

ALASKA LEGISLATURE COMMITTEE FILES 1987-1988 8672  
5299 SJUD SB 32 (file 1)

87

STATE OF ALASKA 1987 LEGISLATIVE SESSION  
FISCAL NOTE

Bill Version: CSSB 32 (HESS)

Publish Date: \_\_\_\_\_

REQUEST  
Revision Date: \_\_\_\_\_  
Title: "An Act relating to the re-criminalization of marijuana.."  
Sponsor: Sen. Fischer  
Requestor: Senate Judiciary

Agency Affected: Public Safety  
BRU: Alaska State Troopers

Components: Detachments & CIB  
Narcotics

EXPENDITURES/REVENUES: (Thousands of Dollars)

OPERATING	FY 87	FY 88	FY 89	FY 90	FY 91	FY 92
PERSONAL SERVICES						
TRAVEL						
CONTRACTUAL						
SUPPLIES						
EQUIPMENT						
LAND & STRUCTURES						
GRANTS, CLAIMS						
MISCELLANEOUS						
TOTAL OPERATING		0	0	0	0	0
CAPITAL						
REVENUE						

FUNDING:: (Thousands of Dollars)

GENERAL FUNDS		0	0	0	0	0
FEDERAL FUNDS						
OTHER						
TOTAL						

POSITIONS:

FULL-TIME		0	0	0	0	0
PART-TIME						
TEMPORARY						

ANALYSIS: (Attach a separate page if necessary)

No fiscal impact is anticipated.

Prepared by: Francis C. Allan  
Division: Alaska State Troopers

Phone: 269-5691

Date: 4/8/87

Approved by Commissioner: William R. Nix  
Agency: Public Safety

Date: 4/8/87

Distribution (by preparer):

- Legislative Finance
- Legislative Sponsor
- Requestor
- Office of Management and Budget
- Impacted Agency(ies)
- Senate Secretary

page \_\_\_\_ of \_\_\_\_

*JWA*  
*4/8/87*

**STATE OF ALASKA 1987 LEGISLATIVE SESSION  
FISCAL NOTE**

Bill Version: SB 32  
Publish Date:

**REQUEST:** \_\_\_\_\_

Revision Date:  
Title: An act relating to marijuana

Agency Affected: Alaska Court System  
BRU: Trial Courts

Sponsor: Fisoner  
Requestor: Senate Judiciary

Components:

<b>EXPENDITURES/REVENUES:</b>		(Thousands of Dollars)				
	FY 87	FY 88	FY 89	FY 90	FY 91	FY 92
OPERATING						
Personal Services	. . . .	143.6	143.6	143.6	143.6	143.6
Travel	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
Contractual	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
Supplies	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
Equipment	. . . .	11.5	. . . .	. . . .	. . . .	. . . .
Land & Structures	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
Grants & Claims	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
<b>TOTAL OPERATING</b>	<b>0.0</b>	<b>155.1</b>	<b>143.6</b>	<b>143.6</b>	<b>143.6</b>	<b>143.6</b>
<b>CAPITAL</b>	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
<b>REVENUE</b>	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .

<b>FUNDING:</b>		(Thousands of Dollars)				
	FY 87	FY 88	FY 89	FY 90	FY 91	FY 92
General Funds	0.0	155.1	143.6	143.6	143.6	143.6
Federal Funds	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
Other	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .
<b>TOTAL</b>	<b>0.0</b>	<b>155.1</b>	<b>143.6</b>	<b>143.6</b>	<b>143.6</b>	<b>143.6</b>

<b>POSITIONS:</b>		FY 87	FY 88	FY 89	FY 90	FY 91	FY 92
Full-time	. . . .	4.0	4.0	4.0	4.0	4.0	4.0
Part-time	. . . .	1.0	1.0	1.0	1.0	1.0	1.0
Temporary	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .	. . . .

**ANALYSIS:** (Attach a separate page if necessary)

See attached fiscal analysis.

Prepared by: Karla Forsythe, General Counsel  
Division: Alaska Court System  
Approved by: *Stephanie J. Cole* Stephanie J. Cole, Deputy Director  
Agency: Alaska Court System

Phone: 264-8228  
Date: 4-23-87  
Date: 4-23-87

- Distribution (by preparer):  
Legislative Finance  
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Requestor  
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Impacted Agency(ies)  
Senate Secretary

ALASKA COURT SYSTEM  
SB 32 - Fiscal Analysis

The Court System's fiscal note is based on the assumption that this bill will be enforced if enacted into law. The fiscal note submitted by the Department of Law reports that enforcement personnel anticipate several thousand new cases. This figure does not include prosecution resulting from municipal enforcement. Municipal police will generate a significant volume of cases for the courts, since they are responsible for enforcement in Alaska's urban communities and are more likely to arrest a large number of individuals than state troopers who focus on organized drug activity.

Using a conservative estimate of 2,000 cases annually, it appears that the increased caseload could be absorbed with existing judicial resources, but additional clerical support would be needed to process the high volume of paperwork attributable to these new criminal offenses which will be entering the criminal justice system.

ALASKA COURT SYSTEM  
SB 32 - Fiscal Analysis

Personal Services:

	Salary	Benefits	Total
2 - Court Clerk II, Range 10B, Anchorage, PFT - 12 months	\$45,672	\$16,580	\$62,252
1 - Court Clerk II, Range 10B, Fairbanks, PFT - 12 months	25,740	8,936	34,676
1 - Court Clerk II, Range 10B, Juneau, PFT - 12 months	22,836	8,290	31,126
1 - Court Clerk II, Range 10B, Ketchikan, PPT - 6 months	11,418	4,145	15,563 -----
Total Personal Services			143,617

Equipment: (one-time cost)

Desk, chair, typewriter, and filing cabinet for each new position	11,540 -----
Total First-Year Cost	\$155,157 =====

# Marijuana and Health

Report of a Study  
by a Committee of the  
INSTITUTE OF MEDICINE  
Division of Health Sciences Policy

NATIONAL ACADEMY PRESS  
Washington, D.C. 1982

NOTICE The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 Congressional charter responsibility to be an advisor to the federal government, and its own initiative in identifying issues of medical care, research, and education.

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Study of the Health-Related Effects of  
Cannabis and Its Derivatives

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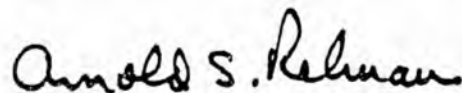
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- Arthur Zimmerman, University of Toronto

## PREFACE

This report is the work of the many people identified in the preceding pages, and to all of them I am very grateful. I particularly wish to thank my distinguished colleagues on the study committee, upon whose expert knowledge and critical judgment this report rests. They responded conscientiously to all the demands placed on them, and they did so with a promptness and grace that made my task easy.

No study of this kind can be carried out without the help of a skilled staff. We were fortunate to have had the assistance of a devoted and highly capable staff team led by Enriqueta C. Bond and Linda S. Dujack. They coordinated the efforts of the committee, the panel, the consultants, and the Institute of Medicine staff, and they played the key role in keeping everything on schedule. Moreover, they carried out this formidable task with tact and common sense. On behalf of the committee, I wish publicly to acknowledge our indebtedness to the IOM staff, and I also wish to express my personal thanks to Drs. Bond and Dujack for their unfailing support and cooperation.

Finally, I wish to acknowledge my appreciation of the editorial assistance of Wallace K. Waterfall, whose expert touch is evident throughout this document. Our aim was to write a report in "a clear and incisive form for the general public." Any success that we may have achieved is due in no small measure to his efforts.



Arnold S. Relman, M.D.  
Chairman

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# Marijuana and Health

## SUMMARY

The Institute of Medicine (IOM) of the National Academy of Sciences has conducted a 15-month study of the health-related effects of marijuana, at the request of the Secretary of Health and Human Services and the Director of the National Institutes of Health. The IOM appointed a 22-member committee to:

- analyze existing scientific evidence bearing on the possible hazards to the health and safety of users of marijuana;
- analyze data concerning the possible therapeutic value and health benefits of marijuana;
- assess federal research programs in marijuana;
- identify promising new research directions, and make suggestions to improve the quality and usefulness of future research; and
- draw conclusions from this review that would accurately assess the limits of present knowledge and thereby provide a factual, scientific basis for the development of future government policy.

This assessment of knowledge of the health-related effects of marijuana is important and timely because marijuana is now the most widely used of all the illicit drugs available in the United States. In 1979, more than 50 million persons had tried it at least once. There has been a steep rise in its use during the past decade, particularly among adolescents and young adults, although there has been a leveling-off in its overall use among high school seniors in the past 2 or 3 years and a small decline in the percentage of seniors who use it frequently. Although substantially more high school students have used alcohol than have ever used marijuana, more high school seniors use marijuana on a daily or near-daily basis (9 percent) than alcohol (6 percent). Much of the heavy use of marijuana, unlike alcohol, takes place in school, where effects on behavior, cognition, and psychomotor performance can be particularly disturbing. Unlike alcohol, which is rapidly metabolized and eliminated from the body, the psychoactive components of marijuana persist in the body for a long time. Similar to alcohol, continued use of marijuana may cause tolerance and dependence. For all these reasons, it is imperative that we have reliable and detailed

information about the effects of marijuana use on health, both in the long and short term.

What, then, did we learn from our review of the published scientific literature? Numerous acute effects have been described in animals, in isolated cells and tissues, and in studies of human volunteers; clinical and epidemiological observations also have been reported. This information is briefly summarized in the following paragraphs.

#### EFFECTS ON THE NERVOUS SYSTEM AND ON BEHAVIOR

We can say with confidence that marijuana produces acute effects on the brain, including chemical and electrophysiological changes. Its most clearly established acute effects are on mental functions and behavior. With a severity directly related to dose, marijuana impairs motor coordination and affects tracking ability and sensory and perceptual functions important for safe driving and the operation of other machines; it also impairs short-term memory and slows learning. Other acute effects include feelings of euphoria and other mood changes, but there also are disturbing mental phenomena, such as brief periods of anxiety, confusion, or psychosis.

There is not yet any conclusive evidence as to whether prolonged use of marijuana causes permanent changes in the nervous system or sustained impairment of brain function and behavior in human beings. In a few unconfirmed studies in experimental animals, impairment of learning and changes in electrical brain-wave recordings have been observed several months after the cessation of chronic administration of marijuana. In the judgment of the committee, widely cited studies purporting to demonstrate that marijuana affects the gross and microscopic structure of the human or monkey brain are not convincing; much more work is needed to settle this important point.

Chronic relatively heavy use of marijuana is associated with behavioral dysfunction and mental disorders in human beings, but available evidence does not establish if marijuana use under these circumstances is a cause or a result of the mental condition. There are similar problems in interpreting the evidence linking the use of marijuana to subsequent use of other illicit drugs, such as heroin or cocaine. Association does not prove a causal relation, and the use of marijuana may merely be symptomatic of an underlying disposition to use psychoactive drugs rather than a "stepping stone" to involvement with more dangerous substances. It is also difficult to sort out the relationship between use of marijuana and the complex symptoms known as the amotivational syndrome. Self-selection and effects of the drug are probably both contributing to the motivational problems seen in some chronic users of marijuana.

Thus, the long-term effects of marijuana on the human brain and on human behavior remain to be defined. Although we have no convincing evidence thus far of any effects persisting in human beings after cessation of drug use, there may well be subtle but important physical and psychological consequences that have not been recognized.

## EFFECTS ON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

There is good evidence that the smoking of marijuana usually causes acute changes in the heart and circulation that are characteristic of stress, but there is no evidence to indicate that a permanently deleterious effect on the normal cardiovascular system occurs. There is good evidence to show that marijuana increases the work of the heart, usually by raising heart rate and, in some persons, by raising blood pressure. This rise in workload poses a threat to patients with hypertension, cerebrovascular disease, and coronary atherosclerosis.

Acute exposure to marijuana smoke generally elicits broncho-dilation; chronic heavy smoking of marijuana causes inflammation and pre-neoplastic changes in the airways, similar to those produced by smoking of tobacco. Marijuana smoke is a complex mixture that not only has many chemical components (including carbon monoxide and "tar") and biological effects similar to those of tobacco smoke, but also some unique ingredients. This suggests the strong possibility that prolonged heavy smoking of marijuana, like tobacco, will lead to cancer of the respiratory tract and to serious impairment of lung function. Although there is evidence of impaired lung function in chronic smokers, no direct confirmation of the likelihood of cancer has yet been provided, possibly because marijuana has been widely smoked in this country for only about 20 years, and data have not been collected systematically in other countries with a much longer history of heavy marijuana use.

## EFFECTS ON THE REPRODUCTIVE SYSTEM AND ON CHROMOSOMES

Although studies in animals have shown that  $\Delta$ -9-THC (the major psychoactive constituent of marijuana) lowers the concentration in blood serum of pituitary hormones (gonadotropins) that control reproductive functions, it is not known if there is a direct effect on reproductive tissues. Delta-9-THC appears to have a modest reversible suppressive effect on sperm production in men, but there is no proof that it has a deleterious effect on male fertility. Effects on human female hormonal function have been reported, but the evidence is not convincing. However, there is convincing evidence that marijuana interferes with ovulation in female monkeys. No satisfactory studies of the relation between use of marijuana and female fertility and child-bearing have been carried out. Although  $\Delta$ -9-THC is known to cross the placenta readily and to cause birth defects when administered in large doses to experimental animals, no adequate clinical studies have been carried out to determine if marijuana use can harm the human fetus. There is no conclusive evidence of teratogenicity in human offspring, but a slowly developing or low-level effect might be undetected by the studies done so far. The effects of marijuana on reproductive function and on the fetus are unclear; they may prove to be negligible, but further research to establish or rule out such effects would be of great importance.

Extracts from marijuana smoke particulates ("tar") have been found to produce dose-related mutations in bacteria; however,  $\Delta$ -9-THC, by itself, is not mutagenic. Marijuana and  $\Delta$ -9-THC do not appear to break chromosomes, but marijuana may affect chromosome segregation during cell division, resulting in an abnormal number of chromosomes in daughter cells. Although these results are of concern, their clinical significance is unknown.

#### THE IMMUNE SYSTEM

Similar limitations exist in our understanding of the effects of marijuana on other body systems. For example, some studies of the immune system demonstrate a mild, immunosuppressant effect on human beings, but other studies show no effect.

#### THERAPEUTIC POTENTIAL

The committee also has examined the evidence on the therapeutic effects of marijuana in a variety of medical disorders. Preliminary studies suggest that marijuana and its derivatives or analogues might be useful in the treatment of the raised intraocular pressure of glaucoma, in the control of the severe nausea and vomiting caused by cancer chemotherapy, and in the treatment of asthma. There also is some preliminary evidence that a marijuana constituent (cannabidiol) might be helpful in the treatment of certain types of epileptic seizures, as well as for spastic disorders and other nervous system diseases. But, in these and all other conditions, much more work is needed. Because marijuana and  $\Delta$ -9-THC often produce troublesome psychotropic or cardiovascular side-effects that limit their therapeutic usefulness, particularly in older patients, the greatest therapeutic potential probably lies in the use of synthetic analogues of marijuana derivatives with higher ratios of therapeutic to undesirable effects.

#### THE NEED FOR MORE RESEARCH ON MARIJUANA

The explanation for all of these unanswered questions is insufficient research. We need to know much more about the metabolism of the various marijuana chemical compounds and their biologic effects. This will require many more studies in animals, with particular emphasis on subhuman primates. Basic pharmacologic information obtained in animal experiments will ultimately have to be tested in clinical studies on human beings.

Until 10 or 15 years ago, there was virtually no systematic, rigorously controlled research on the human health-related effects of marijuana and its major constituents. Even now, when standardized marijuana and pure synthetic cannabinoids are available for experimental studies, and good qualitative methods exist for the

measurement of  $\Delta$ -9-THC and its metabolites in body fluids, well-designed studies on human beings are relatively few. There are difficulties in studying the clinical effects of marijuana in human beings, particularly the effects of long-term use. And yet, without such studies the debate about the safety or hazard of marijuana will remain unresolved. Prospective cohort studies, as well as retrospective case-control studies, would be useful in identifying long-term behavioral and biological consequences of marijuana use.

The federal investment in research on the health-related effects of marijuana has been small, both in relation to the expenditure on other illicit drugs and in absolute terms. The committee considers the research particularly inadequate when viewed in light of the extent of marijuana use in this country, especially by young people. We believe there should be a greater investment in research on marijuana, and that investigator-initiated research grants should be the primary vehicle of support.

The committee considers all of the areas of research on marijuana that are supported by the National Institute on Drug Abuse to be important, but we did not judge the appropriateness of the allocation of resources among those areas, other than to conclude that there should be increased emphasis on studies in human beings and other primates. Recommendations for future research are presented at the end of Chapters 1-7 of this report.

#### CONCLUSIONS

The scientific evidence published to date indicates that marijuana has a broad range of psychological and biological effects, some of which, at least under certain conditions, are harmful to human health. Unfortunately, the available information does not tell us how serious this risk may be.

Our major conclusion is that what little we know for certain about the effects of marijuana on human health--and all that we have reason to suspect--justifies serious national concern. Of no less concern is the extent of our ignorance about many of the most basic and important questions about the drug. Our major recommendation is that there be a greatly intensified and more comprehensive program of research into the effects of marijuana on the health of the American people.

## INTRODUCTION

The Institute of Medicine (IOM) of the National Academy of Sciences has undertaken this review and analysis of the health-related effects of marijuana\* at the request of the Secretary of the Department of Health and Human Services (DHHS) and the Director of the National Institutes of Health (NIH).

~~Scientific controversy and public confusion about marijuana continue unabated and perhaps even are expanding,~~ notwithstanding numerous reports on the topic from authoritative agencies and organizations (Fifth, Sixth, Seventh, and Eighth Annual Reports from the Secretary of Health, Education and Welfare to the Congress on Marijuana and Health; Fehr, et al., Cannabis: Adverse Effects on Health, 1980a; Tinklenberg, Marijuana and Health Hazards and Marijuana in the '80s, a report of the Council on Scientific Affairs, the American Medical Association, 1980). Increasing use of this substance and growing concern about its possible long- and short-term consequences for human health have added some urgency to the need for reassessment of the available data. Interest has been further heightened by recent suggestions that marijuana may also have some medical therapeutic value, which only intensifies the debate about what our public policy towards marijuana ought to be.

With this as background, the Secretary of Health, Education, and Welfare, Joseph A. Califano, Jr., in a press statement on April 18, 1979, announced the intention of his department to undertake a review that would ". . . assess the information and scientific work now available on the effects of marijuana." He followed that with a memorandum on May 16, 1979, to Donald S. Fredrickson, Director of NIH in which he further stated:

This review must be undertaken by an independent scientific body that has not staked out a position in this highly controversial field. This review should be conducted by a

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\*The terms marijuana and cannabis will be used interchangeably in this report. Strictly speaking, they are not synonymous; cannabis is the more general term. (See Glossary, page 9.)

group of distinguished biomedical and clinical scientists and should involve thorough, systematic review and analysis of the research literature. . . . The report should identify the most urgently needed and promising lines of inquiry to build a firmer base for decision-making in years to come. The information should be available in a clear and incisive form for the general public.

While the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and its National Institute on Drug Abuse (NIDA) have provided leadership in research related to biological and health effects of marijuana, it is most important that we have a review by an independent nongovernmental body, such as the Institute of Medicine. In order to avoid even the appearance of a conflict of interest, inasmuch as this review will cover part of the research plan of ADAMHA-NIDA, I believe it is important that the National Institutes of Health serve as the responsible DHHS agency for seeing that such a review is conducted.

Following Mr. Califano's resignation, subsequent secretaries have confirmed to the Director of the NIH their desire to see this review carried forward. Accordingly, a contract between the NIH and the IOM was executed to provide for a study to commence September 30, 1980, and be completed by December 29, 1981.

#### THE COMMITTEE'S TASK

Under this contract, the IOM agreed to appoint a committee to:

1. analyze existing scientific evidence bearing on the possible hazards to the health and safety of users of marijuana;
2. analyze data concerning the possible therapeutic value and health benefits of marijuana;
3. assess federal research programs in this area;
4. identify promising new research directions, and make suggestions to improve the quality and usefulness of future research;
5. draw conclusions from this review that would accurately assess the limits of present knowledge and thereby provide a factual, scientific basis for the development of future government policy. Such an assessment also should be helpful to private citizens who want to make their own informed decisions about this subject.

The committee's charge specifically excluded the analysis or formulation of public policy.

#### PROCEDURE FOR THE STUDY

Primary responsibility for the conduct of the study was vested in a steering committee of 22 biologists, behavioral scientists, and

clinicians. Although they all were experts in relevant disciplines, only a few had previously been involved in the study of marijuana or had taken public positions on the subject. The committee was divided into six panels, each concerned with major scientific areas: cardiovascular and respiratory system effects; neurobiological effects; epidemiological, behavioral, and psychosocial effects; reproductive biology and effects on the fetus; pharmacology, cell biology, and immunology; and genetic and oncogenic effects. Each panel was chaired by a member of the committee and usually had one or more additional committee members and several expert consultants, whose names appear in the front of this report. The committee also consulted with many other experts in the course of its work and received valuable help from many persons and organizations.

The full committee met five times to coordinate and assess its progress. In the intervals between these meetings, the panels held their own independent sessions and various ad hoc working groups met as necessary. The chairman and members of the committee staff were invited observers at the Conference on Adverse Health and Behavioral Consequences of Cannabis Use, which was sponsored by the Addiction Research Foundation (ARF) of Ontario and the World Health Organization (WHO) and held in Toronto, Canada, from March 30 to April 3, 1981. Other members of our committee served as working members of that conference. We were also fortunate in being able to work closely with members of the ARF/WHO conference staff and having access to all the documents prepared for the Canadian meeting as well as the revised draft of the summary report of the conference (1981).

The committee began by systematically reviewing all the literature published since 1975 on marijuana and related subjects, which had been collected by our staff through a Medline computer search. Earlier literature was selectively examined, as were a variety of other documents, reviews, and monographs on the subject. Our objective was not merely to compile and summarize, but also to evaluate the evidence critically and, with the aid of our consultants, form some judgment of the quality and reliability of the work. Our report is an assessment of what is and is not known, based on our best interpretations of the scientific literature. We confined our attention to published scientific articles as the primary sources of information, relying heavily on experts in each field to select the relevant papers and help us interpret the data.

To obtain additional information and opinions from the public and from professional groups on the health-related effects of marijuana, we solicited written responses in a notice in the Federal Register of February 24, 1981. Responses were received and incorporated into the records of the committee. (See Appendix A for a complete description.) The responses fell into three categories:

1. The dangers of marijuana. Letters in this category came from mothers whose children were using or had used marijuana. These parents believed that drug use by their children led to a lack of motivation and loss of interest in school and other activities. Letters about the harmfulness of the use of marijuana were also received from physicians and scientists.

2. The therapeutic potential of marijuana. Half of the responses were from people who used marijuana illegally for various medical problems and who urged that it be made easily available to patients. Several letters submitted by legislators and doctors described problems in obtaining marijuana for therapeutic use (see Appendix B). A group interested in the legitimate medical use of cannabis emphasized the need for continuing investigation into the numerous constituents of the marijuana plant for therapeutic uses.

3. Support of general use and legalization of marijuana. Letters were received from individuals and groups favoring the use of marijuana and actively promoting its legalization.

This report covers most of the concerns expressed by the public, except the question of legalization. The various statements included many opinions and much anecdotal evidence from laymen and scientists. The committee took note of this material, but has not cited any of it in this report unless it was supported by published data in the scientific literature.

#### THE ORGANIZATION OF THE REPORT

This report is divided into eight chapters and a summary. The summary includes the principal findings and conclusions of the study, together with suggestions for future research.

The first chapter reviews what is known about the chemistry and pharmacology of marijuana. Chapter 2 deals with the epidemiology and demography of the use of marijuana in the United States. The next three chapters discuss the effects of marijuana on cells, tissues, organs, and biological systems. Chapter 6 deals with behavioral and psychosocial effects. Chapter 7 discusses the present status of marijuana as a therapeutic agent. Chapter 8 describes and analyzes the federal research program on marijuana.

This report is intended to be intelligible to readers who are not expert on the subjects at hand. We have tried to use technical language only where accuracy would be compromised by less precise terms, and to keep the discussions as brief and as clearly stated as is consistent with our obligation to present a valid critique of the state of knowledge in this field. Although we have surveyed the literature as thoroughly as possible, our citations are selective rather than exhaustive, because they are intended to illustrate or document only the key points in the discussion. For comprehensive bibliographies, see Waller et al., 1976; Abel, 1979; and Kalant et al., 1980.

#### GLOSSARY OF TERMS FOR MARIJUANA-RELATED PRODUCTS

CANNABIDIOL (CBD) and CANNABINOL (CBN) are major cannabinoids generally present in cannabis (see CANNABIS and CANNABINOIDS).

CANNABINOIDS are a class of 21-carbon compounds present in Cannabis sativa. The basic structure contains a six-membered hydroaromatic ring and a benzene ring joined by a pyran moiety (see Figure 1-1 in Chapter 1). Derivatives include a number of carboxylic acids, their analogues, and transformation products.

CANNABIS is a general term for any of the various preparations of the plant Cannabis sativa and the cannabinoids obtained from it. "Cannabinoid" is a generic term for a class of compounds. Cannabis sativa, also called hemp, is an herbaceous annual plant that readily grows in temperate climates. Depending on the geographic region, and other considerations, the various natural preparations of cannabis possess different physical characteristics and concentrations of cannabinoids. Cannabis preparations may contain over 420 different compounds; of these, 61 have been identified as cannabinoids, many of which possess some biological activity. Marijuana, hashish, and tetrahydrocannabinol are examples of different forms or components of cannabis.

HASHISH is a resin, generally more potent than marijuana, which is obtained from Cannabis sativa by shaking, pressing, or scraping the leaves and flowers of the plant and usually contains some of the latter.

MARIJUANA is a general term for crude preparations obtained from the plant Cannabis sativa and is a mixture of crushed leaves, twigs, seeds, and sometimes the flowers of this plant. In the United States, the term "marijuana" has often been used interchangeably with cannabis to refer to any part of the plant or extract therefrom or any of the synthetic cannabinoids that induce somatic and psychic changes in man.

SINSEMILLA is a seedless variety of high-potency marijuana, originally grown in California.

TETRAHYDROCANNABINOL (THC) is one of the major groups of cannabinoids. Delta-9-THC is the principal active constituent in natural cannabis preparations. Delta-9-THC is also known as  $\Delta$ -1-THC, by a different system of nomenclature. (In the United States, the  $\Delta$ -9-THC content of marijuana ranges from unmeasurable amounts to about .6 percent.) Another active isomer,  $\Delta$ -8-THC, is less often present in marijuana and typically occurs in minute amounts. Many derivatives of  $\Delta$ -9-THC have been synthesized.

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# I

## CHEMISTRY AND PHARMACOLOGY OF MARIJUANA

The cannabis plant (Cannabis sativa) thrives under a variety of growing conditions. It has been cultivated for centuries, mainly for hemp fiber, but also for its psychoactive and putative medicinal properties (Abel, 1980; Turner et al., 1980). Although the behavioral and psychological effects were well described in literature of the nineteenth century (Kalant and Kalant, 1968), the complex chemistry and pharmacology of the cannabis plant discouraged extensive investigation until about 15 years ago.

The most prominent effects of cannabis are on psychological phenomena and behavior. Psychopharmacology and behavioral pharmacology have developed as divisions of scientific inquiry only over the past 25 years; therefore, the older cannabis literature, no matter how valuable for observations on other matters, does not provide a basis for quantitative pharmacological analysis and evaluation.

Early pharmacologists could work only with crude extracts of the plant. Although the general structure of the cannabinoids (Figure 1) was known by the turn of the century, the particular cannabinoids that were identified early and were available as pure substances were largely devoid of the characteristic psychoactive and other pharmacological effects of cannabis. Synthetic cannabinoids with cannabislike activity became available in the 1930s. It was not until 1964 that an active ingredient of cannabis was identified as  $\Delta$ -9-tetrahydrocannabinol (THC) and synthesized (Figure 1) (Gaoni and Mechoulam, 1964; Mechoulam and Gaoni, 1965, 1967). In the mid-1960s, the isolation and synthesis of the main psychoactive component of cannabis and related cannabinoids, together with a rapid increase in the use of marijuana by middle class North American students, stimulated scientific activity (Waller et al., 1976; Waller et al., in press). This chapter, an overview of cannabis chemistry and pharmacology, emphasizes difficulties in the study of this drug (explored further in subsequent chapters) and in evaluating the literature.

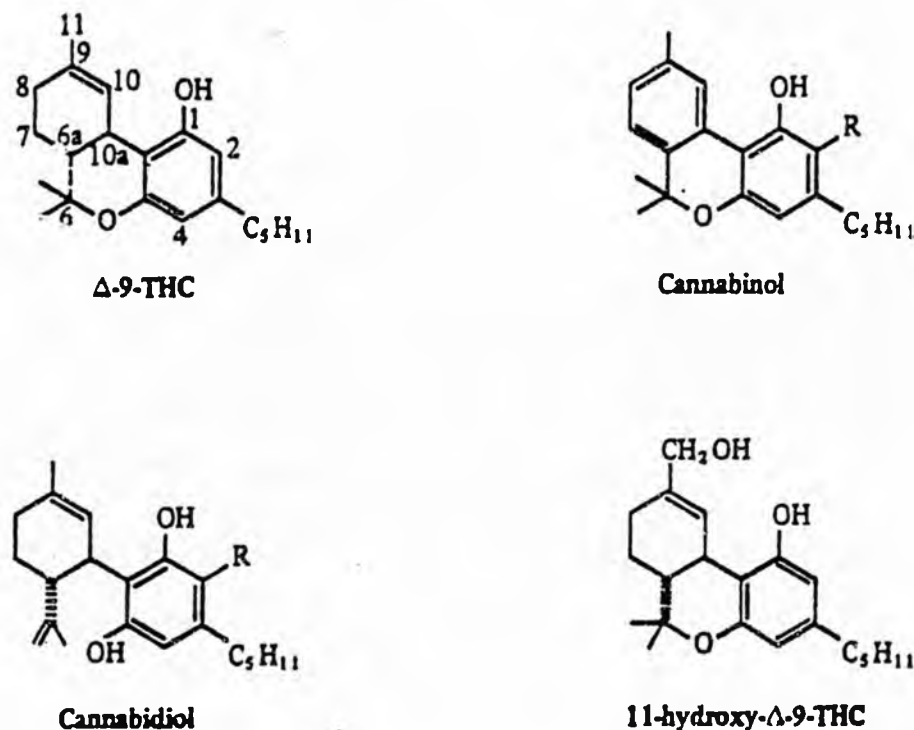


FIGURE 1 Cannabinoid structures.

## CANNABIS CHEMISTRY

### Chemistry of the Plant

Cannabis, the crude material from the plant *Cannabis sativa*, contains hundreds of chemicals. Most of these are found in other plants, but 61, termed cannabinoids, are unique to the cannabis plant (Table 1). Natural and most synthetic cannabinoids are relatively insoluble in water, but dissolve in fats and fat solvents and are therefore called lipid soluble.

A single cannabinoid, Δ-9-THC, produces almost all the characteristic specific pharmacological effects of the complex, crude cannabis mixtures. A number of synthetic cannabinoids have pharmacological effects similar to Δ-9-THC. Other cannabinoids in the plant, for example, cannabinol (Figure 1), are almost inactive pharmacologically or interact with Δ-9-THC to modify its actions. One cannabinoid, cannabidiol (CBD), can influence the metabolism of another, Δ-9-THC (Siemens et al., 1976). A few cannabinoids have effects quite different from Δ-9-THC. For example, cannabidiol (Figure 1) has relatively little psychoactive and cardiovascular effect but is an active anticonvulsant (Karler and Turkonis, 1981).

Investigators have chemically altered the Δ-9-THC molecule in an attempt to determine which of its structural elements are required to produce behavioral or other effects (Mechoulam et al., 1980). Studies of structure-activity relationships indicate that, to produce

TABLE 1 Chemical Constituents of Cannabis Preparations

1. Cannabinoids: 61 known
  - a. Cannabigerol (CBG) type: 6 known
  - b. Cannabichromene (CBC) type: 4 known
  - c. Cannabidiol (CBD) type: 7 known
  - d.  $\Delta$ -9-Tetrahydrocannabinol ( $\Delta$ -9-THC) type: 9 known
  - e.  $\Delta$ -8-Tetrahydrocannabinol ( $\Delta$ -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
  - j. Cannabitriol (CBT) type: 6 known
  - k. Miscellaneous types: 9 known
  - l. Other cannabinoids: 4 known
2. Nitrogenous compounds: 20 known
3. Amino acids: 18 known
4. Proteins, glycoproteins, and enzymes: 9 known
5. Sugars and related compounds: 34 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
15. Noncannabinoid phenols: 16 known
16. Flavanoid glycosides: 19 known
17. Vitamins: 1 known
18. Pigments: 2 known

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SOURCE: Adapted from Turner, 1980.

effects on behavior, a pyran ring must be part of the three-ring system, a free phenolic hydroxyl on the aromatic ring at C-1, and a lipophilic side chain ( $C_5H_{11}$ ) at C-3 (Figure 1). Understanding chemical structure-effect relationships is important to guide the synthesis of cannabinoids with differing pharmacological effects. Different effects of  $\Delta$ -9-THC activity by chemical design will require further syntheses and pharmacological study of a large number of cannabinoids.

### Chemistry of the Smoke

It is impossible to understand the effects of cannabis without quantitative control of the composition and the amount of the active substances, that is, control over the dose. Systematic pharmacology must therefore be performed using pure compounds. In the United States, cannabis usually is smoked, which complicates the pharmacology.

The smoke from any burning plant contains hundreds of chemicals that may have biological effects. This poses a dilemma for researchers, because consequences of smoking cannabis cannot be fully determined by studies only of the pure cannabinoids. Studies also are needed with doses of  $\Delta$ -9-THC delivered, however imperfectly, by smoking.

The dose of  $\Delta$ -9-THC obtained from smoking cannabis varies greatly, depending on many factors (Table 2). First, the content of  $\Delta$ -9-THC depends on the genetic background or phenotype of the plant, the sex of the plant, conditions of growth and storage, and the plant preparation smoked. Second, much of the  $\Delta$ -9-THC in fresh leaves that can be detected by gas-liquid chromatography (GLC) is in inactive carboxylated form. Decarboxylation to the active  $\Delta$ -9-THC occurs slowly during storage and rapidly during heating, such as occurs in smoking or GLC analysis. Third, the way in which a cigarette is smoked can greatly affect how much of the  $\Delta$ -9-THC content is absorbed by the smoker.

Cannabis smoke is similar to tobacco smoke in that it is a mixture of very small particles and a gas-vapor phase. Both the particulate and vapor phases contain many identified and probably some still unidentified constituents that, based on clinical experience with tobacco smoke, must be assumed to be potentially harmful (Leuchtenberger and Leuchtenberger, 1976). The amounts of some materials in tobacco cigarette and marijuana cigarette smoke are compared in Table 3. Toxic substances, such as carbon monoxide, hydrogen cyanide, and nitrosamines occur in similar concentrations in tobacco and marijuana smoke; so do the amounts of the particulate material known collectively as "tars."

It is not easy to compare the toxicity of a given number of marijuana cigarettes to a given number of tobacco cigarettes. There are general similarities in the composition of the smoke, but the variations in composition of both tobacco and marijuana cigarettes and differences in smoking techniques make simple extrapolations of risks of tobacco versus marijuana smoking not valid.

TABLE 2 Concentrations of  $\Delta$ -9-THC in Different Varieties of Marijuana

Type	Percent $\Delta$ -9-THC (Percent by Weight)	Normalized Averages <sup>e</sup>
Nepal <sup>c</sup>	2.81	
Mexico <sup>e</sup>	1.68	1.00
Pakistan <sup>e</sup>	1.30	
Colombia <sup>e</sup>		3.00-3.50
India <sup>f</sup>	0.46 (grown above 2000 m)	
	1.39 (grown below 2000 m)	
Jamaica (Ganja) <sup>h</sup>	2.80 (mean)	
United States <sup>e</sup>	0.35	
Sinsemilla (fiber) <sup>d</sup>	0.21	
Sinsemilla (intermediate) <sup>d</sup>	3.58	
Sinsemilla (drug) <sup>d</sup>	6.28	3.00-11.00
Hashish (U.N. standard) <sup>d</sup>	2.22 (7.40) <sup>b</sup>	1.90
NIDA (cigarette 1) <sup>d</sup>	0.84	
NIDA (cigarette 2) <sup>d</sup>	1.86 (2.8) <sup>g</sup>	
Crude marijuana extract <sup>g</sup>	20.00	
Illicit hashish oil <sup>g</sup>	10.00-30.00 (up to 60) <sup>a</sup>	20.00
Research harvests <sup>g</sup>	0.90-2.80	

SOURCES: (a) Jones, 1980; (b) Braenden, 1972; (c) Turner, 1974; (d) Turner, 1980; (e) Turner, 1981; (f) Turner et al., 1979; (g) Rosenkrantz, 1981; (h) Marshman et al., 1976.



### Other Preparations

Besides the crude plant leaf material for smoking, usually called marijuana, resinous material from the plant, called hashish, and solvent extracts of the plant, termed hashish oil, sometimes appear on the illicit market. In many parts of the world, hashish is more commonly used than marijuana. As with all cannabis preparations, the  $\Delta$ -9-THC content of hashish varies enormously, but the upper limits of  $\Delta$ -9-THC content are usually much higher than for marijuana: 7 percent or higher and even higher for hashish oil (Table 2). However, even these generally more potent forms of cannabis may occasionally contain much less  $\Delta$ -9-THC.

The mere designation of the nature of a cannabis preparation is an unreliable predictor of its  $\Delta$ -9-THC content. The practical consequence of this for the clinical researcher is that the exposure to cannabis users is not known.

### What Potency of Marijuana Is Available From Street Samples?

Because of the many confounding variables mentioned above, it is difficult to know what potency of psychoactive drug is in marijuana sold illicitly. The concentration of  $\Delta$ -9-THC in a given sample will vary (Ritzlin et al., 1979). The content of  $\Delta$ -9-THC from various street samples has been assayed. Marijuana from Drug Enforcement Administration confiscated samples; samples received through psychiatrists, police departments; and state crime laboratories, and fugitive\* samples were quantitatively analyzed for  $\Delta$ -9-THC and other cannabinoids. A physical description of the sample was made--e.g., buds, sinsemilla. The plants were also categorized by origin--where they were cultivated. The analysis showed that tremendous variability exists in the potency of  $\Delta$ -9-THC on the street; normalized samples ranged from zero to 11 percent  $\Delta$ -9-THC (Turner, 1981).

### Analytic Methods

Detection and measurement of cannabinoids and their metabolites in body fluids is far more difficult than with such drugs as alcohol. The blood and tissue levels resulting from use of ordinary "cannabis" are very low--nanograms per milliliter or lower. In addition, compounds like steroids, occurring normally in body fluids interfere with the measurement of cannabinoids in blood and can make the test much less sensitive than if pure cannabinoids in an uncontaminated

\*Samples received, when no arrests were made.  
One billionth of a gram.

solution are being analyzed (Harvey et al., 1980; Harvey and Paton, 1980).

A combination of gas-liquid chromatography and mass spectrometry is the most sensitive direct method of measuring cannabinoids. That, however, requires skilled technicians and expensive equipment not readily available. Using modifications of this experimental technique, one can measure as little as 5 picograms\* of  $\Delta$ -9-THC in a milliliter of plasma (Harvey et al., 1980; Harvey and Paton, 1980). Radioimmunoassay and enzyme immunoassay techniques also are available, the lower limits of sensitivity of these methods now are not adequate for reliable measurements of  $\Delta$ -9-THC in human blood more than a few hours after drug administration. A readily available enzyme immunoassay will detect cannabis metabolites in the urine for as long as a week after the smoking of a single marijuana cigarette. Thus, a positive urine test by this method is not necessarily indicative of use within the previous few hours and does not provide evidence of recent intoxication as a breath test does for alcohol. Assays for cannabinoids are likely to remain far more complicated than for alcohol and many other drugs.

#### PHARMACOLOGY OF CANNABIS

Implicit in a discussion of the effects of any drug is some determination of dose. The intensity and duration of effects in relation to drug dose must be determined or inferred from adequate pharmacologic study. The intensity and duration of a drug effect depends on at least three major factors:

1. The concentration of the drug at the sites of action in the body. This is determined by the dose, what the drug is dissolved in or mixed with, the route of administration, and the pharmacokinetics of the drug.
2. The sensitivity of the cells the drug acts upon.
3. The physiological state of the bodily systems being affected. This, in turn, depends on interactions with other systems and, especially for drugs with behavioral and psychological effects, as well as environmental and experiential factors, including the presence of other drugs.

With cannabis, ~~any or even most of these factors are not always measurable or under the control of an investigator.~~

\*1 pg =  $10^{-12}$  grams.

## Potency and Pharmacokinetic Considerations

Pharmacokinetic studies of the absorption, distribution, metabolism, and elimination of  $\Delta$ -9-THC determine how long  $\Delta$ -9-THC and its metabolites remain in the body. Pharmacokinetics vary with the route of drug administration and such factors as lipid solubility;  $\Delta$ -9-THC tends to remain for long periods of time in fatty tissue.

When smoked,  $\Delta$ -9-THC is rapidly absorbed by the blood in the lung. If taken orally,  $\Delta$ -9-THC is not absorbed into the blood as rapidly. The rate of disappearance of  $\Delta$ -9-THC from the blood varies with time (Lemberger et al., 1971a,b, 1972; Ohlsson et al., 1980). High blood levels fall rapidly for the first 30 minutes, as the  $\Delta$ -9-THC distributes to tissues with high blood flow. After the initial distribution, the blood level falls much more slowly with a half-life\* of 19 hours or more (Hunt and Jones, 1980). Metabolites of  $\Delta$ -9-THC have their own independent rates of elimination. Typically, metabolites are eliminated more slowly, having a half-life of approximately 50 hours (Hunt and Jones, 1980).

After an injection of a single dose of  $\Delta$ -9-THC, approximately 25-30 percent of the compound and its metabolites remain in the body at 1 week (Lemberger et al., 1971b; Hunt and Jones, 1980). Essentially complete elimination of a single dose may take 30 days or longer (Jones, 1980). Thus, repeated administration of even small doses may lead to an accumulation of drug higher than levels reached at any time after a single dose.

### Absorption

Inhaling smoke from a cannabis cigarette or pipe is pharmacokinetically different from ingesting cannabis. Smoking is a far more efficient way of delivering cannabinoids to the brain than ingestion because of the large surface area of the lungs. Inhaled, the cannabinoids in the smoke go rapidly from the lungs into the blood to the left side of the heart and are carried in seconds to the brain and other organs before passing through the liver. When smoked, a drug reaches the brain with relatively little time for metabolism or dilution. Many substances with high lipid solubility such as cannabinoids go quickly from blood into tissues, including brain tissues. Psychological and cardiovascular effects of cannabis are

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\*The half-life is a measure of how rapidly a drug is eliminated. It is the time required for the level of a drug to be reduced by one-half. If starting levels are ten units and the half-life is 24 hours, then 1 day after administration, the level will be 5 units, 2 days after administration 2.5 units, etc.

†There are more than 45 metabolites of major cannabinoids identified in different species, at least one of which, 11-OH- $\Delta$ -9-THC, is psychoactive.

evident within a few seconds of inhalation. Peak effects occur about the time smoking is completed.

When taken by mouth, cannabinoids usually are in solutions or suspensions. The material they are mixed with affects the rate of absorption. For example, blood levels of  $\Delta$ -9-THC were higher and lasted longer when given in an oily solution than in an ethyl alcohol solution (Perez-Reyes et al., 1973). This suggests that cannabis eaten in food mixtures containing fat is better absorbed.

An important difference between smoking and ingestion is that when cannabinoids are absorbed from the gut, the blood-containing them first goes directly through the liver. The liver rapidly clears the  $\Delta$ -9-THC from the blood and enzymatically changes much of the  $\Delta$ -9-THC to other metabolites before it reaches the brain (Hunt and Jones, 1980). A large amount is metabolized to 11-hydroxy- $\Delta$ -9-THC (Figure 1). It is unknown if the spectrum of effects of this metabolite is identical to that of  $\Delta$ -9-THC. When taken by mouth, in contrast to when smoked, two or three times more  $\Delta$ -9-THC is required to obtain equivalent acute psychological and physiological effects. After oral doses the effects develop more slowly, last longer, are more variable, and cannot be controlled by the recipient once the cannabis has been swallowed. In contrast, the smoker feels the effects quickly and can modify inhalation at any time, although overdosage is still possible. Unpleasant reactions to overdose are more common following ingestion than inhalation.

A variety of other routes of administration have been used experimentally in humans and in animals, including intravenous, intraperitoneal, subcutaneous, intramuscular, topical (on the skin), and into the conjunctival sac (eye). These various routes influence the time to onset of effect, duration and peak intensity, and the rate with which the effect disappears. Direct comparison of findings in studies using differing administration routes is difficult and must take these factors into consideration.

Human users of cannabis vary in their preferred routes of use. In some countries and cultures cannabis is mainly taken by ingestion (for example, India) and in others by inhalation (for example, the United States). Because of the effects of route of administration on pharmacology, it is reasonable to expect different health consequences of the different routes of administration; therefore, comparisons of health statistics among countries must be made with care.

Although smoking avoids many of the absorption problems discussed above, a host of other variables affecting dose are introduced, such as the size and packing of the cannabis cigarettes, the way the smoke is inhaled, the number of puffs and the interval between puffs, the temperature produced in the burning cigarette, and whether a cigarette is shared. Because of the progressive concentration of cannabis constituents in the cigarette butt, the last few puffs yield considerably more  $\Delta$ -9-THC and particulate matter than do the earlier puffs. All these and other factors affect the dose received, and only rarely have they been measured. Only some of these factors are under the conscious control of the cannabis smoker. About half of the  $\Delta$ -9-THC originally in a cannabis cigarette is lost by

combustion, by butt entrapment, in smoke not inhaled, and in smoke exhaled (Fehr and Kalant, 1972; Rosenkrantz, 1981).

It has been reported that, like nonsmokers of tobacco, individuals in a poorly ventilated room where cannabis is smoked may passively inhale active components (Zeidenberg et al., 1977). Because only trace amounts of cannabinoid metabolites are present in urine of these passive inhalers, it is unlikely that the low levels of the absorbed cannabinoids from the ambient air account for the so-called "contact high." Experiencing subjective cannabis effects in the presence of cannabis smokers could be explained by psychologic factors in addition to any pharmacologic ones. But, because studies have shown that children of parents who smoke tobacco are more likely to have respiratory infections during the first year of life—which may be due to their being exposed to cigarette smoke in the atmosphere (U.S. Department of Health, Education, and Welfare, 1979)—the issue of passive inhalation of marijuana smoke is worth further study.

#### Distribution

The lipid solubility of  $\Delta$ -9-THC and other cannabinoids, including those with highest pharmacologic activity, facilitates distribution readily into tissues and cells throughout the body so blood levels drop rapidly. Initially, cannabinoid concentrations are highest in such tissues as lung, liver, and kidney that have a high blood flow (Agurell et al., 1969, 1970; Klausner and Dingell, 1971). Delta-9-THC crosses the placenta and enters the fetus of experimental animals (Kennedy and Waddell, 1972). Cannabinoid levels in the human fetus have not been studied. Small amounts are also found in the milk of experimental animals and can be transferred to progeny (Jakubovic et al., 1973; Chao et al., 1976). After initial distribution, concentrations of cannabinoids in tissues, cells, and subcellular compartments are highly nonuniform, determined no doubt by solubility and other physicochemical characteristics. Therefore, blood concentrations do not reflect concentrations at pharmacologically active sites, as they do with alcohol.

#### Metabolism and Elimination

Elimination of drugs and their metabolites is mostly through excretion by the kidney into the urine or by the gall bladder via the bile into the intestine and out with the feces. Cannabinoids do not pass out of the blood into the lungs and do not appear in breath in appreciable quantities. Some cannabinoids going into the intestine with bile are reabsorbed. Some also diffuse back through the kidney tubules during the process of urine formation, so the amounts finally excreted per unit of time are small. The net result of this recycling is that the cannabinoids are only slowly eliminated from the body.

Studies of the disappearance of  $\Delta$ -9-THC from human plasma have led to reports of values of half-lives that ranged from 19 hours in experienced users (Hunt and Jones, 1980) to 57 hours in naive users (Lemberger et al., 1971b). Whether this difference in half-life is due to the experience of the user has not been established. Because of their high lipid/water partition coefficients,  $\Delta$ -9-THC and some of its metabolites can be sequestered in fatty tissues. Following the intravenous administration of radioactive  $\Delta$ -9-THC to human volunteers, however, 67 percent of the radioactivity was excreted in 1 week, 22 percent in the urine and 45 percent in feces (Lemberger et al., 1971a). Almost no  $\Delta$ -9-THC itself was excreted in the urine. There may be fairly rapid and complete metabolism of free  $\Delta$ -9-THC followed by slow release and metabolism of sequestered  $\Delta$ -9-THC and retained metabolites. Because no direct measurements of cannabinoid levels have been made in tissue samples from human cannabis users and the data are limited in experimental animals, one can only infer from blood levels what metabolites are accumulating and where.

In rats, after inhalation or intravenous administration of radioactive  $\Delta$ -9-THC, radioactivity persisted in the brain for at least 7 days, mostly as metabolites (Ho et al., 1970). When given subcutaneously in rats, even at intervals as great as a day or two apart,  $\Delta$ -9-THC will accumulate as metabolites (Kreuz and Axelrod, 1973). Accumulation of some cannabinoids with even less frequent intake appears likely. Although most metabolites are concentrated in fatty tissues, they will slowly pass into plasma and circulate through all parts of the body, particularly including such organs as the brain, and generally all membranes. The health consequences of the continued presence of such foreign molecules are not known. The marked persistence of the cannabinoids is quite unlike other widely consumed agents, such as alcohol, nicotine, and caffeine, that are rapidly metabolized and leave no trace a few hours after moderate intake.

#### WHAT IS A LARGE OR SMALL CANNABIS DOSE?

Large and frequent doses of any drug are more likely to produce adverse health effects than small infrequent doses of the drug. Thus, judgments of health consequences of the use of cannabis can only be made with implicit or explicit knowledge about dose. For the reasons discussed above, the range of cannabinoid doses consumed varies widely. Investigators usually report dose in terms of marijuana cigarettes per unit of time, or they give some estimate of the concentration of  $\Delta$ -9-THC used for oral application. This is not an adequate way to quantify the amount of cannabinoids actually entering the body. Only one epidemiologic study provides a breakdown of varying dose levels in excess of one cannabis cigarette daily (Bachman et al., 1981). Epidemiologic surveys have not quantified  $\Delta$ -9-THC levels. When reporting less frequent use patterns than one cigarette per day, investigators use measures that make it difficult to compare studies. In this report, any general or average dose estimates are approximations.

It is generally agreed that smoking five or six 1-gram cannabis cigarettes daily is a large dose (Dornbush et al., 1971; Rosenkrantz, 1981). Because of the variability of  $\Delta$ -9-THC content of cannabis available from street samples, it would be more appropriate to consider this heavy use. The definition of a low dose is more controversial. Some consider one marijuana cigarette a day to be a large dose. Others think even one cigarette a week is regular, frequent, and a high dose.

With tobacco and alcohol, for which dose is easier to quantify, it took many years to establish what a small or large dose might be in terms of specifying doses that significantly increased the risk of various behavioral and health consequences. Even with those drugs, there is still disagreement as to precisely what a small and "safe" dose might be. There will be even more problems in specifying typical cannabis doses and predicting their likely health consequences.

In controlled laboratory conditions, ingested doses of more than 20 mg of  $\Delta$ -9-THC generally are considered by both investigators and cannabis users to be large doses. Doses of less than 10 mg are considered small. Marijuana cigarettes containing more than 20 mg of  $\Delta$ -9-THC seem to be a large dose, and those with 10 mg produce effects generally considered the result of a small dose. When volunteers were allowed to select their own self-determined smoked doses in controlled experiments, some smoked only one or two 20-mg cigarettes daily, while other similar volunteers smoked six to ten or more cigarettes per day. Variability in smoking patterns is great and not easily quantified; only broad range estimates of dose are possible.

#### GENERAL TOXICOLOGY

Delta-9-THC and related cannabinoids have very low lethal toxicity. That is, a very high single acute dose of  $\Delta$ -9-THC is required to kill half of a population of experimental animals. This lethal dose for 50 percent of the animals is called the LD<sub>50</sub>. The lack of well-authenticated cases of human deaths from acute  $\Delta$ -9-THC or cannabis overdose is consistent with the experimental animal data. The lethal dose increases as the phylogenetic tree is ascended. The rat has an LD<sub>50</sub> of 40 mg/kg intravenously, in contrast to a 125 mg/kg in the monkey (Rosenkrantz, 1981). Death is usually due to cardiac dysfunction. Delta-9-THC appears to be the most toxic of the cannabinoids.

Studies of chronic cannabis administration to animals have demonstrated delayed lethality. Animals die after several days of a repeated high dose (Rosenkrantz, 1981). The reason for this pattern is unclear. It could be related to accumulation of  $\Delta$ -9-THC or metabolites in tissues.

A 1-year chronic treatment of rats with lower doses of cannabinoids produced a pattern of toxicity consisting of weight loss, pulmonary pathology when the drug is inhaled, and slowly

developing behavioral toxicity characterized by hyperactivity, vertical jumping, fighting, and seizures (Rosenkrantz, 1981).

#### RELEVANCE OF NONHUMAN ANIMAL MODELS

Much of what is known about cannabis comes from experiments in animals. Some aspects of the pharmacology of any drug can only be studied in animals other than human beings. Findings from animal experiments have been criticized because of what were thought to be unreasonably high doses of cannabis given to the animals as compared with doses commonly used by human beings. Although extrapolation of human effects from animal data must be done with caution because of species differences in metabolic pathways and differing sensitivity and physiology, a blanket criticism of animal studies because of high doses is inappropriate. When an effect of a drug occurs consistently in several species, it is likely to occur in human beings. Comparisons of  $\Delta$ -9-THC blood levels in human beings and in several species suggest roughly similar intensity of effects at similar blood levels in the various species (Rosenkrantz and Fleishman, 1979).

#### CANNABIS CONTAMINANTS

On occasion cannabis has been reported not only to contain the herbicide paraquat, but also salmonella bacteria and aspergillus fungus. Deliberate addition of such drugs as lysergic acid diethylamide (LSD), heroin, and phencyclidine (PCP) has been claimed. A plant material such as cannabis is not always handled in the most sanitary way, and a variety of contaminants are possible.

#### Paraquat

There is no question that large doses of paraquat by mouth or by aerosol can cause pulmonary fibrosis, but no cases in human beings have yet been proved to result from paraquat-contaminated cannabis. Few cannabis smokers are expected to be exposed to the large amounts of paraquat known to cause severe lung damage. This is not to say that no lung damage will occur from such exposure. A more extensive discussion of paraquat is in Appendix D.

#### Bacteria and Fungi

A few outbreaks of salmonellosis epidemiologically linked to marijuana use were reported from Ohio and Michigan (Schrader et al., 1981). Marijuana was found to be contaminated with the same type of salmonella that was obtained from the 62 patients experiencing diarrhea, fever, and abdominal pain.

Aspergillus, a fungus, is a common contaminant of some cannabis (Llewellyn and O'Rear, 1977; Llamas et al., 1978). The spores pass easily through contaminated marijuana cigarettes and when smoked are presumed to enter the body.

#### CELLULAR TOXICITY

A variety of effects on cellular processes have been reported, usually based on studies of in vitro systems. The low water solubility of the cannabinoids and the need to add solvents and emulsifiers, along with a common tendency to use higher in vitro concentrations than occurs in living animals, makes interpretation of such experiments difficult.

In related studies,  $\Delta$ -9-THC alters the actions of a number of intracellular enzyme systems. The biological relevance of these drug/enzyme interactions is still unclear at this time, but, together with the cytotoxicity, it suggests that  $\Delta$ -9-THC is producing marked effects on cell membranes and intracellular processes.

Almost nothing is known of the molecular mechanisms by which cannabinoids produce their effects in cells.

#### TOLERANCE AND DEPENDENCE

Repeated administration of most psychoactive drugs leads to the development of tolerance. This state of increased drug resistance results from two general mechanisms (Kalant et al., 1971):

- Dispositional tolerance resulting from lower drug concentrations at sites of action, usually because of increased rates of drug metabolism or elimination
- Functional tolerance arising from decreased sensitivity of the target cells.

Tolerance to most cannabinoid effects has been demonstrated both in animals and human beings (Jones, 1981). Tolerance can develop rapidly after only a few small doses. It disappears at an equally rapid rate for many effects, although after large doses in experimental animals some tolerance may persist for long periods (Jones, 1981). Systematic studies of tolerance loss have rarely been done. Many characteristics of tolerance to  $\Delta$ -9-THC, particularly its pattern of rapid acquisition and loss, are similar to that occurring with opiates, nicotine, and cocaine (Jones, 1981). Most evidence suggests functional rather than dispositional means of acquiring tolerance.

The development of such tolerance to cannabis does not necessarily have health implications. However, if tolerance should lead to higher or more frequent doses, adverse consequences, e.g., respiratory effects, associated with higher usage could result.

Physical dependence, manifested by withdrawal signs and symptoms, can develop rapidly in animals and in human beings (Jones, 1981). The withdrawal syndrome is not life threatening. It is similar in many respects to the mild dependence produced by low doses of other sedatives. Withdrawal symptoms can include restlessness, irritability, mild agitation, insomnia, and sleep EEG disturbance.

Cannabis dependence does not mean the same thing as cannabis addiction. Dependence means only that a withdrawal syndrome can occur when drug taking is stopped. Addiction implies compulsive behavior to acquire the drug. The relationship between dependence and increased drug seeking or drug using is more theoretical than well documented, particularly in experiments with human beings. Given the appearance of tolerance and dependence with almost any psychoactive drug, it would be unusual not to find tolerance and dependence with the right dose and dosage schedule of cannabis. Good studies of the relationship of dependence, if any, to persistent drug use are important.

#### DRUG INTERACTIONS

Because cannabis often is consumed with other drugs, interactions can be expected. Other illicit drugs, tobacco, caffeine, alcohol, and over-the-counter or prescribed medications should be studied in combination with cannabis, because  $\Delta$ -9-THC and its first metabolite are strongly bound to proteins in the plasma (Garrett and Hunt, 1974) and may interact with other drugs similarly bound. Cannabis and many other drugs share disposition by the hepatic metabolic enzyme systems, and there are possible interactions at the drug metabolism level. For example, drugs such as alcohol or pentobarbital can inhibit metabolism of  $\Delta$ -9-THC by enzyme substrate competition. Or, if after a period of inhibition one drug is removed, the enzyme activity can increase so that faster than expected metabolism follows. If given simultaneously with other drugs,  $\Delta$ -9-THC can slow metabolism of drugs such as theophyllin, antipyrine, ethanol, and pentobarbital (Benowitz and Jones, 1977; Jusko, 1979). Cannabidiol can also inhibit the metabolism of a variety of drugs normally metabolized by the shared hepatic enzyme systems.

Drug interactions also can occur by means of functional mechanisms. These can be additive, resulting in enhancement or prolongation of behavioral and psychological effects by cannabis when combined with other central nervous system depressant drugs, such as alcohol and barbiturates. Animals less tolerant to cannabis will also be less sensitive to other central nervous system depressants. This phenomenon is known as cross-tolerance. Drug interactions will be mentioned in subsequent chapters.

## SUMMARY AND CONCLUSIONS

Cannabis is not a single drug, but a complex preparation containing many biologically active chemicals. The psychological and physiological effects produced by  $\Delta$ -9-THC probably result from actions at sites within the central nervous system and elsewhere in the body, leading to the likelihood of complicated effects depending on dose, duration of use, and many other considerations.

The intensity of effect an individual experiences varies considerably according to the cannabis preparation and the amount taken, route of administration, frequency of use, and probably other not-well-recognized biological considerations. Dose variability must be considered both in conducting and in interpreting any studies of the effects of cannabis, particularly when trying to predict health consequences.

In research the use of pure  $\Delta$ -9-THC avoids some problems of dose control but cannot provide a complete picture of cannabis effects, because the effects of  $\Delta$ -9-THC in crude preparations of the plant may be influenced by other components. Other consequences of cannabis use, for example, exposure to harmful components in its smoke, will have deleterious health consequences in addition to anything produced by the  $\Delta$ -9-THC.

The long persistence of cannabinoid metabolites in the body may have delayed effects or health implications not yet recognized, because, even with relatively infrequent use, there is chronic exposure to biologically unknown materials. In this respect, cannabis differs fundamentally from such drugs as alcohol, nicotine, and caffeine, which are rapidly metabolized and eliminated from the entire body.

Cannabinoid effects can be modified by many events, including interaction with other drugs and the development of tolerance. Both tolerance and dependence develop to many effects of the drug. The health significance of tolerance and dependence, particularly their importance in drug-seeking and drug-using behavior, has not been studied properly.

It is unlikely that adequate epidemiologic data will be available (soon) to enable good estimation of the health consequences of various usage levels.

A prerequisite is that adequate chemical analytical methods be applied on a large-scale basis to monitor actual exposures. Continued studies in experimental animals will play an essential role in the assessment of the health risks of cannabis. For example, the biological activities of  $\Delta$ -9-THC metabolites can be assessed in experimental animals, but these tests are technically more difficult to do in human beings.

## RECOMMENDATIONS FOR RESEARCH

Several research priorities are identified by the preceding discussion:

\* Cannabinoids and their metabolites persist for relatively long periods in the body. More information is needed on the biological significance of that persistence in human beings. As a first step, the toxicological effects of the various metabolites need to be determined.

\* Drug interactions alter the actions of cannabis. Cannabis use alters other drug effects. More information is necessary to make the combined effects of cannabis and other licit and illicit drugs more predictable, especially with respect to behavioral impairment and toxicity to lungs, liver, and other organs.

\* Studies of the mechanism of action of cannabis should continue. Knowledge of mechanism is likely to provide powerful insights into the potential health effects.

\* Improved chemical analytical methods are necessary. Epidemiologic appraisal of the health effects of cannabinoids requires methods suitable for wide-scale assays of exposures. Pharmacological verification of the self-reported extent of use will make experimental and clinical results much easier to interpret. A chemical "marker" of the frequent user would be useful. Screening techniques for the purpose of identifying and discouraging cannabis-impaired driving would also be valuable.

\* Characterization of the toxicological significance of common cannabis contaminants such as paraquat and other chemicals, fungi, and bacteria should be continued.

\* The development of tolerance is a factor that potentially modifies the expression of all psychoactive drug effects. Additional studies on the rates of acquisition and loss of tolerance and the relationship of these phenomena to dependence are necessary. The biological significance of the changes that underlie the development of tolerance should be established. The relationship, if any, between tolerance and dependence and drug-seeking behavior should be established.

\* Cannabis products are variable and complex. More information on the amount, nature, and potency of the various preparations used around the world would facilitate calculations of exposures to its constituents. For example, what is the biological and toxicological significance of the minor components of cannabis smoke?

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### USE OF MARIJUANA IN THE UNITED STATES

Epidemiologic studies provide information on the use of drugs in various subgroups of the population and on the changes in patterns of use over time. The epidemiologic approach is particularly useful in defining patterns of use of marijuana in American society and in describing and analyzing the behavioral and psychosocial antecedents and consequences of that use. One of the more difficult questions is whether particular behavior or effects that are associated with use of a drug are the consequences of that use, or whether attitudes, values, and behavior develop about the use of drugs to constitute factors that may actually lead to the use of drugs. One of the more useful epidemiologic study designs is a cohort study that follows the same individual with repeated observations at regular intervals over time. Such longitudinal studies have the potential for obtaining the most compelling evidence on the antecedents of known patterns of use of marijuana, as well as possible long-term psychosocial and biological outcomes for these individuals.

The committee, with the help of consultants, sought answers in the epidemiologic literature to the following five questions:

1. What are important patterns of use of marijuana in the American population including special groups?
2. What are the general characteristics of users of marijuana?
3. What is the profile of a user of marijuana on a "daily"\* basis?
4. What is known about the antecedents of use of marijuana?
5. How is use of marijuana related to the use of other drugs?

The epidemiologic and survey literature have been extensively reviewed and the major longitudinal studies are summarized in a table in Appendix C. Much of our recent knowledge derives from two well-designed major, continuing nationwide monitoring efforts

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\*When placed in quotation marks, "daily" is used as defined by Johnston et al. (1980b), i.e., those individuals using marijuana 20 or more times in the preceding 30 days.

sponsored by the National Institute on Drug Abuse. One is based on general household population samples, the National Household Surveys. The second is based on populations of high school seniors and is called Monitoring the Future.

The National Household Surveys of the general population are conducted on an annual or biannual basis by Response Analysis Corporation and The George Washington University (Fishburne et al., 1980). There have been six cross-sectional studies since 1971. The latest one was in the winter of 1979-1980, and the next one will be initiated in 1982. The subjects are classified as youth (12-17), young adults (18-25), and older adults (26 and older). The questions relate to marijuana and other psychoactive drugs, including inhalants, hallucinogens, cocaine, heroin, stimulants, sedatives, and analgesics. Samples vary from about 3,000 to more than 7,200 new respondents at each survey. These are samples that document patterns of use of drugs in the specified populations at a given time.

Monitoring the Future (Johnston et al., 1980b) uses a cohort-sequential longitudinal design, in which a new cohort of high school seniors is surveyed each year, and a representative panel selected from that senior class is also followed over time in successive annual or biannual testings. The earliest panel has now been reinterviewed six times. This survey design makes it possible to disentangle antecedents from consequences of use as well as to distinguish changes due to increased age from changes due to cohort peculiarities or historical circumstances. Initiated in 1975 by the Survey Research Center of the University of Michigan, and directed by Lloyd Johnston and Jerald Bachman, the survey involves a questionnaire self-administered each year by more than 16,000 high school seniors in 130 public and private schools throughout the United States, and longitudinal mail follow-ups of about 2,000 former students drawn, as panels, from each of the previously participating senior classes (Johnston et al., 1979a,b; 1980a,b).

Because the National Household Surveys and Monitoring the Future are surveys of persons in households or in high school, they exclude persons most likely to be using drugs—the transients, those without regular addresses, the school absentees or drop-outs, or those living in institutions or group quarters. These persons constitute a small proportion of the general population, and their exclusion does not significantly bias the epidemiologic estimates reported for the total population (Kandel, 1975a). However, data on the very heavy use of drugs may be underrepresented.

## PATTERNS AND TRENDS OF USE OF MARIJUANA

### General Population

The National Household Surveys found that marijuana was the most commonly used of all the nonlegal psychoactive drugs investigated, including inhalants, hallucinogens, cocaine, heroin, stimulants, sedatives, tranquilizers, and analgesics (Fishburne et al., 1980).

In 1979 more than 50 million persons had tried marijuana at least once in their lives: 68.2 percent of young adults (18-25), or about 21 million; 30.9 percent of youth (12-17), or more than 7 million; and 19.6 percent of older adults (26 and older), or 25 million. The young adult age-group (18-25 years) has consistently showed the highest rates of current use (used in past month) and ever use (lifetime prevalence), and the older adult groups (26 and older) had the lowest user rates. Male users outnumbered females in all age groups. Between 1977 and 1979, significant increases in current use and ever use of marijuana were observed among the young adult and older adult cohorts (Figure 2). In 1979, in the young adult cohort, the most significant increases in use in the past month were found in males, whites, high school nongraduates, people in the southern United States, and those living in nonmetropolitan areas. In the older adult groups, the most significant recent increase in current use of marijuana was observed in males, whites, college graduates, and people living in the southern states (Miller and Cisin, 1980).

In the early 1960s, illicit drug use in the United States was chiefly a phenomenon of large coastal cities. But since then, rates in other regions of the country and in cities of all sizes have rapidly increased until patterns of use are becoming increasingly comparable for all sectors in the United States. At current levels of use, some experience with marijuana in adolescence is becoming the norm rather than the exception throughout the United States. Other major survey studies have confirmed the findings of the National Household Survey for comparable cohort populations (Gallup Opinion Index, 1976; O'Donnell et al., 1976).

#### Military Personnel

Much attention has recently been focused on what appear to be high rates of use of illicit drugs among military personnel. Studies of drug use among male army veterans of the Vietnam War in 1972 showed that marijuana was the most commonly used illicit drug before and after the war (Robins, 1974). A random sample of 470 men was selected from the 13,760 enlisted men who returned to the U.S. in September 1971. Of the 451 men who were interviewed, 69 percent had used marijuana while in Vietnam, with 28 percent stating this was their first use of the drug. The lifetime prevalence of use of marijuana was 41 percent prior to Vietnam; 45 percent of the veterans reported using marijuana in the 10 months following return to the United States. Among this group the prevalence of weekly use doubled from 12 percent prior to Vietnam to 25 percent following the war.

A worldwide survey of nonmedical use of drugs and alcohol among U.S. active duty military personnel was conducted in 1980 under the sponsorship of the U.S. Department of Defense (Burt et al., 1980). In an anonymous, self-administered questionnaire given to a representative sample of more than 16,000 persons, marijuana was found to be the most commonly used illicit drug. Twenty-six percent admitted to having used "marijuana/hashish" within the past 30 days and 35

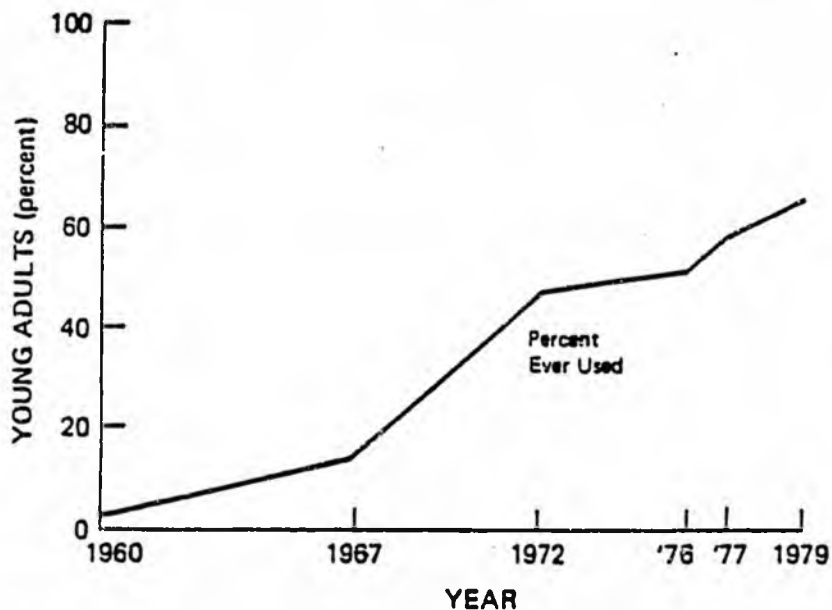
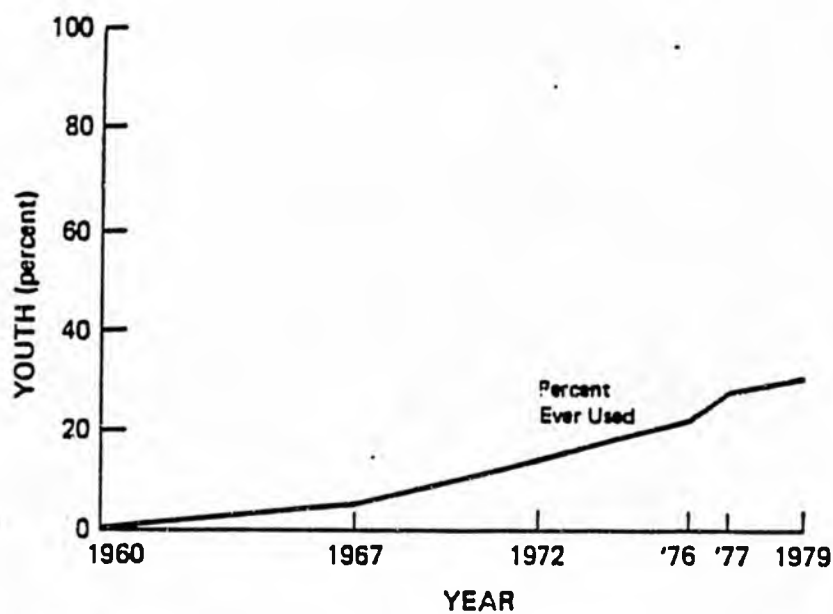


FIGURE 2 Marijuana: trends in lifetime experience, youth, and young adults. Adapted from J.D. Miller and I.H. Cisin. Highlights from the National Survey on Drug Abuse: 1979. Washington, D.C.: U.S. Government Printing Office, 1980. Youth = 12 to 17 years old; young adults = 18 to 25 years old.

percent to having used it in the past 12 months. Five percent of the sample reported use of marijuana daily.

When users of drugs were itemized according to military pay classifications, the largest percentage of current use of marijuana was in the lowest ranks of the military.

### Adolescents and Young Adults

#### Patterns and Trends

One of the compelling reasons to focus on adolescence in studying marijuana is the pervasive and increasing use by this age group. As was mentioned earlier, in 1980 all geographical regions of the United States and all socioeconomic classes had high and increasingly comparable involvement in use of marijuana.

The year 1960 has been taken as a baseline year that represents the stable level of overall use of marijuana that had characterized the United States for most of its history. Figure 2 shows the trends for use of marijuana from 1960 through 1979, revealing the sharp upward climb of use of marijuana starting in 1967. The dramatic rise in use of marijuana by adolescents has recently slowed, and the lifetime prevalence rates (ever use) of marijuana have remained at approximately 60 percent of all high school seniors for the years 1979 and 1980 (Figure 3). To put it another way, in 1979 over 2.5 million high school seniors had tried or were users of marijuana. (This figure is derived from calculations based on 1979 Census Bureau data that give a figure of 4,276,000 for number of 18-year-olds in the population. The committee is aware that all 18-year-olds are not high school seniors and that such a calculation may underreport the numbers of users of marijuana, particularly heavy users who have been shown to be more likely to have dropped out of school. Similar calculations have been attempted throughout this chapter.)

The use of other types of drugs by young people also increased beginning in 1967 (Miller and Cisin, 1980). Figure 4 gives the most recent nationwide figures for use of 11 types of drugs among American high school seniors (average age 18 years). With the exception of negligible use of heroin, the figures for use of all other drugs are substantial. Increases in patterns of use have not been as dramatic for other drugs (except for recent cocaine increases) as they have been for marijuana. Use of marijuana, tobacco, and alcohol far outstrips that of all other drugs. In 1980, the lifetime prevalence (ever use) for these substances by high school seniors was marijuana--60 percent, tobacco--71 percent, and alcohol--93 percent.

Of even greater interest are the percentages of high school seniors who use the 11 types of drugs "daily." In 1980 marijuana was used "daily" by 9.1 percent (about 390,000), alcohol by 6.0 percent (about 256,000), and tobacco cigarettes by 21.3 percent (about 900,000) of high school seniors (Johnston et al., 1980a). No other substance was used that frequently by as many as 1 percent of the

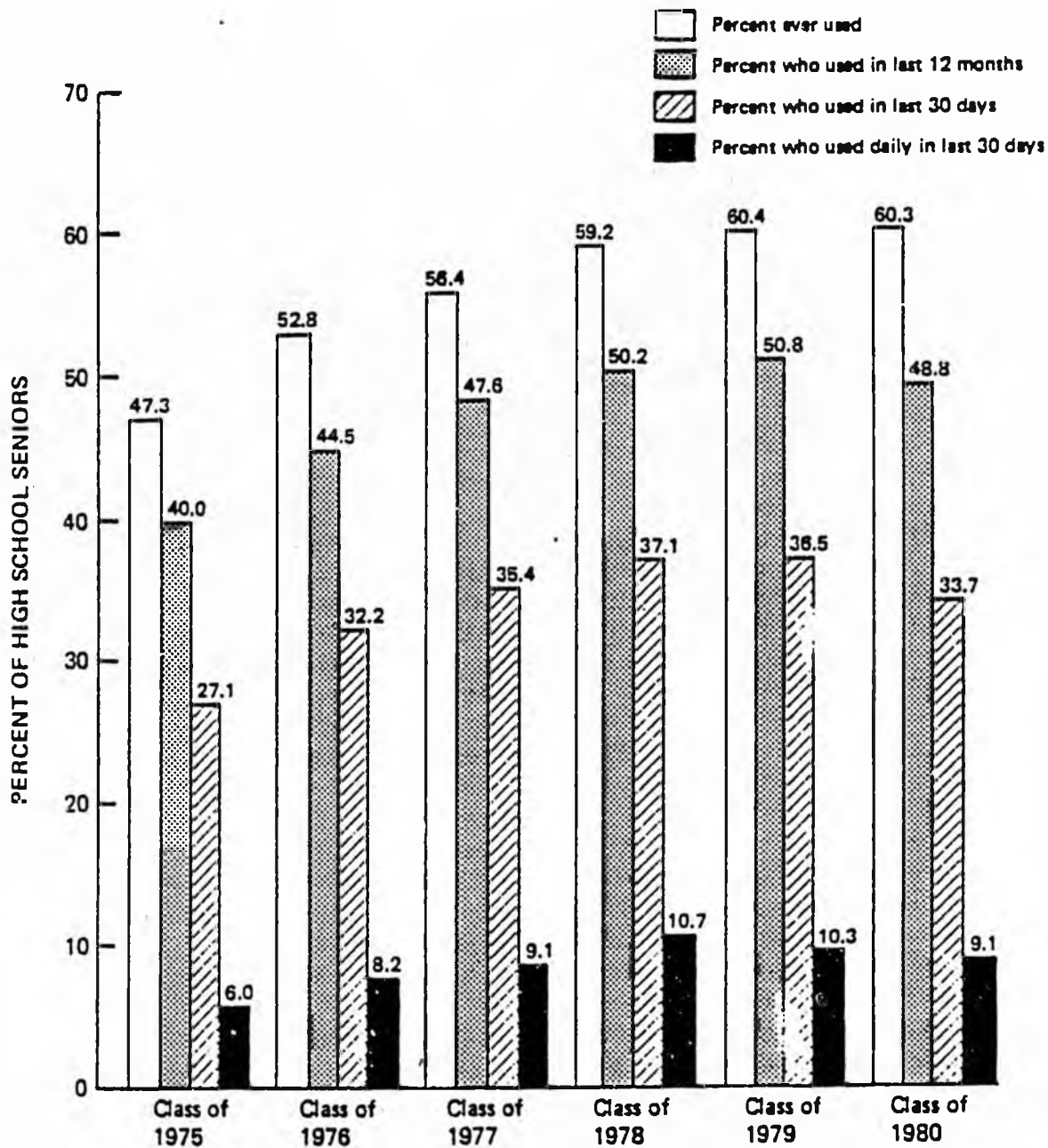
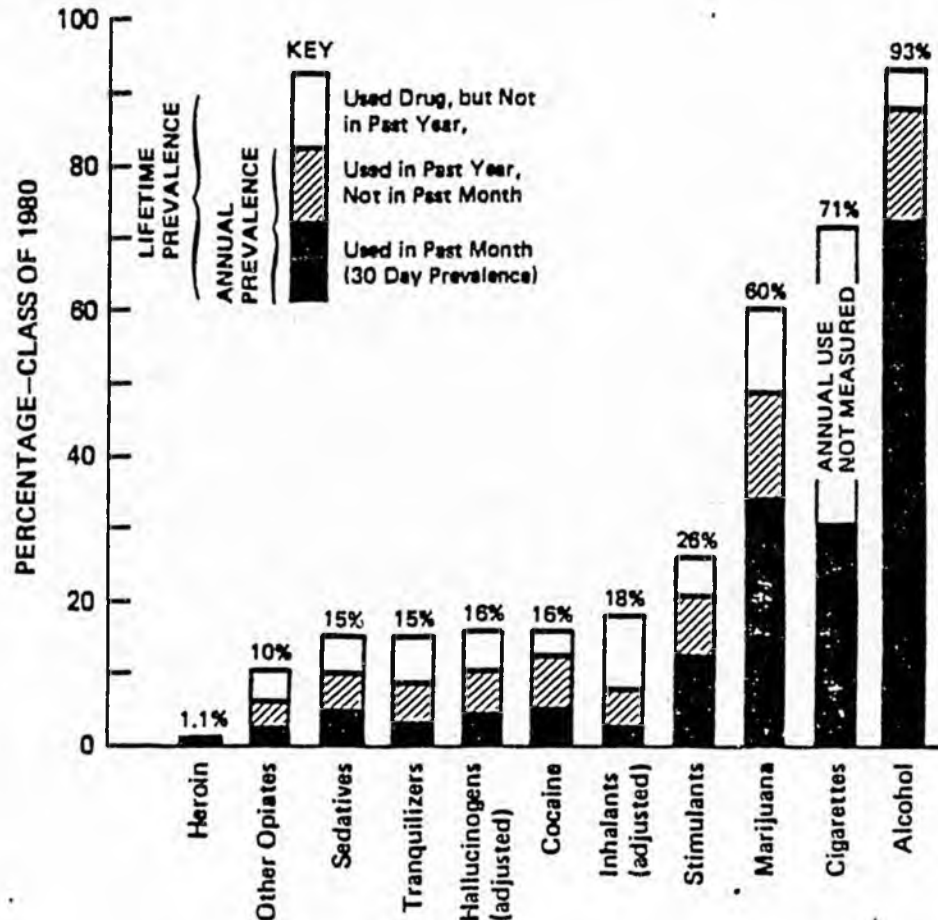


FIGURE 3 Trends in prevalence of marijuana use by high school seniors, 1975-1980 (in school). Adapted from L.D. Johnson, J.G. Bachman, and P.M. O'Malley, Highlights from Student Drug Use in America, 1975-1980. DHHS Publication No. (ADM) 81-1066. Washington, D.C.: U.S. Government Printing Office, 1980a.



NOTE: The bracket near the top of a bar indicates the lower and upper limits of the 95% confidence interval.

FIGURE 4 Prevalence and recency of use. Eleven types of drugs, class of 1980. SOURCE: Johnson, L.D., Bachman, J.G., and O'Malley, P.M. Highlights from Student Drug Use in America, 1975-1980. DHHS Publication No. (ADM) 81-1066. Washington, D.C.: U.S. Government Printing Office, 1980a.

students. These figures show that legal (for adults) drugs are used much more frequently than illegal ones. Reports of illegal use of drugs show that experimentation with marijuana has, by far, the highest prevalence. It should be noted, also, that "daily" use of marijuana (9 percent) among high school seniors is now more prevalent than "daily" drinking (6 percent) of alcoholic beverages.

In 1980, for the first time since 1975, when the Monitoring the Future data collection began among high school seniors, the percentage of "daily" users of marijuana among seniors in high school declined significantly from 10.2 percent in 1979, to 9.1 percent in 1980 (Figure 3), and there was a leveling of lifetime prevalence at approximately 60 percent. Furthermore, the proportion of current users among those who ever used marijuana also showed a statistically significant decline in 1980 as compared to 1979, from 60 percent to 56 percent. However, "daily" users may be increasingly underrepre-

sented in recent senior high school classes due to absenteeism and drop-out associated with increasingly earlier and extensive involvement in use of marijuana. The extent to which long-term "daily" users have dropped out of school by the senior year of high school cannot be ascertained from monitoring the future. Kandel (1975a) found that absentees differed from students attending school regularly. Fifty-six percent of absentees reported use of marijuana as compared to 38 percent of in-class students. Studies that document the patterns of marijuana use in school drop-outs are needed.

### Correlates of Use

Overall levels of use of marijuana have been shown to correlate with patterns of use of the drug.

1. Increased prevalence is associated with younger age of initiation into use of marijuana. As successive cohorts of high school seniors have shown increasingly higher levels of experience with marijuana from 1975 through 1980, these cohorts also report increasingly earlier ages at first use of marijuana. For example, in the senior class of 1980, which had a lifetime prevalence of 60 percent by senior year, 25 percent of those using marijuana had begun in the eighth grade (average age 14) or below. In 1975 when lifetime prevalence was 47 percent, 15.3 percent of marijuana users had begun in eighth grade or below. It is of some interest to compare reported age of use of marijuana by grade for the senior class of 1980 (lifetime prevalence 60 percent) and alcohol (lifetime prevalence 93.2 percent). The more prevalent drug, alcohol, is used at earlier ages than marijuana. Thirty-three percent of alcohol users had started at eighth grade as compared to 21.5 percent of marijuana users (Johnston et al., 1980a).

2. Earlier onset of use of any drug is associated with greater involvement in use of all other drugs. The earlier the introduction to legal (for adults) drugs, the greater the probability that the adolescent will also experiment with illicit drugs. For example, among young adults 18-25 years of age surveyed from the general population in 1979-1980, the proportion who had experimented with any illicit drug other than marijuana ranged from 87 percent among those who reported having first tried alcohol or marijuana at ages 13 or 14, to 47 percent among those who first tried these drugs at ages 15-17, and 5 percent among those who first experimented at age 18 or over (Rittenhouse, 1980). The finding that the earlier the experimentation with marijuana, the greater the intensity of involvement and the greater the likelihood of using more serious drugs has been confirmed in many studies (e.g., Miller and Cisin, 1980; Johnston et al., 1980a; Kandel et al., 1981).

3. Greater overall prevalence of use of marijuana is associated with greater persistence of use of marijuana into later years of adult life. The current prevalence rates for use of marijuana by persons in their mid-30s are increasing (Cisin et al., 1978). Many

studies have not sampled this population in the belief that use of marijuana drops off sharply in the mid-20s. Among males, the prevalence rate for use of marijuana in the past month for over-26-year olds went from 4 percent in 1977 to 9 percent in 1979. It will be exceedingly important to monitor the trends in all older adult age groups.

### Marijuana and the Use of Other Drugs

One of the key questions asked over the years is, does marijuana lead to the use of other drugs. In any population, the use of various drugs appears interrelated and users of any type of drug, whether legal or illegal, are much more likely to use other types of drugs than nonusers. For example, young people who smoke tobacco are also much more likely to have used alcohol or marijuana than nonsmokers (Fishburne et al., 1980). Similarly, there is a strong association between the use of marijuana and of other illicit drugs. Young people who use marijuana are more likely to be consuming other substances, such as alcohol and tobacco, as well as other illicit drugs (Johnston et al., 1980b). The association increases with extent of marijuana involvement and is especially striking among those young people who use marijuana on a "daily" basis, as will be discussed below.

Results from the National Household Surveys and from samples of high school seniors had indicated that the ratio of rates of use of illicit drugs other than marijuana to use of marijuana declined through 1979 (Kandel, 1980; Miller and Cisin, 1980). In 1980, however, the ratio started to rise again. Thus, in 1980, 65 percent of marijuana users among the high school seniors had also used other illicit drugs as compared to 61 percent in 1979 (Johnston et al., 1980a).

### "Daily" Users in High School

Because any health risks resulting from the use of marijuana would be most likely to appear first in chronic users of the drug, the young persons who are chronic and heavy users are of special interest. The committee reports in some detail the findings on this group. The ranks of "daily" users are large. In 1980 they represented more than 9 percent of high school seniors or over 390,000 18-year-olds in the United States. One out of 11 seniors fitted the definition of "daily" users (20 or more occasions of reported use within the preceding 30 days). Collection of systematic data on such users began in 1975 with the annual monitoring of in-school high school seniors. There are many gaps in our knowledge about this group, but sufficient data have been accumulated that it is now possible to describe many of the behavioral attributes of the "daily" users. Most of these data come from Monitoring the Future. Some of the findings recently reported by Johnston (1980, 1981) and Bachman et al. (1981) are as follows:

### Demographic Findings

Rates of "daily" use do not vary among regions of the country, but "daily" use shows a strong positive relationship to the size of the community and is more prevalent in urban areas. Males are "daily" users at almost double the rate of females (13 percent versus 7 percent). "Daily" use among white students is double that for blacks (11 percent versus 5 percent). "Daily" use is spread evenly across socioeconomic levels as defined in terms of parents' education. "Daily" use is only slightly higher among those from homes in which one or both parents are absent.

### Academic Performance and Goals

"Daily" use is associated with poor school achievement. Among non-college-bound seniors the rate of "daily" use is almost double that found among the college-bound (13 percent versus 7 percent). There are strong and positive correlations of "daily" use and cutting classes, school absences, and truancy.

Much of "daily" use takes place within the school setting. A statewide study of seventh through twelfth grade pupils in New York, conducted in 1978 by the New York State Drug Abuse Commission, found that 50 percent of those using marijuana within the last 6 months had been intoxicated one or more times while in class (Johnson and Uppal, 1980). In contrast, alcohol tends to be used most frequently after school and on weekends.

### Religious Commitment

A commitment to religion and self-ratings of strong belief in law-abiding behavior are associated with lower than average rates of "daily" use.

### Dating and Social Life

Dating and social life show strong relationships with "daily" use of marijuana. Those who spend more time on dates have the highest rates of "daily" use of marijuana. Among those students who go out 6 or 7 nights a week and are practically never at home, 34 percent are "daily" marijuana users.

### Use of Other Drugs

"Daily" marijuana users are much more likely than their peers to be extensive users of other drugs. Thus, of seniors in the class of 1979, 27 percent of "daily" users of marijuana drank alcohol as frequently, versus 7 percent for the age-group as a whole; and 59

percent of "daily" users of marijuana smoked cigarettes as frequently versus 25 percent for the group as a whole (Johnston et al., 1980b).

With respect to use of other illicit drugs, the rates for "daily" users of marijuana generally run five to seven times the average for the age group as a whole; 47 percent of "daily" users are current\* users of amphetamines; 31 percent of cocaine; and their current usage figures run from 15 to 17 percent for barbiturates, for lysergic acid diethylamide (LSD), for phencyclidine (PCP), for methaqualone, and for tranquilizers. Since nearly two-thirds of daily marijuana users (64 percent) are current users of hashish, they have substantial exposure to a high-potency form of marijuana.

We also know from data on age at first use that many of these "daily" marijuana users began their use of cigarettes, alcohol, and various other illicit drugs at quite an early age. To illustrate, by the end of eighth grade 40 percent of them had smoked cigarettes "daily" and 50 percent had taken their first drink. Just about half of them (48 percent) first tried marijuana by the eighth grade, and most of the remainder (another 30 percent) started in ninth grade. These are very early ages of initiation for all three drugs. Similarly, these youngsters tend to take up the other illicit drugs at an earlier than average age--though most of that use still is initiated after ninth grade. "Daily" use tends to persist longer into adult life than anticipated. In 1979, 4 years after graduation from high school, 51 percent of marijuana users of the senior class of 1975 were still "daily" users and an additional 34 percent were current although not "daily" users (Johnston, 1980).

#### "Daily" Users After High School

Using a national sample of 19- to 22-year-olds derived from the follow-up surveys of Monitoring the Future, Johnston (1981) reported on "daily" use of marijuana after high school. (These findings are reproduced nearly verbatim below.)

#### College Student Status

Student status after high school correlates negatively with "daily" use; that is, full-time college students have the lowest rate (8 percent), part-time students the next lowest (10 percent), and nonstudents the highest rate (13 percent). However, although full-time students have a lower than average rate of "daily" use, they showed the greatest increase after high school (up from 4.5 to 8.3 percent); they simply started from a very low level and in a sense were "catching up."

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\*A current user is one who has used the drug in the thirty days preceding the surveys.

### Living Status

Young people who are living away from home have a higher proportion of "daily" use than those still living with their parents (12 percent versus 10 percent), probably reflecting the result of reduced social control by parents. Those who remained living with their parents (nearly half) showed relatively little increase in use (up 1.3 percent), while those who moved out increased their daily use rate substantially (up 3.9 percent).

### Marital Status

Those who are single are almost twice as likely to be "daily" users as those who are married (11.4 percent versus 6.6 percent), and those without children are somewhat more likely to use marijuana than those with children (11 percent versus 8 percent). It appears that these role responsibilities have a dampening effect on use. In the face of an overall 2.6 percent increase in "daily" prevalence after high school for the whole sample, those who were married showed virtually no increase (up 0.2 percent) and those with children actually had a decline in use (down 1.5 percent).

### Type of dwelling

"Daily" use is highest for those living in a rented room (14 percent) or apartment (12 percent), and lowest for those living in a college dorm (8 percent). Obviously one's dwelling arrangement is highly correlated with his or her major activity after high school, as these differences reflect.

### Employment

Employment status is unrelated to "daily" use. For those in military service, "daily" use dropped slightly after high school (from 13.4 percent to 12.4 percent). The activity group with by far the lowest "daily" use rate are the full-time homemakers (4 percent), which certainly occurs, in part, because they nearly all are female, married, and in many cases have young children.

## Reasons for Using or Abstaining

### Reasons for "Daily" Use of Marijuana

What reasons do "daily" users give for their use of marijuana? They tend to use marijuana to produce an intoxicated feeling, to cope psychologically with feelings of distress, to augment the effects of other drugs, and to participate in drug-using friendships. On a

checklist of 13 possible reasons, nearly all of the seniors who were "daily" users checked "to feel good or get high" (94 percent) and "to have a good time with my friends" (79 percent). Two-thirds said they used it to relax (67 percent) and nearly half said they used it to relieve boredom (45 percent). Roughly a quarter of the "daily" users checked each of the following: "to get away from my problems" (27 percent), "because of anger or frustration" (23 percent), and "to get through the day" (22 percent). These psychological coping motives in particular seem to distinguish the "daily" users from the less frequent users. A fairly high proportion (30 percent) also said that they used marijuana to increase the effects of other drugs, while only 10 percent of the other current users gave this reason. Only 11 percent of the "daily" users, or 1 percent of the total sample, stated that they used it because they felt "hooked" or had to have it. All of these responses for seniors were closely replicated among the "daily" users in the 19- to 22-year-old sample (Johnston, 1981).

Nearly all "daily" users (over 85 percent), whether in high school or past high school, say (1) that most or all of their friends smoke marijuana, (2) that most or all of their friends drink alcohol, (3) that more than a few of their friends get drunk every week, (4) that more than a few of their friends smoke cigarettes, and (5) that at least a few of their friends use a number of other illicit drugs. This degree of immersion in a drug-using friendship circle contrasts sharply to what we observe for their peers, even those who are current but less frequent users of marijuana. Clearly the social supports and the social pressures are there, both during and after high school, for the "daily" user to continue his or her habit.

#### Reasons for Quitting and Abstaining

A number of users of marijuana stop using the drug (Johnston, 1981). Among students (in the classes of 1978 through 1980 combined), those who have used marijuana 40 or more times but have stopped by their senior year give as their most commonly mentioned reason on a comprehensive list of 17 reasons that "they don't feel like getting high" (56 percent mentioned). Also frequently mentioned, however, are concerns about possible physical effects (41 percent); concern about possible psychological effects (38 percent); and, more specifically, concern about loss of energy or ambition (41 percent). These reasons also ranked high among those young people who smoked less than 40 times before they stopped, as did two additional reasons—concern about parental disapproval and finding that use of marijuana was not intrinsically enjoyable.

Concern about possible health effects appears to play a role in young people's giving up the drug and is mentioned considerably more often among quitters now than in 1976. Concern about physical health increased substantially between 1976 and 1980 among all high school seniors, from 35 percent to 57 percent, while concern about psychological damage went from 34 percent to 53 percent. A similar analysis of the reasons given for abstaining by the minority (about

40 percent) of seniors who have never tried marijuana reveals concern about physical (71 percent) and psychological (68 percent) consequences, which are mentioned far more often than any other type of reason. Social or ideological constraints or disinterest in getting high are infrequently mentioned. There also has been a significant increase in health concerns among the abstaining segment since 1976, though not as large as among quitters.

In summary, many "daily" users themselves see some negative consequences of their habit, and there perhaps are some consequences of which they are unaware. The fact that the "daily" smoking of marijuana is proving to be more enduring and stable than many may have thought increases the probability of cumulative, long-term effects. The fact that so many young people are becoming "daily" users now puts a substantial number of people at risk of whatever the long-term consequences may prove to be.

#### Sequence of Drug Use

Regardless of the age of onset, there is a predictable sequence in the patterns of initiation into the use of available drugs. Independent longitudinal studies have confirmed and identified a stable sequence of drug use (Hamburg et al., 1975; Kandel, 1975b; Kandel and Faust, 1975). The legal drugs for adults, such as alcohol and tobacco, are an early, integral, and crucial part of the sequence. Their use precedes the use of all illicit drugs. At least four distinct successive stages of adolescent involvement with drugs can be identified: (1) use of beer or wine, (2) use of tobacco cigarettes or hard liquor, (3) use of marijuana, and (4) use of other illicit drugs (Kandel, 1975b). A fifth stage, problem drinking, may take place between marijuana and other illicit drugs (Jessor et al., 1980). Adolescents rarely proceed from beer and wine to illicit drugs without use of either hard liquor or tobacco cigarettes as an intermediate step. Furthermore, there is an additive effect such that the highest proportion of adolescents who move to marijuana are those who have experience with both hard liquor and tobacco. For example, among 12- to 17-year-olds in the general population, the proportion who have ever experimented with marijuana is 81 percent among current tobacco cigarette smokers as compared to 24 percent among nonsmokers (Fishburne et al., 1980). However, position on a particular point in the sequence does not indicate that the young person will necessarily progress to other drugs higher up in the sequence. Participation in each stage is a necessary but not sufficient condition for participation in a later stage. There is no evidence to support the belief that the use of one drug will inevitably lead to use of any other drugs. In other words, persons at the top of the ladder of use of drugs typically will have used all substances at lower levels, including marijuana. However, those at lower rungs may stay there and not move to higher rungs of the ladder. For example, data from the National Household Surveys (Fishburne et al., 1980) indicate that of those 18-25 years old who have tried

marijuana, almost all are users of tobacco or alcohol; however, only slightly more than one-fourth of this 18- to 25-year-old population report having gone on to try any illegal drug other than marijuana. Of those who try other illegal drugs, only a very small percentage report being current users (Fishburne et al., 1980).

Although it is of great interest, relatively little is known about the factors that determine which persons will choose to go through the sequence of drug use or the rapidity with which they will do so. Existing research gives us some clues that users of illicit drugs possess some distinguishing features.

There are four clusters of variables--parental influences, peer influences, adolescent involvement in deviant behaviors, and adolescent beliefs and values--that assume differential importance for predicting involvement at each stage of drug behavior (Kandel et al., 1978a,b).

Involvement with drugs legal for adults is the earliest level of drug use. Adolescents who start to drink are exposed to peers and parents who drink, suggesting that these youths learn drinking patterns from their parents. Adolescents who have engaged in a number of delinquent or deviant activities, and who seek high levels of sociability with their peers are likely to become involved with alcohol. Similar patterns are found with tobacco smoking, also one of the earliest drugs to be tried.

The use of marijuana follows that of alcohol and tobacco. It is preceded by acceptance of a cluster of beliefs and values that often reflect disavowal of many standards upheld by adults. Involvement in a marijuana-using peer environment strongly predisposes to its use and is the best predictor (Becker, 1953; Goode, 1970). Participation in minor forms of deviant behaviors, such as those that also precede the use of hard liquor, is also an important precursor.

#### Antecedents of Adolescent Use of Marijuana

When use of marijuana first came under research scrutiny in the late 1960s, very few youths had experimented with illicit drugs. Much was made of the deviant status of use of marijuana and of the counter-cultural and rebellious meaning that came to be attached to using the drug (Suchman, 1968). Yet even today, when over 60 percent of all high school seniors have used marijuana, those youths who use marijuana are quite different from nonusers. The marijuana users in 1979 show the same patterns of disaffection from major institutions that characterized the users in 1967. The most recent data show that marijuana users perform more poorly in school, are less diligent, have performed more delinquent acts, are in trouble with the law, have more traffic accidents, and use more illicit drugs than nonusers. Those persons who also use several illicit drugs show the highest involvement in deviant behaviors. There is a linear relationship with degree of involvement with illicit drugs, such that persons using marijuana exclusively are only quantitatively different from those who have also used harder drugs (Johnston et al., 1980b).

In two cross-sectional national samples of high school students, surveyed in 1974 and 1978, Jessor et al. have found that not only are the patterns of association between use of marijuana and deviant characteristics similar in both surveys, but also that the strength of the associations, as reflected in the sizes of the correlation coefficients, are almost identical. The very same conclusions derive from analyses based on five successive cohorts of high school seniors, sampled at yearly intervals in Monitoring the Future (Bachman et al., 1981).

Longitudinal studies of students aged 12-21 have done much to extend our understanding of the precursors of using various forms of drugs. Studies have been reviewed in detail by Kandel (1978a,b; 1980a; also see Appendix C) and document that many of the factors found to be associated with use of drugs at one point in time, such as low academic performance, crime, low self-esteem, depressive mood, rebelliousness, and other personality characteristics, precede the use of drugs (see in particular Mellinger et al., 1976; Jessor and Jessor, 1977; Johnston et al., 1978; Kandel, 1978a; Kandel et al., 1978b,c; Kaplan and Pokorny, 1978; Smith and Fogg, 1978; Wingard et al., 1979; Kaplan, 1980). Some of the predictive factors can be identified in childhood, such as aggressiveness with or without association with shyness (Kellam et al., 1980, in press) and rebelliousness (Smith and Fogg, 1978).

Other longitudinal studies also document that many of the factors found to be associated with use of drugs at one point in time, such as low academic performance, delinquency, low self-esteem, and depressive mood actually precede the use of drugs (O'Malley, 1975; Mellinger et al., 1976; Jessor and Jessor, 1977; Johnston et al., 1978; Kandel et al., 1978a; Kaplan and Pokorny, 1978; Wingard et al., 1979; Kaplan, 1980).

One study shows not only that certain behaviors predict use of marijuana, but also that drugs may aggravate or exaggerate certain behaviors. A cohort of high school students was followed at annual intervals throughout the four years of high school (Jessor and Jessor, 1977). During this time annual scores for various attributes were charted in four groups of students distinguished by differing drug histories: veteran users, who used drugs pre-high school; early initiates, who began relatively early in their high school career, i.e., between the first and second year of testing; late initiates, who began relatively late, i.e., between the second and the third year; and nonusers, who had not started to use marijuana at the last testing in the senior year of high school (Jessor and Jessor, 1977, 1978). These four groups of students differed on measures, such as general deviant behavior (a 12-item scale measuring frequency of involvement in stealing, fighting, property destruction, truancy, or other delinquent activities in the last year) or value on academic achievement (a five-item scale, measuring the value placed on the attainment of success in school work), at the beginning of the study. Scores predicted if and when students initiated use of marijuana. Those students already involved in use of drugs before high school scored highest on deviance and lowest on achievement motivation at

initial testing and throughout subsequent retests. The scores of all groups of users converged over time so that all three groups increased in deviance scores and decreased in their achievement orientation over the four years. ~~The sharpest changes in scores occurred in the year preceding the drug use.~~

### Peer Influences

The most consistent and reproducible finding in drug research is the strong relationship between an individual's drug behavior and the concurrent use of drugs by his friends. The relationship is stronger when based on adolescents' perceptions of the friends' behavior than on the friends' self-reports (Goode, 1970; Johnson, 1973; Kandel, 1973; Goldstein, 1975; O'Donnell et al., 1976; Brook et al., 1977; Jessor and Jessor, 1977; Kandel et al., 1978a; Orcutt, 1978; Smart et al., 1978; Huba et al., 1979). ~~On no other characteristic except age and sex is the similarity within adolescent friendship pairs as high as it is for use of marijuana (Kandel, 1978c).~~ Such similarity results not only from socialization, the influence of one friend on the other, but also from a process of interpersonal selection (assortive pairing), in which adolescents with similar values and behavior seek each other out as friends. Longitudinal data on the formation and dissolution of friendships indicate that selection and socialization contribute about equally to the similarity in values and behaviors (Kandel, 1978d). Available data on sex differences in peer influence indicate that females are more susceptible than males to such influence (Jessor et al., 1973; Margulies et al., 1977). Susceptibility to peer influence is related to involvement in peer-related activities, e.g., dating or getting together with friends, and to degree of attachment to and reliance on peers rather than parents (Jessor and Jessor, 1978; Kandel et al., 1978a; Brook et al., 1980). Contact with other users increases the likelihood that the individual will have increased opportunities to get the drug. ~~Peer-mediated approaches have been shown to be an effective vehicle for interventions to prevent smoking of tobacco in adolescents (Evans, 1977; McAlister, 1979).~~ ~~The powerful role of peer influence on the use of marijuana would seem to suggest that it would be also useful for preventive marijuana programs.~~

### SUMMARY

There has been a steep rise in the use of marijuana and other illicit drugs in the past decade. So far it is primarily a youth phenomenon. Since 1971 there has been at least a doubling of lifetime experience with marijuana in every cohort in the 12- to 24-year age group. Of all psychoactive drugs investigated (including inhalants, hallucinogens, cocaine, heroin, stimulants, sedatives, and tranquilizers), marijuana is by far the most commonly used illicit drug. Legal drugs for adults, such as alcohol and tobacco, are the most widely used of

all drugs among adolescents. Although substantially more students have ever used alcohol in their lifetime than have ever used marijuana, more high school seniors use marijuana on a "daily" basis (9 percent) than use alcohol that frequently (6 percent). "Daily" users report the use of marijuana in school, whereas daily use of alcohol tends to occur after school and on weekends.

Some trends in use of marijuana are apparent. The continuing dramatic rise in the use of marijuana has recently slowed. It is too early to tell whether this decrease will continue or is merely a pause in the rise. The overall prevalence of use of marijuana has remained at approximately 60 percent of high school seniors for the years 1978, 1979, and 1980. Between 1975 and 1978 there was an almost twofold increase in "daily" use of marijuana from 6 percent in 1975 to a peak rate of 11 percent in 1978. In 1980 the "daily" use rate of high school seniors dropped by 1.2 percentage points, or more than 10 percent. This may signal a reversal of the upward trend in "daily" use unless higher absenteeism and school drop-out of daily users are significant factors in the decline. Multiple sources suggest that out-of-school age mates are heavier users than those in school. Other trends have not slowed. There was a continuing rise in 1980 of the proportion of high school seniors who during the year had used some illicit drug other than marijuana, from 28 percent in 1979 to 30 percent in 1980.

Throughout the 1970s, as a correlate of continuing rise in prevalence rates, there was a trend toward younger ages of first use of all of these drugs. For marijuana this age trend continues but has slowed somewhat. In 1979, 23 percent of seniors who had used marijuana started their use in the eighth grade or below as compared to 25 percent in 1980.

"Daily" use of marijuana in high school and in early adult life is very high and merits special attention. Drawing on data from Monitoring the Future, characteristics of "daily" users were described. For high school seniors the rate of "daily" marijuana use in 1980 was 9.1 percent. Such users have very high involvement with other drugs and begin their use of drugs at very early ages. "Daily" users are predominantly urban although rates do not vary by geographical regions of the country, whereas use among white students is double that for blacks. "Daily" use is only slightly higher in disrupted or single parent homes than in nuclear families, and use is associated with poor school achievement, absenteeism, and dropout. Non-college-bound students are twice as likely to be "daily" users as were students planning to attend college. Religious commitment and self-ratings of strong belief in law-abiding behavior are associated with lower "daily" use rates. "Daily" users are involved in more automobile accidents and delinquency.

Post-high school "daily" user rates are lowest among full-time college students and those living in a college dormitory. "Daily" use among non-college students was not related to joblessness, employment, or military service. Single persons are twice as likely as married persons to be "daily" users. Among the married, those with children had very low rates of "daily" use. The "daily" use

habit has a remarkable stability. By 4 years after high school, 85 percent of "daily" using seniors in the class of 1975 were still using marijuana, with 51 percent of them continuing to be "daily" users.

In these studies, students report reasons for using marijuana: to have a good time with friends, to get "high," to relieve boredom, to enhance the effects of other drugs, and to cope with stress.

"Daily" users are deeply immersed in a drug-using circle of friends. Some "daily" users have discontinued their habit. Reasons given for stopping use of marijuana are ~~loss of interest in getting "high,"~~ concern about harmful physical or psychological effects, and concern about their loss of energy or ambition.

More is known about the antecedents of using marijuana than is known about the consequences of using marijuana (to be discussed further in the chapters that follow). Longitudinal studies have established that ~~use of marijuana is preceded by acceptance of a~~ cluster of beliefs and values that are favorable to use of marijuana and also by the adoption of deviant behaviors. The deviant psychosocial attributes of marijuana users that were described almost a decade ago, when use of marijuana was a rare event, are just as characteristic of marijuana users today, when 60 percent of all high school seniors report some experience with the use of marijuana. Daily users show the extremes of these deviant behaviors but less deeply involved users also exhibit some deviancy. Friendship patterns and peer influence play a uniquely powerful role in determining youthful marijuana use. ~~Negative parental relationships~~ do not appear to be associated as an antecedent to use of marijuana.

#### RECOMMENDATIONS FOR RESEARCH

Additional research needed includes (1) epidemiologic studies on patterns of use of drugs among young adolescents, including those who leave school, (2) longitudinal studies to investigate the antecedents and consequences of use of marijuana, and (3) studies of the effects of marijuana in combination with use of other drugs.

Because samples of high school seniors exclude youths most at risk for high marijuana involvement, namely adolescents not regularly attending the high school, additional cohort-sequential epidemiologic surveys beginning with prepubertal children are needed in order to follow development and behavior from early in life. An all-conclusive approach would be both a prospective (concurrent) cohort study and a retrospective case-control study of possible outcomes of and risk factors for marijuana use (this recommendation is described in detail in Chapter 6).

"Daily" users have been understudied and may have the most severe risk in terms of loss of learning potential, biological risk, and psychosocial handicap. Studies should be undertaken to predict who among the large numbers of young people who try marijuana are at risk of becoming "daily" users.

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

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

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

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

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# 3

## EFFECTS OF MARIJUANA ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEMS

### RESPIRATORY SYSTEM

#### Performance (Pulmonary Function)

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

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

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

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

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

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

### Acute Effects

Marijuana affects the control of the breathing pattern in different ways depending upon the dose, the preparation, and its psychotropic effect on the consumer. ~~Smoking marijuana cigarettes generally stimulates ventilation (air exchange between the lungs and the ambient air) in conjunction with an increase in the metabolic rate and a heightened response to carbon dioxide (CO<sub>2</sub>) as a regulatory stimulant (Vachon et al., 1973; Twilich et al., 1978).~~ On the other hand, larger doses of smoked marijuana may depress the ventilation and responsiveness to the CO<sub>2</sub> stimulus (Weil et al., 1968; Bellville et al., 1975). ~~The intravenous administration of Δ-9-THC in equivalent doses has such less of an effect either on the ventilation or on the effectiveness of CO<sub>2</sub> as a respiratory stimulant (Marr et al., 1975).~~

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

~~Except for bronchodilation, acute exposure to marijuana has little effect on breathing as measured by conventional pulmonary tests. Thus, in young marijuana smokers (21-30 years of age), the spirometric measures of lung volume, flow, and resistance, as well as the measures of respiratory mechanics and gas exchange were normal by conventional methods (Tashkin et al., 1976). In contrast, heavy marijuana smokers, at least 4 days per week for 6 to 8 weeks, did exhibit mild airway obstruction (Tashkin et al., 1976).~~

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

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

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

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

#### Subacute Effects

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

#### Chronic Effects

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

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

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

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

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

Another study was of 200 American soldiers stationed in West Germany who voluntarily sought medical attention for such respiratory symptoms as pharyngitis, sinusitis, bronchitis, and asthma related to chronic heavy hashish smoking (Henderson et al., 1972). Analysis of the hashish available and in use in the locale of this study showed concentrations of 5 to 10 percent 4-9-THC. Two to 1 percent of samples were contaminated with cocaine, opium, morphine, spices, or feces. Two aspects of hashish smoking are relevant to the question of lung injury produced by hashish: 1) hashish is usually smoked in a pipe (occasionally in a water pipe), although it is occasionally eaten, drunk as a tea, or rolled into a cigarette and smoked, and 2) hashish smoke generally is regarded by users as burning much hotter than tobacco smoke.

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

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

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

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

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

#### Defense Mechanisms (Alveolar Macrophages)

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

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

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

### Carcinoma of the Lung

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

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

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

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

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

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

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

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

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

#### Summary: Respiratory System

##### Lung Function and Defense Mechanisms

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

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

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

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

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

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

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

### Carcinoma of the Lung

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

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

### Recommendations for Research

#### Lung Function and Defense Mechanisms

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

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

## Carcinoma of the Lung

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

- an epidemiological survey to determine over the next 20 to 30 years if there will be an increased incidence of primary lung, laryngeal, oropharyngeal, esophageal, nasal, or sinus cancer in chronic marijuana smokers;

- epidemiologic and pathological studies in humans and experimental studies in animals to evaluate the carcinogenic potential of chronic marijuana smoking on the lung, larynx, oropharynx, nasal, and sinus epithelium.

## CARDIOVASCULAR SYSTEM

### Normal Heart and Circulation

#### Heart (Direct Effects)

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

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

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

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

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

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

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

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

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

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

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

#### Autonomic Nervous System

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

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