempted to study human reproductive effects directly.

With respect to human males, some have found a decrease in levels of serum testosterone correlated with heavy marijuana use, although several others have not. One explanation for this apparent discrepancy in experimental findings is that after smoking marijuana the temporarily depressed levels of testosterone may rapidly return to more usual levels. Depending on the time schedule in which sampling is done, the effect may be missed. Even when testosterone decreases have been found, the levels have been within normal limits. Whether more persistent chronic use of marijuana might result in permanently depressed levels of serum testosterone is not known at this time.

Two studies of the semen of male chronic users have found abnormalities in sperm count, motility and in the structural characteristics of the sperm examined (44,45). In one of these, the semen of 16 healthy young males smoking marijuana under controlled conditions was studied (44). The levels of use while "high"--eight to twenty "joints" per day--were comparable to those of other very heavy users in the general population. Decreases in sperm count and motility were found, together with evidences of structural abnormality in the user's sperm. A second study of Greek chronic users also found structural abnormalities in sperm that were associated with heavy use (45). While the clinical implications of these animal and human findings are by no means certain, decreased fertility might well result, especially in those of already marginal fertility. In the more controlled laboratory study there was an apparent gradual return to normal functioning when marijuana use was discontinued (44). To date (late 1979), there have been no published reports of abnormal offspring of fathers which have been related to their marijuana use. Whether or not alterations in reproductive function might have greater

significance for the developing child or adolescent is not known at this time, although this is a concern since the younger user is probably more vulnerable.

When we turn to the question of marijuana's effects on the female reproductive system, there is some recent animal experimentation with doses comparable to those in actual societal use that suggests possible adverse consequences. Results to date are, however, far from definitive. One study, using THC at levels which the authors describe as "equivalent to moderately heavy marijuana usage in the United States," found that the rate of "reproductive loss" in THC-treated female rhesus monkeys was about four times greater than that in drug-free controls. The majority of these losses represented deaths, abortions, or resorptions of the fetus. No clear pattern of fetal abnormality was evident. The authors conclude that their experimental results "raise the possibility that exposure of the human female to marijuana in amounts in relatively common use may be associated with an increased risk of reproductive loss" (46).

A study of female "street users"--women using marijuana on their own and of unknown potency--has also raised questions about the possible reproductive effects of cannabis on women. In this research 26 women in their twenties who used marijuana three times a week or more for six months or more were compared to a nonusing group of women of similar age. The experimental group had a significantly higher frequency of abnormal menstrual cycles in which they failed to ovulate (i.e., produce a ripened egg) or showed possible evidence of a shortened period of potential fertility--shortened luteal phase of the menstrual cycle. Lowered prolactin levels--a hormone important after childbirth in producing adequate mother's milk--were also found, suggesting that nursing might be impaired in marijuana-using women following childbirth (47). While such findings are of considerable interest, they must be regarded as preliminary. The drug-using women also used larger amounts of alcohol than did the controls, which may have contributed to the result, and there may have been other differences in lifestyle which contributed to the experimental outcome. Nevertheless, both animal and human data raise the distinct possibility that fertility may be impaired in heavy marijuana users as a result of their use. Studies which have been done in countries of more traditional cannabis use are of little value in clarifying this question since male use overwhelmingly predominates among traditional users.

Experiments with radioactively labelled THC (enabling its progress through the body to be traced) clearly indicate that the drug appears in the milk of nursing monkey mothers and in their offspring when the drug is administered to the mothers (48). There is also good evidence that THC and other cannabinoids pass through the placental barrier, reaching the fetus during uterine development where they tend to concentrate in the fetus' fatty tissue

(including the brain) (49). While pre- and postnatal changes related to maternal use have usually only been found with larger doses in animals and have not been reported in humans, the distinct possibility that marijuana use during pregnancy might result in abnormal fetal development makes its use during pregnancy very unwise.

While much remains to be learned about the possible effects of marijuana on reproduction, several points are reasonably clear. Marijuana at higher doses has a range of effects relevant to reproduction in animals. These appear to result from a variety of mechanisms, including the drug's effects on adrenal function and hormone production in testes and ovaries. More recently, at dose levels that might be encountered in the heavy, regular user, possible adverse consequences for fertility in both males and females have been identified. Such effects may be of greater importance for the marginally fertile or the developing adolescent than for the mature, healthy adult. Finally, given the many unknowns concerning possible effects on the human fetus, use of marijuana during pregnancy should be especially discouraged.

Cardiovascular Effects

Although cardiovascular effects of marijuana have been investigated extensively, such research in humans has been largely restricted to healthy young male volunteers in whom the effects appear to be limited in duration and generally benign. One such study examined the short range effects of smoking one to three marijuana cigarettes on 21 male experienced smokers participating in a 94-day in-hospital study of heavy marijuana smoking. They found, as have others, a significant increase in heart rate after smoking although not as clearly dose related as previous findings. They attribute the lack of a clear dose relation to tolerance that developed for the cardiovascular effects of the drug as a result of chronic use. The changes they found in heart functioning were secondary to temporarily increased heart rate and appeared to be free of adverse consequences (50). As previous editions of this report emphasize, however, there is evidence that in patients with already impaired heart function use of marijuana may precipitate chest pain (angina pectoris) more rapidly and following less effort than tobacco cigarettes (51). This possible difference in the response to marijuana in heart disease patients may prove to be of considerable practical significance if use expands to include older populations or if presently young adult users continue to use cannabis as they progress through middle life. Despite the limited evidence to date, a warning to heart patients and others who may have impaired cardiac function not to use marijuana, continues to be justified.

Marijuana and the Immune Response

Because of the importance of the body's natural defenses against illness, principally the immune response, in preserving the health of the individual, reports of impairment of this vital function must continue to be carefully considered. There have been contradictory reports of impairment of this response in humans (52, 53,54,55,56). The animal data, using generally higher doses, have consistently indicated a definite suppression of the test animals' immune responses (51,58). In humans, even when there have been indications of a diminished response, it has not been found in all users and the clinical implications are in doubt. As yet, there has been no epidemiological research undertaken to determine whether marijuana smokers suffer from infections and other diseases to a greater extent than others of similar lifestyle who do not use the drug. For the present, this important question must be regarded as unresolved and the evidence far from clear cut.

Chromosome Abnormalities

There is no new evidence in this area. While there were early reports of increases in chromosomal breaks and abnormalities in human cell cultures, more recent results have been inconclusive. The three positive studies in humans that have been reported have decided limitations (50,60,61). All were retrospective--i.e., studies of those already using marijuana who were compared to nonusers. Such variables as differences in lifestyle, 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 (62,63,64). All are negative, but the results could have been influenced by the fact that all the subjects had at least some prior experience with marijuana. It is possible that the baseline levels of chromosome deficits may have been elevated by earlier casual marijuana use, thus masking a drug-related effect.

A team investigating the effect of marijuana smoke on human lung cells in laboratory culture has found an increase in the number of cells containing an abnormal number of chromosomes (65). Another investigator who previously reported a high proportion of cells in marijuana smokers with reduced numbers of chromosomes has more recently reported that the addition of delta-9-THC (the principal psychoactive ingredient of marijuana) to human white blood cell cultures also resulted in an increased frequency of cells with abnormally low chromosome numbers (66). The implications of these findings continue to be uncertain.

323-754 0 - 80 - 3

Overall, there continues to be no convincing evidence that marijuana use causes clinically significant chromosome damage. However, it should be emphasized this year as last that the limitations of the research to date 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. Adding delta-9-THC to various types of human and animal cell cultures has been found to inhibit DNA, RNA, and protein synthesis. No effect on DNA repair synthesis was found although the uptake of the chemical precursors within the cells was reduced by half (67).

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 earlier reported research. 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, marijuana might prove of value as an anticancer drug. It should, however, once again be stressed that there is no evidence to date that cannabis or any of its synthesized or naturally occurring constituents is of value in inhibiting human cancer growth. If animal findings of a depressed cell immunity response which is also related to cell metabolism are substantiated in humans, cannabis, its synthesized components or chemically related drugs might prove useful in preventing organ rejection in human organ transplant surgery.

Brain Damage Research

A British research report, which originally appeared in 1971, attributed brain atrophy to cannabis use in a group of young male users. In the original study, 10 patients, with histories of from 3-11 years of marijuana use, were examined by air encephalography, a neurological technique used to detect gross brain changes. The authors concluded that their findings suggested that regular use of cannabis may produce brain atrophy (68). This research was faulted on several grounds: all of the patients had used other drugs, making the causal connection with marijuana use questionable; and the appropriateness of the comparison group and diagnostic technique was questionable. The potential seriousness of the original observations justifies a brief review of several subsequent studies bearing on the original British observations.

In a study of chronic Greek users, a different technique (echoencephalography) was employed to determine whether brain atrophy

might be present in heavy users. The findings from the Greek study were negative; that is, users were not found to differ from nonusers in evidence of gross brain pathology (69).

Two studies were subsequently conducted in Missouri and Massachusetts (70,71). They examined 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 both studies, the resulting brain scans were read by experienced neuroradiologists independent of the drug histories. In neither was there any evidence of cerebral atrophy. As was emphasized last year, however, several additional points should be stressed. Neither study rules out the possibility that more subtle and lasting changes of brain function may occur as a result of heavy and continued marijuana 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 1979) show no evidence of chronically impaired neuropsychologic test performance in humans at dose levels experimentally studied.

A researcher who used electrodes implanted deep within the brains of monkeys instead of more conventional scalp recording techniques has found persistent changes related to chronic use (72). This same investigator has reported that rhesus monkeys administered marijuana smoke from one joint daily for five days per week for six months show persistent microscopic changes in brain cellular structure following this treatment (73). While both these experiments demonstrate the possibility that more subtle changes in brain functioning or structure may occur as a result of marijuana smoking in animals, the implications of these changes for subsequent human or animal behavior are at present unknown. Other studies, using more conventional EEG techniques to measure brain electrical activity, have found changes temporarily associated with acute use, but no evidence of persistently abnormal EEG findings related to chronic cannabis use (74,75).

Psychopathology

Although this has been discussed in previous editions of this report, and there is little new evidence since the seventh edition, a reiteration of what is known may be useful to those unfamiliar with the area. The most common adverse psychological reaction of marijuana-use represents an exaggeration of the more usual marijuana 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 (e.g., a higher potency variety of marijuana) can cause such a response even in the more experienced user. The symptoms generally 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. It has been repeatedly 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; by setting is meant 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. Additional research support for this clinical impression is found in a field survey which used a questionnaire to measure acute adverse drug reaction. 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 marijuana and other psychoactive drugs (79).

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 (80). 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. This set of acute symptoms has not been frequently reported in the United States, possibly because until recently very strong cannabis materials were 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 from cultures where use

is typically more frequent and at much higher doses than those generally consumed in the United States (81). It continues to be difficult to interpret such reports because the diagnosis of mental illness is partly dependent upon sociocultural factors. In addition, the diagnostic picture is frequently complicated by use of other drugs and earlier evidence of psychopathology not necessarily associated with drug use. While the overseas studies conducted under United States 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 clinical study in India has contrasted the features of a paranoid psychosis arising in the course of long ten cannabis use with that of paranoid schizophrenia. Twenty-five consecutive patients admitted with each diagnosis were compared. The cannabis users, reportedly, had used the drug for 5 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 82).

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

Some further indication of this is to be found in a paper reporting on four cases of well documented schizophrenia in which the use of marijuana is believed to have led to an exacerbation of psychotic symptoms in patients whose psychoses were in at least partial remission prior to use. The author concludes that "While marijuana can perhaps be safely used by many persons, this is not so with the schizophrenic." He urges that schizophrenics be alerted to the special hazards he feels marijuana poses for them in the same way other patients would routinely be alerted to possible hazardous interactions between their illness and substances they might use (83).

In a detailed review of the relationship between cannabis and violence the author concludes that while marijuana probably does not precipitate violent behavior in the majority of users, nevertheless there may be some individuals with a prior history of poor impulse control or special circumstances of stress which combined with pre-existing personality may make use inadvisable.

It is not clear, however, he points out, whether it is specifically marijuana which might have the undesirable effect of releasing violence or any of a variety of other drugs including alcohol 84).

Based on his experience with some five thousand drug-related psychoses encountered while medical director of many youth festivals, one author has summarized his clinical experience including that with marijuana users. In his experience, serious adverse reactions to marijuana are rare, but he offers several sources of concern about its widespread and indiscriminate use. Specifically, he feels that the possibly unexpectedly high potency of some of the cannabis preparations may pose a hazard for those used to weaker materials. Although he believes it to be very rare, he thinks that it is possible to have a psychotic reaction to marijuana. He also believes that persistent psychiatric symptoms after psychotic drug experiences are more common than is generally believed, as many as 5 to 10 percent of those cases which he was able to follow up. While some patients reporting "flashbacks" had their initial "bad trip" on drugs other than marijuana, the flashback recreation of the disturbing aspects of the original experience frequently occurred following alcohol or marijuana use. He concludes by advising that "Those with a history of emotional disturbances and especially 'bad trips' (i.e.. previous drug precipitated emotional disturbances) should avoid intoxicants including alcohol and marijuana." Finally. this author advises that present emergency room and psychiatric hospital procedures should be altered to make the situation less judgmental, less frightening and coercive, more compassionate and more acceptable to youth, with more homelike and reassuring surroundings (85).

Marijuana flashbacks--spontaneous recurrences of feelings and perceptions similar to those produced by the drug itself--have been reported. A survey of United States Army users found that flashbacks occurred in both frequent and infrequent users and were not necessarily related to a history of LSD use. Such occurrences may range from the quite vivid recreation of a drug-related experience to a mild evocation of a previous incident. The origin of such experiences is uncertain but those who have had them typically appear to require little or no treatment (86).

One source of information about possible adverse reaction to drugs, including marijuana, 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 contacts with such facilities as hospital emergency rooms.

During a 1-year period beginning in May 1976 and ending in April 1977, marijuana ranked thirteenth among the drugs mentioned in drug-related emergency room contacts. But during the year 1978, the most recent year for which complete data are available, marijuana had risen to sixth place. While such figures are not always easy to interpret, they do suggest that marijuana is not an uncommon factor in causing individuals to seek help and that its importance may be rising, possibly because of an increase in the number using the drug or because of the increased availability of stronger materials more likely to precipitate adverse reactions.

Effects of Chronic Use on Intellectual Functioning

The question of whether or not enduring effects on memory and other aspects of intellectual functioning occur as a result of chronic use is a difficult one to answer. While three more carefully controlled studies of heavy users in Jamaica, Greece, and Costa Rica failed to find evidence of this, several caveats should be mentioned. The numbers studied were small, the testing procedures with the populations studied may have been insensitive to drug-induced decrements, if any, and even the mode of drug use may have differed from American use. Overall, the majority of studies have suggested impairment does occur. Unfortunately, the quality of studies in this area leaves much to be desired. Thus the issue still remains in significant doubt, especially with reference to American users.

A retrospective study of an Egyptian prison population of cannabis users compared 850 chronic users with 839 noncannabis-using controls, using a number of tests of psychological functioning. Users were reported to be slower in their psychomotor performance and to show impaired visual coordination and memory for designs. These performance deficiencies were found to be more common in younger, better educated users from urban backgrounds than in older, illiterate users from rural areas (87,88). This study has been sharply criticized for alleged sampling and psychometric deficiencies and equally sharply defended by its author (89,90). Despite the apparent disagreement on many points, there was agreement on the desirabflity of replicating the work and possibly. doing further analysis of the original data. The large samples employed, despite some of the methodological deficiencies, might well make the original Egyptian study more sensitive to modest differences between smoker and nonsmoker groups which smaller studies may well have missed. At present the information available does not permit a conclusive judgment of the adequacy of the study's findings particularly if the data were subjected to more elaborate analysis designed to take some of the criticisms leveled against the study into account.

A study of chronic cannabis users in Northern India has been published based primarily on a comparison of 11 male users (out of a larger sample of 23, in turn chosen from 139 long term cannabis users) with 11 male nonusers who were matched in terms of age, occupation, and marital status. Users had all used cannabis equivalent to about 50 mg THC per day (about the equivalent of 5 to 10 "joints" of typical 1 to 2 percent THC content marijuana) for 5 years or more. They were given physical examinations including various laboratory tests of blood and urine as well as chest X-rays, electrocardiogram (EKG), and electroencephalogram (EEG). Subjects were also given a range of psychological tests of intelligence, memory, and other intellectual functions sometimes impaired in the brain-damaged.

The physical examinations including all but one of the laboratory tests (for uric acid blood levels which were found to be somewhat elevated in users) were normal for both users and controls. On the psychological tests, however, users did significantly less well than did nonusers on: two measures of intelligence (9 to 11 I.Q. points lower for users), a measure of memory, a task requiring reproduction from memory of geometric figures, a test of combined cognitive psychomotor speed, and a test of time perception (91).

Unfortunately, several questions of methodology which might have had an influence on these findings are not clear from the report. Twenty-three users more carefully examined were selected from a larger sample of 139 long-term heavy cannabis users and of these only 11 were then matched with 11 nonusers. It is not clear whether the basis for selection of the initial 23 was random or whether some non-random criteria were used such as ready availability, willingness to be further tested, need for possible inducements to participate, etc. The authors themselves raise the question whether the impairments found in user functioning were caused by drug use or if the impairments detected existed prior to such use. They argue for the desirability of doing a prospective study if the question of cannabis-related impairment of function is ultimately to be resolved. The possibility that other aspects of lifestyle such as inadequate diet might have played a role cannot be dismissed as a factor in the poorer performance of the users. Since users were from among the poorer groups in the society, the cost of their cannabis might well significantly reduce the amounts available for food purchases. At present, the results must be regarded as provocative and should be more carefully explored.

American studies comparing college student users with nonusers have found little in the way of evidence of intellectual performance decrement associated with cannabis use at least as such performance is measured by college grades. As was pointed out in previous reports, the higher levels of motivation of students

in the schools studied, the rather modest levels of use compared with that overseas and the possibility that those whose performance was impaired by marijuana use had dropped out earlier, all limit broader interpretation of these more limited findings.

Tolerance and Dependence

Tolerance to cannabis--i.e., a diminished response to a given repeated drug dose--is now well substantiated. Tolerance development was originally suspected because experienced overseas users were able to use large quantities of the drug that would have been toxic to United States users accustomed to smaller amounts of the drug. Carefully conducted studies with known doses of marijuana or THC leave little question that tolerance develops with prolonged use.

Several more detailed reviews of tolerance development to the behavioral and physiological effects of marijuana in both animals and humans have been published (92,93,94). A report detailing tolerance development of 30 young adult subjects in a 94-day closed experimental ward environment has also been published which stresses tolerance to both the effects on heart rate and the subjective "high "(95). The practical implications of this work are that experienced, frequent users of marijuana experience less pronounced physiological and psychological changes at a constant level of use than would less experienced users. This is in some contrast with the original impression that users had a "reverse tolerance"--i.e., a greater sensitivity to marijuana upon repeated use. The latter impression probably derived from the relatively low dose, infrequent use that characterized some of the earlier observations. Under those conditions neophyte users may have become more aware of marijuana's subjective effects with repeated use partly as a result of social learning of what was to be expected from the experience and thus subjectively believed that its effects were enhanced. Since marijuana's metabolites (the transformation products which result as marijuana is metabolized) are also persistent in body fat, it is also possible that repeated low dosage use released some of the previously stored material, enhancing the effects. Whatever the ultimate explanation of these earlier impressions, under conditions of heavier, more regular use, tolerance now appears to be well established.

When one turns to the question of "cannabis dependence" the term has often been used in an imprecise way with meanings ranging from a vague desire to continue use, if available, to the manifestation of physical withdrawal symptoms following its discontinuance. If "dependence" is defined as experiencing definite physical symptoms following withdrawal of the drug, there is now experimental evidence that such symptoms can occur at least under conditions of extremely heavy research ward administration that

are atypical of social marijuana use in the United States. The changes noted after drug withdrawal under these experimental conditions include one or more of the following symptoms: irritability, restlessness, decreased appetite, sleep disturbance, sweating, tremor, nausea, vomiting, and diarrhea (96,97). Some of these symptoms were experienced in a similar research study by users who selected their own smoked marijuana doses (98). Such a "withdrawal syndrome" has thus far been reported clinically in only one formal research report.

THERAPEUTIC ASPECTS

A "fringe benefit" of the past decade's marijuana research has been a renewed interest in its potential as a therapeutic agent. As earlier editions of these reports have indicated, cannabis has a very ancient history of use for the treatment of an unusually wide range of human ills. Almost from the dawn of history, cannabis has been used in many parts of the world as a pharmaceutical preparation. As recently as 1937, tinctures of cannabis were still listed in the United States Pharmacopoeia and presumably used therapeutically in the United States. One limitation of these earlier preparations was the extreme variability of drug potency--ranging from inert or nearly so to unexpectedly potent.

Renewed interest in the potential usefulness of cannabis or of some synthetically related drug has led to experimentation with these drugs for a wide range of symptoms and disorders. Although several of these applications have shown promise, much remains to be learned about even the most promising applications.

Control of Nausea in Cancer Chemotherapy

Use of marijuana, THC, or related drugs for the treatment of the extreme nausea and vomiting which often accompany cancer chemotherapy is probably the single most promising application of these drugs. While by no means invariably effective, they are sometimes valuable when other standard antinausea drugs are not. One of the earlier studies done in 1970 found that THC-treated cancer chemotherapy patients showed improved appetite and diminished weight loss (99). A subsequent study done in Boston found that when compared with a placebo--that is, an inert substance--in a double-blind study in which neither patients nor physicians knew which drug was being administered, THC had an antiemetic effect in seven out of ten patients. The placebo-treated patients showed no improvement (100). In one recent study of 15 patients receiving methotrexate for their bone cancer, THC or placebo was randomly assigned. Fourteen of the 15 patients showed improvement following the use of THC. The amount of reduction in nausea and vomiting was closely related to the dose of THC given. At the highest THC dose employed, in 6 percent of the treatment sessions, patients experienced nausea and/or vomiting, compared to 44 percent when half the dosage was used. Such adverse symptoms were found in 72 percent of the sessions in which the pharmacologically inert placebo was employed. In a second phase of the same experiment, four patients who had shown excellent therapeutic response in the first phase were again treated with THC, but this time much less favorable results were achieved. The reasons for this are unclear, although the authors suggest the possibility that these patients developed a tolerance to the effect during the first phase of the experiment (101). Other studies have attempted to compare marijuana-related drugs to other standard antinausea medication to determine their relative effectiveness. Nabilone, a drug chemically related to marijuana constituents, was compared to

prochlorperazine, a standard antinausea drug, in a series of 113 patients receiving cancer chemotherapy. Eighty percent responded to nabilone, compared to 32 percent who responded to prochlorperazine (102). Use of this experimental drug has, however, since been suspended because of toxic effects observed in dogs.

A partial analysis of the response of the first 66 patients of a series of 200 receiving prochlorperazine and THC in an experimental design in which each patient received trials of both found that equal numbers--25--preferred each, 12 had no preference, and four patients did not respond to the question. Sleepiness was the most common side effect of both drugs (103).

Overall, marijuana, THC, and related drugs show promise for treating the nausea and vomiting which are common side effects of chemotherapy, Although thus far, THC and marijuana do not appear to be invariably superior to other medication, they may be useful with patients for whom other drugs are relatively ineffective.

Glaucoma

A second treatment application which has received wide publicity in the mass media is to reduce the vision-destroying intraocular pressure which occurs in open-angle glaucoma. This use is based on the original observation, both in normal young men and in test animals, that such pressure reductions occur (104). Initial trials with oral THC alone found the drug to be of variable success. When used as a supplemental drug with other standard intraocular-pressure-reducing drugs, greater success was achieved. Because of the desirability of developing a more convenient dosage form with fewer side effects, an eye-drop preparation has been tried. Although it showed initial promise in reducing intraocular pressure in rabbits, it produced eye irritation and was ineffective in humans in one trial. Additional human testing is planned.

A recent study employing smoked marijuana with 16 glaucoma patients, eight of whom were hypertensive and eight of whom were not, found that the hypertensive patients showed a significantly greater drop in eye pressure than did those with normal blood pressure (105).

At present, marijuana-related drugs have been shown capable of reducing intraocular pressure in people with glaucoma, alone and in combination with more conventional anti-glaucoma medications. However, the long-term safety and efficacy of marijuana-related drugs administered chronically to glaucoma patients has not been established, nor is there any data from long-term controlled studies to demonstrate whether these preparations can actually preserve visual function in such individuals.

As with other clinical applications, a synthesized drug with fewer of the side effects found with the natural material may ultimately be more useful. Continued clinical trials to determine the most useful combinations with other drugs could be desirable.

Other Therapeutic Uses

A variety of other clinical uses of marijuana have been suggested or experimentally employed. While marijuana's ability to dilate the lung's air passages (bronchodilation) has been thought to have promise in treating asthmatics, the drug's lung-irritating properties seem to have offset this potential benefit. Aerosol preparations for inhalation have shown some promise, but have produced lung irritation and may not be commercially feasible (106). Despite these problems, a marijuana-related drug may still prove to be of limited usefulness since its different mechanism of action from that of conventional drugs may make it useful with some patients with whom other drugs are ineffective.

The paradox that THC and marijuana have both convulsant and anticonvulsant properties has led both to concern about the implications of marijuana use by epileptics and to speculation about its possible value in controlling seizures. In animal experimentation, these drugs have reduced as well as increased seizure activity, depending on how the experiment was conducted. As in the treatment of glaucoma, the possibility that one or more of marijuana's constituents may be useful in combination with other standard antiseizure medication exists, although its usefulness, if any, appears limited at this time. Although a small survey of youthful epileptics did not disclose any particular effect of cannabis use upon their seizure patterns, our present limited knowledge and the possibility that marijuana might adversely affect these patients suggests that caution be exercised in use (107).

While there have been some clinical reports of marijuana reducing muscular spasticity in paraplegics and patients with multiple sclerosis, such work is still in an early stage, and a definite usefulness has not yet been found on a more systematic basis (108).

Still other applications of marijuana in the treatment of depression, pain, and of alcoholism and drug dependence have been variously considered. Although these applications have not been adequately explored, there is little evidence that they are likely to prove useful at this time.

While marijuana and/or its synthesized constituents have shown some promise as therapeutic agents, it should again be emphasized that additional work is necessary before such agents become generally approved as standard medications, even for limited purposes.

If consistently useful medical applications for marijuana are found, it is quite likely that the product or products resulting will be chemically related to but not identical to the natural material's constituents.

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 the 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 to their use arise.

EFFECTS OF MARIJUANA IN COMBINATION WITH ALCOHOL AND OTHER DRUGS

Since marijuana is so commonly used in combination with alcohol and other drugs, the combined effects of these drugs has potentially important implications. Given the extremely wide range of possible doses and interactions, it is not surprising that our present knowledge is still quite limited. This is true even of the most commonly used combination, alcohol and marijuana.

A related issue is the extent to which marijuana use might displace alcohol use were both drugs equally available. Although some marijuana users in the 1960s were ideologically opposed to alcohol, it now appears that use of both has generally increased. While it is not possible to be certain what would occur under conditions of equal availability, there is no indication that increased marijuana use among teenagers and young adults has resulted in a decrease in alcohol use. In fact, several researchers have noted a positive correlation between heavy marijuana use and that of alcohol; that is, those using marijuana heavily were more likely to use alcohol than those who either did not use it or used it less frequently. One large scale longitudinal study of children from elementary school to high school age has found that the early use of alcohol (and tobacco) is more common in those who also begin marijuana use early or use it more regularly and heavily (109). In one study of marijuana use in young men conducted in a closed experimental ward setting, marijuana smoking increased regardless of the availability of alcohol, although, conversely, alcohol use decreased when marijuana was available (110). Thus the larger question of what would happen in American culture were marijuana more freely available cannot readily be answered. It might well depend on the kinds of informal social attitudes and controls which developed among users.

Animal studies of the behavioral effects of the alcohol-cannabis (or THC-alcohol) combination have generally found that the combined effect is greater than that of either alone (111). For example, the duration of alcohol-induced sleep increased as much as three-fold when rats or mice also received a marijuana extract or THC prior to being given alcohol (112, 113, 114, 116). Animals receiving THC in doses that ordinarily did not interfere with their ability to remain on a moving belt showed increased alcohol-related impairment of their performance (117). When animals have been simultaneously administered both drugs, conditioned avoidance (i.e., a learned avoidance of a noxious stimulus), general activity level, heart rate, and body temperature have been more affected than when either was used alone (118).

The limited human research to date is generally consistent with the results of animal research. Experiments at alcohol levels within the range commonly used socially showed that performance reductions from combined use are greater than those from the use

of either alone. Such decrements have been detected in reasoning, manual dexterity, and standing steadiness (119,120). Although the effects after 40 minutes were greater than either drug separately, 2 hours and 40 minutes later some of the changes were less than those of THC alone. This apparently antagonistic action under some circumstances may result from the different rate at which the two drugs are metabolized. In more recent experiments, when alcohol was given one hour after THC, the effects of the drugs were clearly additive. Combined use reduced reaction time, cognitive performance, standing steadiness, and psychomotor coordination more than that of either alone (121).

In measuring glare recovery--the time it takes for light adaptation after exposure to bright light--it was only slightly greater for the combination than for either alone (122).

The authors of a research paper dealing with the side effects of alcohol and marijuana caution that the use of the two simultaneously may be dangerous for those with cardiac disorders. In a study of seven healthy male volunteers aged 20 to 29, they found that four of the seven developed intense nausea and vomiting when they smoked a marijuana cigarette after drinking a moderate amount of alcohol. The doses of alcohol involved (1 gm ethanol/kg. of body weight or about 57 cc. of pure alcohol for an average man weighing 154 lbs.) represented about the equivalent of three drinks containing one and a half ounces each of 90 proof liquor. All four men were markedly incapacitated during the height of the adverse effects, although they recovered in three to four hours. The fact that not all seven subjects were equally affected illustrates large individual differences in response. One subject, for example, experienced a marked drop in heart rate under the influence of the drugs--from 150 to 36 beats per minute. When the experiment was repeated with half the amount of alcohol originally used, no adverse effects occurred. The volunteers acknowledged that similar adverse consequences had sometimes occurred when they had used the drug recreationally (123).

Taking the total of animal and human research simultaneous use of both alcohol and marijuana typically has more profound effects than the use of either alone. However, the magnitude and duration of the effect may vary depending on the dosages of the two drugs involved, the type of effect measured, and the time intervals involved in administering the drugs. As with either drug alone, there are also undoubtedly individual differences in response to the drugs in combination,

Animal research has raised the question of a possible cross tolerance between alcohol and marijuana. By this is meant regular administration of one drug may result in a decreased response to another drug, even though the other has not been given. A recent experiment has found that when both alcohol and THC were administered to rats, they developed tolerance to alcohol much more quickly than when

they received only alcohol (124). In humans the question of cross tolerance has not yet been resolved. While there is some evidence that the performance of male heavy marijuana users is less affected by drinking four to five ounces of 100 proof alcohol than is that of nonusers, a later study of performance under similar conditions found the trend to be statistically insignificant (that is, the difference found may well have been the result of chance rather than due to prior marijuana use) (125).

There have been few human studies of the interactive effects of marijuana with drugs other than alcohol. However, limited evidence suggests that such interactions may be significant. A study in which high doses of THC were given to young adult males indicates that chronic marijuana use may affect the persistence of barbiturates in the body as well as their rate of absorption (126). Only limited studies of combined use of amphetamines and marijuana in humans have thus far been done. One study found that simultaneous use resulted in an increase in the intensity and duration of the subjective "high" greater than use of either alone produced (127).

The possibility that absorption, distribution, and the metabolism of therapeutic drugs might be modified by marijuana use has been raised. In rats, aspirin has been found to decrease the rate of disappearance of THC in their blood as well as to increase the THC brain levels (128). Since there are many therapeutic drugs in widespread use which are used in many different forms and dosages, much work remains to be done.

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THE HAZARDS OF MARIJUANA VERSUS OTHER RECREATIONAL DRUGS

A question that frequently arises is how hazardous is marijuana as compared to alcohol and tobacco. As appealing as such a comparison is, it is also misleading on several grounds. Any comparison of alcohol and tobacco use and that of marijuana compares drugs with great differences in social acceptability, period of use, and degree of availability. The hazards of alcohol and tobacco are reasonably well known and the social and public health costs quite high. For example, fully 10 percent of alcohol users have been described as having an alcohol problem, and alcohol has been implicated in half the automotive fatalities in the United States. The health costs of alcohol in terms of cirrhosis, mental illness, crime, and industrial accidents can also be documented. A similar analysis can be done for tobacco. By contrast, marijuana has only recently become a popular substance; it remains illegal and most use is not habitual at present. Moreover, unlike cigarettes and alcohol, for which the health hazards can be reasonably well specified, much less is known about the implications of marijuana use.

Any consideration of the hazard a drug poses must take into account not only its present use, but also use that might be reasonably expected in the future. At present, this involves many imponderables such as the parameters of risk for various groups in our society at different levels of use, the likely circumstances of use, effects on user functioning and motivation of heavier use patterns, degree of use restriction possible, combined use with other drugs--to name but a few. As the history of the introduction of alcohol demonstrates, it is very difficult to anticipate the problems which will arise in a given society in advance. Thus, any attempt to compare the health impact of marijuana with that of alcohol and tobacco at current levels of use is certain to minimize the hazards of marijuana. But any comparison at levels of anticipated use involves many assumptions that are at best dubious and at worst may be dangerouly misleading. Such a comparison seems, therefore, useless and undesirable until such time as the parameters of risk are better specified than they can be at present.

FUTURE DIRECTIONS

The past decade's priority emphasis on Federal marijuana research has brought about an impressive increase in our knowledge concerning cannabis and its effects. Our understanding of the basic chemistry of marijuana, its mode of action in the body, and some of the acute and chronic effects of the drug have all expanded rapidly. Nevertheless, there are still many areas in which our knowledge continues to be modest. For example, we know little about the implications of use by girls and women both for their own health and for possible offspring. Since nearly half of the

American users are females of childbearing age, this is an important area for further research.

As marijuana use has come to include much younger ages--a decade ago use was largely restricted to young adults, now significant numbers use it in their early teens--the need to understand the implications of use by this group has also become imperative. Unfortunately, teasing out the effects of marijuana from that of both other drugs and other aspects of lifestyle is not always easy. Heavier users of marijuana at any age are more likely than nonusers or light users to take other drugs as well. As we have seen, "street" marijuana can also vary in potency from inert or nearly so to material with high THC content, which is very psychoactive.

While carefully controlled animal experimentation in which factors as disparate as genetic and learning history can be specified is very useful, there are important differences between animals and humans. While marijuana, for example, slows heart action in most animals, in humans it accelerates it. And, while significant progress has been made through special apparatus to induce animals to smoke the material, it is not easy to replicate typical conditions of human use.

The National Institute on Drug Abuse (NIDA), the agency within the Department of Health, Education and Welfare* which has principal responsibility for marijuana research, makes repeated use of non-government scientists serving as consultants to assist in determining new directions for research. One of the central questions that has been considered is the desirability of conducting large-scale, long-term epidemiological studies analogous to those which were done to determine the effects of cigarette smoking. Because the level of marijuana use for most of the population has been modest and because the potency of the material has been so variable, this approach is unlikely to produce results in proportion to its high cost. Instead, the Institute has elected to support a large variety of smaller studies focusing on some of the already identified specific effects as well as exploring implications of use in high risk groups.

Following the recommendations of its consultants, NIDA is particularly concerned with studying the implications of use during periods of likely maximum sensitivity. These include childhood, adolescence, and prenatal development. The study of groups receiving standardized health care is being investigated to determine cost-effective means of doing larger scale studies likely to detect effects in children, adolescents, and young adults. Development of standardized data collection methods which will enable researchers to effectively pool data from several sources is also being pursued. This enables us to detect use implications employing samples larger than are available in any single study. Such standardized methods also make it possible to compare data from different sources.

* Now the Department of Health and Human Services (1980)

Because of the increasing importance of multiple drug use patterns, the implications of that type of use are also being studied. While simultaneous use of alcohol and marijuana is the most common pattern, many users use the drug with other licit and illicit drugs. Such patterns of use and their implications must be explored.

It is unlikely that any single approach will be sufficient. Methods as diversified as the study of the impact of marijuana's constituents on cell membrane metabolism to psychosocial research on changing patterns of use are all essential to developing a well-rounded picture of the implications of marijuana use. It is also unlikely that any single piece of research will provide the definitive answers to our concerns about marijuana's effects. As with other drugs, it is probable that our understanding will increase gradually and that the effects of the drug will not be uniform, but will vary significantly depending upon the age, mental and physical health of the user, and the individual differences in vulnerability to the drug's effects.

Finally, given the marked increase in use by children and adolescents, it is important that we develop more effective means of discouraging use. While some progress has been made in this area, much more needs to be learned about individuals and groups at high risk of becoming seriously involved with marijuana use. Through an improved understanding of the factors which play a role in individual vulnerability we may ultimately be better able to "target" prevention efforts toward those most likely to suffer serious adverse consequences rather than at a more general population.

An important step in the ongoing process of exploring the implications of cannabis use and the best ways of coping with it is an independent review of the marijuana area being sponsored by the Department to be conducted in 1980. This review will provide a fresh look at our present knowledge and possible future directions of effort. It will encompass research into the physiological effects of marijuana use as well as behavioral research into such use-related problems as intervention strategies to help adolescents resist peer pressure. A report is expected to be produced in about one year.

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Human Effects: An Overview

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INTRODUCTION

Each year it becomes more difficult to write a reasonably brief review of the effects of cannabis on humans. Since the early 1960's cannabis research literature has grown rapidly. Increased research activity is a consequence of both increased public interest and increased support for cannabis research In 1951 the United Nations Division of Narcotic Drugs, Geneva, had approximately 1,000 publications in its cannabis files. Their bibliography issued in 1965 included 1,860 titles. In 1968 the Addiction Research Foundation in Toronto, Canada, published a bibliography containing almost 2,000 publications (Kalant et al 1968). The Foundation currently has about 5,000 articles on cannabis in its archives. Over 1,000 are directly relevant to human health consequences, many of the others have indirect implications. As a result, a review such as this must be selective.

Because the review is selective, it is more apt to reflect the author's biases. One of the interesting things about the cannabis research literature, particularly that dealing with human effects, is that personal views and bias often seem to cloud the judgment of otherwise reasonable scientists. A nonscientist may well puzzle over what appear to be contradictory opinions and results from research studies, particularly when the research is reviewed by others. However, careful study of the original literature often suggests relatively little disagreement over the facts, that is, the findings and the data. The area of greatest disagreement and controversy involves interpretation of these findings and speculation about long range health consequences. This is not unique to cannabis research. It occurs in many areas of medicine.

This large and rapidly growing literature demonstrates that all relevant information on all effects of cannabis will probably never be available. Because of the nature of science, usually facts change as experience accumulates. As more people use any

drug for more time, as analytic instruments become more sensitive, and as researchers ask more focused questions, new facts appear and the significance of older facts is continually revised (Edwards 1974). For those who believe that our knowledge of cannabis effects is unreasonably modest, a review of progress or lack of progress in determining the full spectrum of effects of such drugs as tobacco or alcohol or of many therapeutic drugs will give a sense of perspective. Such a review should induce some humility and make one aware of the imperfections of the scientific process in predicting the ultimate consequences of widespread and relatively uncontrolled use of a drug.

For interested readers who desire an entree into the cannabis scientific literature, a number of review articles, books, and proceedings of meetings have been published in recent years which cover in great detail aspects of cannabis (Harris, Dewey and Razdan 1977; Harris 1978; Nahas 1979; Graham 1976; Fried 1977). Some reviews discuss research findings in the context of making political-social decisions (Edwards 1974). Others emphasize adverse effects of cannabis (Nahas 1979), or legal versus health issues (Brecher1975), or the chemistry of cannabis (Harris, Dewey and Razdan 1977). The reports issued by two national commissions (the Canadian and the United States) along with the eight annual reports on "Marijuana and Health" that have been presented to the U.S. Congress by the Secretary of Health, Education, and Welfare provide some historical perspective concerning issues and earlier data.

THE DRUG: BOTANY AND CHEMISTRY

Cannabis sativa, the plant from which marijuana and hashish are derived, has been cultivated for at least 5,000 years, spreading originally from Central Asia to all temperate and tropical areas of the world. As with any plant material, the pharmacology and chemistry are necessarily more complicated than those of pure drugs. Among plants, cannabis sativa is more variable than most, due to its genetic plasticity. The plant has been cultivated for fiber, oil, or its psychoactive resin. Fiber strains have lower concentrations of the psychoactive substance delta-9-tetrahydrocannabinol(THC) than those cultivated for drug content. The fiber type commonly contains less than .5 percent THC; the drug type may contain as high as 4 or 5 percent THC. Thus, when considering expected effects of using marijuana, immediate distinctions must be made regarding the plant's characteristics. Is it a fiber strain or a drug-rich strain?

In addition to THC, the major source of psychoactivity, there are over 400 other chemicals in this plant. About 60 of these are called cannabinoids, found only in cannabis sativa. There is increasing evidence that these other natural cannabinoids such as cannabidiol (CBD), cannabinol (CBN), cannabickcmene and cannabicyclol, although they have little or no psychoactive effect, do have biological activity.

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THC is most concentrated in the upper small leaves, bracts, and flowering tops of the plant. To make marijuana cigarettes, the leaves and flowering tops are finely chopped, rolled in cigarette paper, and smoked much like a deeply inhaled tobacco cigarette. Although the size of a marijuana cigarette varies in the United States, a 0.5 to 1 gram cigarette containing 1 to 2 percent THC (5 to 20 mg) is fairly typical.

Hashish, the concentrated plant resin, may contain up to 12 percent THC. "Hash oil," which is easily extracted from cannabis plant material using a variety of solvents, can contain up to 60 percent THC. The oil is customarily added to plant material to enhance its pharmacologic potency, or it can be used in baked gods or otherwise eaten.

Thus, when considering the possible human effects of cannabis, distinctions must depend partially on THC content. The dose of any drug is a very basic and necessary bit of information in understanding its pharmacology and effects. With marijuana, doses vary widely, based initially on the concentration of THC in the plant. As will be discussed in other sections, this beginning dose may be complexly modified so as to determine the final ingested dose. Uncertainty as to dose is but one factor that makes it difficult to answer questions and make predictions regarding long term cannabis effects.

Cannabis preparations can also be eaten, or drunk in mixtures of resin and water or milk, a form known as bhang in India. The pharmacology of such dosage forms has not been researched. In North America, cannabis is probably eaten most often in cookies or other baked goods. No exact figures are available, however, as to what percentage of users consume what form. Because THC is virtually insoluble in water at room temperature, the fatty substances in baked goods in bhang may be necessary for a pharmacologically active dose.

The mix of cannabinoids in the plant is probably controlled more by the type of seed than by soil or climatic conditions, but after a few generations this my change. The success of illicit growers in producing high THC content plant material in a variety of locations illustrates the plasticity and adaptability of both the plant and those who grow it.

Compared to many other psychoactive drugs, the chemistry of the cannabinoids is complex (Harris, Dewey and Razdan 1977). The amount of THC absorbed by an individual, of course, depends on the method of administration. After absorption, because THC is so fat soluble, it leaves the bloodstream very rapidly. Initial, plasma THC concentrations of about 100 nanogram per milliliter decrease with in an hour after smoking to 5 to 10 nanograms per milliliter of blood, even though the obvious signs and symptoms of intoxication last 2 or 3 hours. The THC in the blood is rapidly changed to 11-hydroxy-THC, a metabolite that is also psychoactive, and to at least 20 other known metabolic products

that are either relatively inactive or have unknown activity. This metabolism mostly occurs in the liver (Lemberger and Rubin 1978).

Only in the last few years have there been reliable methods for assaying the levels of THC and its metabolites in bodily fluids and tissues (Willette 1976). Some earlier studies depended on measurement of radioactivity in blood and tissues after the administration of a radioactive dose of THC. The data from those studies perhaps has been overinterpreted, and the more precise metabolic studies are still underway. Species differences in metabolism complicate our understanding of this important aspect of a drug's pharmacology. Rats, for example, metabolize cannabinoids far more rapidly than do humans, thus partially accounting for the need to administer larger doses to rats to get what seem to be human equivalents of drug effects.

THC leaves the blood rapidly, not only because it is metabolized but also because of its efficient uptake by tissues. An understanding of the pharmacologic properties of THC is necessarily complex because of its complicated pharmacokinetic behavior: that is, its apparent entry into multiple body compartments, THC's multiple metabolites, the formation of both active and inactive metabolites, and the tendency for THC and metabolites to bind tightly to proteins in the blood and to remain for long periods of time in fatty tissues (Harris, Dewey and Razdan 1977). While stored in body fats, THC and its metabolites are slowly released back into the bloodstream. Thus, 5 days after a single injection of THC, 20 percent of the THC remains stored, while 20 percent of its metabolites remain in the blood. Complete elimination of a single dose can take 30 days. After the passage of about 6 hours, the step that limits the rate of elimination of unchanged THC in the blood is not its metabolism but rather the very slow return to the plasma of THC that has been sequestered in the tissues. As more sensitive analytic techniques are developed, one might predict the measurement of even slower rates of plasma decline of THC in humans. Measurable levels of THC in the blood of chronic users can be detected for up to 6 days after their last marijuana cigarette. The terminal half-life for THC, that is, the time it takes for half of the amount to be eliminated from the blood, was reported to be 56 hours in subjects who had never had cannabis and 28 hours in those who had used it chronically (Lemberger et al. 1971a, 197lb). More recent studies using slightly different analytic techniques suggest a terminal half-life of about 19 hours in frequent users (Hunt and Jones 1980). Another possible source of the uncertainty as to half-life is a confusion between THC and THC metabolites, since the metabolites seem to have a much longer half-life -- in the range of 50 hours.

No matter what the precise clearance rate, there is general agreement that THC and its metabolites are cleared from the body more slowly than some other psychoactive drugs. Thus, there is the theoretical possibility of accumulating biologically active metabolites. Increased toxicity may result, like that of chronic

exposure, because the drug is sequestered in the body even when it is used intermittently (for example, every few days).

In studies where repeated doses of THC or marijuana were given (Hollister and Reaven 1974; Mendelson et al. 1974; Jones et al. 1976), there did not appear to be any significant accumulation of drug or metabolites, at least as judged by behavioral and physiologic measures. This would suggest that the biological activity of metabolites is not obvious, but it does not rule out the possibility, of course. Biochemical studies have not yet been done.

Given the slow clearance of cannabinoids, one might predict that repeated administration of marijuana at intervals of less than 8 to 10 days should result in accumulation of THC or its metabolites in the tissues. This would be impossible to measure from levels in the blood. One explanation for the lack of such human data is that tissue biopsies are more difficult to obtain from humans than from experimental animals. The body's storage capacity for THC and other cannabinoids is enormous. Thus, what is termed by pharmacologists as a steady state level, where elimination is equal to absorption, would be reached only after about 4 weeks of daily or more frequent administration.

Elimination of the THC metabolites is largely through the feces. Relatively little is eliminated in the urine. Both urinary and fecal metabolites, of course, can be detected for weeks, and there is some recycling through the enterohepatic circulation.

The very strong protein binding of THC in the blood and the low level of drug free in the plasma means that the uptake by the tissues of THC and metabolites will be limited mainly by blood flow. Thus, it is not surprising that tissues with high blood flow (for example, lung, liver, kidney, and spleen) take up the drug so quickly. Testes and ovaries also take up the drug rapidly. However, one must be careful not to conclude that because an organ takes up the cannabinoids quickly they necessarily have any action there. Hair follicles, for example, have considerable affinity. Despite some understanding of the half-life of THC and metabolites in the blood, the lifetime in the human brain and other relevant tissues is unknown. Regional levels of THC and THC metabolites may be far more important in terms of predicting toxicity than blood levels are. Accumulation of THC itself in human body fat has not been demonstrated.

Drugs that are slowly cleared are not necessarily inherently more toxic than drugs that are rapidly cleared. However, slow clearance may make for cumulative toxicity (assuming that some of the metabolites have biological activity). Many useful therapeutic drugs are cleared slowly from the body; for example, many benzodiazepines. Therapeutic drugs having this characteristic sometimes cause problems when their dosage schedules are not properly regulated. Thus, slow elimination and the possibility of drug accumulation become even more significant with a drug such as

marijuana which is administered in doses and on a dosage schedule controlled by the individual user and by custom rather than as recommended and monitored by a physician.

ASSAY TECHNIQUES

Much effort has gone into developing practical assay techniques to determine cannabinoid and cannabinoid metabolite levels in humans (Willette 1976). Such techniques are needed not only for research purposes, but also for law enforcement and medical diagnostic purposes. The very low level of THC in the blood and the even lower levels of its numerous metabolites makes quantifying and identifying cannabinoids in bodily fluids a far more complicated undertaking, compared, for example, to assessing alcohol blood levels. The only completely accurate and sensitive method is mass spectrometry combined with either high pressure gas or liquid chromatography. While these are superb techniques in the research laboratory, they are too slow and costly for more general use. Although not fully developed because of the problem of crossreacting cannabinoids, immunoassay is also a promising technique, particularly for determining total cannabinoid levels, THC, or the 11-hydroxy metabolites, which seem to be the most psychoactive ones identified thus far.

Although the pharmacokinetics of THC are becoming better understood, simple techniques for identifying THC levels in the body and predicting driving impairment or other abnormal behavior are still far from the stage of any practical application. There are theoretical reasons why such a technique will never be practical, at least in terms of using blood levels to predict driving impairment or abnormal behavior. For example, the very rapid disappearance of THC from the bloodstream is severely limiting. That is, the levels of psychoactive drug one is really interested in are not blood levels but rather brain or other tissue levels not easily accessible to a convenient assay. This is quite different from alcohol, in which blood levels do reflect brain levels. Also, the very low levels that one must measure, the low levels eliminated in urine, and the prolonged period of elimination all make it difficult to correlate a given level of THC metabolites measured in the urine with specific behavioral or physiological abnormalities. These analytic and theoretical complexities have been extensively discussed in a recent monograph (Willette 1976).

DOSE CONSIDERATIONS

The ease with which the ingested dose of THC in smoked marijuana can be controlled is one of cannabis' most attractive attributes to the user. It is also a complication in health-related research. The very wide marijuana potency range has already been emphasized. Because of varied smoking techniques, the range of actual ingested doses per experience or per unit time is equally broad. In free access studies, the amount that humans will voluntarily consume is enormous. While in general surveys one or

two marijuana cigarettes a week is a common dose, in free access chronic studies 20 or more marijuana cigarettes per day may be consumed (Babor et al. 1975). Volunteers in the free access studies as well as "street users" may use upwards of 200 micrograms per kilogram per day.

To accurately predict or to measure long term health consequences of drug ingestion, it is necessary to identify populations using known dosage levels. Such data are difficult, if not impossible, to obtain from large populations of marijuana users. Similar problems are encountered in detemining the health consequences of tobacco use. Even in that situation, with the advantage of commercially produced, relatively standard cigarettes, there is considerable dosage variability, depending on brand, amount of inhalation, puff frequency, etc.

In North America, smoking appears to be the most common way to consume marijuana. A little less than half the THC in a marijuana cigarette is delivered to the lungs in the smoke (Lemberger and Rubin 1976). Lung absorption and transport to the brain are quite rapid, with THC probably reaching the brain within about 14 seconds of inhalation. This very efficient and very rapid delivery of a smoked drug to the brain may be important in determining the positive reinforcing characteristics of marijuana and other smoked material such as tobacco. For many marijuana users, the rapid onset of intoxication makes smoking it far more attractive than consuming it orally. THC has been estimated to be 3 to 5 times more potent when inhaled than when ingested. This also undoubtedly makes smoking the preferred route. Smoking is even more efficient than intravenous injections for efficient delivery of a drug to the brain. To avoid confusion when interpreting scientific data from various studies, some of which involve oral administration, some smoking, and some intravenous administration of THC or other cannabinoids, one must keep these dose efficiency differences in mind.

A marijuana cigarette containing 2 percent THC would deliver slightly less than 10 milligrams of THC to the lungs where must is probably absorbed. But to reach an equivalent state of intoxication when taken orally, from 30 to 50 milligrams of THC would have to be consumed. The slower absorption via the oral route and the resulting slower onset of intoxication make comparisons imprecise, since the time course of the intoxication is so different. As the user is just beginning to become intoxicated from an oral dose, a person who simultaneously smoked it instead is becoming less intoxicated.

Although used in laboratory experiments, the intravenous route of THC administration is rarely used illicitly. The few case reports of intravenously administered marijuana describe injections of various crude plant extracts. The results reflect a generalized toxicity from the foreign material, bacteria, etc., rather than THC effects as such. When given intravenously in 1 or 2 milligram intravenous doses, THC produces effects similar to

smoking marijuana, containing about 20 milligram of THC. Should intravenous THC become available on the illicit market, one might anticipate more acute behavioral and physical toxicity because of the great potency when administered by that route.

The actual dose delivered with each puff on a marijuana cigarette is partially determined by the acummulation of THC in the "butt" or roach as the cigarette is smoked down. Thus, in a group of marijuana smokers sharing a cigarette, the last person taking a puff on the joint receives considerably more THC than does the first. The relatively low incidence of intoxication levels greater than the user anticipates suggests that reasonably efficient titration of level of intoxication is common, probably because of the extremely short time between a puff and its psychological and physiological consequences. The experience from laboratory experiments suggests that some adverse psychological reactions are more often the result of encountering marijuana stronger than previously experienced than of the presence of adulterants (Jones1973). Oral ingestion poses more dose control problem because of the user's inability to control the level of intoxication after the dose has been ingested.

In recent years them have been attempts to determine doses of alcohol that could be used with acceptable levels of toxicity. Although open to some dispute, such levels can be specified. While that would be a reasonable goal for cannabis as well (that is, the specification of a certain dose of THC per unit time resulting in certain expected effects and not resulting in toxicity), at present there is insufficient scientific data to allow such a specification or prediction.

Even the precise specification of what is a high, moderate, or low dose, or what heavy frequent use or intermittent use is, has not been well established in North American studies. Most laboratory investigators use marijuana cigarettes containing from 10 to 20 milligrams of THC. This is determined as much by the availability of standardized marijuana cigarettes from the National Institute on Drug Abuse as on any more rational basis. Very little systematic data has been published from well-defined marijuana user groups that would help one decide that 20 milligram is indeed a "large" and 10 milligrams a "modest" dose. Things are even more unsettled when it comes to specifying oral doses. A tremendous range of oral doses has been administered in experimental studies, with some investigators routinely giving 50 milligram oral doses with the implication that those are "realistic." Other studies are often referred to as "high dose studies," although doses of only 10 to 30 milligrams were administered orally.

One can conclude from the literature that approximately a 30 milligram oral dose is needed to produce easily measurable physiologic and subjective effects. Intravenously, most investigators have administered 1 to about 3 milligram per 70 kilograms of body weight, though no systematic dose effect studies

have been done with the intravenous route.

The problem of specifying dose is compounded by the fact that THC disappears from the bloodstream rapidly and is also rapidly metabolized. Thus, one might expect that the effects from a given dose would last for only a short time unless the metabolites themselves are active. In most human laboratory studies this, in fact, seem to be the case. Most measurable effects tend to disappear 3 to 6 hours after a dose of marijuana, or THC (Harris 1978). Since in the usual social situation repeated doses are used, the issue arises how often a repeated dose should be given in the laboratory to mimic the social setting. A best guess based on incomplete data would suggest that repeat dosing every 3 to 4 hours is probably realistic. Thus, whatever the reinforcing attributes of marijuana, the dose needs to be repeated every 3 to 4 hours to produce acceptable levels of continued intoxication. Of course, most users dose themselves with cannabis less often. Compared to our knowledge of alcohol, tobacco, or almost any therapeutic drug, we are still woefully ignorant of cannabis dosage considerations.

GENERAL PSYCHOLOGICAL EFFECTS IN HUMANS

Although this review emphasizes recent research findings, a book first published in 1845 by Moreau still provides one of the more vivid and detailed descriptions of the psychological effects of cannabis (Moreau 1973). More recent research activity really has extended the descriptions in that book and, to some extent, only adds a better understanding of the dose-effect relationships reflected in Moreau's descriptions. In that early study Moreau considered the need for dose differences and for control groups, as well as to take into account individual suggestibility and setting in greater detail than in some contemporary psychopharmacologic studies. In the book, Hashish and Mental Illness, he wrote, "By its mode of action on the mental faculties, hashish gives everyone who submits to its strange influence the power of studying on himself, the moral disturbances of mental illness, or at least the principal intellectual disorders from which all kinds of mental disturbances originate." Moreau deliberately used cannabis to produce psychotic or psychotic-like symptoms in normal people. He was probably orally administering cannabis doses containing 50 to 100 milligrams of THC, while most, of our current North American users are describing the effects of only 1 to 10 milligrams.

Moreau described dose-related phases of cannabis intoxication. The initial feeling of "happiness" or euphoria was mixed with excitement and a dissociation of ideas. This was quickly followed by an altered sense of time and space relationships, a subjective enhancement of senses, particularly hearing, and, with higher doses, the appearance of delusions, labile emotions, particularly anxiety, decreased impulse control and, at the highest doses, profound sensory illusions and hallucinations.

Many current users of marijuana in the United States may argue that the sense of well-being or euphoria, the relaxation, drowsiness, mild perceptual changes and altered time sense that follow the smoking of a marijuana cigarette are not what Moreau was describing. One explanation for these differences is the dose taken. The brief and relatively mild "high" that follows the smoking of 10 to 20 milligrams of THC can be altered by many nonpharmacological variables. Prior drug experience, expectations, the setting, and other enviromental factors, as well as user's personality can all shape the experience both qualitatively and quantitatively. Interpretation of many physiologic findings is complicated by the initial and relatively brief period of stimulation, autonomic arousal and sympathetic activity followed by a longer period of 2 to 3 hours of a drowsy, relaxed, often dream-like state with decreased sympathetic activity. A similar pattern occurs in or out of the laboratory, thus supporting the validity of much of the laboratory data.

Because of exposure to a wide range of plant material and because of the cultural labeling (almost like advertising) of much of the marijuana experience, many marijuana users are particularly subject to the effects of nonpharmacologic variables that alter the intoxication. A number of studies suggest that experienced marijuana users are more subject to "placebo reactions"; that is, a degree of intoxication disproportionate to the THC content of the material, particularly if they are exposed to low potency marijuana. This is presumably a result of experience and practice at recognizing minimal physiologic cues together with the smell, taste and other sensations associated with smoking a marijuana cigarette (Jones 1971).

A misinterpretation of this finding may be the simplest explanation of so-called "reverse tolerance." Reverse tolerance refers to an apparently increased sensitivity to cannabis in the experienced user and a lack of sensitivity in the novice. Although it is conceivable that metabolic considerations cause this, a more parsimonious explanation is that with very mild threshold levels of intoxication, practice, recognition and set influence the subjective intoxication more than at higher levels. Given sufficiently potent plant material, it is well established that even the first-time novice smoker will experience all the characteristics of the expected marijuana intoxication, although in some instances the interpretation of the pleasantness of that state may be altered.

PSYCHOLOGICAL EFFECTS

The most striking acute effects of cannabis are alterations in cognition, thinking, sensation and psychomotor functions. Many of these are reviewed in more detail elsewhere in this volume. These psychological effects are more predictable, and, depending on dose, of greater magnitude than most of the physiologic effects that will be discussed later.

Although users report subjective feelings of enhanced sensory acuity, sensitivity, and interpersonal closeness, in fact, as measured in the laboratory and observed in the real world, generally there are either no effects or an impairment of performance, sensation, and behavior. For the most part, the degree of impairment is dose-related. In studies where psychological effects were not readily measured, generally low doses of the drug or subjects with high levels of tolerance appear to have beenused. When large doses of marijuana in any dosage form are combined with testing at the time of peak intoxication, it is possible to show dramatic alterations very reliably.

PHYSIOLOGICAL EFFECTS

As with psychological effects, observed physiological effects depend on dose and all the other factors already discussed. Some years ago it was not uncommon for reviewers to comment on the preponderance of psychological effects and the relative paucity of physiologic effects from a given dose of cannabis. This, of course, is only true if one is talking about relatively low doses of THC. At moderate to high doses, many physiologic systems are altered. Whether the alterations indicate adverse or potentially dangerous effects is a far more complicated question to answer. As with many, if not all, drugs, acute effects (that is, effects following a single dose) are not necessarily similar to chronic effects (that is, effects following repeated use, sometimes for many years). It is around "chronic effects" that marijuana "experts" most disagree, with resulting confusion to the non-specialist.

If proper attention is paid to dose, setting, route of administration, etc., there is fair consistency from laboratory to laboratory as to many physiologic effects. It is the long-term biological significance of many of these effects that is debated. Given very sensitive, sophisticated and refined test procedures and instruments, a research scientist is now able to detect very subtle and formerly unmeasurable effects on many bodily systems. Thus, the most difficult task in judging cannabis research findings is to decide whether a measurable effect has biological or practical health significance. Such decisions are particularly a problem for those in social policymaking or public health positions (Edwards 1974). In addition, incompletely understood factors such as past history of cannabis exposure, variations in genetic background of the user, current or prior use of other drugs, and metabolic differences, all partially determine the magnitude and spectrum of physiologic drug effects.

Even in therapeutic drug administration, where careful monitoring of effects is possible, surprising, unpredicted and not well understood effects sometimes develop only after years of exposure. For example, consider the cardiovascular effects associated with tobacco stoking or consider the occurrence of vaginal carcinoma in the offspring of mothers treated with diethylstilbestrol,

where a 20-year lag may pass between exposure to the drug and the disease, or consider the appearance of increased carcinoma of the breast in women treated with reserpine, a cardiovascular drug used for treating hypertension (AMA article current).

What follows is not an exhaustive listing of all effects. Some are mentioned because of their obvious health implications. Others are mentioned just because they are interesting. Many other effects of cannabis are disscused in more detail in a number of review articles (Stimmel 1979; Harris, Dewey and Razdan 1977; Fried 1977).

Cardiovascular Effects

Cardiovascular effects are among those most easily measured (Stimel 1979). Increased heart rate proportional to dose of THC is one of the more reliable consequences of ingesting marijuana. During the early phase of cannabis intoxication, heart rate can increase up to 160 beats per minute or more, along with decreases in standing (that is, orthostatic) blood pressure. Myocardial contractility is probably unaffected, though the myocardial oxygen demand, coupled with decreased myocardial oxygen delivery, produces problems in people with coronary artery disease. These problems range from a decrease in exercise performance before the onset of angina to the theoretical possibility of myocardial infarction in predisposed individuals.

Even with easily measured cardiovascular phenomena, there are inconsistencies in reports of various research groups; for example, regarding blood pressure. These can generally be reconciled by a careful reading of the reports, as they usually reflect differing experimental procedures, doses, techniques of measurement, etc. For example, blood pressure has been reported to be increased, decreased, or unchanged after the smoking of marijuana. More often than not, if the subject was in a standing position when blood pressure was measured, it was decreased; in a sitting position, it was unchanged; and in a prone or supine position, slightly increased. Lack of attention to things like body position can needlessly confuse the uninitiated reader of such research reports.

To predict chronic from acute effects is problematic. The long term administration of oral THC, for example, can result in a decrease in heart rate and a persistent mild lowering of blood pressure, with the initial orthostatic hypotension disappearing, probably became of a marked expansion in plasma volume (Benowitz and Jones 1975). While these changes in themselves may be of no particular biological or functional significance, after years of drug exposure they could be associated with lasting health consequences. The lessons learned from chronic tobacco use are worth considering. It was only after many years of use by millions of people that cardiovascular disease associated with tobacco use was recognized. Even now the exact mechanisms are scientifically debatable. Assuming that smoking cannabis has some similarity to

smoking tobacco (in fact, THC seems to have far more profound effects on the cardiovascular system than does nicotine), one may assume that long term chronic effects will be different from the more commonly reported and easily studied acute ones. The many problems in measurement of the results of chronic exposure to marijuana are discussed in a later section.

Respiratory and Pulmonary Effects

Like tobacco, marijuana is commonly smoked. It would be surprising if there were not some effects from repeated inhaling of combustion products. When tobacco is smoked, approximately 70 percent or more of the total particulate matter in the smoke is retained in the lung (Huber et al. 1976). There is reason to assume that with marijuana, because of deeper inhalation, a still greater percentage is retained. Smoke is a mixture of tiny particles suspended in gas, mostly carbon monoxide. These solid particles carbine to form a residue called "tar." Cannabis produces more tar than an equivalent weight of tobacco and is smoked in a way that would facilitate tar deposition in the lung.

Alveolar macrophages that play a role in clearing debris from the lung appear to have their bacteria-inactivating activity impaired when exposed cannabis smoke. Early reports that cannabis improved lung functionby increasing the diameter of air passages received much publicity. Subsequent data indicate that chronic use has different effects from those found in heavy cigarette smokers. Significant worsening of pulmonary function was evident after only 6 to 8 weeks of smoking a few marijuana cigarettes daily in an experimental situation (Tashkin et al. 1976a, 1976b). A similar pattern of change was noted in an earlier study where volunteers smoked cannabis while living on a research ward (Mendelson et al. 1974). Chronic exposure to marijuana smoke appears to impair many of the lung's defense mechanisms and to produce cellular changes in lung tissue that may be precancerous (Leuchtenberger et al. 1976). This is one area of research in which the test tube and laboratory data are consistent with clinical experience. The cellular changes noted in laboratory studies and the changes in laboratory pulmonary function tests are consistent with clinical observations that cannabis users often have laryngitis, pharyngitis, bronchitis, asthma-like conditions, cough, hoarseness, and dry throat after periods of frequent use.

Although the acute administration of THC or marijuana produces bronchodilatation (that is, an increase in airway diameter), chronic use produces obstructive airway disease of the sort that is often seen in cigarette smokers, Cellular changes often termed precancerous have been found in the bronchial biopsies of heavy smokers of hashish and tobacco in their early twenties. Such changes are ordinarily seen in tobacco smokers only after the age of 40. The pattern suggests either a potentiation of tobacco-related changes with marijuana smoking or a result of increased tar inhalation from combined use (Tennant et al. 1979).

The biological and the health significance of similar tobacco-related cellular and functional changes was in dispute for some years and still remains a topic of dispute by some scientists. A long period of observation of a sizeable group of chronic cannabis smokers will be needed to establish the health implications of such pulmonary changes. In North America most cannabis users do not have the high level of exposure of cigarette smokers; thus making for a longer period of incubation before any pathology becomes clinically apparent. The increase in cannabis smoking by very young people might provide the necessary period of years of exposure. The limitations of interpreting the absence of serious pulmonary disease in the few chronic studies undertaken thus far will be discussed later.

NEUROLOGICAL EFFECTS

As with any psychoactive drug, there is no question that cannabis produces neurological effects. What are called psychoactive effects are, of course, neurologic effects as well. Cannabis clearly alters brain function. The perceptual, cognitive, and mood changes, the memory alteration, the alterations in time sense, alterations in behavior, and other effects sought by the user of cannabis and predictably apart of the acute intoxication are presumably a result of changes in nervous system activity. Some might even argue that such altered, usually impaired, brain function is prima facie evidence of temporary brain and nervous system damage, at least during the few hours of acute intoxication after a dose of marijuana. As with drugs deliberately ingested to produce intoxication, that viewpoint is not usually shared by their users. The more important health issue is whether the neurological alterations last only for the few hours during the period of acute intoxication or whether they persist or become cumulative over longer periods of time. The scientific data on this issue is not consistent.

There are various techniques for measuring neurological effects. Subjective and behavioral changes are perhaps the most sensitive. Electrical, biochemical, radiographic or cellular anatomic alterations are other approaches. All of these have been used to study marijuana-related changes. Some techniques can only be used in animal or test tube studies and their human implications judged only by inference.

Acute cannabis intoxication includes not only the pleasant state of relaxation, euphoria, and sought-after sensory alterations, but also impairs judgments of distance and time, memory for recent events, ability to learn new information, and physical coordination. At slightly higher doses the acute intoxication includes tremor, transient muscular rigidity, or myoclonic muscle activity. The subjective feelings of muscular "weakness" or stiffness can be measured objectively. Low doses produce no changes in tendon reflexes, but high doses cause hyperexcitability of knee jerks with clonus (Tassinari et al. 1976). At even higher doses a full blown acute brain syndrome is possible.

As is often the case with psychoactive drugs, the scalp-recorded EEG; changes at ordinarily used doses are minimal and brief (Klonoff et al. 1973). They tend to resemble those associated with drowsiness and relaxation. Modest increases in alpha activity and slowing of alpha frequency are the most commonly observed changes. Cannabis has no unique qualities as measured by scalp EEGs. There are no published reports of scalp EEG; changes that would indicate any specific gross central nervous system abnormalities following the smoking of cannabis. The occasional reports of convulsions associated with marijuana use have not been corroborated by the EEG changes incontrolled laboratory studies, though, of course, the latter studies usually involve lower doses given to healthy volunteers not prone to seizures.

Although scalp EEG changes are minimal, marked alterations in electrical activity have been recorded from electrodes implanted in deep brain structures, particularly in the septal and amygdala areas (Heath et al. 1979). These areas are involved in regulation of emotion and memory. The functional significance of such acute changes is not entirely understood, though similar electrical activity has been noted in some patients with schizophrenia or epilepsy. Normal people have not had electrodes implanted in such areas, of course. Similar EEG changes are seen in the brains of monkeys exposed to marijuana smoke or given THC intravenously. Exposure to the smoke from the equivalent of about 3 marijuana cigarettes per day produced the electrical changes after 2 to 3 months of daily administration. After 3 to 6 months exposure, the electrical abnormalities persisted for up to 8 months. Anatomic changes at the brain synapses were apparent in electron microscopic studies, suggesting long-lasting changes related to the THC exposure.

Perhaps one of the more important observations from these studies was that throughout this experiment scalp EEGs of the monkeys were not altered, despite the changes in deeper brain structures. This indicates that the measurementtechniques used in human subjects may sometimes miss changes that would be made apparent by the use of more sensitive measurement techniques. Although the behavioral significance of these lasting neurological changes is yet to be determined (Jones 1975), they provide clear-cut evidence of THC-induced alterations in brain function and structure that could plausibly occur in human users.

Sleep EEG; recordings are often more sensitive indicators of drug effects than are EEG recorded in a waking state. Loss of rapid eye movement sleep appears to be a predictable effect of cannabis (Feinberg et al. 1976). Total sleep time increases, although tolerance develops to this effect. Unlike the situation with other drugs, stage four or slow wave sleep is relatively unaffected. When cannabis use is stopped after a period of prolonged administration, rapid eye movement sleep stages and eye movements show a rebound above baseline measures like that seen with a variety of sedative hypnotic drugs. In contrast to the relatively small changes in waking EEGs, the sleep EEG changes are

fairly large.

A number of studies of cannabis or THC effects on sensory evoked potentials recorded from scalp electrodes have demonstrated changes consistent with alterations in brain function (Herning et al. 1979). However, the pattern of change varies with dose and measurement technique, and between laboratories. The biological or functional significance of these alterations remains obscure. Although there was some hope that these evoked potential techniques might provide direct measures of attention deployment or motivation, it appears that, like so many neurophysiologic measures, their interpretation is far more complicated than was originally assumed (Jones 1975).

An earlier study done in England, which reported enlarged brain ventricles consistent with the presence of cerebral atrophy in a group of ten young marijuana users, stands alone as indicating anatanic changes in human marijuana users (Campbell et al. 1971); Recent studies in this country, in Missouri and Boston, examined equally small groups of marijuana users aud nonusers for evidence of brain atrophy using computerized transaxial tomography (CAT), a relatively new brain scanning technique for visualizing brain anatomy (Co et al. 1977; Kuehnle et al. 1977). These studies found no evidence for brain anatomic changes in the marijuana-smoking groups. Such findings are reassuring in that they demonstrate the possibility of regularly consuming fairly large amounts of marijuana without obvious evidence of cerebral atrophy. However, the results demonstrate one of the recurring problem in interpreting many marijuana effects. The earlier Campbell study that reported changes consistent with brain atrophy used a different measurement technique, pneumoencephalography, rather than tomography. An important difference in the earlier study was that the population of marijuana users were mostly sick people, neurologically impaired or with neurological symptoms. In the more recent studies finding no evidence of brain damage, the subjects were preselected as healthy, normal marijuana users. A populationof abnormal, neurologically impaired, marijuana users might show evidence of brain abnormality while a group of healthy and normal users would not.

It is possible to demonstrate organic toxicity from alcohol or not to demonstrate it, depending on the sample of alcohol users. The sampling or selection process is a general problem that confuses simple interpretation of many studies of chronic cannabis users. Depending on the sampling techniques, the populations of research subjects who finally appear in the laboratory may represent selected subgroups who are relatively more resistant or less resistant to marijuana-induced changes (assuming there are such changes of course). None of the three X-ray studies just mentioned either confirms or totally rules out the possibility that subtle changes in brain function may follow marijuana smoking. With many psychoactive drugs it is quite possible to have severe impairment of brain function that is not apparent on gross

examination, microscopic examination, or by any physical testing of brain tissue.

One indirect but sensitive measure of neurological alterations is change in mental and psychomotor perfomance. In previous reviews and in other sections of this monograph the many studies reporting impaired functioning on cognitive and performance tasks while intoxicated have been discussed. The magnitude and character of these alterations are generally dose-related. Interactions between dose and task difficulty, practice, motivation, and setting are as complex with cannabis as with any other psychoactive drug. Performance on complex taks requiring vigilance and optimal nervous system functioning, such as driving, flying, instrument operation, etc., are altered, whether in a laboratory setting or outside. Since survey data indicates more cannabis users are now driving while cannabis intoxicated than was true a few years ago, this drug-induced impairment assumes great public health significance. The great weight of evidence is that cannabis does have detrimental effects on such complex psychomotor-cognitive performance.

A major area of controversy among scientists is the issue of impaired neurological functioning beyond the period of acute intoxication. Many survey and laboratory studies comparing user and nonuser populations have reported no differences in cognitive, intellectual, or perceptual function between these two groups (Grant et al. 1973). Such results are reassuring only to the extent that they demonstrate that impairments are not inevitable. In science, particularly when dealing with drug effects, it is impossible to prove the absence of something or to prove that something will not happen. Many of the studies reporting no neurological differences between users and nonusers have compared very selected people using 1, 2, or 3 marijuana cigarettes per week to those using none (Grant et al. l973). It may well be that lasting impairment will be evident only at a greater dosage level or that the marijuana use interacts with some other unrecognized factor to produce lasting effects. The impairment will thus be missed in such limited studies. On the other hand, when deleterious, possibly marijuana-related, effects on function have been noted in groups of cannabis users, it is very difficult to determine whether the cannabis use caused the impairment, or was simply associated with it, or followed it. For example, in one of the few longitudinal studies of college students examining the relationship between cannabis use and psychosocial adaptation and academic performance (Brill and Christy 1974), the users and nonusers did not differ on grade point average or educational achievement, but the marijuana users dropped out of college more often and seemed to have more difficulty in deciding on career goals. Fewer of them planned to seek advanced academic degrees. They considered themselves to have poorer academic adjustment. It is impossible to decide whether these attributes were simply associated with marijuana use or caused by it. In fact, some would argue that such differences do not reflect impairments nor should they be considered harmful.

Studies done oveseas comparing chronic cannabis users with nonusers not infrequently report slower psychomotor performance, poorer perceptual motor coordination and memory in the user group (Soueif 1975). Other studies comparing cannabis users and nonusers in Jamaica (Rubin and Comitas 1975), Costa Rica (Coggins et al. 1976), and Greece (Stefanis et al. 1976) concluded there were no long-lasting neuropsychological impairments. Sampling problems and difficulties in interpreting psychological test performance in illiterate, rural, older, and less intelligent subjects make any simple interpretation of the findings from abroad inherently controverisal. It is an area where the total weight of evidence must be considered as well as such things as scientific design, control groups, etc. If one considers neurochemical data from test tubes, animal data, clinical case reports, survey data, controlled laboratory data, and semicontrolled field studies, the weight of the evidence so far is that lasting neuropsychological impairments are possibly but not inevitably associated with some undetermined level of heavy, prolonged cannabis use. However, the many factor that would determine the appearance of clinically evident cannabis-induced neuropsychological changes in any given user are so complex as to make any simple pronouncement of risk almost meaningless.

CANNABIS AND PSYCHOPATHOLOGY

The evidence for cannabis as a specific cause of psychoses or other mental illness is confusing. A variety of psychiatric disorders are associated with cannabis use, but whether the psychopathology preceded use, is a consequence of it or coincident with it is still open to question and likely to remain so, as it has for LSD, amphetamine, PCP, alcohol, and many other drugs. Past reviews have pointed out many of the methodological and theoretical shortcomings of published work and no definitive new studies have been done (jones 1975; Meyer 1975). Use of cannabis, like so many other psychoactive drugs, probably can precede, result from, or occur coincidentally with psychopathology, depending on the person, the culture, and many other variables.

The acute anxiety reaction that may occur during marijuana intoxication remains the most common adverse psychological reaction (Halikas 1974; Meyer 1975). This reaction, which usually starts off with an exaggeration of normal cannabis effects, can range from mild anxiety and restlessness to panic with paranoid delusions, to a full-blown acute toxic psychosis with loss of contact with reality, delusions, hallucinations, and agitated and inappropriate behavior. The reaction is more likely to occur in inexperienced users or in the user who unknowingly consumes more potent cannabis material than is anticipated. Preexisting psychological difficulties may also contribute. The symptoms usually diminish over a few hours and are somewhat alleviated by reassurance, a quiet environment, and generally supportive atmosphere.

These acute reactions seem to occur most frequently in individuals who are under stress, depressed, or have a history of schizophrenia. The relationship to schizophrenia is becoming clearer as more case reports are published (Treffert 1978; Thacore and Shukla 1976). Patients with schizophrenia, or perhaps patients who have the genotype for schizophrenia, may be more prone to develop schizophrenic-like psychoses after consuming only modest amounts of cannabis. The clinical signs and symptoms resemble schizophrenia. The usual treatments for schizophrenia appear to be effective, and thus it is not surprising that the literature reflects some uncertainty as to whether case reports are really discussing schizophrenia or a cannabis-induced psychosis. Since schizophrenia is not a rare disease, if there is a special vulnerability of such people for adverse cannabis psychological reactions, this has obvious implications.

The descriptions of long-lasting cannabis psychosis are drawn 1argely from Middle Eastern and Asian cultures where cannabis use is more frequent and at higher dosage levels than is typical for the United States. The cannabis psychosis often lasts for 1 to 6 weeks or longer. Some authors distinguish its symptoms from those of paranoid schizophrenia. The patient said to be suffering from cannabis psychosis shows more bizarre behavior, more violence and panic, and a relative absence of schizophrenic thought disorder. Such patients tend to relapse when cannabis use is resumed. As is often the case with clinical reports, studies describing cannabis psychosis rarely present data in a way that would withstand rigorous scientific scrutiny. A number of reports finding no evidence of links between cannabis use and psychoses unfortunately have the same methodologic problem as studies claiming drug-related associations, making it very difficult to draw unequivocal conclusions.

The studies of chronic marijuana users in Jamaica, Greece, and Costa Rica failed to document the existence of such psychoses. However, these studies used very small, select samples; in their selection process they could have missed the relatively rare occurence of such a psychosis. In addition, these retrospective studies used recruiting procedures that would tend to screen out subjects with a high likelihood of psychosis.

Psychopathology is an area of cannabis research where there is a need to depend on so-called "clinical" studies. Such data are necessarily inexact, only partially controlled, and heavily dependent on the hunches, wisdom, and good judgment of clinical investigators. Many of the reported cases may ultimately reflect interacting nutritional, genetic, or coincident disease factors that are more important than the simple use of cannabis in determining the onset of a cannabis psychosis. Because of the obvious difficulties in experimentally producing such states in human subjects, however, it may well be that such imprecise clinical data is all that can be obtained.

Marijuana flashbacks, that is, spontaneous recurrences of the feelings and perceptual state similar to that produced by the drug, are still occasionally reported (Brown and Stickold 1976). Their etiology is still unexplained. Either medical investigators have ceased reporting flashback experiences or they have become uncommon.

Relatively little new information is available on the relationship between cannabis and violence. An extensive review of that issue has recently been published (Abel 1977). Most commissions and review groups that have specifically studied the relationship between cannabis and violence have concluded that the use of marijuana is not a major cause of aggression. There is little new that would change that conclusion. However, as Abel points out, such conclusions are based on "typical" or average marijuana users and tend to underemphasize individuals who may be at some special risk and who may react atypically and violently as a consequence of their marijuana use. It might be the rare individual, perhaps someone with a prior history of violent behavior and impulse control problems, in whom cannabis might reduce control even further and lead to violent behavior. In laboratory studies and in many surveys, such people maybe screened out by the selection process. This may be yet another area where clear-cut human data must depend on clinical reports and the slow accumulation of clinical experience rather than on experimental studies. The literature from animal studies suggests that with proper combinations of stress and environmental conditions, cannabis can produce aggressive behavior. Scattered case reports (Thacore and Shulka 1976; Treffert 1978) describe explosive, agitated, and violent behavior in some patients. A more complicated issue is whether such behavior is a specific consequence of marijuana or due to the combined use of marijuana and other drugs such as alcohol and possibly to other unrecognized factors. Aggressive behavior is not a common consequence of marijuana use in this country, however.

AMOTIVATION

Apathy, a lack of concern over the future, and loss of motivation have been described in populations of cannabis users. The term is deceptively simple but is difficult to operationally define. In laboratory studies, in some respects subjects seem activated during the acute phase of intoxication, but in others they work very hard at the assigned experimental tasks. In chronic studies of people living on research wards, some types of work output decreased as the level of intoxication increased (Mendelson etal. 1976a, l976b; Miles etal. 1974). To ascribe these changes simply to changes in motivation, however, ignores the complexity of drug effects, even in a relatively simple experimental environment. Artificial work conditions and artificial tasks make generalizations imprecise. In the studies of chronic users in Greece, Jamaica and Costa Rica, work output of marijuana users did not appear to be lower than that of nonusers. Particularly in the Greek study, however, the employment histories of the

cannabis users were such that one might suspect some level of amotivation. Uncontrolled clinical reports from areas of the world where cannabis is readily available continue to report decreased work output and initiative in chronic cannabis users (Sharma 1975). Similarly, uncontrolled reports from observations of users in this country suggest a similar pattern.

TOLERANCE AND DEPENDENCE

Tolerance, that is, a diminished response to a repeated cannabis dose, is clearly associated with repeated use (Fried 1977). The magnitude of the tolerance and the rapidity with which it develops depend on the size and frequency of the repeated dose, just as with opiates, alcohol, barbiturates, and virtually any other psychoactive drug. The pharmacokinetics of THC are complex enough so that simple predictions as to the characteristics of tolerance are not possible. If one assumes that THC is cleared rapidly; that is, if one focuses on the rapid or alpha phase of clearance, then the prediction would be that frequent doses of THC are necessary to clearly demonstrate tolerance. If one focuses on the terminal half-life of THC and metabolites, a period of time which can be 50 hours or more, then less frequent administration should be necessary to produce tolerance. It appears now, both in animals and in humans, that tolerance develops quite rapidly to many of the effects of THC. The more frequent the administration and the higher the dose the more rapidly it develops, but even subjects smoking as little as one marijuana cigarette per day in a laboratory experiment demonstrate tolerance on some behavioral and physiologic dimensions when they are carefully measured. As with many other drugs, tolerance does not develop to all THC effects. Some of the more prominent effects, for example the "high" and the tachycardia, show tolerance far more rapidly than such effects as the reddening of the conjunctival blood vessels or weight gain. Most of the tolerance seems to be lost rapidly, but this rate may vary with the sensitivity of the measures used.

In outpatient studies where frequent and infrequent users or other populations with differing drug histories are compared, marked tolerance is less obvious, if evident at all. However, with sensitive and reliable measures, even infrequent outpatient use produces some tolerance (Borg and Gershon 1975; Cohen and Rickles 1974). Drug-seeking behavior in experimental studies is not clearly related to the degree of tolerance (Babor et al. 1975), but in free access studies with smoked marijuana material research subjects do tend gradually to increase their dosage over a 2 or 3 week period. Just how many cigarettes per day are smoked seem to be governed by many other pharmacologic and nonpharmacologic factors in addition to tolerance.

With many drugs, the development of tolerance is associated with dependence, that is, the appearance of withdrawal signs and symptoms following discontinuation of drug use. In those instances where definite cannabis tolerance develops in humans,

mild physical dependence seems to be associated. Healthy volunteers given in divided doses the oral equivalent of several marijuana cigarettes a day so as to maintain constant blood levels of THC show within hours after the last dose of THC, irritability, restlessness, decreased appetite, sleep disturbance, sweating, tremor, nausea, vomiting and diarrhea (Jones et al. 1976). These signs and symptoms are reversed by small doses of marijuana and possibly by other sedative hypnotic drugs. Such dramatic psychologic and physiologic changes have not been commonly observed in other chronic administration studies in the United States involving smoked material. Less intense and fewer symptoms, but still including restlessness, sleep disturbance, loss of appetite, mild nausea, and general irritability, were evident in subjects who had on an average smoked five marijuana cigarettes per day for a 64-day period (Nowlan and Cohen 1977). Although the investigators did not conclude that dependence was present, restlessness, anorexia, and a sudden weight loss were described in one group of inpatient volunteer subjects at the end of a 21-day smoking period (Mendelson et al. 1974;. Greenberg et al. 1976).

In the group of Greek hashish users that was studied in some detail, irritability, anxiety, and unpredictable emotional outbursts followed when they failed to obtain hashish each day. This was replaced by a relaxed and drowsy state after the smoking of hashish (Stefanis et al. 1976b). Such symptoms have not been commonly reported in nonexperimental studies in this country, though one German study described withdrawal symptoms in nonlaboratory cannabis users (Kielholz and Ladewig 1970). The detailed studies of marijuana users in Costa Rica and in Jamaica did not describe withdrawal symptoms in those user populations (Coggins et al. 1976; Rubin and Comitas 1975).

The most important question regarding dependence is the clinical significance of drug dependence particularly as manifested by a mild transient withdrawal syndrome of the sort that can, under some circumstances, be produced by cannabis. The relationship between withdrawal symptoms and drug-seeking behavior is not a simple one (Jones and Benowitz 1976). There is much to suggest that dependence and drug-seeking behavior are not necessarily associated. Drug-seeking behavior is shaped by a multitude of social, economic, psychological, and other factors. For example, if we better understood the role of the relatively mild symptoms of withdrawal from tobacco as a determinant of tobacco-seeking behavior, and if we understood why the relatively mild withdrawl syndrome associated with low potency doses of illicit heroin generally available in the United States should be associated with heroin-seeking behavior, then we could better answer the question about the significance of a mild abstinence syndrome following frequent cannibis use. Of course, the information to answer such questions about any of these drugs does not exist. In the past, medical researchers have had little success in predicting dependence liability of drugs that become available for widespread, relatively uncontrolled use.

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Chemistry and Metabolism

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SUMMARY

Marijuana is not a simple drug. It is a complex mixture of over 400 individual chemicals. In some cases, pharmacological data on pure Δ^9-THC, referred to as the "most active" compound in marijuana, may be irrelevant, since some marijuana contains very little Δ^9-THC. (–)–Δ^9 -Trans-tetrahydrocannabinol is only one of 61 cannabinoids known to occur in the Cannabis plant. Cannabinoids are chemicals indigenous to the Cannabis plant and are found in all crude drugs derived from it, i.e., marijuana, hashish, sinsemilla, etc. Marijuana chemistry is, therefore, not synthetic cannabinoid chemistry nor the chemistry of analogs and homologues of cannabinoids. Marijuana chemistry is the chemistry of: 1) all classes and subclasses of chemicals found in Cannabis and their interactions; 2) pyrolysis of these individual chemicals and classes when smoked to produce tars and other compounds; 3) absorption of chemicals and distribution of these chemicals in systems of the body; and 4) subsequent reactions of these chemicals during metabolism, storage, and elimination from the body.

Much progress has been made in identifying and quantitating cannabinoids found in marijuana. Today ten cannabinoids are routinely quantitated. Pharmacologists can now design studies with marijuana of better known composition.

Although analytical data can routinely account for ten cannabinoids, no method exists to routinely quantitate the other 411 constituents found in Cannabis, and no method has been developed to fill the forensic need for determining sample origin. Reports indicate certain analytical tools and methods can identify the origin of Cannabis; however, dynamic fluctuation of cannabinoids and the existence of three basic types of Cannabis plants have prevented any positive identification. Nevertheless, progress in the chemical classification of marijuana has been made.

Refinement of procedures and techniques continues to be noteworthy in the identification of unknown components in marijuana. Gas, thin layer, column, high pressure liquid, and plasma chromatography are being used, but X-ray methods are playing a significant role in understanding the crystal and molecular structures of known and unknown cannabinoids. These structural data enable scientists to develop a more accurate understanding of the nature and distribution of cannabinoids at the cellular level.

The chemistry and pharmacology of individual cannabinoids play a role in understanding marijuana. Recent findings suggest the interactions between cannabinoids and other components along with the cellular action of cannabinoids may be very significant. These factors may explain why the percent of Δ^9-THC in a marijuana sample is not an absolute indication of potency. The interaction between cannabinol and Δ^9-THC has been known for some time. Recently the decomposition of Δ^9-THC to the less psychotropic cannabinol has been elucidated. Compounds of the cannabitriol type are intermediates in this process and may have pharmacological actions that mimic Δ^9-THC or other cannabinoids. Two other classes of compounds indigenous to Cannabis have recently been discovered. Cannabisativine type alkaloids of the spermidine class and cannabispiran, a spiro-compound, have been found. Several of the spiro-compounds have been identified from different Cannabis samples and two cannabisativine type alkaloids have been found.

Synthetic cannabinoids and improvements in synthetic procedures continue to be of major interest. With these advances many new analogs have been synthesized and are being tested for their pharmacological profiles. Cannabichromene, one of the four major cannabinoids, has been synthesized in quantity. The use of microorganisms to produce metabolites is promising.

Metabolic studies are significant. No major breakthrough has occurred in this area but some progress has been made. Gas chromatography-mass spectrometry, radioimmunological assays, electron capture gas chromatography and thin layer chromatography remain the methods of choice for metabolic studies. None of these methods solves the problem of determining levels of intoxication in humans. Radiolabeled compounds are being used in studies on total distribution of cannabinoids in animal models.

Constituents found in marijuana smoke are being investigated. Considerable pyrolysis work has been done on cannabidiol and many pyrolytic products have been identified.

Chemical interactions between constituents of marijuana and/or their metabolites and other drugs may create toxic reactions. Progress has been slow in this area. The chemical changes in brain chemistry caused by marijuana constituents continue to be investigated as does the therapeutic potential of cannabinoids and analogs.

In the future marijuana chemical and metabolic research will, by necessity of ongoing programs and unanswered questions, be focused on providing a constant supply of standard marijuana of known composition, and a program to provide synthetic cannabinoids, their metabolites, and analogs.

THE DRUG MARIJUANA

Continued research into the synthetic chemistry and pharmacology of individual cannabinoids has clouded the natural chemistry of preparations from the Cannabis plant. The chemistry of (-)-Δ^9-trans-tetrahydrocannabinol (Δ^9-THC) is not the chemistry of marijuana, and the pharmacology of Δ^9-THC is not the pharmacology of marijuana, although Δ^9-THC is referred to as "synthetic marijuana."

Marijuana chemistry is complex and cannot be simplified or extrapolated to any one or two "active compounds." As early as 1974 this fact was recognized (UN Doc 1974), and it was recommended that all research reports on marijuana list a minimum of three cannabinoids: 1) Δ^9-THC, 2) cannabinol (CBN), 3) cannabidiol (CBD). Cannabinoids are compounds indigenous to the Cannabis plant and therefore, to all crude drugs prepared from this plant. Prior to 1964 only three cannabinoids were known to exist even though prominent chemists had attempted to elucidate "active principles" since the 1870's (Preobraschensky 1876). Today 61 cannabinoids are known.

Since 1964 many procedures to produce synthetic Δ^9-THC, other cannabinoids, and their respective homologues and analogs have been developed (Waller et al. 1976, Pitt et al. 1979). However, the chemistry of marijuana and other crude drugs from Cannabis was not well defined, and consequently not adequately understood. This progress report is designed to bring the reader up to date on natural marijuana chemistry and will, therefore, review the complex crude drugs prepared from Cannabis, i.e., marijuana, hashish, sinsemilla, dagga, etc.

The chemistry of marijuana can best be understood by breaking all known constituents of the Cannabis plant down into classes of chemicals. The total number of constituents known from Cannabis is 421 (Turner, Elsohly, and Boeren 1980) (Table 1).

Table 1. Chemical Constituents of Cannabis Preparations

1. Cannabinoids: 61 nown
   a. Cannabigerol (CBG) type: 6 known
   b. Cannabichromene (CBC) type: 4 known
   c. Cannabidiol (CBD) type: 7 known
   d. Δ^9-Tetrahydrocannabinol (Δ^9-THC) type: 9 known
   e. Δ^8-Tetrahydrocannabinol (Δ^8-THC) type: 2 known
   f. Cannabicyclol (CBL) type: 3 known
   g. Cannabielsoin (CBE) type: 3 known
   h. Cannabinol (CBN) type: 6 known
   i. Cannabinodiol (CBND) type: 2 known

Table 1. Continued.

j. Cannabitriol (CBT) type: 6 known
k. Miscellaneous types: 9 known
l. Other cannabinoids: 4 known

2. Nitrogenous compounds: 20 known
   a. Quarternary bases: 5 known
   b. Amides: 1 known
   c. Amines: 12 known
   d. Spennidine alkaloids: 2 known
3. Amino acids: 18 known
4. Proteins, glycoproteins, and enzymes: 9 known
5. Sugars and related compounds: 34 known
   a. Monosaccharides: 13 known
   b. Disaccharides: 2 known
   c. Polysaccharides: 5 known
   d. Cyclitols: 12 known
   e. Aminosugars: 2 known
6. Hydrocarbons: 50 known
7. Simple alcohols: 7 known
8. Simple aldehydes: 12 known
9. Simple ketones: 13 known
10. Simple acids: 20 known
11. Fatty acids: 12 known
12. Simple esters and lactones: 13 known
13. Steroids: 11 known
14. Terpenes: 103 known
    a. Monoterpenes: 58 known
    b. Sesquiterpenes: 38 known
    c. Diterpenes: 1 known
    d. Triterpenes: 2 known
    e. Miscellaneous compounds of terpenoid origin: 4 known
15. Noncannabinoid phenols: 16 known
16. Flavanoid glycosides: 19 known
17. Vitamins: 1 known
18. Pigments: 2 known

Not only is the chemistry of marijuana complex because of the large number of chemical constituents, it is compounded by three distinctly different Cannabis chemovariants: each producing a distinctly different marijuana. The three types are fiber, intermediate, and drug. Cannabidiol is the major cannabinoid found in fiber type; the percent by dry weight of cannabidiol is equal to or greater than Δ^9-THC in intermediate Cannabis; and Δ^9-THC is the major cannabinoid in the drug type with CBD being absent or present in trace amounts. Cannabichromene is always present in drug types. Ratios of cannabinoids vary hourly, daily, etc.; thus there are dynamic changes over time (Turner et al. 1979).

To understand Cannabis chemistry it is best to observe analyses of several samples of crude drugs from Cannabis available on the street, from NIDA and from the UN (Table 2)

Table 2. Cannabinoid Analyses

Cannabis Prep	CBDV[1]	Δ^9-THCV	CBL	CBD	CBC	Δ^8-THC	Δ^9-THC	CBN
Sinsemilla[2](Fiber)	0.07	0.02	0.03	4.68	0.47	0.09	0.21	0.06
Sinsemilla(Inter.)	t[3]	0.08	9.01	3.69	0.61	0.07	3.58	0.21
Sinsemilla(Drug)	-[4]	0.15	0.02	0.02	0.20	-	6.28	0.22
Hashish (UN Stand.)	0.03	0.03	0.03	2.89	0.38	0.22	2.22	2.50
NIDA[5] (Cig 1)	0.01	t	t	t	0.12	0.09	0.84	0.30
(Cig 2)	-	0.02	0.02	0.02	0.18	0.15	1.86	0.13

[1]CBDV=cannabidivarin; Δ^9-THCV=(-)-Δ^9-trans-tetrahydrocannabivarin; CBL=cannabicyclol; CBD=cannabidiol; CBC=cannabichromene; Δ^8-THC=(-)-Δ^8-trans-tetrahydrocannabinol; Δ^9-THC=(-)Δ^9-trans-tetrahydrocannabinol and CBN=cannabinol. Cannabigerol (CBC) and cannabigerol monomethylether (CBGM) were excluded but are routinely included in all analyses.

[2]Sinsemilla-a crude drug from the flowering tops of female Cannabis plants that have not been pollinated: "Seedless marijuana." Same as Dagga from the Republic of South Africa. These samples were grown in Calif.

[3]t=trace (less than 0.009%).

[4]absent

[5]Standard NIDA Mexican marijuana cigarette from Cannabis grown in Mississippi.

The preparations listed in Table 2, with the exception of hashish, are dry forms of Cannabis commonly called marijuana and illustrate the fact that the chemistry of marijuana is not just the chemistry of Δ^9-THC, but at a minimum? a combination of cannabinoids. For example, observe the cannabinoid ratios in the three types of Sinsemilla listed. Moreover, Δ^9-THC is not the only psychomimetically active compound: Δ^8-THC, Δ^9-THC, and CBN are active (Holister 1974, Perez-Reyes et al. 1973). Kinetic interactions have been reported to occur among cannabinoids since the early 1970's (Karniol and Carlini 1972, Borgen and Davis 1974, Siemens, Kalant and deNie 1976). Therefore, other cannabinoids play a role yet to be determined in the pharmacology of marijuana.

Recently a new subclass of cannabinoids called cannabitriols were discovered. Chan, Magnus, and Watson (1976) provided the first of these compounds: (-)-cannabitriol. Elsohly, El-Feraly, and Turner (1977), Elsohly et al. (1978), and Boeren, Elsohly, and Turner (1979) quickly confirmed this work and found four additional cannabitriols. Boeren, Elsohly, and Turner (1979) determined the

stereochemistry of one compound, cannabiripsol, and determined the presence of other "cannabitriols." These compounds may be of pharmacological significance since they decompose to CBN and are produced when Δ^9-THC decomposes to CBN (Turner and Elsohly 1979).

For many years it was believed that alkaloids were responsible for the biological activity found in Cannabis preparations (Preobraschensky 1876, Humphrey 1902). Until recently no alkaloids of significance were found in marijuana. El-Feraly and Turner (1975) reported the structure of hordenine and Lotter et al. (1975) reported the finding of a spermidine class alkaloid: cannabisativine. In 1978 Elsohly et al. found anhydrocannabisativine. These three alkaloids are present in marijuana produced from many variants of Cannabis (Elsohly and Turner 1977). Pharmacological studies on cannabisativine and anhydrocannabisativine have not been carried out. These compounds are unique and believed to be indigenous to Cannabis.

Discovery of a new class of spiro-compounds in marijuana (Ottersen et al. 1976, Bercht et al. 1976, Boeren et al. 1977, Kettenes and Salemink 1978, Shoyama and Nishioka 1978, Crombie, Crombie, and Jamieson 1979) may solve some of the inconsistencies reported in hormonal research with marijuana since compounds of the spiro type have exhibited estrogenic properties (Bailey et al. 1976). Moreover these compounds may be more abundant in marijuana than previously thought (El-Feraly et al. 1977).

Burstein et al. (1976) reported that eugenol and p-vinylphenol may contribute to the overall activity of marijuana. Both of these compounds are noncannabinoid phenols as are the spiro-compounds. In research programs using only synthetic cannabinoids, these compounds are excluded.

The contribution of X-ray crystallography to research in the field of marijuana chemistry has been demonstrated by Ottersen et al. (1976, 1977a,b); Jones et al. (1977); and El-Feraly et al. (1977). Structural data obtained by X-ray methods will allow more investigation into the possible structural correlations with other classes of drugs. These correlations are presently underway with anticonvulsant drugs (Jones et al. 1977).

Synthetic Progress

Synthetic production of new analogs of naturally occurring cannabinoids continues at a rapid pace. Handrick et al. (1977) synthesized the cis isomers of cannabidiols and Uliss et al. (1979) reported a procedure to convert cis cannabinoid isomers to trans. The synthesis of novel cannabinoids (Uliss et al. 1977a,b) along with other synthetic procedures reported (Handrick et al. 1979) provide new approaches to the synthesis of metabolites and some elusive cannabinoids (Boeren, Elsohly and Turner 1979).

Microbiological oxidation of the pentyl side chain to provide a series of metabolites was a significant accomplishment. Refinements of this method (Robertson et al. 1978) combined with synthetic programs as described by Pitt et al. (1979) and Ohlsson et al. (1979) provide a route to side chain metabolites.

Another significant development since the last report was the synthesis of a C-glucuronide of Δ^8-THC. C-glucuronides may be very significant in determining the nature of water soluble conjugates (Yagen, Levy, and Mechoulam 1977). These conjugates are of particular interest since Harvey, Martin, and Paton (1977) reported the identification of 0-glucuronides of seven cannabinoids.

With the synthesis of CBC by Elsohly, Boeren, and Turner (1978a) it is now possible to study CRC and its influence on the pharmacology of other cannabinoids. Cannabichromene is one of the four major naturally occurring cannabinoids. Pharmacological studies were previously restricted because of an insufficient supply. Further work on the separation and quantitation of CRC and CBD (Fifth Marihuana Health Report 1975, Sixth Marihuana Health Report 1976) was carried out and again confirmed that CBC is a major cannabinoid (Coutts and Jones 1979). The report by Coutts and Jones (1979) also has important forensic significance since all extracts of suspected Cannabis preparations found to be positive using 1) microscopic-examination of the material, 2) modified Duquenois-Levine color reaction, and 3) a thin layer chromatographic examination of the extracts were confirmed in blind experiments using GC-mass spectral data.

Chemistry of Marijuana Smoke

Marijuana chemistry is the chemistry of smoke from natural marijuana or special products prepared by coating placebo marijuana with individual synthetic cannabinoids. Research programs may use both products whereas users consume natural material. In this connection, Mikes and Waser (1971) suggested that the cannabinoid composition of marijuana smoke may differ from the leaf analysis. Reports on the amount of Δ^9-THC available in marijuana smoke have been inconsistent (Truitt 1971, Manno et al. 1970); however, smoking conditions normally employed by the marijuana user may provide up to 62 percent of the original Δ^9-THC in the smoke (Fehr Land Kalant 1972). Also, more tar will be produced from a marijuana cigarette than from a tobacco cigarette deliberately chosen to produce high tar levels. Many variables affect the amount of drug (cannabinoids) available to the user via the smoking method (UN Doc 1975). Lee, Novotny and Bartle (1976) identified 150 compounds in marijuana smoke using a capillary GC column. Further work on the acidic fraction of marijuana smoke was done by Maskarinec, Alexander, and Novotny (1976). Novotny, Lee and Bartle (1976) concluded that benzopyrene, a known carcinogen found in tobacco smoke, was 70 percent more abundant in marijuana smoke. Pyrolysis of cannabinoids or nonpolar higher terpenes abundant in marijuana (Turner et al. 1979) was thought to be the source of the elevated amounts of polynuclear aromatic hydrocarbons found in

323-754 0 - 80 - 7

marijuana smoke. Hoffman et al. (1975) provided a detailed comparison between marijuana and tobacco smoke.

Some of the products formed in the pyrolysis of pure CBD have been isolated and characterized (Küppers et al. 1975, Spronck and Salemink 1978, Luteyn, Spronck and Salemink 1978). The pyrolysis of pure CBD produced many new cannabinoid-like compounds. Rosenkrantz and Hayden (1979) found marked changes in animal testicular tissue during acute and subacute inhalation of Turkish marijuana, CBC, and CBD. These findings are indicative of variation in smoke content. Moreover, in a one-year study Fleischman, Baker and Rosenkrantz (1979) found focal granulomatous inflammation and cholesterol-like clefs in rats exposed to marijuana smoke. These two studies illustrate the variable results obtained when smoke from different types of marijuana and synthetic cannabinoids is delivered to research subjects. A striking finding by Rosenkrantz and Hayden (1979) was that Turkish marijuana smoke was more lethal than placebo impregnated with 10 percent CBC or CBD which was more lethal than 9 percent Δ^9-THC on placebo. Using standard Mexican marijuana, Zwillich et al. (1978) found marijuana had stimulatory effects on metabolic rate, ventilation, and the ventilatory response to CO_2.

Current analytical data on cannabinoids in marijuana is sufficient but an adequate understanding of the chemical composition of marijuana smoke and interactions of the cannabinoids within smoke is lacking. Progress in impregnating and preventing the decomposition of synthetic cannabinoids on placebo produced from natural marijuana will contribute to the ultimate understanding of marijuana chemistry and pharmacology.

Metabolism

Progress has been made in understanding mechanisms for distribution, storage, and disposition of cannabinoids and their metabolites. This progress is the key to illuminating the short and long term effects of marijuana and individual cannabinoids on the body.

Initial metabolism of cannabinoids in marijuana smoke takes place in the lungs, whereas initial cannabinoid metabolism of orally consumed marijuana takes place in the liver. Since different enzymes are involved, different initial metabolites are produced. Major lung metabolites are usually side chain hydroxylated metabolites whereas major liver metabolites are usually hydroxylated derivatives of the cyclohexene ring system. There are over 35 metabolites of Δ^9-THC, 22 metabolites of CBD, and 22 metabolites of CBN known. Considerable species variation exists (Harvey, Martin and Paton 1978, Yisak et al. 1978, Harvey and Paton 1978). These metabolites were formed by in vivo and in vitro metabolism and were found in feces, plasma, urine and homogenized tissues and organs.

We now know several of the biotransformation pathways for Δ^9-THC. These include allylic and aliphatic hydroxylations; oxidation of methyl groups to acids, aldehydes, and ketones; conjugations with

fatty acids or ß-glucuronic acid; epoxidation of double bonds; and reduction of the terpene double bond.

Many of these metabolites are "psychoactive," but most are not. This does not mean, however, that these "cannabinoids" will not have biological activity. Recent findings on the nonspecific membrane binding properties of Δ^9-THC (Roth and Williams 1979), the interaction of cannabinoids with model membranes (Tamir, Lichtenberg, and Mechoulam 1978), and the complex pharmacokinetics of distribution, storage, and disposition of cannabinoids and metabolites (Garrett 1978) strongly suggest biological activity.

Data shows that cannabinoids and their metabolites are distributed throughout the body. Recent experiments using radiolabeled Δ^9-THC in rats by Schou et al. (1977) have demonstrated that 11-hydroxy-Δ^9-THC penetrates the blood-brain barrier more readily than Δ^9-THC. Possibly the affinity of 11-hydroxy-Δ^9-THC for plasma albumin accounts for this. Δ^9-THC is bound to lipoprotein.

Progress in finding and isolating new metabolites (Harvey, Martin and Paton 1978, Yisak et al. 1978, Harvey and Paton 1978) has been significant. These advances provide much information on how metabolites are stored and disposed of by the body. Synthesis of these individual metabolites and subsequent toxicological testing can add much to accurately define the long term effects of marijuana.

Determination of cannabinoids and metabolites in biological fluid can be accomplished by the following principal methods: 1) gas chromatography-mass spectrometry, 2) thin layer chromatography, 3) high pressure liquid chromatography, 4) radioimmunoassay (RIA), and 5) gas chromatography. Of these, the gas chromatography-mass spectrometry method provides the most specific and sensitive assays for cannabinoids in biological fluids (Agurell, Lindgren and Ohlsson 1978). Both chemical and electron impact ionization methods are used. Fentiman, Foltz and Foltz (1978) have provided a manual and Rosenthal et al. (1978) have compared the methods for quantitating Δ^9-THC in biological media. Foltz (1978) also discussed the use of gas chromatography chemical ionization in the quantitative analysis of Δ^9-THC. Pirl, Papa and Spikes (1979) have used this method to detect Δ^9-THC in postmortem blood samples.

Thin layer and high pressure liquid chromatography have been used to detect and separate cannabinoids and metabolites but recently, Kanter, Hollister and Loeffler (1978) developed a method to quantitate Δ^9-THC by combining thin layer and high pressure liquid chromatography. Maximum sensitivity at 215 mm is about 30 times greater than at 280 mm.

Radioimmunoassay, in general, lacks the specificity and precision of other methods, but it does offer certain advantages due to cross activity between Δ^9-THC and its metabolites and other cannabinoids. A recent report by Gross and Soares (1978) illustrated a RIA method for determining Δ^9-THC in plasma which gave levels corresponding to intoxication.

Ahomogenous enzyme immunoassay (EMIT) for cannabinoids in urine has been used (Rodgers et al. 1978) and may prove useful in rapid screening programs.

Progress has been slow in the quantitation of pure Δ^9-THC and its metabolites in biological systems. Moreover, when marijuana is used no practical method has been developed as a forensic tool for determining levels of intoxication based on detectable cannabinoids and metabolites.

Our knowledge of how pure Δ^9-THC and its metabolites, as well as the crude drug marijuana, affect certain systems of the body is constantly increasing. It is known that the cannabinoids affect brain amine levels (Johnson and Dewey 1978); platelet monoamine oxidase activity (Stillman et al. 1978); and ultrastructural changes in neurons (Myers and Heath 1979). The cannabinoids interact with ethanol (Siemens and Khanna 1977, Siemens and Doyle 1979, Belgrave et al. 1979); cross the placental barrier (Vardaris et al. 1976); cross the blood-brain barrier (Schou et al. 1977); and, are transferred from the milk of lactating animals to nursing pups (Chao et al. 1976). These diverse examples illustrate the complex ways in which pure Δ^9-THC and marijuana affect body chemistry and metabolism. A comprehensive understanding of "marijuana chemistry" is just beginning. The future of marijuana chemical and metabolic research will continue to focus on a "standard" supply of the crude drug marijuana and studies of synthetic metabolites.

The broad spectrum of biological activity found in marijuana and its components may provide chemical leads for developing therapeutic drugs. However, current knowledge on the chemistry of marijuana precludes the use of this crude drug.

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Acute Effects of Marijuana on Human Memory and Cognition

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A person who smokes or ingests marijuana will generally exhibit an impairment in memory and cognitive functions, such as attending, speaking, thinking, problem solving, and forming concepts. These marijuana-induced impairments in psychological functioning are apparently quite robust as they were easily identified by early clinical investigators of the psychological syndrome of marijuana intoxication (Ames 1958; Bromberg 1934; Halpern 1944; Williams et al. 1946). These early clinical accounts have been remarkably well verified by subsequent psychological descriptions of marijuana intoxication in man (e.g., Tart 1971).

Wikler (1974) has noted that the most obvious feature which permeates all descriptive accounts of acute marijuana intoxication is the difficulty the observer has in understanding what the intoxicated person is saying. Speech is fragmented, thought patterns are disjointed, and the speaker quite often forgets what is being thought or what was recently said. On this basis, Weil and Zinberg (1969) hypothesized that the acute effects of marijuana on speech are due primarily to a drug-induced impairment of the user's memory.

COGNITIVE TASKS

Early laboratory investigations of the effects of marijuana on cognitive functioning in man also indirectly suggest that many of the cognitive deficits produced by marijuana can be attributed to memory failures. These early experiments established empirically that marijuana can impair performance on a wide variety of cognitive tasks including: digit-symbol substitution (Weil, Zinberg and Nelsen 1968), choice reaction time (Clark and Nakashima 1968), digit span and goal directed serial alternation (Melges et al. 1970a, 1970b, 1971) serial subtraction (Manno et al. 1970), time estimation (Jones and Stone 1970), production of time intervals (Tinklenberg, Roth and Kopell 1976), spatial location (Clark and Nakashima 1968), concept formation (Klonoff, Low and Marcus 1973),

abstraction (Pearl, Domino and Rennick 1973), attention (Dittrich, Battig and Von Zeppelin 1973, Casswell and Marks 1973b) and reading comprehension (Clark, Hughes and Nakashima 1970).

The inference that a drug-induced memory disruption occurs in these experiments is drawn from the requirements of the cognitive tasks themselves. For instance, under the digit span task, the subject is presented with a number of digits and then is immediately asked to recall them in order. Under the serial subtraction task, the subject is given some starting number and then is asked to subtract some constant number, such as seven, until zero is reached. In other words, at any given moment in time the subject needs to remember what the current number is and to perform, from memory, previously learned arithmetic operations. Likewise, the goal directed serial alternation task requires the subject to hold a number in memory and to perform cognitive functions directed toward a remembered goal. It seems apparent that one could infer that marijuana impairs memory directly from marijuana-induced performance decrements under these cognitive tasks.

The inference that memory impairment mediates marijuana-induced performance decrements on cognitive tasks is less direct in the case of cognitive tasks involving, for example, concept formation, abstraction, or reading comprehension. Nevertheless, in each of these latter cases the inference is appropriate since each involves the acquisition of some cognitive behavior, and the process of acquisition may be viewed cognitively as consisting of memory processes and retrieval processes. A possible exception to this interpretation is any cognitive task that involves the fundamental process of attention (DeLong and Levy 1973, 1974). It should be noted, however, that there are several considerations which have served to mitigate the inference, drawn from cognitive task performance, that marijuana impairs memory or that memory impairment mediates marijuana-induced impairments in cognition.

The primary consideration is that subsequent research did not always empirically confirm the earlier findings of marijuana-induced performance decrements on these same cognitive tasks. For example, in selected experiments, marijuana did not affect performance on such cognitive tasks as: digit-symbol substitution (Hollister and Gillespie 1970), choice and concept formation (Peters et al. 1976), reaction time (Rossi, Kuehnle and Mendelson 1977; Kvalseth 1977), digit span (Waskow et al. 1970; Rafaelsen et al. 1973), goal directed serial alternation (Tinklenberg et al. 1972), serial subtraction (Melges et al. 1970a), time production (Jones and Stone 1970; Tinklenberg et al. 1976), card sorting (Beautrais and Marks 1976), and attention (Sulkowski, Vachon and Rich 1977, Vachon and Sulkowski 1976; Vachon, Sulkowski and Rich 1974).

Comprehensive reviews of the experimental literature pertaining to marijuana's effects on cognitive tasks of the types discussed herein are available elsewhere (see especially: Abel 1975; Braude and Szara 1976; DeLong and Levy 1974; Jones 1976; Miller 1974; 1976). A general perusal of these earlier reviews indicates that

marijuana most often impairs cognitive functioning. Additionally, evidence favors interpreting these marijuana-induced impairments in cognitive functioning in terms of memory disruption although, as noted above, the data are too equivocal to be definitive in this regard.

It is well established that most drug effects on memory and cognition depend upon a host of pharmacological and extrapharamcological factors. Marijuana is similar to other psychoactive drugs in this regard. Indeed, part of the above-described discrepancy in experimental findings regarding marijuana's effects on performance under cognitive tasks may be accounted for in terms of such factors. Furthermore, the early reported finding that marijuana's cognitive effects are not consistently present within a subject but instead tend to wax and wane across the duration of a single drug intoxication may be similarly explained (e.g., Clark and Nakashima 1968; Tinklenberg et al. 1970; Rafaelsen et al. 1973).

With respect to pharmacological factors? for example, the adverse effects of marijuana on cognitive functions including concept formation, convergent and divergent thinking, goal direction, attention, choice, and decisionmaking have been shown to be directly dependent upon the magnitude of the drug dose (Borg and Gershon 1975; Klonoff, Low and Marcus 1973; Klonoff and Low 1974; Schaefer, Gunn and Dubowski 1977), although performance on some cognitive tasks may paradoxically improve at low drug doses (Weckowicz et al. 1975). Further pharmacologically, propranolol pretreatment can block a marijuana-produced impairment of performance on a digit-symbol substitution task (Sulkowski et al. 1977), but no drug interactions are found between marijuana and cannabidiol (Dalton et al. 1976) or marijuana and dextroamphetamine (Evans et al. 1976) on cognitive behavior. Neither cannabidiol or dextroamphetamine alters marijuana's effects on cognitive performance when administered simultaneously with marijuana. On the other hand, drug combinations involving marijuana and alcohol produce additive effects at first (Belgrave el al. 1979) and later may produce a possible antagonism in that cognitive functions may eventually be less impaired under an alcohol-marijuana combination than under marijuana alone (Chesher et al. 1977).

With respect to behavioral factors that have been shown to alter marijuana's effects on cognition, Casswell (1975) has shown that monetary incentive can attenuate marijuana's adverse effects on goal directedness, choice, and memory. However, other experiments have questioned the efficacy of monetary reward in modulating marijuana's effects (Galanter et al. 1973) or have shown that motivational factors may reduce drug effect on some tasks (e.g., time estimation) but not on others (e.g., memory - cf. Cappell and Pliner 1973; 1974). Peeke, Jones and Stone have shown that prior practice on a cognitive task can eliminate the marijuana-produced impairment on that task. In this latter context, Beautris and Marks (1976) and Miller et al. (1977c) have disagreed in suggesting that training in a nondrug state confers no advantage to the marijuana user when subsequently drugged. Still other research (Cohen

and Stillman 1976; Rafaelsen et al. 1973) has shown that marijuana's cognitive effects are directly related to the difficulty or the complexity of the cognitive task.

Cappell and Pliner (1974) have reviewed the evidence that relates amount of prior marijuana usage to marijuana's effects on cognition. This review leaves no doubt that a prior history of marijuana use can mitigate the drug's effects on cognitive performance. Indeed, Cohen and Rickles (1974) and Cohen, Rickles and Naliboff (1975) have proposed the construct of "cognitive tolerance" in order to account for the fact that the very cognitive impairments which are produced by marijuana in infrequent marijuana smokers (Rickles et al. 1973) are not manifested by individuals who smoke marijuana frequently.

Individual differences and psychologically dynamic factors have also been shown to modulate marijuana's effects on cognition. For example, Linton, Kuechenmeister and White (1976) suggest that a person's individual preference for marijuana is the most potent determinant of the individual's response on cognitive tasks. Furthermore, the effects of marijuana intoxication on cognition are related to the individual user's extent of depersonalization (Melges et al. 1970), cognitive style (Harshman, Crawford and Hecht 1976; Weckowicz et al. 1975), and personality (Miller et al. 1978b).

Last, but by no means least, there is no gainsaying that the cognitive set of the marijuana user and the physical and social setting in which the marijuana is consumed have considerable influence over the subjective and cognitive effects of the drug (cf. Cappell and Pliner, 1974; Jones 1976). In one of the more recent studies of this sort, for example, it was found that the smoker's cognitive expectancy and verbal labelling determine the level of intoxication to marijuana (Pihl, Segal and Shea 1978).

To summarize briefly up to this point, marijuana clearly impairs speaking, thinking, attending and other cognitive functions. One possible interpretation of some of these drug-induced impairments is that marijuana acts primarily to disrupt memory, and it is through this behavioral mechanism of action that marijuana causes cognitive dysfunction. The evidence favoring this interpretation, which can be drawn from experiments using cognitive tasks, is inferential and sometimes equivocal. Some of the variability between experimental outcomes, which pertains to marijuana's effects on cognition, may be attributed to pharmacological and extrapharmacological factors, although this is not always so readily done (cf. Abel 1975, Miller 1976).

There is one other source of variance which complicates the interpretation of marijuana's effects on cognitive task performance. This complication stems from the different dependent variables used to measure performance on these tasks. Taking the above-described serial subtraction task as an example, different dependent variables are possible. Specifically, these dependent variables are: time to complete the task, number of errors made in completing it, and a combination of completion time and

number of errors. Interestingly, the majority of studies that have observed marijuana-induced impairments on the serial subtration task have given equal weight to time and errors as dependent variables (Casswell and Marks 1973a, Manno et al. 1970), whereas when errors alone are considered, no impairment may be observed (Pearl, Domino, Rennick 1973; Rafaelsen et al. 1973).

The issue of which dependent variable is appropriate to measure cognitive performance on these tasks is exacerbated when the tasks are assumed to represent, or to be isomorphic with, different memory functions (Melges et al. 1970a). For example, if the serial subtraction task involves only long-term memory, or both long-term and short-term memory, then the question arises as to which dependent variable should be taken to represent which memory function (Rafaelsen et al. 1973).

Taken together, the variability in experimental outcomes, the unidentified pharmacological and extrapharmacological determinants of performance, the confusion regarding appropriate dependent variable(s), and the lack of an adequate theoretical framework under which to interpret the existing marijuana research on cognitive tasks have led researchers, particularly those interested in marijuana's effects on memory, to pursue alternate research paradigms. By and large, psychopharmacological researchers have now adopted the conventional methodologies used by experimental psychologists to study memory and the corresponding theoretical frameworks (e.g., Atkinson and Shiffrin 1968; Kintsch 1970) in order more directly to study the effects of marijuana on memory.

MEMORY TASKS

The procedures that have been used experimentally to study marijuana's effects directly on memory have not been as multifarious as those used to study marijuana's effects on cogniticm. Indeed, the procedures used to study marijuana's effects on memorial functioning can be dichotomized between those procedures involving free recall and those involving recognition memory.

Under the free recall procedure, subjects are first presented with verbal or pictorial material to be learned. Subsequently, the subjects are asked to recall the previously presented material in the absence of that material. The procedure is called free recall because there are no strictures placed on the subject as to the method or order of recalling the material. The recall phase can occur immediately after learning (immediate free recall) or after an intervening period of time (delayed free recall). Of course, either original learning, or subsequent recall, or both learning and recall (or neither one) can occur under marijuana intoxication.

There are two typically used measures of free recall performance. One measure is the overall amount or percentage of original material that is correctly reproduced. The other is the serial position curve, which is a graphical representation of the amount of material

recalled plotted as a function of the material's serial or&r of presentation during learning. That is, the serial position curve provides an answer to the question of whether the amount of material freely recalled depends upon the order in which the material was presented during learning. Under typical, nondrug, immediate free-recall conditions, the serial position curve has a U-shape; the best recall occurs for material that had been presented first (primacy effect) and last (recency effect).

The recognition memory procedure differs from the free recall procedure in that during the recall phase following original learning, the subject must identify the previously presented material from an array of old and new material. That is, rather than reproduce the previously presented material, the subject is asked to recognize which of the material presented during the recall phase was previously presented during the learning phase, and which was not. Obviously, recognition memory may be tested immediately after learning or following a delay, and it may be tested in a drug or nondrug state. The usual dependent variable under this procedure is some measure of the total amount of material correctly recognized. However, it has often been found useful to analyze the errors of recognition into those instances where the subject failed to recognize previously presented material (misses) and those instances where the subject purported to recognize material that had not been previously presented (false alarms).

For ease of exposition, the ensuing review of the empirical literature pertaining to marijuana's acute effects on human memory will deal separately with free recall and recognition memory. It will be noted, however, that in some experiments these two memory procedures have been used in the same subject following a common learning experience (with the free recall procedure usually preceding the recognition memory procedure). Similarly, the free recall data will be arbitrarily divided between those situations where the original material was learned in a nondrug (or placebo) state and where original learning occurred in a marijuana-intoxicated state, even though in some experiments subjects have served as their own drug or nondrug controls. For other reviews of marijuana's effects on memory, the reader should consult the following: Abel 1975; Darley and Tinklenberg 1974; Miller 1976; and Tinklenberg and Darley 1975, 1976.

Marijuana-Intoxicated Free Recall Following Nondrug Learning

The incisive question that the experiments reviewed in this section were designed to answer is "Does marijuana cause you to forget things you otherwise know?" Stated more functionally the question is, "If an individual learns simple verbal material when not drugged, what acute effect will marijuana have on the subsequent free recall of that material?" The extant literature is unequivocal in its answer to the latter question; marijuana has no effect on the free recall of simple verbal material learned in a drug-free state. This answer was indirectly suggested by the earlier research using cognitive tasks such as serial subtraction and goal directed serial

alternation (e.g., Melges et al. 1970a). However, the first direct answer using an explicit memory task was provided by Abel (1971b, 1971c).

In Abel's free recall experiments, subjects were first presented with several lists of words in a nondrug state. Twenty-five minutes after one-half of the subjects had smoked marijuana, all subjects were given a delayed free recall test. No differences in recall were obtained between drugged and nondrugged subjects. Abel's (1971b, 1971c) experiments contained some possible confoundings, and used marijuana that was not analyzed for Δ-9-THC content. Nevertheless, this research has stood the test of replication. Using a well controlled methodology, Darley et al. (1973b) and Dombush (1974) have directly replicated the finding that delayed free recall of word lists learned in the nondrug state is not altered by marijuana smoking or by oral ingestion of Δ-9-THC. Still further, Darley et al. (1974) have found that neither fixed rehearsal or free rehearsal of word lists during nondrugged learning differentially favors the marijuana or placebo group during subsequent delayed free recall of the lists. Finally, Pickles et al. (1973) found that no significant marijuana-induced impairment in delayed free recall of word responses occurs after prior nondrug learning of a list of verbal paired associates.

Several other experiments have investigated the effects of marijuana on the recall of verbal material that was previously learned outside of the experimental situation. For example, Darley et al. (1977) assessed the free recall of commonly known facts by college students. The recall of the nonexperimentally presented information was not affected by marijuana. The same conclusion was reached by Stillman et al. (1974) who investigated the recall of preexperimentally formed word associations (cf. Hill and Goodwin (1976) for a conflicting finding).

Delayed free recall of material learned in the nondrug state is not as impervious to marijuana when the experimenter imposes a structure on the material during original learning. For example, marijuana significantly impairs the free recall of word lists that are presented as categorized groups of words during original learning (Domino, Rennick and Pearl 1976; Pearl, Domino and Rennick 1973; Eich et al. 1975; Stillman et al. 1976; Weingartner, Murphy and Stillman 1978). Interestingly, in these experiments the marijuana-induced memory impairment is alleviated or eliminated if during recall the subject is presented with retrieval cues in the form of appropriate category names.

A second way to impose structure experimentally on material is to sequence or order it during learning and to require that it subsequently be recalled in order. The delayed recall of ordered material is impaired by the administration of marijuana prior to the recall period. This drug effect on sequential recall has been found for ordered arrangements of pictures, geometric objects , and meaningless strings of words (Hill et al. 1973; Stillman et al. 1974; Weingartner, Murphy and Stillman 1978).

It should be noted that in these latter two general instances where structure was added to the material, the recall procedure used was not actually free-recall. That is, when retrieval cues are presented during recall, or when material is required to be recalled in a particular sequence, the recall is not free in the sense of being unaided or unrestricted. Thus, it is possible to offer a reasonably consistent and general summary of the free recall literature following learning in a nondrug state. Specifically, when compared to a person who learns material and later recalls it in a nondrug state (ND-ND), a person who learns material in a nondrug state but later recalls it in a marijuana drug state (ND-D) exhibits no difference in memory function.

Marijuana-Intoxicated Free Recall Following Marijuana-Intoxicated Learning

The literature reviewed in this section may also be introduced by an empirical question. To wit, "Can a person under the influence of marijuana recall material, which was learned when intoxicated, as well as can a person who does not use marijuana during either learning or recall?" More succinctly, the relevant comparison is between learning and free recall in a marijuana drug state (D-D), and learning and free recall in a nondrug state (ND-ND). As a preview to the relevant literature that follows, it may be stated that in this instance, the marijuana user has a distinct disadvantage.

The initial experiment in this area was again done by Abel (1970). Subjects first smoked either a placebo or marijuana of unknown Δ-9-THC content, and then read some narrative material. Fifteen minutes later the placebo and drug subjects were asked to recall freely what they had recently read. Marijuana had no effect on total verbal output; the marijuana subjects produced as many total words as did the nondrug subjects. However, marijuana significantly decreased the smoker's ability to reproduce the narrative correctly either in terms of words or meaning. In a direct followup to this experiment, Abel (1971a) obtained precisely the same findings when the narrative was read to the subjects rather than having the subjects read the narrative to themselves.

Additional support for the finding that narrative material, which is heard and then later recalled freely, is not remembered as well under the influence of marijuana was provided by Drew et al. (1972) and Miller and Drew (1972). These latter workers made explicit what was first noticed by Abel (1970), namely that marijuana-intoxicated recall of narrative material is typified by distorted intrusions, that is, by the introduction of new and unrelated material that was not contained in the original narrative.

The marijuana-induced impairment in free recall memory observed in these experiments is dose related (Miller and Cornett 1978), but it is by no means specific to the narrative material used. Indeed, under comparable drug and free recall procedures, it has been repeatedly found that the recall of widely varying verbal and

pictorial materials is generally diminished by marijuana intoxication. The generalization that learning and recall suffer with marijuana use applies to materials as diverse as: anagrams (Abel 1971a), auditory consonant trigrams (Dornbush, Fink and Freedman 1971), digits (Galanter et al. 1973), words (Abel, 1971b; Darley et al. 1973b), word associations (Hill et al. 1973), categorized word lists (Pearl, Domino and Rennick 1973), geometric figures (Miller, Cornett and Nallan 1978), pictures (Miller et al. 1977d), and prose (Miller et al. 1977a).

As was the case for narrative material, marijuana-induced disruptions in free recall of other verbal material, such as a word list, are characterized by intrusions of material external to the word list or to the learning situation more generally (e.g., Miller et al. 1976; 1977c; Pfefferbaum et al. 1977). Miller and coworkers have further analyzed these marijuana-engendered intrusions of new material and have found that the increase in intrusions is not dose related (Miller and Cornett 1978), nor is it significantly correlated with total recall (Miller et al. 1977c) or with cognitive style (Miller, Cornett and Nallan 1978). In a related vein, marijuana increases the descriptive novelty of ambiguous stimuli (Roth et al. 1975) but it does not enhance measures of object description (Tinklenberg et al. 1978). On balance, then, it appears that marijuana-induced intrusions do not represent creative or associational thinking.

When material is both learned and recalled under marijuana, as it was in the above-cited experiments in this section, it is not necessarily the case that drug-induced impairments in the free recall of material implicate a memory dysfunction per se. Indeed, it is conceivable that instead marijuana blocks the perception or sensory registration of the presented material in such a way that no material is ever made available to the marijuana user for later recall. It has been clearly demonstrated, however, that marijuana does not affect the sensory registration of presented information in this manner.

One way this has been demonstrated has been to compare the free recall of material immediately after presentation of the material (0 sec delay) with recall following a delay of a few (4-6) seconds (Dombush, Fink and Freeman 1971; Galanter et al. 1973). Under marijuana intoxication, a few seconds can make a difference; immediate recall is not impaired while short-delay recall is depressed. Obviously, the material must have registered in the sensorium to be recalled at all, even immediately, although it is apparently not available from memory after a few seconds.

A similar argument may be made based upon the serial position recall curves that have been obtained in experiments investigating the recall of word lists. When marijuana impairs free recall of word lists, the obtained serial position recall curve necessarily differs from that obtained in the nondrug state. In some experiments, particularly but not necessarily if free recall is delayed somewhat, the serial position curve obtained in the drug state will have the

same shape as that obtained in the nondrug state; but it will be depressed throughout (e.g., Galanter et al. 1973; Miller et al. 1977a; 1977c). In other experiments, the drug state serial position curve will be depressed at all serial input positions except for the very last positions, that is, except for the few words that were presented last during learning. For these most recently presented words, the drug and nondrug serial position recall curves are not different (Abel 1971b; Darley et al. 1973b; Darley and Tinklenberg 1974). Taken all together, these experiments again suggest that marijuana does not interfere with the sensory registration of material, but it does somehow impair memorial registration (see also Darley et al. (1973a) for further supporting data obtained with a different experimental memory procedure).

Some of the research that has investigated the acute effects of marijuana on recall of material learned in the drug state has gone beyond the since identification and description of marijuana's acute effects to investigate the influence of various behavioral factors on the marijuana-induced memory impairment. Among the behavioral factors that have been investigated to date are ones that might reasonably be expected to influence free recall of material when a person is in the nondrug state. Specifically, recent experiments have studied the roles of practice, rehearsal, organization, and retrieval cues on free recall, mostly of word lists, in the marijuana drug state.

The experiments that have investigated the effects of practice on marijuana-intoxicated free recall have done so within an experimental session rather than between experimental sessions as had been done previously with cognitive tasks (e.g., Peeke, Jones and Stone 1976). In the first of these memory experiments (Miller et al. 1977c), marijuana-intoxicated and placebo subjects were presented with 20 word lists, with an immediate free recall memory test being given after each list. The practice component in this experiment was contained in the fact that the same word list was used as lists numbered one, six, eleven, and sixteen. Practice on the word lists did not attenuate the effects of marijuana on free recall; performance under marijuana was consistently inferior to performance under placebo conditions for all word lists. A similar conclusion regarding the ineffectiveness of practice in attenuating marijuana-induced free recall deficits may be drawn from a study by Miller, Cornett and McFarland (1978). These researchers used a technique of restricted reminding in which, following an initial immediate free-recall test of a 30-word list, only those words not recalled were presented again, and again until the word was recalled once. Thus, in subsequent learning trials the subject would be presented with only previously unrecalled words, although the subject was asked to recall the entire list during each memory test. Repeated practice on previously unrecalled words did not alleviate the marijuana suppression of total recall.

Manipulating the subject's rehearsal of words during list presentation also does not erase the deficits in immediate recall evidenced by marijuana-intoxicated subjects. No matter whether the marijuana-

intoxicated individual is asked to rehearse the presentation of a word freely and covertly (Darley et al. 1974; Darley and Tinklenberg 1974), overtly by repeating the word (Darley et al. 1974; Pfefferbaum et al. 1977), or overtly by speaking aloud free-asociates to the word (Pfefferbaum et al. 1977), the marijuana effect remains consistently in evidence.

When a marijuana-intoxicated person is asked freely to recall recently presented pictures and words, the subjective organization of the material recalled does not differ from the subjective organization imposed upon the material by a nonintoxicated person (Miller et al. 1977d). However, if the experimenter imposes an organization on the material, say by presenting categorized lists of words and, perhaps, category names, then the marijuana-intoxicated person will organize the material less during free recall and will recall fewer total words than will the nonintoxicated person. For example, Pearl, Domino and Rennick (1973) found that marijuana-intoxicated subjects less often recall items from the same category together, and Eich et al. (1975) found that they recall fewer categories all together.

Cueing the subject during the recall of categorized lists by providing the subject with appropriate category names has the effect of erasing marijuana-placebo recall differences (Stillman et al., 1976; Weingartner, Murphy and Stillman 1978). However, cueing is not a generally effective method of overcoming a marijuana-induced impairment of memory. For example, Miller et al. (1976) found that cues representative of to-be-remembered words were only mildly effective in reversing the recall deficit in marijuana-intoxicated subjects. In a second experiment dealing with cued recall, Miller et al. (1977a) used questions concerning facts and events in a narrative as retrieval cues for the prose material. No relative cued recall advantage was found in marijuana subjects as compared to nondrug control subjects.

By way of summarizing this section, it may be said that when a person uses marijuana, the person's ability to freely recall events experienced in a marijuana state will be compromised. This drug-induced impairment is pervasive in that it occurs with a wide variety of verbal and pictoral material, and it is resistant to amelioration, in that it is generally insensitive to practice, rehearsal, or cueing. The problem clearly involves memorial functioning in the marijuana smoker inasmuch as indices of sensory registration show that the to-be-remembered material is initially available to the marijuana smoker. Additionally, the marijuana-impaired recall of material is sometimes characterized by a lack of cognitive organization, and frequently involves the intrusion of inappropriate memories.

Finally, in considering the preceding two sections on free recall memory together, it is appropriate to emphasize the importance of the drug state during original learning. If a person learns in a nondrug state, later marijuana usage will have no effect, or only a minimally detrimental effect, on the recall of the learned

material. Apparently, a change in marijuana drug state between acquisition and recall (specifically, nondrug to drug) is not sufficient in and of itself to produce substantially reliable effects on memory. On the other hand, if a person learns under the influence of marijuana and continues to use marijuana, the recall of prior events will be seriously curtailed in comparison to the memory of the nonuser of marijuana. This summarization gives rise to one additional empirical question regarding free recall memory and marijuana usage: "If a person learns material under the influence of mariajuana, will the subsequent recall of this material depend upon the person's drug state at the time of recall?" In other words, "Will the person remember better if marijuana intoxicated, or will the person have better recall if not under the influence of marijuana?"

Nondrug Free Recall Following Marijuana-Intoxicated Learning

The issue here is one of state dependency, that is, whether material learned in the marijuana state is better recalled in the same marijuana state (state dependence) or given a change to a nondrug state. Before proceeding to discuss the literature pertaining to free recall memory and state dependency, it should be noted that marijuana generally does not produce a wide ranging state dependency on cognitive and memory tasks.

For instance, no disadvantage is afforded the nonintoxicated person in performing a wide variety of cognitive tasks that were originally learned while intoxicated, including: visual concept formation and tactile form discrimination (Klonoff, Low and Marcus 1973), reaction time (Peeke, Jones and Stone 1976), and card sorting (Beautrais and Marks 1976). Likewise, marijuana-intoxicated recall is not better than nondrug recall, after original learning in the marijuana state, using a variety of memory procedures including: cued recall (Eich et al. 1975; Stillman et al., 1976; Weingartner, Murphy and Stillman 1978), recognition memory (Darley et al. 1973b, 1974), and tactile and auditory memory (Klonoff, Low and Marcus 1973).

With respect to free recall procedures, there are a number of studies that suggest that marijuana-intoxicated learning is not state dependent, material learned in the marijuana state is not better recalled in the marijuana state than when not under the influence of the drug. No state dependency has been found in free recall of a variety of materials including: word lists (Stillman et al., 1974), paired associates (Rickles et al. 1973), free associates (Hill and Goodwin 1976), pictures (Klonoff, Low and Marcus 1973), and prose (Miller et al. 1977a). Indeed, there exists in the literature only one report of state-dependent memory using a free recall procedure (Darley et al. 1974). In this latter experiment, delayed free recall of word lists learned under marijuana was better in the drug than in the nondrug state.

There are two general experimental procedures that tend to yield

state-dependent recall of material originally learned under marijuana. Interestingly, these are the same two procedures for which a drug-induced recall impairment was obtained following nondrug learning. Recall of material in the same drug (or same nondrug) state seems to be consistently better than recall of material in a changed state when the material has been organized by categories (e.g., Weingartner, Murphy and Stillman 1978) or by sequential order (e.g., Hill et al. 1973) during learning.

Overall then, marijuana does not often produce state dependent performance on cognitive and memory tasks. What state dependency there is for marijuana seems to be task dependent and somehow related to the organization of the material to be remembered.

More generally summarized, it appears that when considering the free recall of learned material there are no advantages, and some distinct disadvantages, for the marijuana user. To begin with, in no memory experiment using a free recall procedure has marijuana ever been reported to enhance the user's memory of material learned in thenondrug state. The weight of the evidence supports the same conclusion for material learned in the drug state. Indeed, as compared to the learning and free recall of material while nondrugged, marijuana intoxication has a generalized detrimental effect on memory just as it does on cognition.

Recognition Memory

Many theories about the processes of memory contend that free recall and recognition memory tasks measure different hypothetical memory functions (e.g., Kintsch 1970; McCormack 1972). Be that as it may, there is no denying that the two memory tasks are operationally quite different. Procedurally, free recall involves the reproduction of previously experienced material, while recognition memory involves the identification of previously experienced material that is presented within the context of new material. As compared to the investigation of marijuana's acute effects on free recall, there has been much less research done on the effects of marijuana on recognition memory. Nevertheless, what research has been done tends to support the generalization that the person who becomes intoxicated with marijuana risks the possibility of an impaired memory. As might be expected from the free recall data, marijuana's acute effects on recognition memory depend, to some extent, upon the drug condition present at the time of original learning and again later during the recognition test. However, in no instance has it been found that marijuana facilitates recognition memory.

Beginning with the situation in which subjects are presented with verbal material in a nondrug state and then are later asked to recognize the material in either a nondrug or marijuana-intoxicated state, the literature is quite consistent in showing that drug and nondrug subjects do not differ in terms of the number of items correctly identified. Apparently marijuana does not impair one's ability to recognize correctly material that was previously experienced in a nondrug state (e.g., Abel 1971b; 1971c; Darley et al.

1973b; 1974; Miller et al., 1977b). This lack of an effect on recognition memory holds across a range of marijuana doses miller and Cornett, 1978), and for material experienced both within and outside the experimental situation (Darley et al. 1977).

There is one drug-related effect which is sometimes reported in the recognition memory context and that pertains to the occurrence of false alarm errors, that is, to the erroneous positive identification of material which, in fact, had not been previously presented. (False alarms in recognition memory bear a conceptual similarity to erroneous intrusions in free recall). When recognition memory of material previously experienced in a nondrug state is tested in the marijuana-intoxicated person, an increase in false alarms is sometimes (Abel 1971b, 1971c; Dornbush 1974), but not always (Miller et al. 1977b; Miller and Cornett 1978), observed.

Recognition memory for material originally experienced while marijuana intoxicated has been studied systematically in only four experiments, all of which used word lists. In one of these experiments (Dornbush 1974), subjects were exposed to the word lists in either a nondrug or marijuana state and then were tested for recognition memory in the marijuana state. The initial drug exposure produced a small decrease in subsequent recognition memory, which was typified by an increase in false alarms.

The remaining three experiments compared recognition memory between subjects who were always in the marijuana-intoxicated state with those who were not drugged during either the initial presentation of the material or the later recognition memort test. The data here are somewhat equivocal. A drug-induced impairment was found in one experiment (Darley et al. 1973b) but not in the other two (Darley et al. 1974; Miller et al. 1977).

Quite obviously, marijuana-induced memory impairments are not as intensive under a recognition memory procedure as they are under a free recall procedure. However, as suggested at the outset of this section, the recognition memory data are well in accord with the data reviewed for cognitive tasks and for the free recall of material from memory. Marijuana's acute effects on memory and cognition are sometimes small, but where there are effects, large or small, they are seemingly always detrimental to the marijuana user.

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Effects of Marijuana on Neuroendocrine Function

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One of the major problems of studying the effects of drugs on neuroendocrine systems relates to an incomplete understanding of mechanisms of neuroendocrine regulation. In general, a neuroendocrine system consists of neural cells which secrete a chemical substance (neurohormone) that exerts its effect on other cells within the body. These target cells may be other nerves or somatic cells. Thus, the neurohormones are often placed into two classes. One class consists of those secretions that are known to be involved in neural function, such as the neurotransmitters. The second class consists of those secretions that are involved in somatic cell function, such as the hypothalamic hormones that regulate anterior pituitary function. The mechanisms that control neuroendocrine activity are thought to be forms of negative or positive feedback, similar to the feedback systems that control the peripheral endocrine glands.

Most of the newer studies of the effects of marijuana on neuroendocrine regulation have examined the effects of the drug on the hypothalamic-pituitary axis. These studies have resulted in part because of the observed effects of marijuana on the peripheral endocrine organs that are regulated by the hypothalamic-pituitary axis. For example, the reproductive consequences of prolonged marijuana use include both 1) alterations in reproductive hormones (Smith et al. 1979) and 2) effects on spermatogenesis (Hembree et al. 1976) or ovulation (Smith et al. 1979). Since both of these reproductive processes are controlled by the hormones from the anterior pituitary gland, and since marijuana is a neuroactive drug, it seemed reasonable to assume that the hypothalamic-pituitary axis was the site of action for the reproductive effects of marijuana.

In attempting to describe a mechanism for the hypothalamic-pituitary effects of marijuana, it becomes apparent that the study of the effects of marijuana on central nervous system neurotransmitters is also important. These neurotransmitters are located along the nervous pathways that regulate the hypothalamic-pituitary axis and, at a cellular level, the effect of marijuana may

be mediated by the drug's effect on these neurotransmitters. Thus, in order to summarize these studies on the effects of marijuana on neuroendocrine regulation, this review will be divided into two parts: 1) evidence for the effects of marijuana on hypothalamic-pituitary function and 2) studies on the role of neurotransmitters in the mechanism of action of marijuana effects on hypothalamic-pituitary function.

EVIDENCE FOR THE EFFECT OF MARIJUANA ON HYPOTHALAMIC-PITUITARY FUNCTION

Effects of THC on Gonadotropin Secretion

Since the initial report by Harks in 1973 of the inhibitory effect of tetrahydrocannabinol (THC) on luteinizing hormone (LH) levels in ovariectomized rats, a number of studies have appeared which confirm this observation and attempt to describe the mechanism. Studies in the ovariectomised rhesus monkey have defined the dose-response relationship of the effect (Besch et al. 1977). In these studies, THC (0.6 - 5.0 mg/kg) or vehicle (3 percent polysorbate 80 [Tween 80] in saline) was given to ovariectomized monkeys by an intramuscular injection. The result was a prompt and significant decrease in LH levels (average 50 - 80 percent decrease) that lasted for 12 - 24 hours depending upon the dose level of THC. These results are in agreement with studies in ovariectomized rats (Tyrey 1978) which showed a suppression in episodic LH secretion following THC administration. In both the monkey and rat studies, the magnitude of the decreases appeared not to be directly related to the dose of THC; but the duration of the responses was shown to be related to the dose, with larger doses of THC producing longer lasting depressions in gonadotropin levels. The suppression of LH secretion appeared to be complete, but the effect was completely reversible.

A comparison of the effects of the various doses of THC on the levels of LH and the levels of follicle stimulating hormone (FSH) in ovariectomized monkeys showed no great differences between the two gonadotropins (Smith et al. 1979). For example, the average maximum decrease in LH and FSH following the 5.0 mg/kg dose of THC was 68 percent and 56 percent respectively. Comparison of the time course of the effects on gonadotropin levels in individual monkeys showed that the maximum decrease in hormone levels occurred at generally the same times for LH and FSH.

It is important to note, at this point, that these studies have examined the effect of Δ^9-tetrahydrocannabinol on pituitary hormone levels. One study has compared the effects of THC and other marijuana derivatives, including the crude alcohol extract of marijuana (CME) containing 25 to 30 percent THC (Smith et al. 1979). THC and CME were administered to ovariectomixed monkeys at equivalent dose levels (based on total amount of THC). The decreases in both LH and FSH levels were equivalent in response to equal doses of THC and CME. That is, the 4.16 mg/kg dose of CME produced an average 40.8 percent inhibition of LH levels that

lasted for 6 hours. The equivalent dose of THC (1.25 mg/kg) produced an average 35.9 percent decrease in LH that also lasted for 6 hours. Other cannabis derivatives that were examined for effects on pituitary hormones included cannabidiol (CBD) and cannabinol (CBN). Neither CBD nor CBN had any statistically significant effect on gonadotropin levels at dose levels up to 10 mg/kg.

The comparison of the inhibition of gonadotropins produced by THC, marijuana extract and the other cannabis derivatives indicates that the inhibitory action of marijuana on gonadotropin levels is produced by THC, and that the other cannabis derivatives contained in marijuana do not contribute to the effect. This is particularly evident because the relative doses of CBN and CBD used in this study were much larger than would be contained in the doses of marijuana extract. In addition, these results suggest, but do not prove, that the inhibitory effect of cannabis derivatives on gonadotropins is related to their psychoactivity. Further studies need to be done with other psychoactive cannabinoids and with cannabis derivatives devoid of psychoactive properties. It should also be noted that while certain cannabis derivatives may not contribute significantly to the endocrine changes caused by marijuana, they may have other direct effects on spermatogenesis, ovulation, and other reproductive functions.

The pharmacological site of action of a single dose of THC on gonadotropin levels was investigated in ovariectomized monkeys (Smith et al. 1979). Synthetic gonadotropin releasing factor (GnRH) was administered to the monkeys 6 hours after the administration of 2.5 mg/kg of THC. This dose of THC produces a statistically significant depression in gonadotropins that lasts for at least 12 hours. GnRH administration resulted in a stimulation of the blood levels of both LH and FSH. The increase in LH and FSH levels was statistically significant at 30, 60, 90, and 120 minutes after the GnRH administration. The stimulation of LH and FSH levels measured after GnRH could be considered as a reversal of the effect of THC since all of the stimulated gonadotropin levels were within the 95 percent confidence interval established for each monkey's control values. The response to releasing hormone in ovariectomised rats was the same as the response in monkeys (Tyrey 1978). Further, the suppression of ovulation in rats (Nir et al., 1973) and in rabbits (Asch et al. 1979) caused by THC can be reversed by the administration of GnRH. These results show that the pituitary gland can respond to hypothalamic releasing hormones by releasing gonadotropins in the presence of THC. This indicates a hypothalamic site of action for THC, and while the exact mechanism of the inhibitory effect of THC on gonadotropin secretion remains unknown, the involvement of hypothalamic neuroendocrine processes seems very likely.

In summary, the effect of single doses of THC on pituitary gonadotropins is a significant inhibition that lasts 12 to 24 hours depending upon the dose of THC administered. The effect appears

to be mediated at the level of the hypothalamus. Little is known about the effects of short-term or chronic administration of THC on these hormones and the possible development of tolerance. The weight of current evidence (described elsewhere in this volume) clearly indicates that the effect of THC on gonadotropins is sufficient to produce disruption of the reproductive process in both males and females.

Effects of THC on Prolactin Secretion

While there are a number of drugs, including narcotics (Tolis et al. 1975). phenothiazine tranquilizers (Frantz 1973), and sex steroids (Robyn and Vekeman 1973), that will inhibit LH and FSH levels, these drugs have a stimulatory effect on prolactin levels. The effect of THC on prolactin levels has been quite controversial with studies reporting either increases or decreases in man (Lemberger and Rubin 1975), rats (Daley et al. 1974), and mice (Raine et al. 1978).

Studies in male and female rhesus monkeys have shown that the acute effect of THC on prolactin levels is a significant, but short-lived inhibition (Asch et al. 1979). THC (2.5 mg/kg) or vehicle (3 percent Tween 80 in saline) was administered to the monkeys, and blood was drawn at 30, 60, 90, 120 and 180 minutes after injection. While vehicle administration produced no consistent change in prolactin levels, THC produced a prompt and significant decrease in prolactin level. The decrease in prolactin levels was significant for both male and female monkeys (average 84 percent decrease) at all of the time intervals from 30 to 180 minutes. The site of action of the inhibitory effect of THC on prolactin was determined by using thyrotropin releasing hormone (TRH). TRH administration stimulates the release of prolactin from the pituitary by a direct action on the pituitary gland. The results indicated that the effect of THC on prolactin levels is mediated by a hypothalamic site of action, since the administration of TRH at 30 minutes after THC injection reverses the inhibitory effect on prolactin levels. Kramer and Ben-David (1974) have shown that the inhibitory action of THC on prolactin secretion in the rat can be abolished by cyprohepatidine (a serotinin antagonist) or perphenazine and pimozine (dopamine antagonists). While the exact mechanism remains unclear, the evidence now shows that the acute effect of THC on prolactin is inhibition. The mechanism most likely involves an effect of THC on hypothalamic, neuroendocrine control of prolactin secretion. A study of the effects of short-term administration of THC on prolactin levels indicates a very different type of response. In this study, THC was administered to normal rhesus monkeys during the luteal phase of their menstrual cycles (Smith et al. 1979). Daily administration of THC (2.5 mg/kg) had no effect on serum progesterone levels or on the length of the luteal phase. However, after discontinuation of the THC administration, the next cycle period was marked by an absence of normal estrogens, gonadotropins, and progesterone. Notably, the prolactin levels recorded during the posttreatment period were 4 to 5 times

greater than prolactin levels in normal ovulatory cycles. Thus, while the acute effect of THC on prolactin levels is a prompt and significant decrease, the short-term effect appears to be chronically elevated prolactin levels associated with the production of anovulatory cycles. Whether this elevation in prolactin levels is a direct effect of THC on the hypothalamic-pituitary control of prolactin or a secondary effect of the disruptive effect of THC on the menstrual cycle remains to be determined.

Effects of THC on Thyrotropin (TSH) Secretion

In 1965, Miras first reported that administration of cannabis resin to rats depressed the uptake of radioactive iodine into the thyroid gland. This inhibitory effect could have been due to a direct effect of the cannabis resin on thyroid gland function or due to a secondary effect of the cannabis resin on the hypothalamus or pituitary function. Later studies confirmed the inhibitory effect of marijuana on thyroid function and identified the hypothalamus as the site of action (Lomax 1970). In these studies, the injection of marijuana distillate extract inhibited the release of radioiodine from the thyroid gland in rats. The administration of thyroid stimulating hormone (TSH) resulted in the reversal of the inhibitory effect of the drug, suggesting that reduced TSH secretion was the primary cause of the thyroid inhibition produced by marijuana. Further evidence of a hypothalamic site of action comes from studies in which bilateral electrolytic lesions in the region of the medial mammillary nuclei of the hypothalamus prevented the decrease in pituitary-thyroid activity induced by marijuana (Lomax and George 1966). These investigators compared the effect of marijuana to the effect of morphine on pituitary-thyroid function, and they postulated that the effect of both drugs may be either inhibition of hypothalamic neurons responsible for thyrotropin releasing factor (TRF) secretion or the stimulation of specific inhibitory centers in the hypothalamus.

Effects of THC on Corticotropin (ACTH) Secretion

Contrary to the effect of THC on gonadotropins, prolactin, and thyrotropin, the apparent effect of THC on corticotropin, and hence, adrenal cortical activity, is activation. Dewey et al. (1970) demonstrated this activation of adrenal function in laboratory rats by measuring depletion of ascorbic acid from the adrenal gland, indicating increased hormonal activity by the adrenal gland. Kubena et al. (1971) reported an increase in plasma corticosterone levels after THC administration. The elevation of plasma corticosterone levels was found at 45 minutes after a dose of THC as low as 2.0 mg/kg. The effect of a single dose of THC lasted less than 8 hours, but the effect was still present at 45 minutes after daily administration of THC for 8 days. This elevation in adrenal cortical hormone was attributed to hypothalamic-pituitary site of action, because the increase in plasma corticosterone was completely blocked in hypophysectomized rats or after pretreatment with anesthetic doses of pentobarbital

and morphine. Additional findings in THC-treated rats (Barry et al. 1973) show that the elevation in adrenal steroids is associated with hyperglycemia at 45 minutes after drug administration and increased sodium retention and potassium excretion measured in the urine at 6 hours after drug administration. The diuresis continued during the 8 days of short term drug administration in these studies. The hyperglycemia and diuresis produced in these animals by THC treatment are the metabolic consequences of pituitary-adrenal activation and elevations in adrenal steroids. These metabolic changes are similar to such responses elicited by the effects of stress on pituitary-adrenal activation in animals.

The pharmacological effects of THC treatment on pituitary-adrenal function are similar to those reported for intoxicating doses of ethyl alcohol (Ellis 1966). Several other CNS depressant drugs can cause pituitary-adrenal activation after a single dose (Marks and Bhattacharya 1970), indicating that CNS depression or sedation may be an important component of the effect of such drugs. Unlike the effects of THC and alcohol, the effects of other CNS drugs tend to disappear with repeated drug administrations, indicating the possible development of tolerance to the effects of certain CNS depressant drugs.

In order to attain a full understanding of the effects of drugs on pituitary-adrenal function, both physiological changes and psychological changes must be considered. Pituitary-adrenal activation can be measured as a nonspecific effect of various types of stress. This activation is mediated by the hypothalamic-pituitary axis by an increase in the secretion of ACTH (corticotropin). Certainly, conscious recognition of the CNS depressant effects of drugs could be considered a stress. Hollister et al. (1970) measured adrenal hormone levels in human volunteers after an oral dose of THC up to 1 mg/kg. Increases in hormone levels were detected only in individuals in which a severe anxiety reaction occurred.

The idea that pituitary-adrenal activation may be a nonspecific stress reaction to CNS depression is further supported by the paradoxical effect of certain CNS drugs (e.g. pentobarbital and morphine) at high doses. At sufficiently high doses, these drugs actually block the pituitary-adrenal activation caused by THC (Barry et al. 1973). Thus, the pituitary-adrenal activation in response to lower doses of certain CNS depressants and in response to THC or alcohol could reflect a normal compensatory mechanism to counteract the stress of the depressant effect on functions of the CNS. Further studies are necessary to fully define the effects of THC on pituitary-adrenal function and to describe the hypothalamic-pituitary action that apparently results in an increased adrenal activity in response to THC administration.

EVIDENCE FOR THE ROLE OF HYPOTHALAMIC NEUROTRANSMITTERS IN THE MECHANISMS OF ACTION OF MARIJUANA EFFECTS ON HYPOTHALAMIC-PITUITARY FUNCTION

Hypothalamic biogenic amines have been demonstrated to exert an important influence on the secretion of pituitary hormones. These transmitters probably act by altering release of hypothalamic releasing factors or release-inhibiting factors from nerve terminals in the median eminence of the hypothalamus into the pituitary portal vessels. Alterations in levels of dopamine (DA), serotonin (5-HT), and norepinephrine have been observed to influence the release of pituitary hormones and may in fact be the physiological modulators of these hormones. Several studies have also indicated a possible role for the recently discovered endogenous opiate peptides (EOP's) in the hypothalamic control of pituitary hormones.

Before discussing the evidence for effects of THC or marijuana on these hypothalamic modulators, it is necessary briefly to review the evidence for the roles of these substances in the control of pituitary hormones. A number of methods have been used to investigate the mechanisms and physiological significance of neurotransmitter-hormone interactions. However, those methods currently available all have limitations. For example, treatment of animals with drugs affects transmitter levels in the whole brain, making it very difficult to distinguish between direct effects on the hypothalamus and secondary effects mediated at other brain levels. Even direct infusion of drugs or transmitters into the brain's ventricles or into the hypothalamus is likely to result in greater than normal physiological concentrations of the transmitters in the hypothalamus and/or cerebrospinal fluid (CSF), resulting in artifacts.

In addition to methodological considerations, it should be remembered that each pituitary hormone can be controlled by several factors such as negative feedback by peripheral hormones, circadian rhythms in hormones, and stress-induced alterations in hormone secretion. Several of these factors may regulate levels of a single pituitary hormone but may operate through alterations in more than one hypothalamic neurotransmitter. Thus, methodological limitations and the complex nature of the neuroendocrine systems make conclusions about the physiological controlling mechanisms tentative at best.

Role of Hypothalamic Neurotransmitters in Gonadotropin Secretion

It has been known for several, decades that the secretions of the anterior pituitary gland are regulated by substances generated by the hypothalamus. The best evidence for this came from the demonstration of the existence of a factor in the hypothalamus that causes the release of the gonadotropin, luteinizing hormone (LH), from the anterior pituitary gland (McCann et al. 1960). This releasing factor actually brings about the release of both the gonadotropins LH and FSH (follicle stimulating hormone), so it is also referred to a gonadotropin releasing hormone (GnRH). It is now recognized that all of the effects of the hypothalamus on the release of both FSH and LH can be explained by variations

in dose, time course, and steroid hormone interactions at the pituitary level with a single releasing factor, GnRH. The mechanisms behind basal or tonic levels of secretion of gonadotropins, the generation of gonadotropin surges, or even the timing of the onset of puberty are not well understood.

There is considerable evidence in experimental animals that the hypothalamic neurons that release GnRH are regulated by biogenic amines. For example, dopamine and norepinephrine content in the hypothalamus change with different stages of the estrous cycle in the rat, and dopamine can stimulate GnRH release when incubated with hypothalamic fragments in vitro (Schneider and McCann 1969). Little is known, however, about the role of biogenic amines in LH or FSH control in primates. Primates and rodents differ in the development of the cyclic LH release mechanism, in that androgen levels early in life suppress this response in the rodent but not in the primate. In the rhesus monkey, both the tonic and episodic secretory mechanisms appear to be localized within the medial basal hypothalamus (Knobil 1974), while in rodents, neural pathways that arise elsewhere in the brain impinge upon the GnRH system. These differences may help explain the differing susceptibility of gonadotropins in primates and rodents to pharmacological manipulation. In general, it can be said that the neuropharmacological studies in primates indicate that norepinephrine, and perhaps dopamine, may be involved in GnRH release. Adrenergic and dopaminergic agonists probably enhance the release of GnRH, and adrenergic and dopaminergic antagonists probably inhibit the release of GnRH. More studies need to be done in primates and humans before the exact role of these transmitters can be defined.

Role of Hypothalamic Neurotransmitters in Prolactin Secretion

Of the hypothalamic mechanisms for the control of pituitary hormones, the mechanisms for the control of prolactin have been most extensively studied. Prolactin secretion is probably controlled by two systems: a prolactin inhibitory factor (PIF) and one or more prolactin releasing factors. Current evidence indicates that dopamine is the inhibitory substance of hypothalamic origin that controls prolactin secretion (Bishop et al. 1972). Drugs that are classified as dopamine anatagonists (pimozide and haloperidol) cause the release of prolactin (MacLeod and Lehmeyer 1974). Infusion of dopamine (Meites et al. 1972) or administration of a drug that increases production of dopamine (such as L-dopa) inhibits prolactin release (Noel et al. 1973). Apomorphine, a drug that interacts with dopamine receptors, mimics the inhibitory effect of dopamine on prolactin release (Anden et al. 1967). Thus it is thought that the dopamine that is released in the hypothalamus is transported to the pituitary and inhibits the release of prolactin.

The existence of a prolactin releasing factor or factors is less well established. Serotonin (5-HT), in contrast to dopamine, has been shown to produce an increase in prolactin release (Meites et

al. 1972); whereas, methylsergide and cyproheptadine (serotonin receptor blockers) decrease prolactin release. In addition, morphine and the endogenous opiate peptides (EOP's) stimulate the release of prolactin (DuPont et al. 1979). This stimulatory effect of morphine and the EOP's is thought to be mediated by interaction with specific receptors, since the narcotic receptor blocking drug, naloxone, blocks the effect of narcotics and EOP's on prolactin release. At least part of the stimulatory hypothalamic influence on prolactin appears to be mediated by thyrotropin releasing hormone (TRH), the hypothalamic peptide that stimulates thyrotropin stimulating hormone (TSH) secretion, and thereby stimulates thyroid gland function. TRH has been shown to stimulate prolactin secretion both in vivo (Jacobs et al. 1973) and in vitro (Labrie et al. 1979). The question remains as to which of these prolactin stimulatory factors is the physiological trigger for prolactin release. Rapidly accumulating evidence suggests that dopamine, rather than these other substances, may be the primary or perhaps the only hypothalamic substance controlling prolactin release. These studies indicate doubt in the existence of a prolactin releasing factor. The inhibitory effects of serotonin antagonists, for example, can be shown in pituitary cell culture studies to be due to their partial dopamine agonist activity (Labrie et al. 1979). The stimulatory effect of morphine and the EOP's on prolactin release has also been shown to involve interference with hypothalamic dopamine activity. Thus, while serotonin and EOP's may be involved in stimulation of prolactin release, it now appears that the control of prolactin levels is directly mediated by increasing dopamine activity (resulting in prolactin inhibition) or decreasing dopamine activity (resulting in prolactin secretion).

Role of Hypothalamic Neurotransmitters in Thyrotropin Secretion

Only a few experimental studies have been reported that have investigated the role of hypothalamic neurotransmitters in the control of the secretion of TRH thyrotropin releasing hormone. Both dopamine and norepinephrine have been shown to release TRH from mouse hypothalamic tissue in vitro, but dopamine was ineffective when conversion of dopamine to norepinephrine was blocked (Grimm and Reichlin 1973). Serotonin inhibited the TRH release, and acetylcholine analogues had no effect on TRH release. The suggestion that serotonin pathways inhibit TRH release is further supported by the observation that injection of 5-hydroxytryptophan (a precursor that increases hypothalamic content of serotonin) inhibits peripheral TSH levels. The exact role of hypothalamic transmitters in the control of thyroid function in response to other factors, including cold and stress, has not been fully defined; it now appears that adrenergic pathways are involved in enhancement of the release of TRH, and serotonergic pathways may be responsible for the inhibitory effects on TRH release. TRH apparently has a direct effect on pituitary TSH release, since these transmitters do not alter the pituitary response to TRH.

Role of Hypothalamic Neurotransmitters in Corticotropin Secretion

The hypothalamic region that controls ACTH release apparently involves a large part of the basal hypothalamus. In addition to the excitatory control, there may be an inhibitory control that is thought to be in the posterior hypothalamus, close to the mammillary bodies. Thus, adrenal response to negative feedback control, to diurnal rhythm and to stress is thought to be mediated by changes in ACTH release from the pituitary. The analysis of the role of hypothalamic neurotransmitters in the CRF (corticotropin releasing factor) control of ACTH has proven to be the most difficult of all of the hypothalamic-pituitary systems. This is because both excitatory and inhibitory pathways appear to exert an influence on ACTH, and several transmitters, including catecholamines, serotonin, and acetyl choline, appear to have important effects on ACTH (viz. Hiroshige and Abe 1973). In man, evidence for the role of catecholamines in ACTH regulation suggests a dual role, with alpha-adrenergic agonists enhancing ACTH release and beta-adrenergic agonists inhibiting ACTH release. However, current evidence for this role of catecholamines in ACTH is not yet conclusive. Serotonin has been implicated in the inhibitory control of ACTH release. Serotonin antagonists interfere with stimulated ACTH release but apparently do not alter basal secretion of ACTH. Serotonin may be responsible for the diurnal variation in adrenal hormone. A cholinergic component has also been suggested in ACTH regulation. Studies in rodents indicate that acetylcholine may be involved in the activation of the adrenal system after stressful stimuli.

It has been very difficult to describe the role of hypothalamic neurotransmitters in the CRF-ACTH control of adrenal functions. The studies that have been described here have examined the effects of neurotransmitters on ACTH rather than CRF. Although CRF was the first releasing factor recognized, its identity is still unknown. In addition, the many physiological and pathological factors that impinge on the hypothalamic-pituitary regulation of adrenal function make the studies that are necessary to understand the process difficult indeed.

Effect of Marijuana or THC on Neurotransmitters

In several studies, the site of action of the effects of marijuana and THC on hypothalamic-pituitary function has been shown to be at the level of the hypothalamus. In general, it has been shown that the pituitary responds to exogenous releasing factors in the presence of the drugs. This inhibitory effect on hypothalamic-pituitary function is not unique to cannabis derivatives but is a property shared by several CNS depressant drugs including narcotics, some tranquilizers and some sedatives. Certain of the cannabis effects, however, are unique, especially the inhibition of prolactin secretion. Virtually every other drug that inhibits LH and FSH levels (including narcotics and sex steroids), stimulates prolactin release. THC inhibits LH, FSH, and prolactin. The hypothalamic-pituitary activity of the cannabis

derivatives also appears to be somewhat associated with the psychoactivity or neuroactivity of the compounds. Among the other CNS depressant drugs, this may not be true. It appears certain that the hypothalamic-pituitary effects of marijuana are somehow related to the effects of the drug on hypothalamic neurotransmitters.

Some neuropharmacological studies have examined the role of hypothalamic neurotransmitters in the neuroendocrine effects of THC. Marks (1973) studied the involvement of a hypothalamic cholinergic mechanism by using oxotremorine, a cholinergic muscarinic agonist, in combination with THC. He concluded that the effect of THC on LH levels was not related to its effect on the cholinergic system. Studies by Kramer and Ben-David (1974) indicate that both serotonin and dopamine disruption may be involved in the inhibitory effect of THC on prolactin. However, experiments that study the combined effects of THC with agonists or antagonists of the various neurotransmitters are particularly difficult to interpret. While some studies have examined the effects of marijuana or THC on transmitter function in various areas of the brain, very few have specifically addressed the effects of the drugs on hypothalamic neurotransmitters (Constantinidis and Miras 1974).

Because of the important role of biogenic amines, especially dopamine, and norepinephrine, in the regulation of hypothalamic releasing factors, it has been postulated that the effects of THC on these transmitters may be important. Several studies have shown that THC can alter levels of biogenic amines in the CNS (Fuxe and Jansson 1972; Truitt and Anderson 1972; and Welch et al. 1971). This effect on these transmitters appears to be mediated by an effect of THC on the reuptake of dopamine, norepinephrine , and serotonin into nerve endings in the brain (Howes and Osgood 1974; Hershkowitz et al. 1977). This effect of THC apparently results in an increase in serotonin levels in certain areas of the brain (Sofia et al. 1971) and a decreased content of catecholamines in certain areas of the brain (Holtzman et al. 1969). It is not clear, however, whether THC acts directly on transmitter levels or even on transmitter uptake or whether its effects are mediated by secondary effects on neuronal activity. THC has also been shown to alter cholinergic activity in certain brain areas. Studies on the turnover rate of acetylcholine in the rat hippocampus indicate that THC (but not the nonpsychoactive cannabidiol) decreases cholinergic activity (Revuelta et al. 1979). This effect of THC appears to be secondary to an increase in the activity of GABA (gamma-aminobutyric acid), another important central transmitter. The effect of THC on central cholinergic pathways is probably important in the psychoactive effects of THC. Its role in the disruption of hypothalamic-pituitary function is not known.

The effects of THC on certain metabolic processes and subcellular structures in the rat brain have also been studied (Jakubovic and

McGeer 1972). These studies showed that THC, but not the nonpsychoactive cannabinoids, decrease protein and nucleic acid synthesis in the infant rat brain. Studies of the subcellular distribution of THC indicate that these metabolic effects may be related to the preferential binding of THC to mitochondrial and microsomal fractions in brain cells.

Certain cell membrane processes have been reported to respond specifically to psychoactive cannabinoids (Greenberg et al. 1978). The plasma membrane-bound enzyme, LPC-acyltransferase, which is thought to be responsible for regulating the proportion of saturated fatty acids in the plasma membrane, is inhibited by the psychoactive cannabinoids only. The inhibition of this enzyme in synaptosomes from mouse brain may be responsible for the effects of marijuana on neurotransmitter uptake mechanisms.

Morphological changes in the ultrastructure of the synaptic cleft region in rhesus monkey brain has also been reported in response to marijuana exposure or THC treatment (Harper et al. 1977). These changes consisted of 1) appearance of opaque granular material in the synaptic cleft region;. 2) widening of the synaptic cleft; and 3) synaptic vesicle clumping. These ultrastructural changes were consistent with lasting EEG changes produced in the monkey by marijuana or THC. They were observed in various areas of the brain, with the most profound effects in the septal region, the hippocampus, and the amygdala (Heath et al. 1979). The impact of morphological changes on the neural effects of THC or marijuana remains to be shown.

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The Effect of Marijuana on Reproduction and Development

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In the years since the effects of marijuana upon reproduction were first reported much research effort has been directed initially to document the changes that occur, and, more recently, to attempt to explain the physiological and pharmacological reasons for these changes. It is now generally agreed that marijuana exerts significant effects on all phases of reproduction and development, on members of both sexes and in all species studied So far. The list of species studied includes rats (Collu et al. 1975, Collu 1976), mice (Dixit et al. 1974), rhesus monkeys (Smith et al. 1976), dogs (Dixit et al. 1977), pigeons (Vyas and Singh 1976), and humans (Cohen 1976, Kolodny et al. 1976). The effects of marijuana are observed in all phases of reproductive physiology, including decreases in the weight and functions of organs associated with reproduction and decreases in hormones that control development of the fetus. These changes may be caused indirectly by the alteration of circulating hormones in blood, directly by an effect of the physiologically active ingredients in marijuana on the reproductive structures, or by a combination of both direct and indirect action.

THE EFFECT OF MARIJUANA ON THE MALE

Bat and mouse testes respond to delta-9-tetrahydrocannabinol (Δ-9-THC) or Crude Marijuana Extract (CME) with a slight decrease in organ weight. This organ is sensitive to THC over many different dosages, given in several different vehicles via several different routes (Bloch et al. 1978, have summarized these). Most of these studies report the effect on testes of young rats and mice, while a few report cannabinoid effects on adult testes weight. Fujimoto et al. (1978) showed that adult rats treated with CME (15 and 75 mg/kg, orally) for 77 days at very high dosages had a significant reduction in ventral prostate, seminal vesicle, and epididymal weight, as well as a decrease in the plasma testosterone levels. The semen of these rats contained smaller numbers of sperm in the epididymis as well as a decreased fructose content (an energy source for sperm) indicating that there were qualitative changes in the semen. Treatment of rats for only 5 days produced none of

these changes. Thirty days after cessation of CME treatment, there appeared to be a return to control levels of organ weights and testicular function.

There are other reports indicating that the quality of sperm is affected by cannabinoids; for the semen of mice treated with THC (5 and 10 mg/kg, i.p.; 5 days) or cannabidiol (CBD) (10 and 25 mg/kg, i.p.; 5 days) had an increase in the number of abnormal sperm (oligospermia) (Zimmerman et al. 1979a), as well as an increase in the number of ring and chain translocations (Zimmerman et al. 1979b). Rats similarly treated with marijuana smoke (Δ-9-THC content .4 to 3 mg/kg) for 75 days had a higher number of abnormal sperm in their semen, including some which showed a separation of the sperm head and the sperm tail, as well as a decrease in epididymal sperm count (Huang et al. 1979).

Recent research has been concerned with clarifying the biochemical and hormonal mechanisms responsible for the morphological changes described above. Attention has also been focused on whether Δ-9-THC has its effect directly on testicular cells themselves or whether the effects observed are due to an indirect action.

It is possible that much of the decreases in male reproductive function documented here could be produced by the action of cannabinoids on the hypothalamus to inhibit release of Luteinizing Hormone Releasing Factor (LHRF) or on the pituitary to inhibit release of the gonadotropins Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH). In fact, there is evidence that Δ-9-THC (5 mg, i.m., twice weekly for 6 weeks) does depress LH in male rats, which presumably is responsible for the lowered testosterone levels observed in the plasma (Symons et al. 1976). When the animals treated with Δ-9-THC were given exogenous LHRF, the Δ-9-THC-injected animals secreted less LH than vehicle-injected control animals. This fact indicated that the pituitary was able to respond to LHRF, but in a sluggish manner (Symons et al. 1976). Also, when ovariectomized rhesus monkeys, whose LH and FSH were suppressed by Δ-9-THC (5 mg/kg, i.m., acute) were provided with LHRF exogenously, they responded with a prompt release of gonadotropins. This evidence suggested that THC had its action primarily on central neural mechanisms to inhibit LHRF release (Smith et al. 1976). Several other studies point to cannabinoid suppression of LHRF release as a major cause of both the observed decreased LH and gonadal hormone secretion. These studies are discussed in this chapter under The Effects of Marijuana on the Female Reproductive System.

Other arguments for an indirect action of THC on testicular function are that rats injected with Δ-9-THC (2 mg/kg, i.p.; 9 days) or cannabidiol (CBD) (2 mg/kg, i.p.; 9 days) had a decrease in both microsomal cytochrome P-450 from Leydig cells of the testes, an enzyme which is involved in biosynthesis of testosterone, and γ-glutamyl transpeptidase, a marker protein for Sertoli cells in the seminiferous tubules of the testes (Schwarz et al. 1977). When exogenous LH, FSH, or LH and FSH together were supplied to THC-treated animals, the testes were able to be

restored to control levels of cytochrome P-450 and γ-glutamyl transpeptidase, indicating that the testes were able to respond in a normal way when gonadotropins were present (Harclerode et al. 1979).

Among the evidence presented for a direct effect of cannabinoids on reproductive tissues is the observation that Δ-9-THC, when incubated with testicular cells grown in cell culture or in cultures of testicular slices, was able to depress certain functions seen in normal intact testicular cells. Protein synthesis is one function that has been shown to be depressed by Δ-9-THC and one which could explain decreased organ size as well as the decrease in spermatogenesis already reported (Jakubovic and McGeer 1977). Also, decapsulated mouse testes grown in culture were less able to release testosterone to the incubation medium with added Δ-9-THC or CBN (12.5 to 25 μg/ml) than were control testes (Dalterio et al. 1977).

The Leydig cells of the testes, which are responsible for testosterone biosynthesis, are less able to synthesize testosterone when treated with Δ-9-THC in culture (Dalterio et al. 1978). Apparently this occurs due to the effect of Δ-9-THC (3.2 to 32 μM) to either decrease the release of precursor cholesterol from ester storage, or inhibit the conversion of cholesterol to pregnenalone (Burstein et al. 1978a, Burstein et al. 1979). Burstein and Hunter (1978) have pointed out that cannabinoids could have direct effects on cell membranes, thereby altering the rate at which materials enter or leave the cell. Also, Purohit et al. (1979) showed Δ-9-THC (10 mg/kg, s.c.) and CBN (10 mg/kg, s.c.) blocked the stimulatory effect of testosterone and dihydroxytestosterone on ventral prostate and seminal vesicle weights in rats.

It was reported that both Δ-9-THC (2 mg/kg/day, i.p.) and CBD (2 mg/kg/day, i.p.) cause depression of an esterase isozyme located in the Leydig cells of the rat testis after 10 days of treatment (Goldstein et al. 1977). Hubbard et al. (1979) showed that cultured rat Leydig cells with Δ-9-THC (16 μM) added had reduced cholesterol esterase activity. This enzyme hydrolyzes the cholesteryl esters of oleic, arachidonic, and palmitic acids.

Jakubovic and his coworkers have shown that low levels of Δ-9-THC (.05 μg/ml) may directly inhibit protein synthesis and testosterone production of Leydig cells grown in cultures stimulated by Human Chorionic-Gonadotropin (HCG) or cyclic andenosine monophosphate (AMP). Since the effect was not observed in nonhormonally stimulated cells, it is possible that the cannabinoids affect the way in which Leydig cells respond to hormones such as LH (Jakubovic et al. 1979a, 1979b; Dalterio et al. 1978).

In view of the relative insolubility of Δ-9-THC in water, the question arises as to how much Δ-9-THC is actually present in the incubation medium of these in vitro systems. Moreover, the effects observed in vitro may not be observed in vivo, since no

attempt has been made to show that the levels of cannabinoid in the testicular blood supply reach the level approaching that of the culture media. There is also the question of whether the intact testes accumulate Δ-9-THC to the concentration used in these in vitro experimental systems.

The liver appears to be affected directly by cannabinoids, for rat liver microsomes were reported by Chan and Tse (1978) to exhibit a competitive inhibition at the 5-α-reduction step, which is involved in the metabolism of testosterone when incubated with either Δ-9-THC (25 μM or Δ-8-THC (50 μM). These liver microsomes contain enzymes which are responsible for the metabolism and inactivation of many hormones and drugs including the cannabinoids in vivo. Moreover, the livers from rats treated chronically (10 days) with Δ-9-THC (2 or 10 mg/kg each, i.p.) had microsomes with increased steroid hydroxylation activity (List et al. 1977). The enzymatic changes in these liver microsomes could, in effect, decrease serum testosterone levels by increasing metabolism and excretion of testosterone from the blood. Thus, Δ-9-THC could depress the already lowered testosterone levels found in the blood due to decreased testosterone synthesis.

Prolactin is another hormone affected by cannabinoid treatment which is related to reproductive activity. Adult rats treated with Δ-9-THC (2-10 mg/kg, i.p.) had a decrease in serum prolactin levels 30 minutes after a single injection, which returned to normal about four hours later (Kramer and Ben-David 1974, Bromley and Zimmerman 1976). In contrast, younger rats (36-day-old) responded with increased serum prolactin levels 24 hours after an injection of Δ-9-THC (16 mg/kg, i.p.) (Daley et al. 1974), and Collu (1976) observed increased prolactin levels in the pituitary of 23-day-old rats when Δ-9-THC was administered intraventricularly. Hughes et al. (1979) report that Δ-9-THC (1 mg/kg, i.v.) did not influence serum prolactin levels in ovariectomized rats with established ectopic-pituitary autografts. This suggests Δ9-THC indirectly affects prolactin secretion through other central nervous structures rather than having a direct action on the pituitary.

C.G. Smith et al. (1979a) have shown that the administration of a single dose (2.5 mg/kg, i.p.) of Δ-9-THC suppressed serum prolactin levels in both ovariectomized and adult male rhesus monkeys. The maximal effect (84 percent in females and 74 percent in males) was obtained between 30 and 90 minutes after drug administration. The inhibitory action of THC on serum prolactin levels was reversed by TRH administration, which suggests an hypothalamic site of action for THC. Interestingly, the administration of daily doses of THC in female rhesus monkeys during the luteal phase of the normal menstrual cycle produced an absence of ovulation which was associated with elevated prolactin levels during the subsequent cycle period.

Human Males

In humans, marijuana is consumed by smoking. This route of administration allows investigators to study the effect of the chemical components found in marijuana after absorption of the smoke by the lungs, its normal route of absorption, and after normal biotransformation in the human body of all of the absorbed constituents in marijuana, In terms of endocrine effects, the human male appears to respond to marijuana in much the same way rats and mice do. Acute marijuana smoking decreased both LH and testosterone levels in the blood, an effect which lasted for up to three hours, whereas no change was detected in FSH levels (Cohen 1976, Kolodny et al. 1975, Kolodny et al. 1976, Jones 1977). Some studies that examined the chronic effects of marijuana in the male found conflicting results. However, this area of research is controversial since an earlier report had shown that marijuana smoking decreased blood levels of testosterone but had no effect on LH, FSH, or prolactin (Kolodny et al. 1974), although some workers were unable to find any change in plasma testosterone concentration (Coggins et al, 1976, Mendelson et al. 1974, Mendelson 1976, Nahas 1976). The differences between the findings of these studies may have been caused by differences in experimental design of the different investigators. For instance, after smoking marijuana, hormone levels in the plasma appear to return to normal fairly rapidly. Studies which sampled hormones in the blood after this time interval may have been missing the effective period. Also, the dosage of marijuana used and the length of administration appear to have important effects on hormonal levels that control testicular function.

Hembree et al. (1979) examined the semen of 16 healthy, chronic marijuana smokers under controlled research ward settings (8-20 cigarettes/day, for 5 to 6 weeks, 2 percent Δ-9-THC). Semen from these men had decreased sperm count and concentration of sperm as well as a decrease in sperm motility. Moreover, there was an increase in the number of sperm which had abnormal morphology (oligospermia) as well as an increase in the number of sperm which had aberrations of the nucleus. The aberrations seen in sperm are viewed as being an effect of marijuana on spermatogenesis although some effects could be due to changes in the sperm as they pass through the epididymus or due to failure of complete sperm maturation. It is interesting to note, however, that once marijuana treatment was stopped there was a gradual return to apparent normal gonadal activity.

Issidorides (1979), using the same population of 47 chronic Greek hashish users and 40 matched controls from a previous study (Stefanis and Issidorides 1976), reported on sperm aberrations in ejaculated semen. The most prevalent abnormality was that a spongy, fuzzy, disorganized layer of acrosomal substance covered what appeared to be normal sperm heads. Also, some sperm had incomplete condensation of chromatin in sperm heads of normal size, but with no acrosomes. Some sperm exhibited morphology of arrested maturation which correlated well with their low protamine content.

Summary

In summary, marijuana affects male reproductive function in all species studied. This is observed as a decrease in organ weight and organ function after both short- and long-term treatment. The mechanism by which this occurs seems to be due to the effect of the active ingredients in marijuana to depress release of LHRF with the subsequent depression of the gonadotropins. This lack of gonadotropin stimulation of Leydig cells is probably responsible for the observed decreased testosterone production. Many of the changes seen in decreased weight of the testes and associated reproductive organs are probably caused by the decreased testosterone production. Apparently when gonadotropins are administered along with THC, the testis is able to overcome the defects observed with THC treatment, indicating that the testis is able to respond when gonadotropins are present.

Cannabinoids appear to alter the quality of the semen as observed in decreases in several important constituents of semen as well as the appearance of decreased numbers of sperm and sperm with abnormal morphology, an observation seen in both lower animals and in man. The effects of marijuana on male reproductive function appear to be reversible and recovery occurs after cessation of treatment.

THE EFFECT OF MARIJUANA ON THE FEMALE REPRODUCTIVE SYSTEM

The effects of cannabinoids on the reproductive system of the female have been examined less intensively than in males. Although most research reports deal largely with the effects on rats and mice, there is some recent work which reports effects of cannabinoids on rhesus monkeys and humans.

There is a similarity in the biological action of Δ-9-THC and estrogens in both males and females, for a number of common physiological processes are affected by both substances (Solomon et al., 1976; Rawitch et al. 1977). It has been shown that both alter prolactin secretion, depress the weights of testes, seminal vesicles, and prostate, depress release of LH from the pituitary, inhibit spermatogenesis and stimulate mammary gland development. Indeed, there are reports of breast development (gynecomastia) in male heavy marijuana users (Harmon and Aliapoulios 1972). Moreover, mammary tissue of rats treated with Δ-9-THC (1 mg/kg 5 days/week, s.c.) was stimulated, to develop (Harmon and Aliapoulios 1974).

The organs that comprise the reproductive tract in nonpregnant females are affected by cannabinoids in several different ways. Uteri of mice treated with cannabis extract (1 mg/day for 64 days) showed decrease in weight, glycogen content, and RNA content (Dixit et al. 1975; Chakravarty et al. 1975a). Since these effects are opposite from what estrogen causes in the uterus, Δ-9-THC may be acting to cause depressed estrogen secretion. Although one report showed that Δ-9-THC (50 mg/kg for 28-180 days, orally)

did not cause a change in the weight or the morphology of the ovaries or uteri of intact adult rats (Rosenkrantz et al. 1975), others report a weak estrogenic effect in ovariectomized adult females (2.5 mg/kg Δ-9-THC). Solomon et al. (1976) described uterine weight gain and cytological changes upon Δ-9-THC administration of about two-thirds of the effect caused by injecting 2 μg estradiol. They later showed the uterine weight gain was associated with hypertrophy and hyperplasia of the uterus and increased stratification of vaginal epithelium (Solomon et al. 1977), and believe the "uterotropic" effect of Δ-9-THC to be a direct estrogenic action on uterine tissue.

Fujimoto et al. (1979) were unable to duplicate the uterotropic effect reported by Solomon et al. (1976, 1977) in Fisher rats using oral doses of either Δ-9-THC (1-5-25 mg/kg) or CME (3-15-75 mg/kg) administered for 72 days. In fact, the higher doses caused a decrease in both uterine and ovarian weight as well as producing an indication that the rats had a prolonged diestrus. Thirty days after cessation of treatment both uteri and ovaries regained about 90 percent of the control weight. C.G. Smith et al. (1979b) also found no direct estrogenic or antiestrogenic effect in rhesus monkeys that were administered Δ-9-THC (2.5 mg/kg, i.m.) for short terms. There was no stimulatory effect on the histology of the uterus or vagina; they found that THC did not bind to rat and monkey uterus cytosols, nor did THC, CBD, or marijuana compete with estrogen for estrogen receptors in these tissues.

If cannabinoids are estrogenic they would be expected to compete with estradiol for binding sites in the cytosol of uterus and other estrogen target tissues. The competition, if it does exist, is very weak and is of questionable specificity (Rawitch et al. 1977). Shoemaker and Harmon (1977) reported a high affinity binding of Δ-9-THC and 11-hydroxy-Δ-9-THC on uterine and mammary gland cytosol, as well as competitive binding with estradiol binding sites. In contrast, Okey and Bondy (1978) found no competition of Δ-9-THC for binding sites in mouse mammary or uterine cytosols. Also, R.G Smith et al. (1979), using cytosol prepared from uteri of rhesus monkeys and humans, showed that Δ-9-THC did not compete with estradiol for estradiol receptors. Instead, radioactive Δ-9-THC bound to macromolecules in the uterine cytosol in the rhesus monkey but was not displaced by estradiol, progesterone, diethylstilbesterol, THC, cortisol, or 5-α-dihydroxytestosterone. They concluded that inhibition by Δ-9-THC of gonadotropin and steroid levels in primates was not caused by THC's interaction with intracellular steroid hormone receptors. Further, Stanely et al, (1979) found that human term placenta lacked both progesterone and estrogen receptors but did contain an androgen receptor in the cytosol. THC was unable to displace androgens from this binding substance.

This evidence and a number of other arguments have been expressed against considering Δ-9-THC as an estrogen. These are (1) lack of a dosage response relationship, (2) the very large amount of Δ-9-THC that was needed to cause the estrogenic response, and (3) in

some of the processes that are stimulated by estradiol, Δ-9-THC may be antagonistic.

Cannabinoids also affect the ovary, for studies have shown an atrophy in ovarian function, including a decrease in ovarian weight and changes in rat vaginal smears which indicated a complete halt of the ovarian cycle (Dixit et al. 1975). Other changes included inhibition of luteinization and corpus luteum degeneration along with a decrease in uterine RNA, protein and glycogen content. The authors suggest that cannabis may be antiestrogenic. In contrast, two Macaque monkeys which were maintained on Δ-9-THC (2.4 mg/kg/day, in diet) for up to a year still exhibited a normal menstrual cycle (Sassenrath and Chapman 1975).

At least some of the changes that occur in the female reproductive tract caused by cannabinoids can partially be explained by their depressive action on LH secretion with the subsequent reduction of estrogen secretion by the ovary. Marks (1972) showed that Δ-9-THC (1-3-10 mg/kg, i.v.) produced a decrease in LH secretion in ovariectomized rats. Δ-9-THC (2 mg/rat, i.p.) was able to prevent the surge of LH into the blood from the pituitary of ovulating rats that occurs just prior to ovulation (Nir et al. 1973). This inhibition may be a direct effect on the ovary, since LH given concurrently with a blocking dose of sodium pentobarbital after Δ-9-THC administration was not as effective in causing ovulation. Most workers demonstrate a depression with Δ-9-THC of serum LH levels in both ovariectomized and normally cycling rats, and there also are reports that serum prolactin levels are decreased in both sexes (Chakravarty et al. 1975b). Kashi et al. (1977) showed that Δ-9-THC depressed the proestrous rise in LH, FSH, and prolactin that occurs in the rat and delayed ovulation 24 hours. LHRF, when administered, was able to reverse these effects. Similar effects were obtained by Ayalon et al. (1977) and Tyrey (1978a,b). The rabbit also responds in this way, for Asch et al. (1979) showed that Δ-9-THC (2.5-5.0 mg/kg, i.m.) was able to block the ovulatory reflex and halt ovulation, but that LHRF was able to produce ovulation in Δ-9-THC-treated rabbits. The rhesus monkey responded to a single injection of D-9-THC (5.0 to .625 mg/kg, i.m.) with a dramatic decrease in plasma LH and FSH that lasted until about 12 hours after injection (Besch et al. 1977), and return of the hormones in the plasma to normal base levels after this time was fairly rapid. The rhesus monkey responds to LHRF similarly to rabbits and rats; a single dose of Δ-9-THC (5.0 to .625 mg/kg, i.m.) decreased serum levels of LH and FSH in ovariectomized rhesus monkey, but LHRF was able to produce release of LH and FSH in the D-9-THC treated animals (Smith, C. G., et al. 1979b). It is interesting to note that greater dosages of THC produced longer hormonal suppression, but the magnitude of the effect was not related to the quantity of Δ-9-THC administered.

C. G. Smith et al. (1979a) also showed that rhesus monkeys which received Δ-9-THC each day of the normal menstrual cycle did not ovulate during subsequent cycles. An elevated prolactin level probably caused this lack of ovulation.

Human Females

Bauman et al. (in press) report that chronic smoking of marijuana (at least three times per week for the preceding 6 months) increased the number of menstrual cycles where no ovulation occurred or menstrual cycles marked by inadequate luteal phase in the human female. This alteration was also marked by lower prolactin and lower progesterone levels, but higher testosterone levels in the blood. This study raises some important questions about the effect of marijuana on the human menstrual cycle, since, if confirmed by future studies, marijuana might contribute to female infertility. Nursing and normal lactation may also be impaired by the lowered prolactin levels in the blood, The study itself, however, should be repeated in a research ward setting similar to that used for males by Hembree et al. (1979). Such a study could control for amount of marijuana consumed (and with a known Δ-9-THC content), variations in diet and environment, and differences in lifestyle between the two groups of females.

Summary

In summary, the major depressive effect of cannabinoids on the female reproductive tract (as well as in the male) would appear to be due to their inhibition of LHRF release with subsequent depression of LH release. It is probable that many of the changes in female reproductive physiology that are observed after cannabinoid treatment are due to lack of LH stimulation of estrogen production by the ovary. It is possible that some of the effects of cannabinoids may be due to direct action of the active ingredients in marijuana on the female reproductive structures. More work is needed to explore this possibility. Moreover, the responses observed may not be identical when Δ-9-THC is used and when other cannabinoid and noncannabinoid constituents found in marijuana smoke are used.

THE EFFECT OF MARIJUANA ON ADRENAL CORTICAL HORMONES

The adrenal cortex secretes honmnes that have important effects on the reproductive system. In rats and mice, acute treatment with cannabinoids generally produces a prompt rise in corticosteroid levels in plasma which is also accompanied by a decrease in the level of ascorbic acid found in the adrenal glands. A wide range of dosages (2-20 mg) of Δ-9-THC is effective in producing this rise (Bloch et al. 1978, summarize these), apparently by direct action on the hypothalamus and pituitary gland to increase adrenocorticotropic hormone (ACTH) (Mäier and Maitre 1975). In this way cannabinoids act like stressors and effectively block the negative feedback of elevated plasma corticosterone on the hypothalamus (Drew and Slagel 1973). Maier and Maitre (1975) have shown that hypophysectomy, which removes the source of ACTH production, also abolished the adrenocortical response to Δ-9-THC. Moreover, pentobarbital (Mitra et al. 1977) and dexamethasone (Kokka and Garcia 1974), two agents which are known to block ACTH secretion, also prevent the adrenocortical response to Δ-9-THC.

Since cannabinoids are thought to interact at the level of the brain and pituitary, several investigators have examined the uptake of radioactive Δ-9-THC by various brain structures. There was some slight uptake of the radioactive compound by the medulla, preoptic areas, hypothalamus, and pituitary; however, the amount was not greater than in other brain structures (Erdmann et al. 1976, Martin et al. 1976). Uptake of radioactive corticosterone by the hypothalamus and thalamus was reduced if rats were pretreated with Δ-9-THC at a high dose (9 mg/kg, i.p.) but smaller doses (3 mg/kg, i.p.) increased corticosterone uptake (Drew and Slagel 1973). These results are in apparent contradiction to a recent study by Johnson et al. (1978), who examined the effect of 11-hydroxy-Δ-9-THC (11-OH-Δ-9-THC), Δ-9-THC, and cannabinol (CBN) on mouse brain uptake of radioactive corticosterone. Higher doses of the cannabinoids (30 and 100 mg/kg) increased ^{3}H-corticosterone uptake by whole brain. Pretreatment with Δ-9-THC (3, 10, 100 mg/kg, s.c.) increased the affinity of the hippocampus for ^{3}H-corticosterone, but decreased its concentration in hypothalamus, midbrain, pons and medulla, The differences between the results of this study and those of Drew and Slagel (1973) are probably due to differences in experimental design and differences in species used.

Injection of Δ-9-THC directly into the ventricles of the rat brain led to anincrease in general activity of cells in the adrenal and pituitary, and also caused an increased corticosterone production (Collu 1976). Chronic treatment in rats and mice with Δ-9-THC led to increased adrenal weight, which appeared to be reversible (Dixit et al. 1974). The adrenal was still able to respond to Δ-9-THC with a plasma corticosterone rise even after two months of cannabinoid treatment (Barry et al. 1972). Also, Jacobs et al. (1979) showed that Δ-9-THC (5 mg/kg, i.p.) does not prevent the release of corticosterone in stressed (electric shock) rats. The adrenal cortical response to cannabinoids seems to be confined to rodents, for rabbits (Maier and Maitre 1975; Thompson et al. 1975), monkeys (Sassenrath and Chapman 1975; Thompson et al. 1975), and guinea pigs (Huy et al. 1975) apparently do not respond to cannabinoids with increased adrenal cortical activity.

In addition to the direct action of cannabinoids on adrenal cortical function through their effect on hypothalamus and thalamus, and subsequent pituitary ACTH production, cannabinoids can exert a direct suppressive effect on adrenocortical activity. When mouse adrenocortical cells were grown in tissue culture with added Δ-9-THC, CBN, or CBD (10^{-6} to 10^{-4} M each cannabinoid), the cells were unable to respond when ACTH was added to the culture medium (Carchman et al. 1976; Warner et al. 1977). This lack of responsiveness was selective and not due to a change in the viability of the cells. Moreover, the cannabinoids seemed to affect the formation of steroid hormones at a biochemical step somewhere between cyclic AMP and pregnenolone production (Warner) et al. 1977. Burstein et al. (1978a) showed that Δ-9-THC (3.2 and 16 μM) added to incubation medium containing homogenized rat adrenal inhibited cholesterol esterase activity similarly to its

action in Leydig cells. The finding of a direct action on adrenocortical cells is important since the adrenal cortex, especially the lipids and the mitochondria, may selectively retain Δ-9-THC (Bloch et al, 1978), thereby maintaining higher concentrations of cannabinoids in the adrenal cortex after the level in the plasma has decreased.

Humans

Several studies have examined the effect of cannabinoids on adrenal cortical activity and function in humans (Kolodny et al., 1974; Hollister et al. 1970). In contrast to the way in which the rat adrenal gland responds to Δ-9-THC, no changes were reported for humans. Cruickshank (1976) found no difference in excretion of major urinary metabolites of cortisol between marijuana smokers (1-24 cigarettes/day, Δ-9-THC content .07-10.3 percent) and controls. Perez-Reyes (1976) examined the way marijuana smoking affects the adrenal cortical response to a synthetic corticotropin in frequent marijuana users compared to nonusers. He concluded that frequent use of marijuana did not alter the capacity of the adrenal cortex to respond to synthetic corticotropin stimulation.

THE EFFECT OF MARIJUANA ON PROSTAGLANDINS

Some of the actions that cannabinoids exert on reproductive processes are possibly induced by changes in prostaglandin synthesis in the reproductive organs. Prostaglandins are substances which regulate functions of many organs throughout the body. In the female reproductive tract, they allow the ovaries to respond to gonadotropic hormones, are active during parturition, and produce normal contractility and motility of the uterus and oviducts. They are also important in the male, where they affect contractility and mobility of the vas deferens and epididymis. In both the male and female they are necessary for the proper tone of the circulatory system that is associated with all of these reproductive structures.

It was postulated by Howes and Osgood (1976) that cannabinoids may affect reproductive structures by altering the way in which prostaglandins are synthesized in these tissues and organs. Certainly LH secretion, the maturation of follicles in the ovary, reduced sperm counts and reduced uterine contractility are affected by changes in concentration of prostaglandins in these tissues, and cannabinoids are known to depress these same reproductive processes. It is possible, then, that cannabinoids may have their depressive effects on some reproductive functions by inhibiting prostaglandin synthesis and there is some experimental evidence to justify these claims. Burstein and Raz (1972) and Burstein et al. (1973) showed that several cannabinoids inhibited prostaglandin synthesis in microsomal preparations from the seminal vesicles of cows. Moreover, Burstein et al. (1975, 1976) showed that other constituents in marijuana (alkaloids, aromatic alkaloids and acids, turpenes) might be more potent in reducing prostaglandin synthesis than Δ-8- and Δ-9-THC, CBD, or CBN.

THE EFFECT OF MARIJUANA ON PREGNANCY

An early study showed that very high doses (1-4 g) of Δ-9-THC caused a prolonged gestation in rats even though the birth weights were normal (Borgen et al. 1971). Since then, other investigators have shown that rats treated daily with Δ-9-THC (25 to 200 mg/kg/day) throughout pregnancy did not have the same weight gain as normal pregnant rats (Pace et al. 1971; Banerjee et al. 1975). Nonpregnant rats showed a decreased rate of growth which was correlated with decreased food consumption (Bartova and Birmingham 1976; Rosenkrantz et al. 1975; Rosenkrantz and Braude 1976). It would appear that moderate and low doses of cannabinoids (5 mg/kg/day) were ineffective in changing either length of gestation, viability of the mother, or amount of weight that was gained during pregnancy (Wright et al. 1976; Pace et al. 1971).

Unlike rats, mice did not seem to be influenced by consumption of Δ-9-THC with respect to pregnancy and fertility (Legator et al. 1976; Mantilla-Plata et al 1975). Fertility, mating, and pregnancy in chimpanzees were not affected by Δ-9-THC (1 and 2.1 mg/kg/day) intake (Grilly et al. 1974).

It is important that the corpora lutea of pregnant mice concentrate radioactive Δ-9-THC, which indicates an affinity of this structure for Δ-9-THC either through binding to proteins in the corpus luteum or merely to the solubility of Δ-9-THC in the lipids of the corpus luteum (Freudenthal et al. 1972; Kennedy and Waddell 1972).

THE EFFECT OF MARIJUANA ON LACTATION

Milk production in pregnant and lactating animals treated with cannabinoids was inhibited. Δ-9-THC (1.2 gm/day, day 10-16 of pregnancy, s.c.) given to pregnant rats decreased the amount of milk produced by the mother after the pups are born. This depression was observed as a decrease in the amount of milk reaching the newborn pups, which resulted in increased neonatal mortality (Borgen et al. 1971; Pace et al. 1971). It is possible that Δ-9-THC suppressed the production of prolactin as well as having a direct effect on the mammary glands themselves to lower milk synthesis or to a combination of both lowered prolactin and the direct effect. Moreover, mammary tissue is effective in concentrating Δ-9-THC from the blood and, as such, mammary tissue may serve as a reservoir which may actually prolong transmission of Δ-9-THC to the young (Jakubovic et al. 1973). Raine et al. (1978) showed decreased prolactin and decreased mammary gland growth in mice treated from Day 13 of pregnancy with Δ-9-THC (25 mg/kg, s.c.). Lower doses (CME; .5 to 5 mg THC/kg content, p.o.; or 5 mg/kg, i.v. or i.p.) did not affect lactation (Wright et al. 1976; Maker et al. 1974). Radioactive Δ-9-THC administered to lactating squirrel monkeys appeared in the milk and in the suckling infants (Chao et al. 1976).

THE EFFECT OF MARIJUANA ON DEVELOPMENT

Radioactive Δ-9-THC was able to leave the maternal circulation and pass the placenta to accumulate inside the fetuses of pregnant rats and mice (Pace et al. 1971). Martin et al. (1977) found radioactive Δ-9-THC (.05 mg/kg) was concentrated in the brain of the dog fetus 20 minutes after injection into the mother. The distribution in the fetus was similar to the distribution found in the mother, although the uptake was only one-third that of the mother. Loss of Δ-9-THC from the fetus and placenta was slower than that found in the mother, which may tend to prolong fetal exposure to Δ-9-THC (Mantilla-Plata and Harbison 1976a,b). Moreover, because of its high lipid solubility, Δ-9-THC accumulates in the adipose tissues of the mother and the fetus (Harbison and Mantilla-Plata 1972). The net effect of this would allow concentration of Δ-9-THC from the circulation and then slower release of it over a prolonged period of time back to the circulation (Mantilla-Plata and Harbison 1976a).

The ultimate effect of the constituents in marijuana upon development and growth of the fetus seems to depend upon the stage of development at which the fetus is exposed to the chemicals. In general, if the fetus is exposed to teratogens during the early part of gestation at a time when the internal organs are undergoing development, there may be organ malformation or fetal toxicity. If exposure to drugs occurs during the latter stages of pregnancy after the organs have been formed, there may be growth retardation in the fetus. In mice, rats, and rabbits Δ-9-THC or CME at very high doses (30-50 mg/kg/day) producedanincrease in the number of fetal and embryonic mortalities if given in the first half of gestation. These mortalities were observed as an increased incidence of resorptions of the fetus, as well as a decrease in the number of pups born (Mantilla-Plata et al, 1973; Joneja, 1976, 1977; Fleischman et al. 1975; Banerjee et al, 1975). Harbison et al. (1977) found no fetal anomalies with pregnant mice treated with Δ-9-THC (50-200 mg/kg, i.p.); however, they found an increase in in utero deaths with decrease in body weight of the surviving fetuses. Fried (1976) showed increased resorptions of rat fetuses from mothers exposed to marijuana smoke (estimated 3.3 mg Δ9-THC) from Day 1 to Day 19 of gestation. Moreover, the pups that were born had smaller birth weights and were less active (Fried and Charlebois, in press). Rosenkrantz (1979) found that oral doses of Δ-9-THC (in mice, 5-50 mg/kg; in rats, 12.5-50 mg/kg) produced embryo toxicity if given after Day 6 of gestation. Cozens et al. (1979) found marijuana extract (1 mg/kg/day, orally) reduced body weight of maternal and fetal rabbits, with only minor changes in the fetus.

If cannabinoids were given later in pregnancy, they did not produce fetal toxicity (Fleischman et al, 1975; Joneja 1976; Haley et al. 1973; Wright et al. 1976). Some studies showed Δ-9-THC (150 mg/kg) decreased survival of mouse fetuses (Day 8-10 of gestation) (Mantilla-Plata et al. 1975; Mantilla-Plata and Harbison 1976a).

Sassenrath et al. (1979) reported that a group of female rhesus monkeys which had received Δ-9-THC (2.4 mg/kg daily, orally) over a five-year period had no decrease in the number of conceptions, but there was an increase in reproductive loss at all stages of development and a reduced birth weight of male infants.

The growth of the fetus was similarly affected by large amounts of CME or Δ-9-THC in mice, rats, rabbits, and hamsters. The same doses that caused increased resorptions resulted in retardation of growth and reduced survival of the fetus (Harbison et al. 1977; Joneja 1977; Mantilla-Plata and Harbison 1976a; Banerjee et al. 1975).

Matsuyama and Jarvik (1977) reviewed the early research that reported a teratogenic effect of cannabinoids. Much of the conflict between these reports was ascribed to several variables, including differences in the species or strain used, the route and time of administration of the cannabinoids, as well as the dosage of cannabinoidused. Bloch et al. (1978) evaluated these early conflicting reports and found evidence of a clear teratogenic response in mice (Mantilla-Plata et al. 1973, 1975; Mantilla-Plata and Harbison 1976a and b; Harbison et al. 1977; Joneja 1976; and Kostellow et al. 1978). The most frequently described developmental lesion was cleft palate and exencephaly. In all of these studies, doses of several hundred mg/kg of body weight were needed to produce congenital defects. Also, agents which affected Δ-9-THC metabolism when given simultaneously with it enhanced activity of Δ-9-THC to interfere with palate closure. Harbison et al. (1977) showed that large doses of Δ-9-THC (50 or 200 mg/kg, i.p.) given to mice led to cleft palate formation if given in combination with certain other drugs such as phenobarbital.

Although an early study by Persaud and Ellington (1968) showed malformation in rat fetuses whose mothers were treated with cannabis resin (4.2 mg/kg/day, i.p.) given between Day 1 and Day 6 of gestation, several other studies were unable to demonstrate a teratogenic action of CME or Δ-9-THC (Banerjee et al. 1975; Uyeno 1975; Wright et al. 1976). For example, Wright et al. (1976) found no evidence of teratogenic activity when pregnant rats were treated orally with Δ-9-THC or CME containing Δ-9-THC equivalent doses of 5-50 mg/kg on gestation Days 6-15. Nor were there any changes over control animals in average number of pups delivered, pup survival, nor on lactation.

Other investigators have shown congenital defects on dental development in rats (Δ-9-THC, 3.3-20 mg/kg/day), including incisor eruption (Fried 1976), and mandibular and maxillary asymmetry (Siegel et al., 1977). Large doses of Δ-9-THC (125-500 mg/kg, i.g.) given to pregnant hamsters produced only minor defects in the fetus (Joneja 1977).

Only two reports exist which examined teratogenic effects on primates. Of two fetuses born to Macaques treated with Δ-9-THC (2.4 mg/kg, orally) for a year; one was hyperactive but otherwise normal, and the other died shortly after birth and was hydrocephalic

(Sassenrath and Chapman 1975). Chimpanzees who were exposed to marijuana smoke prior to mating had eight normal offspring (Grilly et al. 1974).

In view of the relatively large amount of cannabinoids that are needed to produce developmental anomalies in lower animals, it is doubtful that the cannabinoids by themselves are teratogenic. It is possible, however, that they may facilitate the teratogenicity of known teratogens by lowering the threshold at which they have their effect.

THE EFFECT OF MARIJUANA ON REPRODUCTIVE BEHAVIOR

There are not many reports in the research literature which examine the effect of marijuana and its constituents on reproductive behavior. Reproductive behavior is fairly complex and comprises many different components. Most of the reports are concerned with mating and have not examined very intensively sexual behaviors other than mating. Acute studies of male rats treated with Δ-9-THC (8.3 and 16.6 mg/kg, acute) report an increase in the length of times until the first mount, ejaculation, and longer post-ejaculation intervals, as well as a significant decrease in the number of males achieving, intromission (Corcoran et al. 1974). Mice also showed a decreased number of mounts which were of shorter duration, as well as a depression of the investigative behavior exhibited by the male prior to sexual activity (Cutler et al. 1975a,b). Chronic cannabinoid (2 percent resin in diet) administration in rats caused significantly lower reproductive activity than controls and, also, no differences were observed in mating behavior of either males or females (Miras 1965).

These kinds of studies have been criticized by Bloch et al. (1978) for lack of adequate experimental controls, since no attempt was made to evaluate the depressant effects of marijuana on general motor activity and feeding behavior, and low doses of Δ-9-THC might possibly be behavioral stimulants. In some cases the quantification used to analyze reproductive behavior could have been improved, and many times the degree of female receptivity was not constant. When crude marijuana extract was used, no attempt was made to determine what parts of behavior were affected by the various constituents of cannabis.

Very little work has been reported on female behavior. However, Sassenrath and Chapman (1975) reported that chronic treatment with Δ-9-THC (2 mg/kg/day, in diet) presumably produced an irritable rejection in a single female Macaque toward its infant.

If marijuana is to have an effect on sexual behavior, one would assume a direct action of the constituents in marijuana on those brain structures which serve to elicit sexual behavior. The two principal areas in the brain which elicit and regulate reproductive behavior are the preoptic and hypothalamic areas. Certainly sex hormones are concentrated in these areas and reproductive behavior can be elicited by either electrical or hormonal stimulation

323-754 0 - 80 - 11

of these areas. If they are destroyed by lesions, reproductive behavior is abolished. Also, cannabinoids may affect sexual behavior by altering the sex hormones circulating in the blood which elicit sexual behavior by their action on central nervous targets by cannabinoids' effect on other brain structures to depress LHRF release.

A series of experiments were reported which examined the uptake of radioactive Δ-9-THC in different regions of the brain of rats. These studies are not numerous, nor are they very definitive. Some report no difference in concentration between different regions of the rat brain (Layman and Milton 1971), whereas others report a significant uptake between regions of the brain but by areas not directly concerned with reproductive behavior (Martin et al. 1976; McIsaac et al. 1971; Erdmann et al. 1976). A possible exception, however, was the lateral hypothalamus (Shannon and Fried 1972; Erdmann et al, 1976), where there is reasonable evidence to indicate that it may be involved in reproductive behavior.

Two other areas associated with reproductive behavior are the amygdyla and portions of the limbic structure, Three reports show there is heavy accumulation of radioactive Δ-9-THC in amygdyloid nuclei (McIsaac et al. 1971; Shannon and Fried 1972; Martin et al. 1976). However, the exact nuclei are not specified and may be ones which are not involved in regulating reproductive behavior. One thing is clear: there is altered electrographic activity in the amygdyla after administration of cannabinoids in both cats (Hockman et al. 1971; Miller and Brew 1974) and monkeys (Heath 1976). Similarly, altered electrographic activity was reported in the ventromedial nucleus of the cat, an area located in the hypothalamus that may also be involved in reproductive behavior (Myers 1974; Pfaff et al. 1974).

Human

Most of the reports on the effect of marijuana on human sexual behavior are based on subjective self-reports. Several of these report an increase in sexual stimulation, by noting that sexual desire and sexual performance were prolonged in both males and females. However, it is interesting to note that in some countries, such as India, cannabis is used as a sexual depressant (Chopra and Chopra 1957; Chopra 1969). An early experiment by Hollister et al. (1968) reported stimulation of sexual thoughts after cannabis administration. Indeed, a large number of experienced marijuana users report an increase in sexual pleasure after marijuana use (Tart 1971; Berke and Hernton 1974; Traub 1977), and, in contrast to alcohol, marijuana use was reported to decrease sexually assaultive behavior (Tinklenberg et al. 1974). Acute use of cannabinoids at lower doses apparently enhances sex drive; however, high doses lead to depression of sexual desire and even impotence, possibly due to the decreased plasma testosterone levels,

Bloch et al. (1978) have pointed out that many of the reported

effects may not be due to the effect of cannabis directly but may reflect the lifestyle of the marijuana user which tends to be sensation-seeking and risk-taking. Moreover, there may be a placebo reaction involved. One cannot dismiss the possibility of a secondary effect of marijuana to increase vasodilation in the genitals caused by reduction of sympathetic tone. The appreciation of sexual performance might also be affected by an altered perception of time. Moreover, heightened appreciation of sexual activity may be caused by the effect of marijuana to delay ejaculation as well as to perceive tactile stimulation more intensely.

SUMMARY

This review has pointed out the fact that cannabinoids have significant depressive actions on reproduction and development. In the male, cannabinoids produce decreased organ weights and functional levels of the organs associated with reproduction. These changes may be due to the direct action of cannabinoids to depress testosterone production in the Leydig cells of the testes, or through inhibition of LH and FSH release by the pituitary. One of the primary targets of cannabinoids is on central nervous structures, such as the hypothalamus, to shut down production of LHRF. There is evidence that the testes of animals treated with cannabinoids responded in a normal fashion when LH and FSH were provided exogenously; moreover, the pituitary was shown to respond in a normal fashion when exogenous LHRF was provided. Rats, mice and humans treated with cannabinoids had decreased numbers of sperm with an increase in percent of abnormal sperm in their semen. After cessation of cannabinoid treatment, both rodents and humans returned to normal levels of reproductive function fairly rapidly.

Females similarly responded to cannabinoids with a decrease in the function of organs associated with reproduction. The uterus showed changes in weight and morphology, while the ovary had irregular cycles or a complete cessation of cycling. These changes were probably caused by lowered estrogen production in the ovary caused by the cannabinoids' action to depress gonadotropin release from the pituitary. As inthemale, the primary target of cannabinoids would appear to be their action on central nervous structures to shut down release of LHRF. Certainly, when exogenous LHRF was provided, the pituitary was able to release gonadotropins. It seems at this point that the estrogenic action of cannabinoids previously reported is controversial since recent evidence shows a lack of highly specific binding to the cytosol receptors for estradiol.

Cannabinoids also may have an action on reproduction through a variety of other mechanisms including: (1) their ability to stimulate adrenal cortical hormones, an action that is probably due to the cannabinoids' effect on central nervous structures to cause release of ACTH from the pituitary, since agents which block the release of ACTH also prevent the cannabinoid response; (2) cannabinoids may have a direct effect on both male and female reproductive organs to either alter hormone production or to alter the

response of the reproductive organs to hormones; (3) cannabinoids may alter prostaglandin synthesis in reproductive organs, thus affecting reproductive function.

High doses of cannabinoids appear to inhibit reproductive behavior, at least in rodents, while lower doses may facilitate reproductive behavior, possibly through their action on other physiological systems, to alter time perception, delay ejaculation, and alter perception of tactile stimulation during the sex act.

Cannabinoids also decrease prolactin secretion and release in both male and female. This depression has been shown in nursing females to cause a decrease in milk production and lactation. Cannabinoids may have a direct action on the mammary tissues themselves to decrease milk production.

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Effects of Cannabis in Combination With Ethanol and Other Drugs

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INTRODUCTION

It has become progressively more evident in recent years that many people who use cannabis (marijuana and hashish) also may ingest a large number of other drugs in a wide range of combinations, frequencies, and sequences. Studies clearly reveal that individuals who regularly smoke marijuana may also use alcoholic beverages, barbiturates, amphetamines, hallucinogens and opiates (McGlothlin, Jamison, and Rosenblatt 1970; Carlin and Post 1971; Grupp 1972; Whitehead, Smart, and La Forest 1972; Fisher and Brickman 1973; Hochhauser 1977; Sample 1977). Virtually all surveys have revealed that marijuana and alcohol (ethanol) are the most common drug combination, whereas the use of opiates in conjunction with marijuana is comparatively rare. Although McGlothlin, Jamison, and Rosenblatt (1970), Fisher and Brickman (1973), and Tec (1973) observed a positive relationship between heavy marijuana and alcohol use in a variety of populations, Mello et al. (1978) determined that the simultaneous availability of alcohol and marijuana in a clinical research ward did not result in an increase in the use of both drugs by male volunteers. In the latter study, alcohol use decreased when marijuana was available and marijuana smoking increased irrespective of the availability of alcohol. How representative these findings are of the general population is unknown.

The observation that marijuana users do consume other chemical substances has prompted numerous investigators to examine, in experimental animals and man, the consequences of using a variety of drugs in conjunction with cannabis or Δ^9-tetrahydrocannabinol (THC), the major psychoactive constituent of cannabis. This review will deal with the interaction of cannabis and its constituents with a wide range of drugs, with some emphasis being placed on investigations concerning marijuana and alcohol in view of the popularity of these two drugs in our society.

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INTERACTIONS BETWEEN CANNABIS AND ETHANOL

Correlates of Acute Cannabis/Ethanol Treatment in Animals

Studies with animal models have established that the acute depressant effects of a combination of marijuana and ethanol doses are greater than those produced by either drug alone. Administration of a marijuana extract, containing a 10 mg/kg dose of THC (Siemens and Kalant 1974); or THC alone, 8.5-40 mg/kg (Forney and Kiplinger 1971; Phillips, Brown, and Forney 1971; Sofia and Knobloch 1973; Siemens and Khanna 1977) to rats or mice 30-60 minutes before injection of a hypnotic dose of ethanol increased the duration of the loss of righting reflex (sleep) up to 3-fold. Similar results were obtained with Δ^8-THC (Friedman and Gershon 1974), a cannabinoid which is generally present in marijuana at less than 5% of the Δ^9-THC concentration (Waller 1971). However, cannabidiol (CBD), which is found in marijuana in variable concentrations depending upon its geographical source (Jenkins and Patterson 1973; Chiesa, Rondina, and Coussio 1973; Holley, Hadley, and Turner 1975), did not modify ethanol-induced sleep in the rat (Siemens and Khanna 1977). Moreover, CBD, 24 mg/kg, did not alter the influence of THC, 6 or 12 mg/kg, on ethanol sleeping time,

The impairing effects of subhypnotic doses of ethanol were also enhanced by THC. Kalant and LeBlanc (1974) reported that THC, at doses (3-15 mg/kg) which alone did not influence the motor performance of rats on a moving belt, increased ethanol-induced impairment in a biphasic manner. In the lower THC dose range, the magntidue of impairment gradually increased, but at higher doses the enhancement became less marked. Thus, at higher doses THC may have exerted a stimulatory effect.

Esplin and Capek (1976), who compared THC and ethanol alone and in combination for anticonvulsant activity in mice in a maximal electroshock seizure test, found that the effects of the two drugs were additive. Furthermore, Pryor et al. (1977a) determined that treatment of rats with THC, 2.5-10.0 mg/kg, in conjunction with ethanol, 2.0 g/kg, impaired rotarod performance and a conditioned avoidance response, reduced photocell-monitored activity, and depressed the heart rate and body temperature to a greater extent than either drug alone.

It has been established that at doses administered in the cited studies, THC does not inhibit the disappearance of ethanol from the blood (Kalant and LeBlanc 1974; Friedman and Gershon 1974; Siemens and Khanna 1977) or vice versa (Siemens and Khanna 1977). Accordingly, the behavioral and pharmacological interactions which have been observed are probably mediated centrally.

Correlates of Acute Cannabis/Ethanol Doses in Man

Consistent with the results of animal studies, the concurrent use

of cannabis and ethanol by humans at doses encountered socially can produce more marked effects than either drug alone. Ingestion of ethanol, 0.5-0.6 g/kg, by young, healthy, male volunteers 30 minutes before smoking marijuana (THC, 0.04-0.07 mg/kg) (Manno et al. 1971), or oral ingestion of THC, 0.14-0.21 mg/kg, simultaneously with the alcohol dose (Chesher et al. 1976; Chesher et al. 1977) resulted in greater impairment of perceptual, cognitive and motor functions than caused by either drug, depending upon the time of measurement. In the smoking study the peak brain levels of THC and ethanol will probably have coincided shortly after the end of the smoking period (Isbell et al. 1967; Lemberger et al. 1972; Kalant 1971), thus permitting a measure of the maximal effects of the drug combination at that time (Manno et al. 1971). However, following oral ingestion, maximum ethanol brain levels will have been reached in advance of the THC peak since absorption of the cannabinoid is relatively slow from the gastrointestinal tract (Lemberger et al. 1972; Perez-Reyes et al. 1973). Nonetheless, an additive interaction between THC and ethanol on tests of numerical reasoning, manual dexterity and standing steadiness (eyes open) was already detected at 40 minutes after the oral drug doses. Later in the experiment (160 minutes), the effects of the drug combination on standing steadiness (eyes closed) and responses to visual and auditory stimuli (Vienna Determination Apparatus) were less than produced by THC alone (Chesher et al. 1976; Chesher et al. 1977). This apparent antagonism between the two drugs has not been explained, but it is possible that ethanol reduced the amount of THC available to the brain after oral administration as has been demonstrated in the rat (Siemens and Khanna 1977). If so, subjects ingesting only THC might be expected to be more impaired than those taking the drug combination, as the ethanol disappeared in the later stages of the experiment.

In a subsequent study with male and female students, Belgrave et al. (1979a) increased the oral THC dose to 0.32 mg/kg and administered ethanol, 0.54 g/kg, one hour later, thus correcting in part for the anticipated differences in the pharmacokinetics of the two drugs, The effects of the drug combination on reaction speed, cognitive performance, standing steadiness and psychomotor coordination were additive with no indication of antagonism. In contrast, CBD, 0.32 mg/kg orally, did not modify the impairing effect of ethanol on these measures (Belgrave et al. 1979b).

Marijuana and ethanol not only modify mental and psychomotor performance but also influence physiological parameters. For example, the concurrent use of THC and alcohol produced a greater increase in pulse rate and conjunctival reddening than either drug (Manno et al. 1971; Information Canada 1972). It has also been observed that eye movements, quantitated by electro-oculographic recordings of saccades, smooth pursuit and optokinetic nystagmus, which were impaired at blood ethanol levels of 0.05 and 0.1% in college students, were further reduced, albeit not

significantly, upon smoking a marijuana cigarette containing THC, 0.1 mg/kg (Baloh et al. 1979). In contrast, antagonism between the two drugs has been reported on pupil size and glare recovery in young male subjects. Even though a marijuana cigarette (THC, 15 mg) significantly reduced pupil diameter, and ethanol, 0.56 g/kg, was without effect when administered alone, pupil size was not changed significantly when both drugs were used simultaneously (Brown et al. 1977). Furthermore, the time required for light adaptation upon intense light exposure (glare recovery) was only slightly greater following the simultaneous use of marijuana (THC, 15 mg) and alcohol, 0.56 g/kg, compared to each drug individually despite the fact that recovery was delayed about 2 hours by either drug. That the drug combination did not produce a greater effect on eye function could have been partially due to the slight, yet significantly lower peak blood ethanol concentration when the subjects smoked marijuana in conjunction with the alcohol than when the beverage was taken alone (Adams et al. 1978).

The subjective effects of THC-ethanol combinations also appear variable. Some human subjects have suggested that marijuana antagonized the effects of alcohol (Manno et al. 1971), while other subjective ratings have indicated that the influence of the drug combination either did not differ (Information Canada 1972) or was greater than the effect of the individual drugs (Manno et al. 1971; Chesher et al. 1976). Indeed Sulkowski and Vachon (1977) observed "intense psychological distress" in association with severe nausea, vomiting, tachycardia, variations in blood pressure, skin pallor, and profuse cold sweating in four of seven male volunteers who consumed ethanol, 1 g/kg, followed one hour later by a marijuana cigarette (THC, 18 mg). The adverse reaction did not occur, however, when the ethanol dose was reduced to 0.5 g/kg.

Thus a variety of measures have demonstrated that the concomitant use of cannabis and ethanol may have more profound effects than either agent alone. The magnitude and duration of the effects appear to be related to the parameters measured, drug doses, and the time course of action of each drug. As noted above, some signs of antagonism between the two drugs could possibly be accounted for by reductions in either ethanol or THC brain levels (Siemens and Khanna 1977; Benowitz and Jones 1977; Adams et al. 1978). However, the increases in drug effects are not related to elevated blood ethanol levels (Information Canada 1972; Benowitz and Jones 1977; Chesher et al. 1977; Baloh et al. 1979; Belgrave et al. 1979a).

Correlates of Chronic Cannabis/Ethanol Treatment in Animals

Since tolerance develops to the depressant effects of THC (McMillan, Dewey, and Harris 1971; Information Canada 1972; Paton and Pertwee 1972; Jones, Benowitz, and Bachman 1976) and ethanol (Kalant, LeBlanc, and Gibbins 1971; Mendelson 1971; Smith 1977) on the central nervous system in animals and man, a

number of investigators have questioned whether cross-tolerance between the two drugs could occur. Indeed, rats made tolerant to THC exhibited cross-tolerance to ethanol as determined by conditioned avoidance (Newman et al. 1972), lever pressing (Newman, Lutz, and Domino 1974) and rotarod (Siemens, 1978; Siemens and Doyle 1979) tasks. Similar conclusions were drawn from a study with mice on the basis of rotarod performance (Sprague and Craigmill 1974). In contrast, Kalant and LeBlanc (1974) were unable to demonstrate cross-tolerance to ethanol in THC-tolerant rats on a moving belt test. The reasons for the conflicting results are not clear but could be related to drug doses, duration of chronic drug treatment and the measured used.

Although Newman et al. (1972) and Sprague and Craigmill (1976) reported that ethanol-tolerant rats and mice were also tolerant to challenge doses of THC, Siemens and Doyle (1979) failed to detect complete cross-tolerance to THC in rats on rotarod and conditioned avoidance tasks, respectively. That cross-tolerance was not entirely reciprocal suggests that the nature or characteristics of the impairing effects of the two drugs may not be identical. This possibility is supported by the observation that THC could not be substituted for ethanol in a drug discrimination test in gerbils (Järbe 1977).

Other studies have examined pharmacological interactions between challenge doses of THC and ethanol after subacute treatment (6-14 days) of rats with a marijuana extract (THC, 10 mg/kg/day) (Siemens and Kalant 1974) or pure THC, 10 mg/kg/day (Pryor et al. 1977a). The combined effects of THC and ethanol on sleeping time (Siemens and Kalant 1974), conditioned avoidance responding, photocell-monitored activity, rotarod performance, heart rate and body temperature (Pryor et al. 1977a) were greater before than after the subacute treatments. The decrease in the interactive effects of the drugs at the doses studied was attributed, for most measures, to the development of tolerance to THC rather than a cross-tolerance to ethanol (Pryor et al. 1977a).

In a most recent experiment (Siemens et al, 1979), the simultaneous administration of THC, 6-10 mg/kg, and ethanol, 2-4 g/kg, to rats twice daily in gradually increasing doses resulted in an increased rate and magnitude of ethanol tolerance and physical dependence development. Complete ethanol tolerance was established within 12-16 days in animals receiving both drugs, whereas only minimal ethanol tolerance or cross-tolerance was detected in ethanol- or THC-treated rats, respectively, at this time. The number of animals exhibiting signs of physical dependence as well as the magnitude of these signs, quantitated according to Goldstein and Pal (1971), were much greater in the THC plus ethanol group compared to all other groups of animals.

A variety of sedatives, hypnotics and minor tranquilizers which show cross-tolerance to ethanol in animals and man are effective

in counteracting signs of ethanol dependence (Kalant, LeBlanc, and Gibbins 1971; Smith 1977). Correlatively, treatment of ethanol-dependent mice with THC at doses of 1.5-2.0 mg/kg i.v. (Blum et al. 1975) and 10-40 mg/kg i.p. (Sprague and Craigmill 1978) respectively reduced handling-induced convulsions and suppressed the enhanced responsiveness of the animals to electric foot shock during ethanol abstinence. Nabilone, a synthetic derivative of THC, similarly decreased the response to foot shock (Sprague and Craigmill 1978), indicating that marijuana or related drugs may be beneficial in the treatment of alcohol withdrawal. It should be noted, however, that at higher THC doses, handling-induced convulsions were intensified in ethanol-dependent mice (Blum et al. 1975; Kralik, Ho, and Matthews 1976; Sprague and Craigmill 1978). This phenomenon may have been related to the convulsant action of THC in mice irrespective of ethanol (Sprague and Craigmill 1978).

It is generally accepted that drug tolerance or cross-tolerance may be of functional or dispositional origin (Kalant, LeBlanc, and Gibbins 1971). Functional tolerance is characterized by a decrease in the apparent sensitivity of the central nervous system to a drug, whereas dispositional tolerance involves a decrease in the amount of drug available to its sites of action in the brain, resulting from an increase in the rate of drug metabolism or elimination, or a change in drug distribution. Sprague and Craigmill (1976) and Siemens and Doyle (1979) have demonstrated that cross-tolerance between THC and ethanol is not dispositional in mice and rats, respectively, implying that the phenomenon is functionally mediated.

Correlates of Chronic Cannabis/Ethanol Use in Man

The definitive demonstration of cross-tolerance between THC and ethanol in rodents supports the clinical observation (Jones and Stone 1970) that heavy marijuana users, males who used marijuana regularly for a year or more, apparently showed less behavioral and motor impairment than expected after consuming the equivalent of four to five ounces of 100 proof alcohol. Similarly, MacAvoy and Marks (1975) observed that experienced marijuana users were less impaired than nonusers at a blood ethanol level of 96 mg/100 ml as determined by divided attention performance. Although a similar trend was noted in a repetition of this study, the cross-tolerance between the two drugs was not statistically significant. Thus although the issue of cross-tolerance between the two drugs in man has been entertained, the problem has not been fully resolved.

Cannabis has been tried in alcoholism treatment with varying degrees of success. According to Thompson and Proctor (1953), pyrahexyl, an analog of THC, reduced withdrawal signs including restlessness, irritability and sleep disturbances in 84% of the 70 alcoholics treated. Although Rosenberg, Gerrein, and Schnell (1978) concluded that making marijuana available to alcoholics

did not induce alcoholics to enter or remain in treatment, Mikuriya (1970) described a measure of success in substituting marijuana for alcohol in one female alcoholic. Since the clinical experience in treating various forms and stages of alcohol abuse and alcoholism with marijuana or THC is still limited, it is premature to draw a final conclusion on the benefits of cannabis in this area.

INTERACTIONS BETWEEN CANNABIS AND SEDATIVES, HYPNOTICS AND OPIATES

Acute Interactions of Cannabis and CNS Depressants in Animals

Numerous investigators, employing a variety of pharmacological parameters, have provided definitive evidence that cannabis enhances the depressant effects of sedatives and hypnotics on the central nervous system (CNS). Marijuana extracts prolonged sleep induced by barbiturates in rats (Loewe 1944; Bose, Saifi, and Bhagwat 1964; Siemens et al. 1974) and mice (Paton and Pertwee 1972; Chesher, Jackson, and Starmer 1974). Correlatively, the dose of thiopental required to induce anesthesia in rabbits was significantly reduced by pretreatment with a cannabis extract (Paton and Temple 1972).

The THC content in the marijuana extracts was responsible, at least in part, for the modification of barbiturate hypnosis. THC doses, 0.6-80.0 mg/kg, which do not produce severe impairment alone, significantly prolonged drug-induced sleep in a dose-dependent manner when administered to mice or rats shortly before or after (30-60 minutes) injection of hexobarbital (Garriott et al. 1967; Bating et al. 1972; Sofia and Knobloch 1973; Fernandes, Kluwe, and Coper 1974), pentobarbital (Kubena and Barry 1970; Paton and Pertwee 1972; Chesher, Jackson, and Starmer 1974; Frizza et al. 1977), barbital (Kubena and Barry 1970; Sofia and Barry 1970; Sofia and Barry 1973) or thiopental (Frizza et al. 1977). A number of studies with mice and rats have further demonstrated that THC, 0.6-40.0 mg/kg, also prolonged sleep induced by nonbarbiturate sedative/hypnotics including ethanol (Phillips, Brown, and Forney 1971; Sofia and Knobloch 1973; Siemens and Kalant 1974; Kalant and LeBlanc 1974; Siemens and Khanna 1977), zoxazolamine (Sofia and Barry 1973), ethchlorvynol, meprobamate, ethinamate, glutethimide, chloral hydrate, paraldehyde (Sofia and Knobloch 1973), methaqualone (Sofia and Knobloch, 1973; Stone, McCoy, and Forney 1976), ketamine, the steroidal anesthetic CT-1341 (Sofia and Knobloch 1974a), and phencyclidine (PCP) (Murray and Craigmill 1976). Furthermore, THC, 0.5-2.0 mg/kg, produced a dose-dependent decrease in the minimum alveolar anesthetic concentration for halothane in dogs (Stoelting et al. 1973) and cyclopropane in rats (Vitez et al. 1973).

THC not only augments anesthesia but also modifies the cardiovascular effects of anesthetics. For example, the heart rate and blood pressure of conscious dogs were slightly decreased by THC, 1 mg/kg i.v., but pentobarbital, 35 mg/kg, (Cavero et al. 1972) urethane, 1 g/kg, or chloralose, 100 mg/kg (Jandhyala and Buckley 1977), markedly potentiated the depression of these parameters. Although THC also reduced the heart rate in

morphine-sedated dogs, 3 mg/kg, the cannabinoid produced significant tachycardia in animals treated with the combination of morphine plus chloralose (Jandhyala and Buckley 1977). Furthermore, THC decreased the cardiac output and pulmonary blood flow in association with increases in pulmonary vascular resistance, pulmonary arterial pressure and right ventricular stroke volume in dogs under pentobarbital anesthesia (Jandhyala, Malloy, and Buckley 1976; Jandhyala and Hamed 1978). In contrast, THC, administered to dogs anaesthetized with morphine plus chloralose, increased heart rate and cardiac output and decreased pulmonary vascular resistance, pulmonary arterial pressure and right ventricular stroke work. The mechanisms for these effects have not been fully elucidated although a number of hypotheses have been presented (Jandhyala and Hamed 1978).

In addition to enhancing the depressant effects of drugs at their hypnotic or anesthetic dose levels, THC augments responses to much lower, yet behaviorally effective doses. Pryor et al. (1977a, 1977b) evaluated dose-response interactions of THC, 2.5-10 mg/kg, with phenobarbital, 10-40 mg/kg, chlordiazepoxide (Librium), 2.5-10 mg/kg, ethanol, 0.5-2.0 g/kg, and PCP, 1.25-5 mg/kg, on measures of conditioned avoidance, rotarod performance, photocell activity, heart rate, and body temperature in rats. Most measures showed that the combination of THC with either of the four drugs at their highest doses produced a greater depressant effect than any individual compound. At 1.25 and 2.5 mg/kg doses of PCP, the enhancement was apparently more than additive (Pryor et al. 1977b). Similar results were obtained on measures of schedule-controlled behavior (Murray and Craigmill 1976; Pryor et al. 1977b). When administered alone, PCP markedly increased photocell and open field locomotion, an effect which was almost entirely antagonized by THC doses which alone had little influence on these behaviors (Pryor et al. 1977b). Stone and Forney (1978) have also reported that THC partially antagonized the stimulatory effect of PCP on photocell activity in mice.

Cannabinoids such as Δ^8-THC, cannabidiol (CDB), cannabinol (CBN) and cannabigerol (CBG), which are commonly present in cannabis in addition to Δ^9-THC (Jenkins and Pattersen 1973; Chiesa, Rondina, and Coussio 1973; Holley, Hadley, and Turner 1975), have also been evaluated for potential interactions with depressant agents. Rating et al. (1972) reported that Δ^8-THC, 5 mg/kg, increased the duration of hexobarbital-induced sleep almost twofold in rats. Chesher, Jackson, and Starmer (1974) also observed that Δ^8-THC and Δ^9-THC, 10 mg/kg, were equivalently effective in prolonging the pentobarbital-induced sleep in mice. Furthermore, CBD, 10-80 mg/kg, caused a dose-dependent prolongation of pentobarbital and hexobarbital sleeping time in mice and rats, the effect being greater than produced by THC (Loewe 1944; Paton and Pertwee 1972; Chesher, Jackson and Starmer 1974; Siemens et al. 1974; Fernandes, Kluwe, and Coper 1974; Coldwell et al. 1974; Frizza et al. 1977). In contrast, studies in mice showed that THC was more effective than CBD in prolonging the methaqualone

loss of righting reflex (Stone, McCoy and Forney 1976) and, moreover, CBD appeared to antagonize ether anesthesia (Malor, Jackson, and Chesher 1975).

Whereas CBG, 20 mg/kg, antagonized pentobarbital sleep in rats, CBN, 5-80 mg/kg, did not appear to be effective in altering ketamine, pentobarbital, thiopental, propanidid in anesthesia (Frizza et al. 1977). However, CBN did prolong ether anesthesia (Malor, Jackson, and Chesher 1975).

In view of the contrasting influences that the different cannabinoids may exert, it is not surprising that complex interactions occurred when more than one cannabinoid was administered in conjunction with anesthetics. For example, the effects of CBD plus THC in prolonging pentobarbital sleep in mice were apparently additive, (Chesher, Jackson, and Starmer 1974) or potentiative (Frizza et al, 1977), while CBN reduced the effectiveness of either THC alone (Krantz, Berger, and Welch 1971) or the combination of CBD and THC (Chesher, Jackson, and Starmer 1974). Although CBD reversed ether anesthesia, it did not counteract the THC-induced enhancement of the anesthetic effect (Malor, Jackson, and Chesher, 1975). Other, as yet, unexplained interactions between groups of cannabinoids and various anesthetics have also been reported (Frizza et al. 1977). It is likely that the ultimate interactions which may occur are related to factors such as cannabinoid and other drug doses, mechanisms of drug action, pharmacokinetics, and animal species.

Mechanisms of Acute Cannabis/Depressant Interactions

Considerable emphasis has been placed on the assessment of mechanisms which might be involved in the interactions between THC and CNS depressant agents. To determine whether interactions between THC and depressants reflect the summation of two independent drug actions or, alternatively, are due to a common mechanism of action, gerbils (Järbe, Johansson, and Henricksson 1975) and pigeons (Järbe and Ohlin 1979) were studied for their ability to discriminate between the effects of THC and pentobarbital. Although THC and pentobarbital both exhibited depressant effects, the cue properties of THC were not equivalent to those of pentobarbital in gerbils or pigeons. THC administration in conjunction with pentobarbital increased the barbiturate-appropriate responses in gerbils (Järbe, Johansson, and Henricksson 1975), but the opposite was observed in pigeons (Järbe and Ohlin 1979). Unfortunately, a firm conclusion cannot be drawn from these disparate results, but the observation that the two drugs were not interchangeable in either animal species supports the hypothesis that THC and barbiturates have different mechanisms of action, which may be complementary in drug interactions.

Numerous other investigators have evaluated the relationships between observed behavioral interactions and changes in the

disposition of THC or the interacting agent. Since the duration of action of barbital and thiopental is not dependent on the rate of drug metabolism, the enhancement of the depressant effects of these barbiturates by THC is likely mediated by a mechanism within the central nervous system. This conclusion is consistent with the observation that both a marijuana extract (Chesher, Jackson, and Starmer 1974) and THC alone (Malor, Jackson, and Chesher 1975) prolonged anesthesia induced by ether, a drug which is also not dependent on metabolism for elimination.

Sofia and Barry (1970), observing that SKF 525-A, a known inhibitor of hepatic drug metabolism, augmented the THC-mediated prolongation of barbital sleeping time, concluded that unchanged THC rather than its metabolites was likely responsible for the functional interaction with the barbiturate. This conclusion was supported by the studies showing that SKF 525-A did inhibit THC metabolism in vitro (Burstein and Kupfer 1971; Dingell et al. 1973; Siemens et al. 1975) and in vivo (Gill and Jones 1972; Estevez, Englert, and Ho 1974; Siemens, Kalant, and deNie 1976).

Even though interactions of THC with some hypnotics appear to originate primarily in the brain, the cannabinoid and other drugs which are metabolized by the hepatic mixed function oxidase system may mutually inhibit one another's metabolism, thereby prolonging and perhaps intensifying pharmacological effects. Indeed, THC at high doses, 20-40 mg/kg, slightly reduced the rate of hexobarbital disappearance from the blood and brain (Fernandes, Kluwe and Coper 1974) and slowed the urinary excretion of pentobarbital in rats (Coldwell et al. 1974). However, lower doses of THC, 10 mg/kg, which also prolonged hexobarbital sleep, did not change the tissue concentrations of hexobarbital (Rating et al. 1972), again implying that the central nervous system is the major mediator of THC-barbiturate interactions.

Pryor et al. (1977b) similarly concluded that behavioral interactions between THC and PCP in the rat were not related to changes in brain or plasma drug levels. However, this conclusion remains conjectural since the radioassay which was used did not differentiate between unchanged PCP and its metabolites.

The influence of THC on the distribution, metabolism and elimination of many of the other depressant drugs which have been referred to above has not been established. Moreover, only a few studies have examined the influence of psychoactive drugs on the disposition of THC in the rat. Hepatic THC metabolism was inhibited in vitro to varying extents by high concentrations (10^{-4}-10^{-3} M) of the barbiturates, hexobarbital (Burstein and Kupfer 1971), pentobarbital and phenobarbital (Siemens et al. 1975), and the tricyclic antidepressants, desipramine, nortriptyline and iprindole (Dingell et al. 1973). Inhibition of THC metabolism in vitro by meprobamate and morphine was minimal. Consistent with the observation that high concentrations of drugs were required to inhibit THC metabolism in vitro, pentobarbital and phenobarbital, at behaviorally effective doses,

did not modify the biliary excretion of THC (Siemens et al. 1975). Although these results show that THC metabolism can be altered by psychoactive drugs, it is doubtful that this is a major mechanism of interaction at drug doses which have been used in behavioral studies.

CBD, in contrast to THC, does not primarily interact with other drugs at the brain locus, but rather modifies the action of drugs by inhibiting their hepatic metabolism. Upon observing that CBD inhibited phenazone metabolism in vitro, Paton and Pertwee (1972) predicted that CBD prolonged pentobarbital-induced sleep in mice by inhibition of the metabolism of the barbiturate. This prediction was supported by Siemens et al. (1974) and Coldwell et al. (1974) who showed that the magnitude of the prolongation of pentobarbital sleep in the rat was directly related to the inhibition of pentobarbital metabolism in vivo. Interactions between CBD and hexobarbital were similarly attributed to the inhibition of barbiturate metabolism (Fernandes et al. 1973; Fernandes, Kluwe, and Coper 1974). The inhibition of pentobarbital and hexobarbital metabolism was detectable for at least 63 (Siemens et al. 1974) and 48 hours (Fernandes et al. 1973), respectively, following single acute doses of CBD. This long-lasting effect has been attributed to the slow disappearance of CBD metabolites from the liver (Karler et al. 1979; Siemens, Walczak, and Buckley 1980). CBD is clearly a more Potent inhibitor of drug metabolism in vivo and in vitro than either THC or CBN (Paton and Pertwee 1972; Fernandes et al. 1973; Siemens et al. 1974).

Correlates of Chronic Doses of Cannabis/CNS Depressants in Animals

Chronic studies of interaction between THC and CNS depressants, including opiates, have centered upon aspects of cross-tolerance and cross-dependence as previously described for ethanol. Using a measure of shock avoidance behavior in rats, Newman, Lutz, and Domino (1974) determined that the development of tolerance to repeated daily doses of THC resulted in a dose-dependent cross-tolerance to pentobarbital but not to chlorpromazine. Although the effects of THC and chlorpromazine could have been perceived by the animals as being different in nature, it is possible that the challenge doses of chlorpromazine were simply too high.

Pryor et al. (1977a) observed that THC tolerance in rats was accompanied by an attenuation of the depressant effects of a combination of THC and phenobarbital challenge doses on some, but not all behavioral measures which were used. The depressant influence of concurrent challenge doses of THC and chlordiazepoxide was also partially reduced on some behavioral and physiological measures in THC-tolerant animals. Conversely, subacute treatment (6 days) of animals with phenobarbital resulted in partial tolerance development to the barbiturate, and in a slight reduction in the interactive effects between THC and phenobarbital. Subacute treatment with chlordiazepoxide, however, did not result

in tolerance to the tranquilizer or to combinations of THC and chlordiazepoxide. Tolerance to the interactive effects of THC and PCP on behavioral and physiological measures was also demonstrated in THC-tolerant rats (Pryor et al. 1977b). However, subacute treatment with PCP resulted in an enhancement of the behavioral effects of concurrent challenge doses of THC plus PCP, suggesting that PCP had cumulative effects.

Bloom and Dewey (1978) have determined that THC-tolerant rats were cross-tolerant to morphine on a measure of hypothermia and that morphine-tolerant animals were cross-tolerant to the antinociceptive effect of THC. The fact that the cross-tolerance was not symmetrical on these two measures supports the argument. that the drugs act by different mechanisms.

The mechanisms responsible for cross-tolerance development between THC and the various depressant agents have not been elucidated explicitly, but may have functional as well as dispositional components. Although there is little evidence that THC alone induces the metabolism of other drugs (Dewey, Kennedy, and Howes 1970; Kupfer, Levin, and Burstein 1973; Marcotte et al. 1975), substances such as phenobarbital (Wall 1971; Siemens and Kalant 1974), DDT (Kupfer, Levin, and Burstein 1973), 3-methylcholanthrene (Nakazawa and Costa 1971) and marijuana smoke (Lemberger et al. 1971) can stimulate the metabolism of THC.

As may be expected on the basis of cross-tolerance observations, THC has been shown to be effective in counteracting some signs of physical dependence on CNS depressants. Gildea and Bourn (1977) determined that THC antagonized withdrawal convulsions in barbital-dependent rats in a dose-related manner. THC also attenuated some of the behavioral and physiological signs of naloxone-precipitated abstinence in morphine-dependent rats (Hine et al. 1975a; Zaluzny et al. 1979), guinea pigs (Frederickson, Hewes, and Aiken 1976), and mice (Bhargava 1976; Bhargava 1978). Indeed Zaluzny et al. (1979) have concluded that THC was of similar potency to morphine in suppressing the naloxone-precipitated withdrawal in rats.

It is of further interest that CBD and CBN (Hine, Torrelio, and Gershon 1975), at doses which did not modify the withdrawal reactions alone, further augmented the THC attenuation of the abstinence signs in rats. Although Δ^8-THC also counteracted withdrawal signs in rats (Hine et al. 1975b) it was not effective in mice, a discrepancy which may be related to differences in the duration of action of the two THC isomers in the different animal species (Bhargava 1978).

In contrast to the apparent THC-mediated antagonism of morphine withdrawal, Carlini and Gonzalez (1972) observed that THC enhanced aggressive behavior in morphine-dependent rats. Moreover, Deikel and Carder (1976) have reported that the cannabinoid did not counteract naloxone-precipitated withdrawal in methadone-

dependent rats. The latter authors have argued that studies by Hine et al. (1975a) were not adequately controlled and, furthermore, that the antagonistic effects of THC may be related to nonspecific sedative effects (Carder 1975).

The mechanism for the antagonism of morphine abstinence by THC has not been defined, but Zaluzny et al. (1979) have recently concluded that the phenomenon is not solely dependent on the availability of opiate or dopamine receptors in the brain, and that sedation alone, as previously reported by Frederickson, Hewes, and Aiken (1976), cannot account for the effect.

Interactions of Cannabis and CNS Depressants in Man

Studies of interactions between the cannabinoids of cannabis and CNS depressant drugs, other than ethanol, have been much more limited in man than in experimental animals. Nevertheless, a variety of interactions in man have been documented. Dalton et al. (1975), who administered secobarbital, 150 mg/70 kg orally, to young males 50 minutes before a marijuana cigarette (THC, 25 µg/kg), found that the magnitude of the depressant effect of the drug combination on measures of standing steadiness and psychomotor and mental performance represented "additivity of the component effects." In addition, the subjective effects of the drug combination were greater than produced by either drug alone. Similarly, Johnstone et al. (1975) and Smith and Kulp (1976), reported that injection of THC, 27-130 µg/kg i.v., shortly after pentobarbital, 100 mg/70 kg i.v., induced more profound subjective effects, including hallucinations and severe anxiety, than caused by either drug. The slight stimulant and depressant effects of pentobarbital and THC, respectively, on ventilation were mutually antagonized by the drug combination. Pentobarbital in conjunction with THC increased the heart rate and cardiac index and decreased total peripheral resistance.

Johnstone et al. (1975) also observed that THC caused a dose-related enhancement of the sedation and ventilatory depression induced by oxymorphone, 1 mg/70 kg i.v. Although oxymorphone had no influence on cardiovascular parameters, the concurrent injection of THC, 134 µg/kg, increased the heart rate and cardiac index and decreased peripheral resistance. THC also augmented CNS and ventilatory depression caused by diazepam, 5-20 mg/70 kg i.v. However, diazepam apparently counteracted the THC-mediated increase in heart rate and cardiac index. (Smith and Kulp 1976). These studies by Johnstone et al. (1975) and Smith and Kulp (1976) are of significant interest, but it is difficult to assess the magnitude of the interactive effects between THC and the other drugs because the pharmacological effects of THC alone which have been used for comparison were based on a separate experiment (Malit et al. 1975).

In contrast to the effects of THC, inhalation of CBD, 150 or 500 µg/kg, in marijuana smoke, immediately before an oral dose of secobarbital, 150 mg/70 kg, did not produce responses greater

than caused by the barbiturate alone (Dalton et al. 1975). In addition, CBD did not alter the pharmacokinetics of secobarbital in the blood. It is possible that the absence of an interactive effect between CBD and secobarbital was related to the order of drug administration as discussed for THC and ethanol above.

The observation by Benowitz and Jones (1977) that treatment of young males with THC, 60-180 mg/day, for 14 days increased the half-lives of pentobarbital and antipyrine in the plasma and reduced the rate of absorption of the barbiturate, indicates that chronic marijuana use could alter the effects of drugs in man. Furthermore, after THC administration was terminated, the metabolic clearance of pentobarbital was increased, suggesting that a metabolic cross-tolerance between the two drugs could occur. Although studies of potential interactions between cannabis and CNS depressants are not abundant, the evidence obtained to date reveals that significant interactive effects are possible. The findings indicate that caution should be exercised in the use of cannabis in conjunction with other agents and that additional, well-designed studies in man are imperative.

INTERACTIONS BETWEEN CANNABIS AND STIMULANTS

Interactions of Cannabis and Stimulants in Animals

Considerable attention has also been directed toward the examination of potential interactions between THC and stimulants in rodents. THC (Garriott et al. 1967; Phillips et al. 1971; Craigmill, Canafax, and Curtiss 1974) and two synthetic derivatives of THC (Daginnanjian and Boyd 1962) enhanced the amphetamine-induced stimulation of motor activity in mice. Although the results of various studies agree qualitatively, quantitative differences are apparent. For example, Garriott et al. (1967) noted that THC, 25 mg/kg, increased d-amphetamine, 4 mg/kg, -stimulated motor activity for up to 3 days in aggregated mice, whereas Craigmill, Canafax, and Curtiss (1974) reported a very transient (10 minutes) increase in activity after the administration of THC, 18 mg/kg, and d-amphetamine, 5 mg/kg. Evans et al. (1976) found that the influence of THC on methamphetamine-stimulated motor activity in mice was dependent upon whether the animals were aggregated or isolated. In aggregated mice, a maximum augmentation of methamphetamine stimulation was produced by a 15 mg/kg dose of THC, with higher and lower doses having less effect. However, in isolated mice, THC consistently antagonized methamphetamine stimulation.

THC, in a dose-related fashion, antagonized the stimulant action of d-amphetamine (Hattendorf et al. 1977; Pryor et al. 1978) and methamphetamine (Kubena and Barry 1970) in rats, independent of aggregation. Furthermore, THC counteracted the effects of amphetamine on conditioned avoidance responding. Conversely, Grunfeld and Edery (1969) demonstrated that dl-amphetamine reversed a THC-mediated cataleptoid response in rats.

Interactive effects between THC and amphetamine on other measures in the rat are more variable. Whereas Hattendorf et al. (1977) found that THC antagonized hyperthermia induced by amphetamine, Pryor et al. (1978) reported that amphetamine tended to enhance THC-induced hypothermia and bradycardia. In addition, THC prolonged amphetamine-related stereotypy (Hattendorf et al. 1977), a finding which may be consistent with the observation by Waters and Glick (1973) that the combination of THC and amphetamine caused a circling behavior in rats. Some stereotypic effects, however, were reduced by THC in a study by Gough and Olley (1975).

Variable results have also been obtained in determinations of THC's effect on the toxicity of amphetamines in mice and rats. Early studies by Garattini (1965) and Salustiano, Hoshino, and Carlini (1966) indicated that marijuana or THC had little or no effect on amphetamine lethality in mice. However, Howes (1973a) and Blum et al. (1977) have shown that higher THC doses increase, and lower doses decrease, amphetamine toxicity in aggregated mice. Opposing evidence of Evans et al. (1976) revealed that low doses of THC administered to grouped mice enhanced, but high doses decreased, the toxicity of methamphetamine. In isolated mice no change in lethality was detected. Studies with rats showed an antagonistic effect of THC on amphetamine toxicity (Kubena and Barry 1970).

According to Willinsky, DeCarlos, and Longo (1973) and Consroe, Jones, and Aikins (1975), THC enhanced some of the excitatory effects of d-amphetamine and methamphetamine, respectively, in rabbits. Moreover, the combination of THC and methamphetamine caused stereotypic behavior in this species. However, methamphetamine antagonized THC-induced increases in cortical electrogenesis and depression of behavioral activity. Thus both synergism and antagonism between THC and amphetamines have been described.

Other stimulants which have been evaluated in experimental animals for potential pharmacological interactions with THC include cocaine, nicotine, caffeine, apomorphine, phenitrone, and pemoline. As observed for methamphetamine, Consroe, Jones and Laird (1976) noted that acute doses of cocaine, caffeine and apomrphine all reversed the THC-induced depression of behavioral activity in rabbits. In agreement with this finding, Pryor et al. (1978) reported that cocaine tended to antagonize THC's depression of photocell activity and rotarod performance in rats. However, nicotine further decreased rotarod performance and augmented THC-mediated bradycardia and hypothermia (Pryor et al. 1978).

Daily treatment of rats with THC for 6-8 days resulted in tolerance development to the cannabinoid and, consequently, the interactions with amphetamine (Hattendorf et al. 1977), cocaine and nicotine were no longer detectable (Pryor et al.

1978). In contrast, subacute treatment of rats with amphetamine, cocaine or nicotine did not result in tolerance to the stimulant effects of these drugs or a change in their interaction with THC (Pryor et al. 1978).

Phenitrone (Kudrin and Davydova 1968; Spaulding et al. 1972) and pemoline (Howes 1973b) were studied as potential antagonists to THC intoxication. In direct contradiction of the report by Kudrin and Davydova (1968) that phenitrone blocked hashish intoxication in dogs, Spaulding et al. (1972) determined that the drug did not antagonize THC activity in dogs and pigeons, or hypothermia in mice. Although phenitrone was not confirmed as a THC antagonist, Howes (1973b) showed that pemoline counteracted the THC-induced depression of motor activity and perception of noxious stimuli in mice. Unlike amphetamine, there was no indication of an enhanced stimulatory effect. Whether pemoline would be a good antagonist of THC affects in other species is not known.

Mechanisms of Cannabis/Stimulant Interactions

The mechanisms for the interactions between THC and stimulants have not been fully clarified, but could involve alterations in cholinergic (Consroe 1973) and/or catecholaminergic neurotransmission (Waters and Glick 1973; Howes and Osgood 1974; Consroe, Jones, and Laird 1976; Hattendorf et al. 1977) or changes in drug distribution and disposition. Craigmill, Canafax, and Curtiss (1974) reported that THC either decreased or had no effect on amphetamine brain levels. This suggests that the observed potentiation of amphetamine effects in the study was at least not due to an increase in drug level. Unfortunately, the peak potentiative effect had already occurred when the drug level was determined, precluding a firm conclusion. Other studies have demonstrated that THC reduced the rate of disappearance of unchanged amphetamine from the blood of rats (Siemens 1977). Evans et al. (1976) and Pryor et al. (1978), in assessing the effects of THC on the disappearance of radiolabelled stimulants from the plasma of mice and rats, measured levels of total radioactivity only. Thus despite the finding that THC did not modify these levels, it is not known whether the parent compounds or specific metabolites were altered. Similarly, although amphetamine and nicotine altered the plasma levels of total radioactivity derived from ^{14}C-THC, a conclusion regarding changes in unchanged THC or its active metabolites is not possible. It has been reported, however, that amphetamine inhibited the hepatic metabolism of THC in vitro (Siemens et al. 1975). A determination of the significance of the latter findings in relation to behavioral interactions between THC and amphetamine remains to be carried out.

Interactions of Cannabis with Amphetamine and Propranolol in Man

The results of animal studies are quite variable and cannot be

extrapolated directly to the human experience, but they have revealed that the potential for interactions exists. However, Zalcman et al. (1973) who administered an oral dose of d-amphetamine, 200 μg/kg, to marijuana users immediately preceding a marijuana cigarette (THC, 200 μg/kg) did not detect any significant interaction between the drugs on measures of blood pressure, respiratory rate, pupil size, conjunctival injection, cognitive performance or subjective effects. Similarly, Forney et al. (1976) were unable to obtain evidence of an interactive effect between marijuana (THC, 25 μg/kg) and d-amphetamine, 140 μg/kg, which was taken orally 1.5 hours before the cigarette, on measures of cardiovascular function, psychomotor performance and subjective response. Nonetheless, when the marijuana, THC dose was increased to 50 μg/kg, the drug combination produced an additive increase on systolic blood pressure and a greater than additive increase in the intensity and duration of the subjective "high" (Evans et al. 1976). Thus although extensive studies of potential interactions between cannabis and stimulants have not been accomplished in man, the reports to date indicate that interactions may occur depending upon drug doses and the time intervals between ingestions.

Propranolol, a beta adrenergic blocking agent which is devoid of CNS action at the doses used (Dunleavy, MacLean, and Oswald 1971), has been examined for its effectiveness in antagonizing THC-induced impairment of mental functions and tachycardia. In an experiment reported by Drew et al. (1972), young males took 4 oral doses of propranolol, 40 mg, every 6 hours, followed 2 hours after the last dose by a marijuana cigarette (THC, 25 μg/kg). The investigators failed to observe any antagonism of the cognitive dysfunction produced by marijuana alone. In contrast, Sulkowski, Vachon, and Rich (1977) reported that a single dose of propranolol, 120 mg, given one hour before a marijuana cigarette (THC, 140 μg/kg) blocked marijuana-related learning impairment as well as the subjective depressant effect, but did not alter the "high" rating. Furthermore, propranolol antagonized the THC-induced tachycardia, elevation in blood pressure and eye reddening in agreement with an earlier study by Beaconsfield, Ginsburg, and Rainsbury (1972). The discrepancy between the latter studies and that of Drew et al. (1972) is likely a factor of drug doses. This and related evidence suggest that THC may act, at least in part, by modifying neurotransmitter function. A further evaluation of this area is not within the scope of this review.

INTERACTIONS OF CANNABIS AND NONPSYCHOACTIVE DRUGS

Little is known regarding pharmacological interactions between cannabis and nonpsychoactive drugs. The widespread use of cannabis and the frequent use of prescription and nonprescription drugs for a wide range of medical reasons raises the possibility that people may use marijuana concurrently with a

323-754 0 - 80 - 13

nonpsychoactive therapeutic agent. Depending upon the chemical nature and dose of the drug, the cannabinoids in marijuana could modify its absorption, distribution, metabolism and elimination, and vice versa. Siemens, George and McConnell (1979) , in considering this possibility, determined that aspirin significantly decreased the rate of disappearance of THC from the blood of rats, and, moreover, increased the levels of THC in the brain. This finding may account for the potentiating effect of aspirin on the behavioral depression caused by THC in rats (Pryor et al. 1976; G.I. Pryor, SRI International, unpublished observation). Furthermore, phenylbutazone also increased THC levels in the brain and liver, whereas dicumarol was without effect (Siemens, George, and McConnell 1979). Further work in this area is expected.

INTERACTIONS OF THC AND OTHER CANNABINOIDS

As already implied above, it is imperative that the full complement of cannabinoids which are normally present in cannabis must be evaluated individually for their interactions with other drugs to develop a comprehensive understanding of the consequences of concurrent cannabis-drug use. Such an evaluation, however, is complicated by the fact that the various cannabinoids in cannabis also interact. A review of cannabinoid interactions is beyond the scope of this review. It suffices to point out that some of the pharmacological effects of THC in conjunction with other cannabinoids have been shown to be significantly different from those of THC alone in animals (Karniol and Carlini 1973; Borgen and Davis 1974; Fernandes et al. 1974) and man (Isbell et al. 1967; Karniol and Carlini 1972; Galanter et al. 1973; Kamiol et al. 1974; Lemberger et al. 1976). These interactions are likely associated, at least partially, with an inhibition of THC metabolism by cannabinoids such as CBD (Jones and Pertwee 1972; Siemens, Kalant, and de Nie 1976).

INTERACTIONS OF THC WITH MODIFIERS OF NEUROTRANSMITTERS

Many experiments which were designed to determine the mechanisms of action of THC in the central nervous system have depended upon the chemical manipulation of neurotransmitter levels, turnover and function. Thus these studies involve interactions between THC, neurochemical agonists or antagonists, and specific neurotransmitters. Since these interactions are also beyond the domain of this review, the reader is referred to reports by Sofia and Knobloch (1974b), Hollister (1976), Consroe, Jones and Laird (1976) and Ho and Johnson (1976) for an introduction to the subject.

USE OF MARIJUANA IN COMBINATION WITH OTHER DRUGS: UNRESOLVED ISSUES

Despite the extensive efforts which have been made to evaluate the consequences of using marijuana in combination with other drugs, many important questions remain unanswered. Although a variety of significant interactions have been described on the basis of animal models, demonstration of interactive effects in man has been limited. Human studies involving the acute administration of marijuana and other drugs have not evaluated fully the relationships between potential marijuana-drug interactions and the wide range of drug doses and sequences of drug ingestion which are encountered socially. The absence of a drug interaction at one particular dose combination does not ensure that an interactive effect will not occur at other doses.

Furthermore, information is scarce on the consequences of the chronic human use of marijuana together with other agents. Even though studies addressing the latter concern may be precluded in man on ethical and other grounds, experiments with a variety of animal species would provide results which could be rationally extrapolated to humans. At present, it may be presumptuous to predict effects in humans on the basis of chronic experiments which have been restricted almost exclusively to rodent models.

Two other areas which require further attention in both man and animals include an assessment of the efficacy of treating alcohol and other drug dependencies with marijuana or THC, and the determination of potential interactions between cannabis and nonpsychoactive drugs. These are not the only areas of concern which remain, but they are indicative of the wide variety of issues which still must be addressed in dealing with the problem of marijuana use in combination with other drugs.

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Therapeutic Aspects

Sidney Cohen, M.D., D.Sc.

A review of the therapeutic capabilities of cannabis and of delta-9-THC has been published in NIDA Research Monograph 14: *Marihuana Research Findings: 1976* (NIDA 1977). Another volume, *The Therapeutic Potential of Marijuana* (Cohen and Stillman 1976), presented similar information in greater detail.* That material will be only briefly summarized here, while the investigations from the subsequent years will be given more extensive coverage.

It may be appropriate to begin with a quotation from the Introduction to *The Therapeutic Potential of Marijuana* (Cohen 1976):

"The constitutents of Indian Hemp have unusual chemical configurations, and these are coming under scientific scrutiny after millenia of trial and error traditional usage. The possible therapeutic utility of cannabis seems to derive from two general pharmacologic activities: its mood-altering properties and its physiologic actions. In the first instance the euphoriant, relaxed state is exploited in attempts to treat tension, depression and other noxious affects. In the second instance the subjective psychic symptoms are unnecessary: in fact, they often become undesired side effects. Rather, it is the bronchopulmonary, cardiovascular, or opthalmic physiology that merits attention.

"Cannabis is a controversial plant these days. It evokes the widest spectrum of emotional reactions of adoration to revulsion that I have ever witnessed in response to a weed. We must be aware of the debate if only because it makes our findings more newsworthy than they are. Of course, we are deeply

*A recent review article is that of Bhargava (1978b).

interested in any report of adverse effects about cannabis because it relates to our current and future work with the agent. But beyond that, we cannot allow the extreme value judgments from either polar group to affect our studies. There is an appropriate Latin epigram whose author I do not remember. Translated it goes:

"Nothing is of itself good or evil, only the manner of usage makes it so."

The most noteworthy recent activity on therapeutic use has occurred in the legislative arena, not the medical. More than a dozen States have passed legislation and others are considering statutes permitting the use of marijuana or delta-9-THC for clinical research trials. These are being proposed for the management of the anorexia, nausea, and vomiting connected with cancer chemotherapy or for glaucoma, or both. A very few States have active programs in being at this time. The cannabis or delta-9-THC is being supplied by the NIDA: alternatively, confiscated material might be used. Recently the Federal Government has refused to reclassify cannabis or delta-9-THC from Schedule I (no medical usefulness, high potential for abuse) to Schedule II (medical usefulness, high abuse potential). However, new hearings are underway.

The initiatives of various States to make cannabis or its active ingredients available for clinical trial raise certain questions. How much will be learned from such research? Hopefully, each patient will be carefully studied, and the cannabinoids compared with the previously prescribed medications. Combinations of the cannabinoids with the conventional medications should also be considered, but undesired drug interactions would be a possibility. Since most of the patients with glaucoma and malignancies are in the older age groups, the effects of the cardioacceleratory property of cannabis will have to be taken into account (Nowlan and Cohen 1978). Furthermore, the cannabinoids used in treatment are intoxicating, and in many older people, sometimes anxiety-provoking. Questions of driving vehicles and operating other machinery will certainly arise following the use of these drugs if they are not carefully prescribed and supervised.

Another regulatory change has been the decision to permit women to serve as research subjects or patients under restricted conditions. Until recently, cannabis could not be legally administered to females who were capable of becoming pregnant because its teratologic risk had not been definitely assessed. It still has not, but the lack of information on the cannabis-induced endocrine changes that take place in females is considered more risky than excluding women from carefully safeguarded studies.

It may be worthwhile to deal with the therapeutic potential of cannabis by examining each of the various indications for its clinical use. Clearly, some of the reports are quite preliminary while others appear to have been satisfactorily substantiated.

It is evident that cannabis itself will hardly become officially accepted by the Food and Drug Administration. It contains over 400 identified chemical entities, the great majority of which are unnecessary or even undesirable for any therapeutic activity. What is much more likely is that delta-9-THC, cannabidiol or some synthetic variant will turn out to be the approved drug for specific therapeutic purposes.

Open Angle Glaucoma

Since the demonstration in 1971 (Hepler and Frank) that smoked marijuana significantly reduces intraocular pressure (IOP) in normal human subjects, the finding has been amply confirmed by others (Green 1979; Cuendet et al. 1976). Animal studies have also supported the observation. A number of investigations involving glaucoma patients have shown that ocular hypertension decreases of about 20 to 40 percent lasting 4-5 hours are measurable in the majority of those treated with smoked marijuana. Oral THC is also effective although activity is delayed, less reliable and more prolonged.

Oral delta-9-THC has been used in 10 to 20 mg doses in 15 glaucoma patients. (Hepler et al. 1976) When given alone, the drug was variably successful. When administered as a supplement to previously insufficiently effective medical treatment to eight patients, it was effective in five and partially effective in one. The psychic side effects were minor. Green et al. (1976) have attempted to explain the mechanism of action as a beta adrenergic stimulation by delta-9-THC that dilates the efferent blood vessels of the anterior uvea. Alpha adrenergic stimulation may also participate in the effect by reducing capillary pressure in the afferent vessels of the ciliary process. Those effects might be modulated through an inhibition of prostaglandin synthetase (Burstein 1976).

A logical extension of the work with chronic open angle glaucoma has been the development of delta-9-THC eye drops in a light mineral oil base. Their use in rabbits demonstrated an ocular hypotensive effect (Green 1978a), but their preliminary use in humans was found to be associated with irritation of the superficial ocular structures. Furthermore, there is some question whether the molecular configuration of delta-9-THC is small enough to diffuse readily into the uveal tract. A number of investigators have reported reduction in ocular hypertension with the topical administration of delta-9-THC (Green 1978a,b). In fact, Green (1976) also mentions a lesser effect on the untreated eye, indicating systemic absorption. Well-tolerated opthalmic drops (perhaps by decreasing the plasma concentration of delta-9-THC) would circumvent the issue of psychoactivity and tachycardia. Systemic absorption of the eye drops is insufficient to produce the well-known psychophysiological effects.

Another line of investigation is the use of ocular hypotensive cannabinoids with little or no central effects, such as delta-8-THC and 8-11-hydroxy-delta-8-THC. Work with these in glaucoma

remains at a preliminary level. Actually, delta-8-THC is at least as efficacious as the delta-9 analogue, and it is less psychoactive; therefore, it may be preferable as an anti-glaucoma preparation. Nabilone, a synthetic analogue, also produces few psychic effects and reduces the average IOP by 35, percent in glaucoma patients in oral doses of 0.5 mg. Topical nabilone will induce an equivalent ocular hypotension in the rabbit, but the eye drop preparation has been found irritating in humans. Except for its use as an opthalmic topical preparation nabilone is not being actively investigated because some dogs developed seizures and some humans manifested neurotoxicity.

Another important question remains only partially resolved. Does tolerance develop to the IOP-reducing effect? During the initial testing with smoked marijuana tolerance did not appear to occur. A ceiling effect was noted, however, in that the smoking of more than one cigarette (containing 19 mg of delta-9-THC) did not result in an additional decrease in eyeball pressure (Hepler et al. 1976). In a subsequent study, when large amounts of oral delta-9-THC were used, additional ingestion or smoking failed to cause a fall in pressure. It appears that tolerance to the intraocular hypotensive effect of the cannabinoids will depend (as in other instances of tolerance) upon the dose-time exposure. In the small amounts necessary to produce decreases in eyeball pressure, especially in topical preparations, it is not likely that tolerance will be a problem. No tolerance was detected after one year's ocular instillation of SP 106, a synthetic cannabinoid. (Green et al. 1977).

Crawford and Merritt (1979) compared eight normotensive and eight hypertensive glaucoma patients under conditions involving the smoking of 900 mg placebo cigarettes and of a similar cigarette containing 2.8 percent of delta-9-THC. In addition to the increase in heart rate they found a hypotensive effect, more significant in the systemic hypertensives. Although all the patients had a drop in their intraocular pressure, the hypertensive glaucoma patients had a significantly greater fall in eyeball pressure than the normotensive patients. The substantial decreases ($p = 0.01$) in sitting systolic and diastolic blood pressures produced by delta-9-THC in hypertensives has not been reported previously in humans.

Although formal studies have not yet been conducted on the issue, it appears from clinical notations that the effective cannabinoids show an additive effect when they are given with conventional anti-glaucoma medications like pilocarpine and acetazolamide (Diamox). This line of investigation might provide important clinical data in the future.

Asthma

The investigative pursuit of cannabis as a therapeutic tool for bronchospastic disorders has been slowed because of the confirmation that pulmonary complications are associated with

excessive chronic smoking, It is quite clear that the acute smoking of marihuana produces bronchodilation (Tashkir et al. 1974). However, consistent smoking may narrow the larger airways by about 20 percent (Tashkin, et al. 1978). This effect is secondary to the irritant effects of the coal tars that can produce chronic bronchitis in heavy smokers. Whether the bronchitis can evolve into obstructive lung disease (emphysema or fibrosis) remains undetermined experimentally.

Delta-9-THC is the major bronchodilator in cannabis, but it is a tracheobronchial irritant when smoked. Swallowed delta-9-THC has an antiasthmatic action, but it is delayed and unreliable due to variable absorption from the gastrointestinal tract.

Tashkin. et al. (1977) developed a Freon aerosol spray that was successful in producing bronchodilation in nonasthmatic subjects comparable to equivalent smoked dosages. Interestingly, 5 mg of aerosolized preparation provided a bronchodilation that was 80 percent of the 20 mg aerosolized dose. However, when used in patients with asthma, the procedure was not considered satisfactory because some of them complained of severe bronchial irritation. Two of five asthmatic patients developed bronchospasm rather than dilation. Delta-9-THC is so water insoluble that much of the aerosol appears to precipitate out in the upper airway and reaches the bronchioles through the systemic circulation rather than topically.

Vachon et al. (1976) provided a preliminary report of three asthmatics and two normal controls given either delta-9-THC in propylene glycol or the vehicle alone in a microaerosol spray. A significant and prolonged bronchodilation occurred without adverse side effects. When compared to an isoproterenol Medihaler, the latter produced a more rapid but shorter-acting effect on airway conductance. By using a dose of 0.5 mg of delta-9-THC, most of the systemic effects could be avoided. Problems remain, including the need to refrigerate the solution, whether microsprays are commercially feasible, and whether severe asthmatic attacks can be controlled by a delta-9-THC preparation. Williams et al. (1976) reported significant airway dilation in all 10 asthmatic patients using 0.2 mg of an aerosolized delta-9-THC preparation.

Another discouraging aspect of using cannabis for lung disorders is the finding that the smoke, like tobacco, contains carcinogens, co-carcinogens and cilia-toxic components (Cottrell et al. 1973, Hoffmann et al. 1975, Busch et al. 1979). As with tobacco, skin tumors have been produced on mouse skin using coal tars from cannabis. Pulmonary macrophage inhibition after exposure of rats to marijuana smoke has been found (Huber et al. 1978). Intrapulmonary bacterial inactivation to staphylococcus aureus occurred in a dose-dependent manner. The cytotoxin in marijuana is not delta-9-THC but other constituents of the smoke. Impairment of the pulmonary defense system may be clinically significant by decreasing resistance to bacterial pulmonary infections.

Oral delta-9-THC offers no advantages over available antiasthmatic preparations, especially in the light of the cardiac-accelerating and sometimes unpleasant psychic effects of cannabis. Whether an effective aerosol spray of THC can be developed in the future is undeterminable.

In a published letter, Shapiro et al. (1977) make the case for further studies of the cannabinoids for asthma. Despite its obvious disadvantages (tachycardia, mood alterations, impaired behavioral performance, bronchial irritation by the smoked material) there is a compelling reason to continue to study this group of drugs. They seem to have a novel mechanism of action, for it appears that delta-9-THC is neither a beta-adrenergic agonist in the bronchi, an antimuscarinic agent, or a phosphodiesterase inhibitor, as most antiasthmatic drugs are. Finding the mechanism of action may open up possibilities for new treatments of bronchospastic diseases. Other cannabinoids, natural or synthetic, may turn out to be effective and with fewer side effects than delta-9-THC.

Anorexia, Nausea and Vomiting in Cancer Chemotherapy, Irradiation and Anorexia Nervosa

Animal studies have both confirmed and not sustained the impression that the cannabinoids are antiemetics. Nabilone, the synthetic cannabis derivative, was tested against a number of emetic agents including antineoplastic drugs in unanesthetized cats (Borison et al. 1978). Nabilone provided pronounced protection against vomiting, in contrast to prochlorperazine (Compazine) which showed no antiemetic effect against mechlorethamine and against apomorphine (McCarthy and Borison 1977). Utilizing the dog and apomorphine-induced emesis (Shannon et al. 1978), delta-9-THC, chlorpromazine (Thorazine), the vehicle, or saline was given intravenously 30 minutes prior to the apomorphine infusion. Delta-9-THC had no effect upon the emetic dose of apomorphine, whereas chlorpromazine reduced it by 75 percent. Furthermore, delta-9-THC prolonged the total period of emesis and chlorpromazine reduced its duration. A number of mechanisms exist in controlling emesis, so that conflicting results may be expected.

Although antiemetic agents exist--thiethylperazine (Torecan), prochlorperazine, trimethobenzamide (Tigan), etc.--their effectiveness in controlling nausea and emesis caused by the present-day cancer therapeutic agents is variable. A number of studies involving smoked marijuana or oral delta-9-THC have been completed, and 22 are either underway or not yet published. In addition, chemotherapy patients have been known to use their own marijuana to deal with the chemotherapy treatments.

Regelson et al. (1976) in a comparison between delta-9-THC and

a placebo believed that the principal benefits to their cancer chemotherapy patients were improved appetite and the lack of an unexpected weight loss. Appetite enhancement and the lack of it have been mentioned in a few preclinical and clinical studies. Sedation, which in this group may or may not be desirable, occurred frequently. In a double-blind, crossover comparison of delta-9-THC 10 mg/sq meter body surface, Sallan et al. (1975) found an antiemetic effect in 70 percent of 22 patients during the drug course and in none during the placebo course. They believe that the antiemetic effect paralleled the subjective mood elevation. Butler and Regelson (1976) reported a nonsignificant difference between the placebo and delta-9-THC, although those who improved on placebos were all from the medication-first group. Delta-9-THC 0.15 to 0.3 mg/kg daily was given in three doses, the first prior to chemotherapy.

In a very preliminary analysis of their data in which prochlorperazine 10 mg, delta-9-THC 15 mg and both together were compared, Stevens and Goodwin (1979) indicate that "delta-9-THC may be of limited benefit when compared to prochlorperazine."

The National Cancer Institute protocol (Chang et al. 1979) compared 10 mg delta-9-THC/meter^2 with a placebo in 15 osteogenic sarcoma patients receiving high dose methotrexate (250 mg/kg) therapy. The chemotherapy was given every three weeks for 18 months. During Phase I each patient received either a placebo or delta-9-THC in randomized fashion. When an oral dose was not retained, delta-9-THC (17.4 mg) cigarettes or placebo cigarettes were substituted. The dosages were given five times beginning two hours prior to the methotrexate infusion. Delta-9-THC produced a reduction of nausea and vomiting in 14 of 15 patients as compared to the placebo periods. Fifty-three percent had more than an 80 percent reduction in vomiting, volume of emesis, and degree and duration of nausea. It was found that when plasma concentrations of delta-9-THC were 0 ng/ml (the placebo patients) nausea and/or vomiting occurred in 72 percent of the time periods. Concentrations of less than 5.0 ng/ml were associated with 44 percent, 5.0 to 10.0 ng/ml with 21 percent and 10.0 ng/ml with 6 percent of nausea and/or vomiting. Therefore blood levels are an important variable in the therapeutic efficiency of the drug. Only five dysphoric reactions of a total of 281 delta-9-THC drug doses were recorded. It should be remembered that these were hospitalized patients who did not need to ambulate. Sedation was a common side effect (80 percent). Feelings of "high" correlated with favorable results, probably because both co-varied with higher plasma levels of the active drug.

In Phase II four excellent responders to delta-9-THC were given subsequent courses of the drug. The results in all four were noted to be only fair. Two fair responders sustained no benefit from subsequent courses of delta-9-THC. The authors speculate about drug tolerance, but this is unlikely when delta-9-THC is given in short courses at tri-weekly intervals.

Appetite stimulation was not a significant finding. In addition to the methotrexate patients, five additional patients receiving adriamycin and cytoxan were also studied. Of these, two were fair responders and three were nonresponders to the delta-9-THC. This brings up the question of a variable antiemetic effect depending on the cytotoxic drug given.

Herman et al. (1979) did two double-blind studies comparing nabilone with prochlorperazine. Of 113 patients receiving anti-cancer chemotherapy, 80 percent responded to nabilone and 32 percent to prochlorperazine. Complete relief of symptoms occurred in only nine nabilone patients and no prochlorperazine patients. Both nausea and vomiting were less with nabilone, and the patients indicated a strong preference for it. Side effects, consisting of somnolence, dry mouth and dizziness, occurred twice as frequently with nabilone. Three patients on nabilone hallucinated and one became symptomatically hypotensive.

In a partial analysis of their first 66 patients in a 200-patient controlled crossover study of delta-9-THC vs prochlorperazine for the anorexia, nausea and vomiting following cancer chemotherapy, Ungerleider and Andrysiak (1979b) found that 25 patients preferred each of the two drugs, with 12 expressing no preference. Four patients did not respond to that item in the questionnaire. Drowsiness was the major side effect, with 20 patients on the cannabinoid and 15 on prochlorperazine mentioning that symptom.

Davies et al. (1974) report on what may be the first study of delta-9-THC during irradiation therapy for cancer. The problems of nausea and vomiting are not markedly dissimilar to cancer chemotherapy. Ten mg of delta-9-THC or an identical placebo was given prior to radiotherapy for seven days. No difference in appetite was noted between the two courses. The authors were more concerned about the drug's psychic effects than upon nausea. On rating scales the active drug produced more fatigue and confusion and less elation or vigor than the placebo,

Another first use of cannabinoids is a single case report from Ungerleider and Andrysiak (1979a). A woman with an inoperable cancer of the pancreas was treated with autologous bone marrow transplantation and high dose mitomycin. She had been treated with prochlorperazine 25 mg orally and secobarbital 75 mg intravenously with continued nausea, retching, anorexia and vomiting. After being placed on marijuana cigarettes containing 18 mg of delta-9-THC, she obtained good to excellent relief on an average of 1/2 of a cigarette whenever she felt nauseated. Special devices were necessary to provide sterile marijuana smoke in this case because such a patient has no resistance to infection.

In the first trial of delta-9-THC for primary anorexia nervosa, Gross et al. (1980) did a controlled study on 11 patients comparing delta-9-THC with diazepam. In addition, during the four-week crossover study, a behavior modification program was included. No significant changes in caloric intake, weight, the Situational Discomfort Scale scores, depression or anxiety were found between the two drugs. Delta-9-THC provided significantly higher scores for somatization, interpersonal sensitivity and sleep disturbance with the obsessive-compulsive behavior score approaching statistical significance ($p = 0.082$). It would appear that any appetite-enhancing property of delta-9-THC can hardly be expected to influence so profound a psychophysiological disturbance as anorexia nervosa.

Epilepsy

The major effort to determine the anticonvulsant and epileptogenic effects of various cannabinoids has used a variety of animal species. In general, antiseizure activity has been demonstrated to electrically-induced, audiogenic and pentylenetetrazol (Metrazol) seizures (Consroe et al. 1975). The anticonvulsant profile resembles that of phenytoin (Dilantin) more than that of phenobarbital. Antiepileptic effects were recently obtained in amygdaloid-kindled rats with delta-8-THC and delta-9-THC (Corcoran et al. 1978). Both isomers acutely suppressed kindled seizures, but consistent effects were obtained only with subtoxic doses. Repeated dosages of the cannabinoids resulted in tolerance development to the anticonvulsant action.

The hope that delta-9-THC might play a role in certain seizure disorders has been tempered by the reports of its convulsant properties in some animal species. EEG patterns of convulsive-like activity have been reported in rodents, dogs, cats, rabbits and monkeys (Feeney 1977). In addition, behavioral convulsions have been reported on occasion in rats, dogs and monkeys at high doses. Martin and Consroe(1976) present evidence that a strain of New Zealand white rabbits exhibit behavioral convulsions at intravenous doses of 0.05 mg/kg of delta-9-THC, an extremely low dose. Delta-8-THC, SP-111A, cannabinol and 11-hydroxy-delta-9-THC also produced convulsive episodes, but cannabidiol did not. Tolerance to the development of seizures occurred over a period of 4 to 10 days. After a week without exposure to the cannabinoids, sensitivity to behavioral seizures was reinstituted. Feeney (1977) has obtained comparable results in two other species: in the naturally epileptic beagle dog and in cats with focal epilepsy induced by injections of alumina cream. He has also reported temporal lobe seizures and myoclonus in dogs given a single oral dose of 5 mg/kg. The fact that delta-9-THC has both convulsant and anticonvulsant effects is unique.

Cannabidiol (CBD), essentially devoid of psychoactivity, is at least as effective as delta-9-THC as an antiseizure drug (Karler and Turkanis 1976). It apparently does not precipitate

convulsions in animals. However, there is a single case report of an increased epileptiform EEG pattern in a human epileptic after the administration of a relatively large intravenous dose of the drug (Perez-Reyes and Wingfield 1974). Nevertheless, CBD is a cannabinoid of minimal toxicity and proven anticonvulsive activity in animals; therefore trials in humans are definitely indicated. In a preliminary controlled study of 15 patients with generalized epilepsy secondary to a temporal lobe focus, who were poorly controlled on their current medication, Cunha et al. (1979) added 200-300 mg of CBD or a placebo to their current antiepileptic drugs for a period of 4½, months. Mild sedation was the only side effect noted in the CBD group. Three CBD patients showed complete improvement, two partial improvement, two minor improvement, and one was unchanged. Of the placebo patients, one improved markedly and seven were unchanged. It was concluded that CBD can assist certain seizure patients in improving when it is combined with their customary medicine. Whether CBD alone in larger doses could have produced a beneficial effect is unknown.

A third of youthful epileptic patients smoke marijuana, usually without mentioning this to their physicians. In a small survey of these individuals, they reported no particular effect of their cannabis use upon their seizure patterns (Feeney et al. 1976).

Insofar as synthetic analogues are concerned, Mechoulam and Carlini (1978) prepared a series of oxygenated CBD derivatives. They found that both the 6-oxo-CBD diacetate congener and CBD effectively protected mice from transcorneal electroshock convulsions.

Those analogues of dimethylheptylpyran which are soluble, well absorbed orally, and produce no psychotoxicity or tachycardia showed significant anticonvulsant activity against the standard seizure-inducing techniques in mice and rats at least equal to phenytoin. Short term tolerance to the antiseizure effect did not develop. On the other hand marked tolerance to the anti-epileptic activity of delta-9-THC over prolonged exposure has been suggested by Karler and Turkanis (1976).

Retardation of Tumor Growth

In mice inoculated with Lewis lung adenocarcinoma (Harris et al. 1976) a variable reduction in tumor size ranging from 25 to 82 percent depending on dose and duration of treatment with oral delta-9-THC, delta-8-THC and cannabinol was found. Survival time increased 25-34 percent compared to a 50 percent increase in survival with cyclophosphamide. L1210 murine leukemia was not inhibited by delta-9-THC. Replicating the inhibition of specific neoplasms in vitro, Harris et al. (1976) concluded that certain cannabinoids possess some antineoplastic capability. This may occur because these compounds interfere with RNA and

DNA synthesis. White et al. (1976) found that delta-9-THC inhibits replication after thymidine uptake and attributed this to the extreme lipophilia of delta-9-THC, and therefore its effects on the cell membrane. Cannabidiol may have a growth-enhancing effect on Lewis lung adenocarcinoma.

In itself, delta-9-THC cannot be considered an effective anti-tumor agent despite an attractive differential in inhibition of tritiated thymidine into DNA between Lewis lung tumor cells and bone marrow cells (Harris et al. 1976). The possibility remains that certain cannabinoids may prove to be useful as adjuncts to other chemotherapeutic agents. The impression that delta-9-THC and delta-8-THC are inferior to known antineoplastic drugs is reinforced by the equivocal findings of Friedman (1977) who did not find inhibition of thymidine- ^{3}H incorporation into DNA, leucine-^{3}H uptake into protein, or cytidine-^{3}H into RNA in his in vivo Lewis lung carcinoma study.

Antibiotic Action

A number of clinical investigations utilizing cannabis lotions and ointments as topical antibacterial agents were carried out at the Palacky University in Olomouc, Czechoslavakia (Krejci 1961). A variety of conditions were successfully treated including herpes labialis and otitis media. Cannabis irrigations sometimes outperformed tetracycline. A few osteomyelitic fistulas were healed with cannabis irrigations. In two cases of second degree burns, an analgesic effect is mentioned in addition to healing of the skin. More recently, it was found that delta-9-THC and cannabinol (CBN) were bacteriostatic or bacteriocidal against staphyllococci and streptococci in vitro (Van Klingerin and ten Ham 1976). When horse serum was introduced into the broth cultures, the antibacterial activity was essentially eliminated. Presumably, binding of the CBN and delta-9-THC to plasma proteins could have accounted for the inactivation. They were ineffective against Gram-negative organisms.

Even in these days of effective synthetic antibiotics, a role might possibly be found for topical cannabis preparations if further studies corroborate the Czechoslovakian work.

Antianxiety and Sleep-Inducing Effects

Like other sedatives, cannabis prolongs barbiturate sleeping time, reduces REM sleep periods and may increase Stage IV sleep (Freemon 1974). REM rebound could occur after abrupt discontinuance of the drug. When used as an hypnotic, Neu et al. (1976) found that it decreased sleep latency with fewer awakenings. Doses of 10, 20 or 30 mg of delta-9-THC tended to produce hangover effects in some subjects. In a second study utilizing 5, 10 and 15 mg of delta-9-THC, 500 mg of chloral hydrate or a placebo, no particular differences in sleep latency or duration were observed among the various drug schedules.

Cannabis users occasionally relate that the prime reason that they use the drug is to relax, unwind or decrease tensions. A few find it helpful in falling asleep. The sedative effect occurs most frequently; however, anxiety and dysphoria are also reported. This is especially true when intravenous delta-9-THC is taken, but it is also seen during oral ingestion and smoking. Somnolence is also listed as a side effect in many of the research studies in which sedation is not desired.

Muscle Relaxant

Only individual case reports are available to suggest a muscle relaxant effect of cannabis, and animal models for neuromuscular spasm have been only infrequently used (Passatore et al. 1975). A significant decrease of both twitch and tetanic contractions of the gastrocnemius muscle of adult mice following super-maximal stimulation of the sciatic nerve after chronic delta-9-THC treatment has been demonstrated.

When 10 paraplegics were questioned (Dunn and Davis 1974) about the effects of their marijuana use upon their symptoms, four reported a decrease in phantom pain sensations, five mentioned a decrease in muscle spasticity, with three noting no improvement and two not having significant spasticity. The results of smoking also had an inconsistent effect upon bladder spasms.

Fourteen patients with either lower motor neurone lesions due to spinal cord trauma or multiple sclerosis were said to have a reduced muscle spasticity in connection with their cannabis use (Petro and Ellenberger 1979). Neurological examinations before and after cannabis smoking showed evidence of decreased clonus and muscle spasticity.

Preanesthetic

The possibility that delta-9-THC could be employed as a pre-anesthetic agent has been fairly well explored (Smith & Kulp 1976). The consensus is that the drug has no important role to play for this therapeutic application. Problems of syncopal hypotension, respiratory depression and excessive, serious sedation when delta-9-THC is combined with other preoperative medications make for unacceptable adverse reactions. Most of the investigators have reported serious anxiety when delta-9-THC is given intravenously, which it must be for preoperative purposes. The dysphoric response under these conditions may represent a combination of setting, set and the effects of rapid onset of the autonomic and psychic symptoms of delta-9-THC. These problems in addition to the cardiac accelerating property make it an undesirable medication to use prior to surgery.

Pain

The folk use of cannabis includes numerous references to its pain-allaying qualities. It was traditionally given for toothache, dysmenorrhea, difficult childbirth, neuralgia and rheumatism in those lands where it grew wild.

Preclinical tests in general confirm an analgesic property by demonstrating an elevation of pain thresholds and an attenuation of the escape response to painful stimuli (Parker and Dubas 1973). Delta-9-THC was found to be equipotent to morphine in some tests (hot plate, acetic acid writhing), but not in others (paw pressure) (Sofia et al. 1975).

Some nondefinitive human studies have been done. Milstein et al. (1975) reported an increased pain tolerance, but only in the preferred hand. There was a trend for experienced smokers to have elevated pain thresholds as compared to inexperienced smokers although this variable did not achieve significance. Hill et al. (1974) recorded a double-blind study of smoke from a placebo vs. smoke containing 12 mg of delta-9-THC. Delta-9-THC was found to decrease pain tolerance and heighten pain sensitivity in response to electrical skin stimulation.

Raft and associates (1977) gave intravenous diazepam (0.157 mg/kg), delta-9-THC (0.22 mg/kg) and (0.44 mg/kg) and a placebo to ten students undergoing elective removal of all four impacted third molars. Lidocaine was used as a local anesthetic. In addition, measurements of experimental pain were employed: a strain gauge algometer and an electrocutaneous stimulus to the skin. Pain detection thresholds (discomfort) were elevated with the high dose of delta-9-THC, but pain tolerance (unbearable pain) was less than after diazepam and placebo. Delta-9-THC was not considered to be a true analgesic for either experimental or surgical pain. Instead, it was believed to alter pain responsivity on the basis of the emotion evoked (anxiety or euphoria) and a disruption of sensory interpretive capacities.

Similarly, Cooler and Gregg (1976) were unable to demonstrate an analgesic effect of delta-9-THC in human volunteers as measured by periosteal pressure stimulation or by cutaneous pain thresholds utilizing intravenous doses of 1.5 and 3 mg of delta-9-THC, 10 mg of diazepam or a placebo.

Cancer patients requiring analgesics were treated with either a placebo or delta-9-THC, 10 or 20 mg orally, by Noyes et al. (1975). It was concluded from the study that delta-9-THC was a mild analgesic. In a dose of 20 mg it was prohibitively sedating and intoxicating. The 10 mg dose only rarely presented such problems. Blurred vision and impaired thinking were also recorded. Appetite stimulation, mood elevation and feelings of relaxation were occasionally noted.

323-754 0 - 80 - 15

Butler and Regelson (1976) in a broad study of delta-9-THC effects on advanced cancer patients found no appreciable anti-pain response to 0.15 and 0.3 mg/kg of delta-9-THC as compared to a placebo.

It was found that much of the analgesic effect of delta-9-THC was in its 11-hydroxy metabolite (Wilson and May 1974). The 9-nor derivative that cannot form 11-hydroxy compounds in vivo does not possess analgetic action. Synthesis of 9-nor-9-ß-hydroxy-hexahydrocannabinol proved it to be a potent analgesic approximately equivalent to morphine. Harris (1976) attempted to reverse the 9-nor-9-ß-hydroxyhexahydrocannibinol antinociceptive effect with naloxone and was not able completely to reverse its activity. Nor could cross tolerance between this compound and morphine be demonstrated.

Depression

Cannabis has been used for melancholia in many cultures in which it is a folk medicine. Pyrahexyl (Synhexyl) was used by physicians during the 1950s for depression: in fact, Parker and Wrigley's (1950) study may have been the first in which a double-blind design was used with a cannabinoid. The results of this study were negative. Nor did Kotin et al. (1973) find any difference from a placebo in his one-week study using 0.3 mg/kg of delta-9-THC in depressed patients. Many antidepressant drugs require longer periods of time before their therapeutic effect becomes discernible.

The studies performed for the amelioration of nausea and vomiting in cancer patients may be able to make a contribution to the question of an antidepressant action. Regelson et al. (1976) found that delta-9-THC acted as a mood elevator and tranquilizer as measured by the Zung test. Decisive studies of unipolar and bipolar depressions utilizing delta-9-THC have not yet been done.

Alcoholism and Drug Dependence

The use of marijuana as a reward for certain alcoholics to stay on disulfiram (Antabuse) has been suggested by Rosenberg et al; (1978). No drug interaction appears to occur between the two substances. However cannabis alone or in combination with disulfiram was not particularly effective in inducing alcoholics to enter or remain in treatment. Some evidence exists that cannabis and alcohol produce cross tolerance.

After making rats morphine dependent by implanting pellets, Hine et al. (1975a,b) injected them with delta-9-THC, 1,2,5 or 10 mg/kg daily. Naloxone 4 mg/kg was then injected and attenuation of the abstinence syndrome in two of the nine rated abstinence symptoms was noted. The authors believe that a trial of delta-9-THC in opiate detoxification is justified. This study was

partially replicated by Bhargava (1976) in mice with delta-9-, delta-8, and 11-hydroxy-delta-8-THC. Carder (1975) points out that in the Hine study mentioned above, the effects of delta-9-THC and CBD in suppressing only two of nine naloxone-precipitated morphine abstinence symptoms is not impressive. It could be accounted for by the nonspecific depressant activity of the cannabinoids.

Ten morphine-dependent rats were injected with delta-9-THC twice daily in increasing doses for five weeks, reaching 40 mg/kg during the last three weeks (Bhargava 1978a,b). Ten morphine-dependent controls received the vehicle. On the 22nd and 31st days naloxone precipitated an abstinence syndrome, as did cessation of the delta-9-THC on day 35. The most common abstinence signs noted were tooth chattering, defecation, urination, dyspnea and complete palpebral closure. In the delta-9-THC group infrequent tremors, chewing and eating of objects, escape behavior, sniffing, biting of fingers and increased locomotor activity were observed. These symptoms peaked 48 hours after withdrawal.

The value of finding a new detoxification agent to ameliorate opiate withdrawal is not an important clinical need. A more important issue is whether the psychoactive cannabinoids interpose at the endorphin binding sites. This point is not yet settled.

SUMMARY

Twelve categories of symptoms or of disease states have been considered in relation to a potential ameliorative effect by cannabis or one of its derivatives. To sumnarize the state of the art insofar as the cannabinoids' role as therapeutic agents is concerned is difficult, but an overall impression will be attempted here.

Not only the effectiveness of the drug, but also the need for new treatment products will be considered in the evaluation.

1. Glaucoma. An acceptable topical preparation will benefit certain patients not helped by the conventional medications. It will have to contain less than 0.5 percent of delta-9-THC. A superior synthetic analogue may be found.

2. Asthma. Elucidating the mechanism of action of the cannabinoids be more important than attempting to produce a non-irritating aerosol.

3. Antiemetic. It appears that cannabis has definite, but not invariable antinauseant and antiemetic capabilities. It is at least comparable to our standard antiemetics, and may offer relief to those who are currently not benefitted by them.

Combinations of cannabis plus the standard drugs used for vomiting should be tried in future studies.

4. Epilepsy. Cannabidiol deserves further clinical trials in humans as an anticonvulsant alone or with established antiseizure drugs.

5. Tumor Growth Inhibition. Although, of interest, it does not appear that the cannabinoids will make a contribution in this area. What may be of concern is that tumor growth inhibitors are invariably cellular toxins to normal cells depending on the dosage since they interfere with cellular metabolism. Therefore delta-9-THC should be studied further for a possible cytotoxic effect in dosage levels used by humans.

6. Topical Antibiotics. The earlier Czechoslovakian work requires confirmation utilizing double-blind procedures and appropriate controls.

7. Antianxiety and Insomnia. While the cannabinoids seem to have sedative-hypnotic activity, they are inconstant and not comparable to existing medications for that purpose. Sometimes paradoxical anxiety and panic states intervene.

8. Muscle Relaxant. Although the work is quite preliminary, the effort to determine whether cannabis or its derivatives can make a contribution to the management of musculospastic disorders should continue.

9. Preanesthetic. It does not appear that the cannabinoids have any future for this indication.

10. Pain. Unless new synthetic compounds are found, it is difficult to believe that the available cannabinoids can compete with current analgesics.

11. Depression. This indication has not been convincingly investigated, and no conclusions can be drawn.

12. Alcoholism and Drug Dependence. It is not likely, from the work available that the cannabis group will make a substantial impact on the treatment of the alcoholic or the drug-dependent person.

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