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2464 HJ HB 698 2464

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

EMBARGOED FOR A.M. PAPERS
Thursday, August 12, 1982

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Statement by
C. Everett Koop, M.D.
Surgeon General of the U.S. Public Health Service

As surgeon general, I urge other physicians and professionals to advise parents and patients about the harmful effects of using marijuana and to urge discontinuation of its use.

The health consequences of marijuana use have been the subject of scientific and public debate for almost 20 years. Based on scientific evidence published to date, the Public Health Service has concluded that marijuana has a broad range of psychological and biological effects, many of which are dangerous and harmful to health.

Marijuana use is a major public health problem in the United States. In the past 20 years, there has been a 30-fold increase in the drug's use among youth. More than a quarter of the American population has used the drug. The age at which people first use marijuana has been getting consistently lower and is now most often in the junior high school years. In 1978, nearly 11 percent of high school seniors used the drug daily; and although this figure declined to 7 percent in 1981, daily use of marijuana is still greater than that of alcohol among this age group. More high school seniors smoke marijuana than smoke cigarettes The current use (during previous 30 days) of marijuana is 32 percent; 29 percent smoke tobacco.

On March 24, Secretary Schweiker transmitted to the U.S. Congress a report reviewing the health consequences of marijuana use.

(More)

Marijuana and Health: 1982, the ninth in a series, is primarily based on two recently-conducted comprehensive scientific reviews on the subject: one by the Institute of Medicine of the National Academy of Sciences and the other by the Canadian Addiction Research Foundation for the World Health Organization. Both independent reviews corroborate the Public Health Service prior findings of health hazards associated with marijuana use: Acute intoxication with marijuana interferes with many aspects of mental functioning and has serious acute effects on perception and skilled performance, such as driving and other complex tasks involving judgment or fine motor skills.

Among the known or suspected chronic effects of marijuana use are:

- Marijuana impairs short term memory and slows learning;
- impaired lung function similar to that found in cigarette smokers. Indications are that more serious effects may ensue following extended use;
- decreased sperm count and sperm motility;
- interference with ovulation and prenatal development;
- impaired immune response;
- possible adverse effects on heart function; and
- by-products of marijuana remaining in body fat for several weeks with unknown consequences. The storage of these by-products increases the possibilities for chronic effects as well as residual effects on performance even after the acute reaction to the drug has worn off.

I am especially concerned about the long-term developmental effects of marijuana use on children and adolescents, who are particularly vulnerable to the drug's behavioral and physiological effects. The "amotivational syndrome" has been attributed by some to prolonged use of marijuana by youth. The syndrome is characterized by a pattern of

(More)

loss of energy, diminished school performance, harmed parental relationships and other behavioral disruptions. Though more research is required to clarify the course and extent, in recent national surveys up to 40 percent of heavy users report that they observe some or all of these symptoms in themselves.

The Public Health Service review of the health consequences of marijuana supports the major conclusion of the National Academy of Sciences' Institute of Medicine:

> 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.

# # #

Keep Off The Grass

Marijuana: more harmful than you think

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MARIJUANA FACTS

WHY DO CHILDREN ABUSE DRUGS?

- Peer pressure
- It is fun.
- They think it is harmless
- To escape from daily stress
- To create a new image.
- "Pop Culture" promotes it.
- Lack of positive models.
- Experimenting & curiosity.
- To relax.
- High-risk behavior.
- Imitation of parent's drinking and smoking habits.
- Their short-term thinking precluded consideration of long-term consequences.
- For independence.
- Because they feel a need to reject parent's values.
- To boost their self-esteem.
- Drugs are available.

WHAT IS MARIJUANA?

It is a drug made from the dried leaves and flowering tops of the hemp plant (cannibus sativa) containing more than 421 known chemicals.

THC (delta-9 tetra-hydrocannabinol) is the major mind-altering chemical. There are also other active agents in marijuana.

Marijuana varies in its strength of THC. Today it is up to 10 times more potent than prior to 1970.

When combined with other mind-altering drugs such as alcohol, the THC becomes significantly more potent. THC is fat soluable and it *builds up* and is stored in fatty tissues, especially in the brain and in the reproductive organs.

Half of the THC ingested stays in the body for three to five days. It takes up to 30 days for a single dose of THC to be completely eliminated.

Whereas alcohol is water soluable and fully metabolized in 12 hours, marijuana lingers in fatty tissues and causes cumulative effects.

A combination of marijuana and alcohol is particularly dangerous, causing changes in *depth perception, night blindness, concentration and reaction time.*

According to Carlton Turner, one of the world's most knowledgeable experts on marijuana research: *"There is no other drug used or abused by man that has the staying power and broad cellular actions on the body."*

WHAT DOES MARIJUANA DO TO THE BODY?

EFFECTS ON THE BRAIN

- It widens the gap between brain cells, thus slowing down the nerve impulses.
- Short-term memory is impaired.
- It impairs the ability to evaluate situations and sequencing ability.
- It impairs psycho-motor performance.
- It impairs sense of time and depth perception.
- There is decreased dream activity.
- A tendency towards insomnia.
- It produces apathy and lethargic behavior.

EFFECTS ON THE LUNGS

- Marijuana smoke is more irritating and harmful than cigarette smoke.
- Studies show that smoking one joint is more impairing to the lungs than smoking a pack of cigarettes.
- It can cause pre-cancerous lesions in 2 to 3 years (as compared to 20 years for heavy cigarette smokers).
- It makes lungs more susceptible to emphysema and bronchitis.

EFFECTS ON REPRODUCTIVE ORGANS

- There is a decrease in sperm count and mobility.
- Decreased testosterone level.
- It can cause chromosome change, thus slowing down cell renewal (an ongoing process essential for the maintenance of life).
- Prevents synthesis of DNA.
- Marijuana crosses the placental membrane - passing from the mothers' blood to the unborn child.

EFFECT ON BLOOD CELLS

- There is a decrease in white cell production, therefore it interferes with the body's ability to fight off infection and disease.

EFFECT ON PERSONALITY

- Users develop the "amotivational syndrome" which is characterized by apathy, vagueness, withdrawal and lack of motivation.
- There is a tendency toward paranoia (unfounded fear and suspicions).
- Users experience illusions of accomplishments, with unrealistic evaluation.

WHAT ARE THE OUTWARD SIGNS OF MARIJUANA USE?

- Personality changes may occur.
- Lack of agressiveness in males.
- There is a gradual drop in the quality of school work.
- Often over-reaction to criticism.
- Weight loss may occur.
- Unusual money requests.
- Physical evidence: cigarette papers, ashes, odor, roach holders, etc.

- Secretiveness.
- Red eyes.
- Slowing of speech.
- One of these signs is not enough for identification. Most are typical of adolescent behavior. Immediate signs are not always obvious.

HOW MUCH DOES MARIJUANA COST?

- $2.00 for one joint.
- $5.00 for 3 joints.
- $60 to $80 per ounce (dealer price).

HOW TO DEAL WITH THE PROBLEM OF YOUR OWN CHILDREN USING MARIJUANA.

- Be informed and up-date your facts.
- Do not deny the problem.
- Do not condemn the child.
- Keep cool and calm; do not lecture.
- Keep communications open.
- Refer to resources.
- Children need to hear clearly stated values and standards from their family.
- When a child is independent and self-supporting, they can make their own decisions. Up to then, their health is your responsibility.

HOW TO HELP PREVENT YOUR CHILD FROM USING DRUGS

- Hold family discussions about drugs and encourage open family discussion.
- Be an active listener.
- Provide alternative activities: sports, outings, etc.
- Form parental support groups.
- Discuss with family member that stress is normal. Explain how you cope with stress.

- Discuss how we can all cope with stress other than anestetizing ourselves.
- Encourage a good self-image.
- Promote individual interests - not always following what everyone else is doing.

POINTS OF CONSIDERATION

- Any form of drug use has more serious consequences with vulnerable individuals such as children and adolescents.
- The effects of drugs on those in the early stages of mental and physical development can be more pronounced and persistent than on mature adults.
- Learning to cope with stress is a normal and necessary developmental process.
- Marijuana use provides escape from stress and robs the child of developing skills needed to cope with stress.

Animal studies prove that marijuana use causes reproductive and fetal disorders.

- Of all fatal automobile accidents, 16% are marijuana related.
- Marijuana is addictive. The more you use, the more you need.
- Marijuana is more prevalent, more potent and more frequently used today than five years ago.
- Users are getting younger.
- The contents of cigarettes and alcohol are government regulated. However, since there is no regulation of marijuana, each joint is a surprise package.

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The Heritage Foundation Backgrounder

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A-7

May 4, 1981

THE MARIJUANA EPIDEMIC

> I get a sick feeling in the pit of my stomach when I hear talk of marijuana being safe. Marijuana is a very powerful agent which is affecting the body in many ways. What the full range of these consequences is going to be, we can only guess at this point. But from what we already know, I have no doubt that they are going to be horrendous.[1]
>
> Dr. Robert DuPont
> Former Director of the
> National Institute on Drug
> Abuse.

INTRODUCTION

Marijuana smoking has reached epidemic proportions in the United States. Some sixteen million Americans are now regular users; and among high school seniors, about one in ten are daily smokers -- averaging 3½ joints a day.

The extent of current marijuana consumption raises many important concerns. While use of the drug is widespread throughout the world, for instance, only in the United States is it so prevalent among young people of all classes that an entire generation is affected. In other countries, the smoking of marijuana is not usually found throughout the entire society -- generally use is confined to certain religious groups or classes. Only in this country does it involve the whole culture.

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1 Washington Post, July 30, 1978.

The most frightening aspect of the widespread use of the drug is that the overwhelming majority of smokers have no knowledge of the demonstrated medical effects of marijuana. Most regard it as completely harmless, or at least as no worse than alcohol or tobacco. During the 1960s, when the drug became common in America, reliable scientific evidence was sparse. Marijuana seemed harmless enough to most people, and the very expression of doubt by experts was all too often discounted as deriving from opposition to the political and social attitudes of the users.

This absence of hard evidence regarding the consequences of the drug caused many scientists and legislators to take a liberal view of marijuana usage -- how could one condone alcohol and tobacco and then condemn marijuana? But in the last ten years, the climate has changed. Many detailed studies have been published on the medical aspects of the drug, and a body of scientific literature has been assembled which was unavailable only ten years ago. The National Institute on Drug Abuse (NIDA), a division of the Department of Health and Human Services, has taken the lead in sponsoring over a thousand tests, employing sophisticated procedures to control dosage, strength, etc., consistant with patterns of social usage. Other organizations have funded similar research projects.

It took sixty years of studies to establish a strong correlation between tobacco smoking and a number of serious diseases. Yet the results of experiments carried out in the last decade already suggest a strong relationship between the use of drugs and several medical disorders. Marijuana appears to impair memory, learning performance, motivation and may permanently damage brain tissue. It would also seem to have damaging effects on the lung, reproductive organs and the immunity system.

The powerful evidence now available has caused many experts to revise their position from one of indifference to one of great concern. Dr. Robert DuPont, quoted above, is a case in point. In various senior governmental positions, he did much to soften attitudes towards the use of marijuana -- indeed he was often cited in the literature of the decriminalization lobby. But now, as president of the American Council on Marijuana, he is in the forefront of a campaign to end the consensus that marijuana is no worse than many other drugs taken for pleasure. That belief, he says, "is a disaster and I feel very badly to have contributed to [it]."[2] Like so many of those who have changed their minds in light of the evidence, Dr. DuPont is particularly anxious about the long-term consequences of marijuana smoking on the current school population.

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2 "Reading, Writing and Reefer," NBC News Report, broadcast December 10, 1978.

This Backgrounder will review the scientific evidence which has led to the dramatic change of heart by so many people. It will then examine the policy options available to deal with the situation.

THE GROWING USE OF MARIJUANA

What is Marijuana?

Marijuana (also known as pot or grass) comes from the plant Cannabis Sativa (Indian hemp or hashish), which has been cultivated for hundreds of years as a source of rope. The principal psychoactive, or mind-altering, ingredient of marijuana is a substance know scientifically as delta-9-tetrahydrocannabinol (or THC), although several hundred other chemicals with various effects are also present.

An intake of between five and ten milligrams of THC into the bloodstream is usually sufficient to induce intoxication -- a "high." In the 1960s, when the drug was becoming fashionable, most of the marijuana smoked in this country was of domestic origin. At that time, most American marijuana had a rather low THC content (0.2 percent to 1 percent), and so a 1 gram joint might contain in the region of 2-10 milligrams of THC. By 1970, however, Mexican marijuana with an average THC of between 1.5 percent and 2 percent, had begun to dominate the market. By the end of the 1970s, Jamaican and Colombian varieties, with concentrations of 3 percent to 4 percent THC began to enter the country in increasing quantities. In addition, liquid hashish, with a concentration of 30 percent to 90 percent THC, began to appear. At a potency rate of 50 percent THC, an ounce of this oil is sufficient to intoxicate one thousand people. In 1974 alone, 369 pounds were seized by federal agents.[3]

The rise in potency of marijuana available in the United States is central to any discussion of the medical impact of the drug. The early, inconclusive studies carried out in this country were based on the low-potency marijuana then being consumed. But now we are dealing with far stronger varieties, and the studies using these strains of marijuana are far from inconclusive.

Usage of Marijuana

Twenty years ago, marijuana was hardly used in this country. Only in the late 1960s did the drug become widely used, and not until the mid-1970s did it become commonplace. The increase in use has been dramatic by any measure. The most recent major study on usage was conducted by the National Institute on Drug

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3 J. N. Jenson, Testimony before the Senate Subcommittee on Internal Security, May 1975, ref. 51, pp. 431-439.

Abuse, using a national sample carefully broken down by age and other characteristics.[4] As Table I indicates, this study found that 68 percent of young adults in 1979 had tried marijuana, compared with only 4 percent in 1962. Among 12- to 17-year-olds, the proportion had grown over the same period from just 1 percent to 31 percent. Even among 12- to 13-year-olds in 1979, the study showed 8 percent had been introduced to the drug. When NIDA examined current users (those who had used the drug within the last month), the pattern illustrated by Table II emerged. As the figures indicate, widespread use now occurs among children of high school age and 40 percent of the college-aged population are current users.

Among those who reported current use of the drug, the NIDA study found that about two-thirds of young adults and one-half of older adults and youths have used marijuana five or more times in the last month. Of our high school seniors, some 10 percent were found to be daily users, consuming an average of 3½ marijuana joints every day. Not only has the proportion of daily users doubled among high school seniors since 1975, but it now exceeds the number who use alcohol on a daily basis (stable at about 6 percent since 1975).

When one remembers that the potency of the average marijuana joint has increased many fold in the last ten years, it becomes clear that we are dealing with a staggering increase in the consumption of THC, particularly among the student population. In the 1960s, the medical implications of marijuana use were of direct concern only to a small number of people, and the dangers of heavy chronic use to an even smaller group. But today, the drug is so widespread that the medical evidence is important for the entire population.

The volume and market value of the marijuana trade now makes it a major industry. According to the Wall Street Journal even domestically produced marijuana rivals some leading farm crops. In California, the value of production may soon pass the $1 billion grape industry -- the state's number one farm commodity. In Hawaii, the level of marijuana production and sales may exceed the islands' largest business, the $300 million sugar industry.[5] The Federal Drug Enforcement Administration (DEA) estimates that domestically produced marijuana now accounts for up to 20 percent of the value of the entire trade. The American growers have specialized in recent years on developing very high grade varieties, by selective breeding. The most potent California strains

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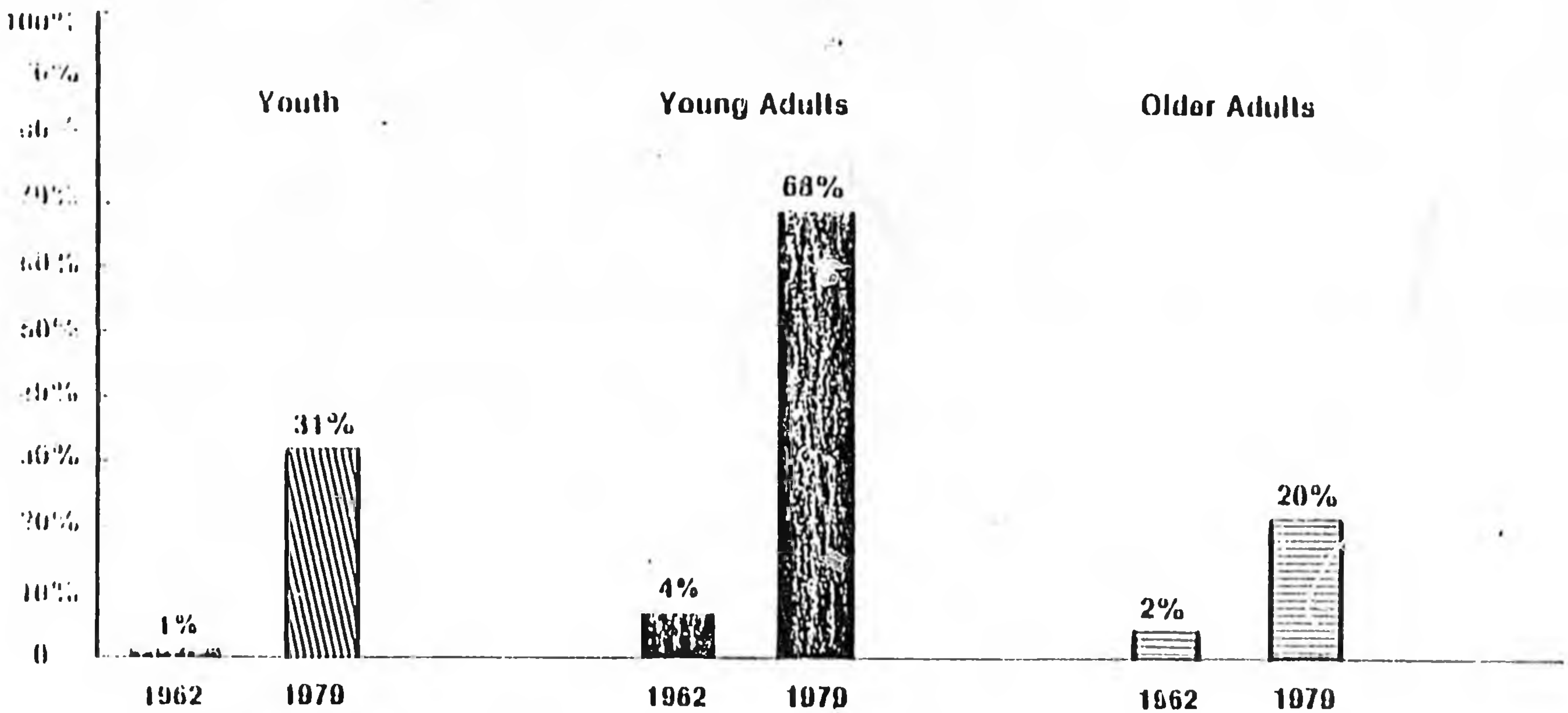
4 National Institute for Drug Abuse, National Survey on Drug Abuse: Main Findings 1979 (Rockville, Maryland: NIDA, 1980).

5 Wall Street Journal, August 4, 1980.

TABLE I

Marijuana Lifetime Prevalence

(i.e., have tried marijuana)



Source: A Drug Retrospective (NIDA, 1980).

Note: Youth: persons 12-17 years old
Young Adults: persons 18-25 years old
Older Adults: persons 26 years and older

40% of young adults who had tried the drug reported that they had done so at least 100 times.

TABLE II

Marijuana 1979
Ages of Current Users

(i.e., have taken drug within last month)

Source: A Drug Retrospective.

can contain as much as 6 percent pure THC. A single plant, on a three-foot diameter plot, can yield $1,000 -- a moderate-sized garden will produce $100,000 worth of the drug.[6] The size of the total American trade, including imports, can only be determined roughly, but it has been estimated that the amount of marijuana coming into this country every year is between ten and twenty thousand tons, with a street value in the region of $20 billion.[7]

The 1970s also saw the rapid growth of what has now become a multi-million dollar industry providing drug-related paraphenalia, magazines and books. Publications such as High Times (which boasts a readership of four million), carry in-depth articles on the use of drugs and legal issues, and are full of glossy advertisements for drug equipment. High Times even provides full listings of the prevailing market prices for many drugs, much as the Wall Street Journal carries the latest stock market quotations.

While the commercial return available on marijuana has been a major contributor to its ready availability, there are other important factors behind the growth in usage. In the late 1960s and early 1970s, the drug was an integral part of the non-conformist lifestyle in universities and elsewhere. The attempt by "authority" to stamp out marijuana consumption, or even discourage it, was seen as an attack on the alternative lifestyle, and the illegality of the drug was quite probably a significant stimulus to its consumption. This mood of resistance was only encouraged by exaggerated claims (on the basis of then available evidence) regarding the health dangers connected with marijuana.

In all probability the most important cause of the explosion in use has been simple ignorance. If, as most people believe, the drug is fairly harmless, then why not use it if it is pleasant? As we shall see in this study, nothing could be further from the truth, but survey after survey shows that while the dangers of alcohol and tobacco are widely appreciated, those associated with marijuana are not.[8]

THE SCIENTIFIC EVIDENCE

General Considerations

Before we examine the evidence regarding the effects of marijuana on the body, it is important to put this evidence in its historical perspective. The early American studies on marijuana, such as they were, were unsatisfactory for several reasons.

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6 Washington Post, February 15, 1981.

7 20,000 tons would be sufficient to make approximately 13 billion joints.

8 See, for instance, L. D. Johnston, J. G. Bachman, and P. M. O'Malley, Drug Use Among High School Students, 1975-1977 (Rockville, Maryland: NIDA, 1977).

The strength of THC in test samples was often not known with precision, and so it was debatable in many instances what was actually being measured. In addition, as has been explained, the THC strength of the average joint has increased dramatically in recent years. We are dealing with a totally different level of consumption than was the case in the 1960s. Using typical test results from the 1950s and 1960s as a guide to the effects of present-day use patterns is rather like trying to determine the consequences of a bottle of gin a day on the average person by testing the effects of a single daily martini!

Given the shortcomings of early tests, it is not surprising that many were inconclusive, and this gave powerful ammunition to the pro-legalization lobby. Even among the scientific establishment, a comparatively sanguine attitude seemed justified.

The first determined challenge to this consensus came from clinical psychiatrists -- particularly from those associated with educational institutions where the drug was in heavy use. Clinicians have often been the first people to warn the world of the unforeseen effects of a drug -- thalidomide being perhaps the most well known case -- and the importance of their front-line role cannot be understated. Typical of such clinicians was Dr. Harvey Powelson, head of the Psychiatric Division of the Student Health Service at Berkeley between 1964 and 1972. Powelson's eight years of extensive exposure to Berkeley students during the period in which marijuana use accelerated greatly make him probably the most experienced campus psychiatrist in the country. Like so many of his associates in the 1960s, Powelson took a tolerant attitude to marijuana in his early days at the University of California; but as he watched individual users over an extended period of time his attitude changed completely, to the point where he came to believe that it is the most dangerous drug with which the nation must contend.[9]

It was the conclusions of observers such as Powelson that created the pressure for the very thorough testing which began in the early 1970s. This series of tests have been far superior to the research of the 1950s and 1960s: more carefully controlled THC doses have been used, for instance, and strength levels in both human and animal tests reflect current usage. It should be noted, however, that there are still some unavoidable obstacles to testing. Marijuana <u>is</u> an illegal substance, and so it is not always easy to obtain statistically perfect volunteer groups. In addition, early studies showed that THC is highly toxic, and that it may pose significant dangers to certain individuals and to the fetus. So there are strong moral and legal impediments to certain important types of study, necessitating the use of animals rather

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9 H. H. Powelson, Testimony before the Senate Subcommittee on Internal Security, May 1974, ref. 30, pp. 18-[illegible], and "Marijuana: More Dangerous Than You Know," Reader's Digest, December 1974.

than humans for test purposes. But in these cases, the animals possess medical characteristics that parallel human functions, and dosages given to the subjects have been equivalent to those taken by humans. Furthermore, the results with appropriate animals correspond closely with clinical observations of human users.[10]

THC and the Body

Unlike water soluable drugs such as alcohol, which is metabolized and "washed out" of the system within twelve hours, THC is fat soluble and remains in the body for a considerable time. The THC in marijuana has a half-life of about three days; that is, it takes three days for half the THC in a joint to leave the body. It may take over three weeks for all the THC to be broken down. According to one expert, observations suggest that the younger the age of first use, the greater may be the long-term effects resulting from the THC in the body.[11]

This pattern of retention in the body means that even the occasional marijuana smoker may never be free of THC. Furthermore, there is strong evidence from animal tests that the toxicity is cumulative -- small amounts of THC administered over a period seem to be far more harmful than the same total quantity in one dose.[12]

The fat solubility of THC, which is exceeded only by substances such as DDT, affects the way in which the substance is distributed within the system. Intravenous injections of radioactive THC confirm that it concentrates in the fatty tissue, and also that it lodges in the liver, lungs, reproductive organs and the brain. It was not until the early 1970s, with the work of Julius Axelrod and others that the pattern of THC absorption by the body, or the period for which it was retained, was known with any real certainty.[13] Until then, it was assumed that THC was broken down and removed from the body as quickly as alcohol.

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10 For excellent reviews of the scientific studies concerning marijuana, see George K. Russell, Marijuana Today (New York: Myrin Institute, 1980 -- published in cooperation with the American Council on Marijuana); Gabriel G. Nahas, Keep Off the Grass (New York: Pergamon Press, 1979); "Twelve Things You Should Know About Marijuana," Consumers Research Magazine, April 1980; I. Lantner, J. O'Brian and H. Voth "Answering Questions About Marijuana Use," Patient Care, May 30, 1980.

11 Carlton Turner, Associate Director, Research Institute of Pharmaceutical Sciences, University of Mississippi, Address to Seminar sponsored by the J.M. Foundation, New York, September 9, 1980, (unpublished transcript).

12 W. D. Patton, Testimony before the Senate Subcommittee on Internal Security, May 1974, ref. 80, pp. 70-79.

13 Ibid.; Also D. S. Kreuz and J. Axelrod, "Delta-9-Tetrahydrocannabinol: Localization in Body Fat," Science, 179 (1973).

This discovery that THC is retained for a considerable time in certain organs of the body is crucial to a proper understanding of its effects. It means that the drug is quite unlike alcohol, with which it is often incorrectly compared. And the moderate user is running far greater risks than the moderate user of alcohol and many other drugs.

Tolerance and Addiction

A discussion of the cumulative effects of a drug leads to the issue of tolerance. One of the popular misconceptions regarding marijuana is that the user develops a "reverse tolerance" -- he needs gradually less and less THC to produce the same "high." It is possible that this belief developed from an examination of the effects of the low dosages commonly used in the 1960s. There may also be a "learning effect" that develops with low doses that leads to a greater appreciation of the high by the user. In addition, it is possible that low doses of THC may cause the release of quantities of the drug stored in the body's organs.

But it has now been firmly established through careful studies with doses typical of current use that a profound tolerance develops -- that is, steadily larger doses are necessary to produce the same effect.[14] Tolerance means that the heavy chronic smoker must increase his THC intake to obtain the same psychoactive results; which in turn means that he must increase the concentration of THC in his brain, lungs and other organs. Tolerance effects also encourage the user to try more potent drugs, such as LSD, and to combine marijuana with alcohol or other available drugs.

One reason why marijuana is considered as relatively safe by so many people is the belief that it is non-addictive. But a misconception regarding the nature of addiction lies at the heart of this impression. If the sole criterion is physical addiction, meaning a physical dependence on the drug followed by severe physical withdrawal symptoms, then the evidence would indeed suggest that marijuana is only mildly addictive, even at high doses.[15] Of much greater concern, however, is the degree of psychological dependence that is associated with marijuana. Many users dismiss the notion of psychological dependence as synonymous with "liking marijuana" in the sense that one might like chocolate ice-cream or tennis. But the term implies a more subtle and dangerous effect on the user. As Gabriel Nahas of Columbia University has explained:

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14 Marijuana and Health: Eighth Annual Report to the U.S. Congress (Rockville, Maryland: NIDA, 1980), p. 25; Marijuana Today, p. [illegible].

15 R. T. Jones and N. [illegible]achman, "Clinical Studies of Cannabis Tolerance and Dependence," Annals of the New York Academy of Sciences, 282:221 (1976). Because of the slow elimination of THC from the body, withdrawal effects are not severe.

> The desire for instant gratification is a profound psychological reinforcer....Addiction to a drug is not a function of the drug to produce withdrawal symptoms. Drug dependence results basically from the reproducible interaction between an individual and a pleasure-inducing biologically active molecule. The common denominator of all drug dependence is the psychological reinforcement resulting from reward associated with past (use) and the subsequent increasing desire for repeated performance.[16]

It is this psychological dependence that makes the marijuana habit difficult to break. It is clear from clinical evidence that it is very common for heavy users to continue smoking even when they concede that it severely impairs their health and motivation, and that professional help is regularly needed to enable a user to give up the drug. The plain fact is that in the case of marijuana, the distinction between physical and psychological addiction is semantic, not real.

Marijuana and Other Drugs

Little could be further from the truth than the idea that a daily joint is merely the equivalent of a lunch-time martini. There are crucial differences. In the first place, as has been pointed out, alcohol leaves the system far more rapidly than marijuana. Even when taken to excess, the effect of alcohol is short-lived. It takes very heavy drinking over a long period to cause irreversible damage to the liver, or to the proper functioning of the brain (and then it is due primarily to a protein deficiency resulting from liver deterioration). The effects of THC, on the other had, occur with only moderate dosage, and it appears to cause damage to more organs in a much shorter space of time.

There is also little evidence to suggest that alcohol and marijuana are in fact considered as alternatives by users. The usage of alcohol among school students, for example, has not fallen during the period in which marijuana smoking has rapidly increased. If anything, there appears to be a small positive correlation between marijuana use and the taking of other drugs, due in large part to the fact that a combination of THC with many other drugs leads to a greater effect than that achieved with either drug alone.[17] Alcohol in combination with marijuana, for example, enhances the sedative result obtained with just the same dosage of alcohol. This is also the case with Valium, Librium, antihistamines, barbiturates, and narcotics such as opium, heroin,

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[16] G. G. Nahas, Marihuana - Deceptive Weed (New York: Raven Press, 1973).

[17] A. J. Siemans, "Effects of Cannabis in Combination with Ethanol and Other Drugs," in R. Peterson (ed.), Marijuana Research Findings, 1980 (Washington, D.C.: U.S. Government Printing Office, 1980).

morphine and codeine. With other drugs, the combination with marijuana increases the stimulant effect, followed by a heavier depression. Such drugs would include cocaine, Benzadrine and Dexadrine.

The reason for this enhancing effect may be that the cells of the liver perform as identifiers and disposers of foreign chemicals in the body through the action of enzymes. When the THC is taken, however, the efficiency of this liver function is impaired and detoxification is reduced. Consequently, the power of the other drug to affect the body is increased.[18]

With some therapeutic drugs, the combination with THC may have the opposite result, leading to a reduction in the effectiveness of the prescribed drug. Taken with anticonvulsants such as Dilantin and Pegamone, for instance, THC antagonizes the drug and lowers the seizure threshold. Similarly, THC can inhibit the results of beta-blockers, used to treat hypertension and some heart conditions. And when taken by a diabetic, marijuana can alter the amount of insulin necessary to maintain balance.[19]

The incidence of marijuana use in combination with other drugs is increasing. Not only is the enhanced effect sought of itself by the user, but it is also a means of obtaining better "value for money" from more expensive drugs. The availability of low-cost marijuana may therefore increase the use of harder drugs.

Psychological Effects

Summary:

There is now a considerable body of scientific data regarding the behavioral effects nad intellectual impairment resulting from marijuana use. Roy Hart and Gabriel Nahas have surveyed the extensive foreign literature. As Hart points out, impairment of memory, judgment, intellectual functions, orientation and motivation have been accepted as consequences of marijuana use for many years.[20] The evidence from this country leads to the same conclusion. Dr. Powelson has summarized the clinical evidence as follows:

> Its early use is beguiling. It gives the illusion of feeling good. The user is not aware of the beginning loss of mental functioning. I have never seen an exception to the observation that marijuana impairs the

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18 Nahas, Keep Off the Grass, p. [illegible].
19 Lantner, "Answering Questions About Marijuana," p. 13[illegible].
20 R. Hart, "A Psychiatric Classification of Cannabis Intoxication [illegible]," Journal of the American Academy of Psychiatric Neurology, [illegible] pp. [illegible]; Nahas, Marijuana, and Keep Off The Grass.

user's ability to judge the loss of his own mental functioning.

After one to three years of continuous use the ability to think has become so impaired that pathological forms of thinking begin to take over the entire thought process.

Chronic heavy use leads to paranoid thinking.

Chronic heavy use leads to deterioration in body and mental functioning which is difficult and perhaps impossible to reverse.

Its use leads to a delusional system of thinking which has inherent in it the strong need to seduce and proselytize others. I have rarely seen a regular marijuana user who wasn't "pushing." As these people move into government, the professions, and the media, it is not surprising that they continue as "pushers," thus adding to the confusion that (the scientific community) is obliged to ameliorate.[21]

Behavioral Effects:

Broadly, light marijuana smoking results in enhanced sensitivity to sensory stimuli. Heavy smoking tends to result in apathy and withdrawal. Research conducted on moderate and heavy smokers shows that a distortion of reality is common, together with confusion, memory loss, diminished concentration, reduced motivation, and hostility towards discipline and authority. Among relatively inexperienced users, acute anxiety can develop as the smoker grows aware that reality is becoming distorted. The same anxiety can also occur when a joint of higher potency is smoked.[22] Heavy usage of marijuana accentuates these effects. Marked memory impairment and confusion is common among such users, and there is evidence that heavy smoking can exacerbate mild and latent paranoia and schizophrenia.[23]

The consequences these effects have on adolescents may be very damaging. At precisely the time that difficult arrangements need to be made, marijuana may distort both the reality that must be faced and the judgment needed to deal with it. The maturing process is inhibited, and a concern with the moment overshadows any assessment of the future. Dr. Mitchell Rosenthal, president of Phoenix House in New York, has summarized the consequences of marijuana use among adolescents as follows:

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21 Powelson, Testimony before the Senate, May 1974, quoted in Russell, Marijuana Today, p. 22.
22 Marijuana and Health, p. 21.
23 Ibid., pp. 21-22.

To grow, to develop, to achieve adulthood, adolescents must cope with the emotional storms and squalls of the troubled teenage period. They turn to marijuana or to alcohol to self-medicate and to relieve the anxieties of the moment. They do not cope and they do not know how to cope. They blow away their troubles in clouds of smoke and they blow away their chance of becoming mature and responsible adults.[24]

Social Behavior:

Marijuana use does appear to foster alientation, towards both the family and society in general. In school and college settings, the tendency of users to form subcultures hostile to prevailing social customs and attitudes is well known. A large-scale study of Boston schoolchildren, for example, showed that early use of the drug was closely correlated with truancy, alienation from authority, poor academic achievement and the early use of alcohol and tobacco.[25]

It remains to be seen what sort of society will emerge as a generation so heavily associated with marijuana attains the position of leadership.

<u>Intellectual Functions</u>

Motivation:

It is all too common to hear of a marijuana user who appears to have lost all will to succeed. The decline in motivation among heavy and moderate smokers -- and even some occasional users -- is probably the effect noticed most often by a user's friends. Chronic heavy use can lead to almost total withdrawal (often rationalized in such terms as "getting out of the rat race"). Clinicians dealing with high schools and colleges report constantly of gifted students who are marijuana users and who lack the drive necessary to reach their full potential.[26] The user is often quite unaware of just how great a decline in motivation he is experiencing, and increasingly, as Dr. Franz Winkler

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[24] M. Rosenthal, "Marijuana and Effects on Adolescents," given at "Marijuana: Biomedical Effects and Social Implications," Second Annual Conference on Marijuana, New York University Post-Graduate Medical School and the American Council on Marijuana, New York, June 28-29, 1979 (unpublished transcript).

[25] G. Smith and C. Fogg, "Psychological Predicators of Early Use, Late Use, and Non-Use of Marijuana among Teenage Students," in D. Kandell (ed.), <u>Longitudinal Research on Drug Use</u> (New York: Halstead Press, 1978).

[26] See, for example, H. Kolansky and W. [illegible] Moore, "Effects of Marijuana on Adolescents and Young Adults," <u>Journal of the American Medical Association</u>, 216 ([illegible]), pp. [illegible]; and "Toxic Effects of Chronic Marijuana Use," <u>Journal of the American Medical Association</u>, 222 ([illegible]), pp. [illegible].

has pointed out, the smoker loses all interest in normal student activities:

> The lasting effects of moderate amounts of marijuana are minimal in contrast to the harmful effects of even a couple of reefers a week....An early effect of marijuana and hashish use is a progressive loss of willpower, already noticeable to the trained observer after about six weeks of moderate use....Soon all ability for real joy disappears, to be replaced by the noisy pretense of fun. While healthy teenagers will eagerly participate in all kinds of activities, such as sports, hiking, artistic endeavors, etc., a marijuana user will show an increasing tendency to talk aimlessly of great goals, while doing nothing about them.[27]

A particularly disturbing aspect of this reduction in motivation is that in some cases it may be permanent. It will be shown later that THC appears to have long-term physical effects on the brain, and clinicians such as Powelson have cited several instances of patients who gave up marijuana and yet are still unable to regain their normal level of motivation and concentration after a year or more of abstinence.[28]

Learning and Skills:

The decline in motivation common among marijuana users is closely related to a general reduction in intellectual performance. Chronic use of the drug can seriously inhibit powers of comprehension, judgment and learning -- and this effect is not confined to the period of intoxication. The most distinctive influence is on short-term memory. THC appears to interfere with the transfer of learned information from the short-term memory, leading to difficulty in recalling material learned when intoxicated.[29] Given the widespread daily use of marijuana among school children, this effect has most serious educational implications.

The use of marijuana has also been shown to have detrimental effects on the smoker's ability to operate certain machinery, such as an automobile or airplane. Several studies have demonstrated a distinct impairment of driving skills, and that users are overrepresented in accidents compared with non-users.[30] It must be emphasized that this impairment does not only occur during a "high"; it continues for many hours after the subjective intoxication. Since judgment itself is affected, a driver may be totally unaware that his skills have diminished and that his

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27 F. E. Winkler, About Marijuana (New York: Myrin Institute, 1970), quoted in Russell, Marijuana Today, p. 40.

28 Powelson, "Marijuana," pp. 95-99.

29 Marijuana and Health, p. 10.

30 Several of these studies are summarized in Marijuana and Health, p. 11.

reactions are slower. And since the influence of marijuana, unlike that of alcohol, is not easily detected by others, passengers travelling with the user may be unaware of their own danger.

There are certain aspects of the effect of THC on skills and intellectual functioning which need to be understood to appreciate the full impact of marijuana use, and the shortcomings of some studies. In the first place, THC has a much greater influence on the performance of less familiar tasks than on well learned activities. The impact on the student, in other words, is likely to be much greater than on the assembly line worker. Furthermore, the effects are dose related -- the heavy smoker experiences markedly greater impairment than the occasional user (although frequent but light smoking does have a cumulative effect). Thus, studies based on the relatively low doses generally used in the 1960s do not provide an accurate guide to the influence of high-potency marijuana currently used.

Another key feature of the drug is that its effect on skills and performance appears to be correlated strongly with the intelligence level of the user. Thus, the impairment seen among students and professionals is usually greater than that among people of average or low intelligence. More generally, the impact of the drug on middle class smokers tends to be more significant than in the case of manual or working class users. This is particularly important when examining evidence from abroad, since in countries such as Egypt, Morocco or the West Indies, the use of marijuana is a habit usually confined to the poorer, less educated classes. Only in the United States is marijuana widely used by better educated segments of society -- the very groups most prone to its damaging effects.

By appreciating these distinctions in the influence of the drug one can appreciate the deficiencies of tests such as the "Jamaica Study," which is widely cited by the pro-legalization lobby as a demonstration of the benign effects of the drug.[31] In this study, the researchers selected a group of thirty ganja (i.e., marijuana) smokers and a control group of thirty non-smokers. The groups were given a battery of psychological and other tests, and their brain wave patterns were examined. No significant differences between the groups were detected.

This study has been faulted on several grounds, some of them technical,[32] and the findings ran strongly against the clinical evidence available in Jamaica.[33] But, more importantly, the

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31 V. Rubin and L. Comitas, Ganja in Jamaica: A Medical Anthropological Study of Chronic Marijuana Use (The Hague, The Netherlands: Mouton Press, 1975).

32 See Russell, Marijuana Today, pp. 2[illegible]-30; Nahas, Keep Off the Grass, pp. 101-102.

33 Russell, Marijuana Today, p. [illegible].

study ignored both the relationship between intellectual capacity and impairment, and the difference in the influence of THC or skilled as opposed to simple and familiar tasks.

Brain Damage

The personality and learning impairment associated with marijuana use leads naturally to the question, "Does marijuana actually cause physical damage to the brain?" There is now a strong body of evidence to suggest that it does -- in ways consistent with clinical observations.

The most important work in this field has been conducted by Dr. Robert Heath of Tulane University Medical School. In the most significant test undertaken by Heath, groups of rhesus monkeys were used to examine the physical effects on the brain resulting from marijuana use. This species of monkeys has a central nervous system very close to that of man, and is widely used as an indicator of the consequences of therapeutic and other drug use on humans. By using monkeys, Heath was able to remove many problems associated with human volunteers -- such as legal issues and the difficulty of keeping a tight control on the level of drug use. He was also able to sacrifice the monkeys and conduct a close examination of the brain tissue of each animal. In the test THC was administered both by smoke inhalation and by injection -- the intake being equivalent to that normally found among human users. The monkeys were exposed to the drug for six months and studied for a further eight months after the drug was withdrawn, using deep and surface electroencephalograms (EEG), after which they were sacrificed and examined.

Heath found distinct changes in the brain wave pattern in the "deep brain sites" of the limbic region -- the area associated with smell, taste, emotion, pleasure, and the control of drives. This change was noticeable after two to three month's use by monkeys subjected to the equivalent of heavy or moderate intake by humans. There was no such effect in the control group. The alteration in the deep brain pattern resembled that associated with conditions such as schizophrenia, and with the reduction of awareness. Heath continued to monitor the deep brain throughout an eight-month period after THC intake was ceased, during which time the change in pattern continued -- suggesting long-term and possibly permanent brain damage.

After the eight-month period the monkeys were sacrificed and their brain tissue carefully studied. Electron microscope analysis revealed distinct damage, particularly at the synaptic junction, where one nerve cell connects with the next -- regions that are crucial to the operation of the central nervous system. This damage included a widening of the synaptic cleft (i.e., the gap between the cells) by an average of 25 percent; which is a condition seen in brain poisoning associated with substances such as carbon tetrachloride and in cases of severe vitamin B deficiency leading to psychosis. Heath also noted that dense material was deposited in the clefts, and, among other effects, there were changes within the cells active in memory function.[34]

The changes in the brain observed by Heath correspond with the behavioral and learning function alterations described earlier. His studies show clearly that THC has a detectable physical effect on the brain, even though the implications of the effect are not known. Most disturbing of all, his experiments suggest that the changes in the brain tissue may be permanent, even among moderate marijuana smokers.

While Heath's experiments have provoked considerable controversy, both regarding the methodology and the meaning of the results, there is supporting evidence. A 1971 study, for instance, used air encephalography to examine the brains of a group of young smokers, each of whom had used marijuana consistently for many years and were experiencing severe personality changes. The study, conducted at the Royal United Hospital in Bristol, England, concluded that there was evidence of as much brain atrophy among the group as would be expected in very elderly people. None of the test group displayed clear evidence of any condition prior to smoking the drug that might have produced such a level of degeneration.[35]

More recent research, using CAT scanners to examine the brains of chronic users, has failed to confirm the Bristol results, however, and so further testing is clearly necessary before any firm conclusions can be reached on the question of brain damage.[36] Nevertheless, the weight of existing evidence does suggest that there is good reason to believe that potentially serious physical effects on the brain do result from chronic marijuana use.

Disease and Cell Division

Recent research has shown that THC seems not only to have very damaging effects on the cells of the brain, but also that it may have an impact on cells related to the immunity system. Work by Gabriel Nahas, for example, showed that the cell division rate

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34 R. G. Heath, "Marijuana: Effects on Deep and Surface Electroencephalograms of Rhesus Monkeys," Neuropharm, 12 (1973), pp. 1-4; Heath and W. Myers, "Cannabis Sativa: Ultrastructural Changes in Organelles of Neurons in Brain Septal Region of Monkeys," Journal of Neuroscience Research, 4 (1979), pp. 9-17.

35 A. Campbell, M. Evans, G. Thompson, and M. Williams, "Cerebral Atrophy in Young Cannabis Smokers," Lancet, 2 (1971), pp. 1219-1224.

36 R. Co, D. Goodwin, M. Gado, M. Mikhael, and S. Hill, "Absence of Cerebral Atrophy in Chronic Cannabis Users," Journal of the American Medical Association, 237 (1977), pp. 1231-1232; J. Kuehnle, W. Mendelson, K. Davis, and R. New, "Computed Tomographic Examination of Heavy Marijuana Smokers," Journal of the American Medical Association, 237 (1977), pp. 1229-1230.

for the lymphocytes of a group of human users was over 40 percent lower than for a control group (lymphocytes are white blood cells that divide rapidly and attack viruses and foreign tissue). This result would mean a drastic reduction in the ability of users to fight diseases -- a reduction comparable with that found in cancer patients and kidney transplant patients receiving immuno-suppressive drugs to prevent rejection (these patients are highly prone to illness).[37]

The influence of THC on cell division seems to extend even further than the immunity system. Research findings presented by twelve different medical groups at a 1978 international conference on marijuana indicated that use of the drug causes strong interference with the synthesis of proteins, DNA and RNA (the basic "building blocks" of cells) in a wide range of cell types. The substance was also shown to impair the rate of tissue growth, to lead to unnatural cell division, and to the production of cells with an abnormal number of chromosomes.[38] Further work is needed in this area, but it should be noted that chromosome damage in certain cells does lead to leukemia and other conditions; and similar damage to gonadal tissue could affect the physical and mental characteristics of children conceived from the sperm or egg cells of a marijuana user.

Reproduction

Several studies have been conducted recently to determine the effect of THC on the male reproductive system. Research by Dr. Robert Kolodny, using a group of young males who were heavy users (averaging 9.4 joints per week), found that the principal male hormone, testosterone, was reduced by 44 percent within the group (although this was still within the normal range for the population).[39] The hormone plays an important role in sexual change during adolescence, and in sperm production. Whether this reduction has a significant effect, or if it is permanent with chronic use, is not yet known.

Two other studies of smokers indicate that chronic heavy use does result in abnormalties in the sperm count, and that it affects the mobility and physical characteristics of sperm.[40]

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37 G. Nahas, N. Suciu-Foca, J. Armand, and A. Marishima, "Inhibition of Cell-Medicated Immunity in Marijuana Smokers," Science, 183 (1974), pp. 419-420; Nahas, Keep Off the Grass, pp. 116-122.

38 G. Nahas, W. Paton and J. Indanpaan-Heikkila (edit.), Marijuana: Chemistry, Biochemisty and Cellular Effects (New York: Springer Verlag, 1976).

39 R. Kolodny, W. Masters and others, "Depression of Plasma Testosterone Levels in Chronic Intensive Marijuana Use," New England Journal of Medicine, 290 (1974), pp. 872-874.

40 W. Hembree, G. Nahas and H. Huang, "Changes in Human Spermatazoa Associated with High Dose Marijuana Smoking," in G. Nahas and W. Paton, Marijuana: Biological Effects (New York: Pergamon Press, 1979); M. Issidores, "Observations in Chronic Hashish Users: Nucleic Aberrations in Blood and Sperm and Abnormal Acrosomes in Spermatazoa," in Nahas and Paton, Marijuana: Biological Effects.

Reports from Jamaica, Morocco, India, and this country also indicate a high level of impotence among long-term users.[41] As yet, there are no published reports of a correlation between marijuana use and abnormal offspring.

Testing the effects of THC on women -- especially pregnant women -- poses ethical and legal problems. Rhesus monkeys have therefore been used for certain of these tests, both to overcome such problems and to enable dosage to be tightly controlled. But there is also a good deal of clinical human evidence available.

Research by Dr. Carol Smith on monkeys has shown that exposure to THC for just a few days during the menstrual cycle can lead to the suppression of ovulation and the disruption of the cycle, due apparently to an interruption in the production of necessary hormones.[42] The menstrual cycle returns to normal two to three months after use of the drug ceases. Dr. Joan Bauman of the Masters and Johnson Clinic in St. Louis, studied the menstrual cycles of young volunteers who were frequent users of marijuana (an average of 4 joints per week), and had been so for at least six months. The group was then compared with a control. Dr. Bauman found that 38 percent of the marijuana users experienced problems with their cycles, compared with 12.5 percent of the control group, and a substantial number of them failed to ovulate. The users were also prone to other irregularities, such as hormone imbalance.[43] Although it is not possible to monitor precisely the drug habits of such volunteers, the human results compared sufficiently closely with more exact animal tests for the conclusion to be reached that marijuana use results in definite irregularities in the cycle.

More serious than the evidence on the menstrual cycle, however, are the strong indications that THC may be very damaging to the unborn. Tests by Dr. Ethel Sassenrath of the University of California Primate Research Center, in which rhesus monkeys were exposed to moderately heavy doses of marijuana (the equivalent of between one and two joints per day), resulted in a 42 percent loss of offspring by the monkeys through spontaneous abortion, fetal death, stillbirths or death in early infancy -- four times the rate in the control group. Post mortem examinations of the offspring, moreover, revealed a number of abnormalties, such as fluid in the brain, together with vascular, liver and kidney

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41 J. Hall, Testimony before the Senate Subcommittee on Internal Security, May 1974, ref. 80, pp. 147-154; H. B. Jones and H. C. Jones, Sensual Drugs: Deprivation and Rehabilitation of the Mind (New York: Cambridge University Press, 1977).

42 C. Smith, M. Smith, M. Besch, R. Smith and R. Asch, "Effect of Delta-9-THC on Female Reproductive Function," in Nahas and Paton, Marihuana: Biological Effects.

43 J. Bauman, "Effect of Chronic Marihuana Use on Endocrine Function of the Human Female," in Nahas and Paton, Marihuana: Biological Effects.

disorders.[44] Experiments using radioactive THC (allowing its progress through the body to be traced) have shown that the drug appears in the milk of the mother and passes into the bodies of the infants being nursed. Furthermore, there is evidence that THC passes through the placental barrier, and lodges in the fatty tissue and various organs of the fetus, including the brain.[45]

These results are very alarming. The consequences of marijuana use by pregnant women and mothers has yet to be fully determined, but the evidence so far indicates that use of the drug may be extremely dangerous or even fatal to the unborn child.

The Heart and Lungs

Marijuana use tends to increase the heart rate, leading to a reduced capacity for exercise -- although this effect does diminish as tolerance to the drug builds up. For young, healthy users this presents no particular danger, but in the case of smokers with pre-existing heart conditions, marijuana can accelerate the development of chest pains and heart irregularities.[46]

Results of test examining the effect of marijuana smoking on the lungs are more disturbing, indicating not only that the drug is connected with lung damage, but also that this damage may be more severe than that associated with tobacco. The U.S. Army's drug program in Europe, between 1968 and 1972, for example, revealed a high incidence of serious respiratory ailments among soldiers with access to the very potent strains of marijuana then available in Europe. Bronchitis and emphysema were seen even among young smokers. Emphysema, in particular, is a disease usually associated with later life, and to find it among young soldiers was most unusual. As Dr. Forrest Tennent, who headed the study, testified to the Senate:

> Even though a person can get bronchitis and emphysema from cigarette smoking, one must usually smoke cigarettes for 10-20 years to get these complications. We became alarmed about this because we began seeing these conditions in 18-, 19-, and 20-year-old men.[47]

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44 E. Sassenrath, L. Chapman and G. Goo, "Reproduction in Rhesus Monkeys Chronically Exposed to Delta-9-Tetrahydrocannabinol," in Nahas and Paton, Marijuana: Biological Effects.

45 R. Vardis, D. Weisz, A. Fazel and A. Rawitch, "Chronic Administration of Delta-9-Tetrahydrocannabinol to Pregnant Rats." Pharmcology, Biochemistry and Behavior, 4 (1976), pp. 249-254.

46 R. Prakash and W. Aranow, "Effect of Marijuana on Coronary Disease," Clinical Pharmacology and Therapeutics, 19, iv (1976), pp. 94-99.

47 F. Tennant, Jr., Testimony before the Senate Subcommittee on Internal Security, May 1974, ref. 30, pp. 288-314.

An examination by Dr. Harris Rosenkrantz of the Mason Research Institute in Massachusetts, found that the exposure of laboratory rats to only moderate amounts of marijuana smoke led to a distinct alteration in lung tissue. These effects included intense inflammation, a breakdown of the air sacs, and the formation of deposits in the lung tissue. The air capacity of the lung was also reduced by 15-20 percent. Control experiments showed clearly that far more damage occurred than with the same degree of exposure to tobacco smoke.[48]

Test conducted with humans have reached similar conclusions. A University of California study, for example, matched a group of healthy users with a control group and found a 25 percent higher airway resistance in the lungs of the marijuana smokers after just two months of heavy use.[49] This level o' resistance rarely occurs among tobacco smokers before fifteen or twenty years of use.

Therapeutic Uses for Marijuana

Like many drugs that exhibit damaging effects with chronic usage, THC does seem to have some useful properties for patients with certain conditions. It appears to be effective, for example, in providing relief for certain glaucoma sufferers -- although non-psychoactive drugs can achieve the same results in many cases.

Of much greater importance is the possibility of using THC as a treatment for severe nausea often associated with chemotherapy. The National Cancer Institute recently embarked on a $1 million program to distribute THC capsules to a large number of cancer patients undergoing chemotherapy. By using THC in capsule form, rather than cigarettes, the possibility of lung damage is avoided. Some critics of the program do, however, maintain that capsules are inferior to smoking the drug, and there is some evidence available to support such a claim in the case of certain patients. Further testing is necessary to determine the cases where inhalation might be an appropriate method of administering the drug until an effective synthetic version becomes available.

The use of THC for therapeutic purposes is not without its problems. Patients run the risk of the damaging results of marijuana discussed earlier, but these risks are much lower in medical programs. Most of the damaging effects associated with the drug appear to result from moderate to heavy use for a longer period than is usual in medical purposes. And the drug can be

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48 H. Rosenkranz and R. Fleischman, "Effects of Cannabis on Lungs," in Nahas and Paton, Marijuana: Biological Effects.

49 D. Tashkin, B. Shapiro and others, "Subacute Effects of Heavy Marijuana Smoking on Pulmonary Function in Healthy Men," New England Journal of Medicine, [illegible]

avoided in the case of high-risk patients. But if THC was widely distributed, even under prescription, it would be difficult to ensure such control. Another problem with the drug is that its psychoactive effects can be very disturbing to some patients, particularly older ones. Again, carefully controlled use allows these side-effects to be detected at an early point. Certain drugs that are chemically similar to THC (such as levo-nantradol) are currently being tested to see if they may be superior in certain instances.[50]

Consideration of THC as a therapeutic drug is not in any way inconsistent with the position that it is very harmful in general. Some highly dangerous drugs are very beneficial in certain circumstances, but this does not imply that they should be made freely available. Occasional use of THC capsules by some carefully chosen patients is not the same as chronic heavy smoking of marijuana.

PUBLIC POLICY CONSIDERATIONS

Marijuana Use and the Law

The inescapable conclusion from the scientific evidence now available is that marijuana is a dangerous substance. The increase in potency in recent years means that we are now dealing with a very different problem than the one faced in the 1960s. The evidence also shows that THC is quite different from alcohol in the way that it lodges in certain organs and causes damage to them in a short period of time.

Yet the question remains, "What, if anything, should be done?" There are many things that we do which are dangerous. Is the use of marijuana any different than these?

There are really four aspects to this question, and each raises important philosophical and practical issues:

1. To what extent should society interfere with the individual's decision to pursue a dangerous activity?

2. Is there harm, or a cost, to non-users?

3. Does society have the right to enforce some collective lifestyle on the individual to preserve some notion of "culture" or "way of life"?

4. Is an effective law possible, given a resolution of the other issues?

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50 Washington Post, November 11, 1980.

Taking each of these questions in turn:

a) Marijuana and Individual Freedom

It has always been a tenet of the idea of liberty that the individual has the right to pursue a dangerous activity, or to knowingly damage his own health. If it were otherwise, we should ban everything from hang-gliding to eating candy.

On the other hand, it has usually been conceded that there may be another justifiable position in the case of certain segments of society. When a person does not realize the consequences of an action, it is reasonable to warn him, and perhaps to physically prevent him from undertaking it. Most smokers of marijuana have very little understanding of the likely consequences of taking the drug. It would seem quite appropriate to embark on a program of education, particularly in schools, to reduce this ignorance. In addition, a policy aimed at making the drug less available, by presenting obstacles to supply, would reduce the liklihood of casual access by the ill-informed -- while the determined user would still be able to obtain supplies.

Drugs do, of course, involve a complication when considering the ability of the user to judge the consequences of his actions. We recognize that children should be protected from many things because inexperience and poor judgment can lead to unforeseen results. But some drugs actually cause reduction in the power of reasoning, or the ability to cease using the substance. This is one reason why we ban heroin but not hang-gliding. Whether there is a sufficient observable effect on the processes of the brain for us to class marijuana with heroin rather than hang-gliding is open to serious question. Yet there is probably sufficient evidence available to suggest that THC does affect motivation and the will to resist higher doses, and other drugs, to justify a policy of active discouragement.

b) Harm and Cost to Others

When a drunk decides to drive his automobile, he poses a physical threat to others, and so it is reasonable for society to impose heavy penalties on such actions for the protection of innocent parties. There is plenty of evidence for us to conclude that the use of marijuana interferes with the reactions and skills of people who drive or fly, and that this is hazardous to other people. In addition, the effects of marijuana usually last longer than those due to alcohol. It is quite reasonable, therefore, for society to punish marijuana users who drive or fly under the influence of the drug. Sophisticated laboratory techniques are now available to enable the level of THC in the body to be known with reasonable accuracy, and routine detection equipment should soon be operational. So it will be possible to provide clear guidelines, and penalties, to deal with the smoker-driver.

The idea of cost is not so simple. If the brilliant scholar becomes a heavy smoker, quits college, and goes on welfare, he is taking from society rather than contributing to it. Yet only a small minority of users could be said to impose costs such as this. Active discouragement would seem to be the most practical way of dealing with the situation.

c) The Imposition of Society's Standards

This is in many respects the most difficult issue of all, and marks a clear difference of opinion between the libertarian and the conservative. If one believes that "society" is simply a collection of individuals, it is difficult to argue that the spreading use of a drug is detrimental to society in any sense, assuming individuals other than the users are not harmed. On the other hand, if one feels that the strength of a society, and the benefits that it can provide to its members, depends on the broad acceptance of certain obligations and customs -- and that the individual is hurt when these customs are eroded -- then it could be legitimate to discourage certain activities.

It is at least arguable that the widespread use of marijuana, leading to a decline in motivation, educational achievement and health, may reduce the benefits of society for us all. If this is so, then it would provide an additional reason for active discouragement.

d) Just and Effective Law

(i) Legislation:

It has been argued by many that we are in a form of "prohibition era" with respect to marijuana. The drug is illegal, but the law is openly and widely flouted, just as it was when alcohol was made illegal. The law is held in disrespect and the punishment of marijuana users is deeply resented. According to this argument, otherwise law-abiding people find themselves dealing with criminals, and only complete legalization will restore faith in the law and get the business of marijuana out of the hands of criminals.

While this argument does have a surface plausibility to it, it is fraught with dangerous implications. In the first place, the almost universal public ignorance of the harmful consequences of marijuana use lies at the heart of the discontent with the law. If the drug were to be legalized, making it available at the corner drugstore, it would confirm the general belief that marijuana was fairly harmless. If the drug were freely available, with the consent of government, it would be virtually impossible to persuade users that they face real dangers. How could one justify a situation where marijuana was made legal when every attempt had been made to ban saccharine?

Illegality may not stop the use of marijuana, but it may serve to hold the line while people are educated as to its dangers. To remove the legal restrictions on its use could also remove any chance of reversing the trend.

(ii) Decriminalization:

There is, of course, a distinction between the issues of legalization and decriminalization. In the one case we are considering making the distribution and consumption of a drug a legal activity; while on the other we are talking about reducing the penalties for taking the drug.

It is a little difficult to justify putting someone in jail when they are probably ignorant of the consequences of taking marijuana. Even if they are fully aware of the possible damage, it does seem unreasonable to apply harsh criminal penalties when no other person is affected. While full legalization would undoubtedly lead to an explosion of use, non-criminal penalities for the possession or use of small quantities of marijuana, together with criminal sanctions for the possession of large quantities or supplying marijuana to children, would be a more just and acceptable position.

There are, however, many experts who feel that even decriminalization would be a grievous error. This view has been put forward very cogently by Dr. Robert DuPont, the former NIDA director:

> For many years, while I was in government, I supported decriminalization of marijuana and was actively publicized by the marijuana lobbying organizations as one of their chief advocates or supporters. I was never this, but I did for some years favor decriminalization of marijuana. I have changed my mind completely on that point and I now strongly oppose decriminalization. I am persuaded that we, as a nation, are dealing with a massive epidemic with grave consequences for our society, and that decriminalization is a signal in this political debate that, however much one might feel that it is not a good idea to put people in prison for possession of small amounts of marijuana, support for decriminalization is seen as support for marijuana. We all need to recognize that the battle lines are drawn and that decriminalization is the major line that is drawn across the political landscape right now.[51]

The argument surrounding the decriminalization issue is thus not so much one of principle as one of practical poltics. If removing criminal penalties for the possession of small quantities

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51 Address to seminar sponsored by the [illegible] Foundation, see note 10.

of marijuana (while maintaining criminal sanctions for distribution) would not lead to a significant increase in use, or to overwhelming pressure for legalization, then decriminalization would have the support of many people who nevertheless consider the drug as very damaging.

ACCESS AND SUPPLY

A policy of active discouragement and education may be pursued in several ways. A number of states, for instance, have banned so-called headshops, where drug-related equipment is sold. The determined user can still find ways of obtaining paraphernalia, but open encouragement to the non-user is reduced by such a measure.

A much more effective form of discouragement, however, would be to actually reduce the level of supplies reaching this country. Enormous quantities of marijuana reach the United States from the Caribbean and South America. It is a multi-billion dollar traffic that involves radio warning planes, large cargo ships, high-speed pickup boats, secret landing strips, and large payoffs to local police. It is not uncommon for seizures of ships to reveal loads of marijuana worth up to $40 million at street prices.

The Coast Guard has been overwhelmed by the volume of the trade, and the tenacity and equipment of the smugglers. Seizures now account for probably less than 15 percent of the total -- making but a small dent in massive profits.[52] If anything is to be done to contain the staggering increase in the quantity of marijuana reaching this country, there must be a significant boost in the resources made available to the Coast Guard, the Drug Enforcement Administration, and other services involved with drug interception. Only by driving up the risks faced by smugglers do we stand much chance of reducing the drug flow.

Some argue that reducing the availability of marijuana in this country might actually be counterproductive. If you deny people marijuana, they claim, they will merely turn to something more dangerous. This is a spurious argument. For the heavy user with psychiatric problems, marijuana is generally only a stepping stone to hard drugs, or a means of enhancing the effect of other substances. If these people are denied marijuana it would make little difference to the damage they will inflict on themselves. Far more important is the person who tries marijuana because it is inexpensive and freely available, and who then becomes a chronic user or moves on to hard drugs. A reduction in the supply of marijuana would lessen the chances of a casual introduction to the drug. Even among existing users, a switch to alcohol or tobacco is far more probable than to hard drugs.

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52 For an account of a typical Coast Guard encounter see the Washington Post, December 20, 1980.

Of course, the marijuana reaching this country has to come from somewhere, and that can present sensitive policy issues. In certain countries, the cultivation of marijuana for export to the United States has become a significant part of the domestic economy, and a major source of foreign exchange. There have been cases of the United States supporting the actions of foreign governments seeking to reduce cultivation, such as Mexico, but this kind of cooperation is rare and not very effective.

Jamaica is a good example of the kind of problem faced by the United States. The country is a major supplier of marijuana to America. The trade is worth well over $1 billion a year, equal to Jamaica's entire foreign debt, and greater than all other exports combined. Jamaica is also unstable and bankrupt, and is a target of Cuban penetration.

When the Jamaican government changed hands in 1980, the United States found itself in a very delicate situation regarding the drug business. The new Prime Minister, Edward Seaga, is a friend of the West, and so the United States is understandably hesitant to undermine what is left of the island's economy. But marijuana is crucial to the economy. As Seaga pointed out recently, "The ganja (i.e., marijuana) trade in the last several months was virtually what was keeping the economy alive."[53] According to him, the trade is "here to stay," and the question is not whether it should be wiped out but whether it should be completely legalized:

> so as to bring the flow of several hundred million dollars in this parallel market through the official channels, and therefore have it count as part of our foreign exchange -- which would mean an extremely big boost to our foreign exchange....

Mr. Seaga's tidy, businesslike approach to the drug trade is complemented by a convenient interpretation of the scientific evidence. Medical reports, he states with authority, "seem to suggest there's no conclusive evidence that ganja is harmful...."[54] Mr. Seaga would be well advised to talk to some of Jamaica's leading psychiatrists at Kingston Hospital, who seem to have reached somewhat different conclusions regarding the effects of marijuana.[55]

While the situation in Jamaica may be outrageous, dealing with it presents many problems. It would be easy to drift into the feeling that really nothing can be done without damaging the

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53 Washington Post, November [illegible], 1980.

54 Ibid.

55 See, for example, the report by Dr. John Hall, Chairman of the Department of Medicine at Kingston Hospital, Jamaica, quoted in Russell, Marijuana Today, p. 25.

fabric of the country. But if the government of Jamaica (or any other country) condones the cultivation and exportation of a drug that is harmful to the people of the United States, it has only itself to blame for the consequences. It is an absurd form of foreign aid for the U.S. government to stand idly by while a country encourages the supply of a dangerous drug to America, simply because that country needs foreign exchange!

In the interests of its own citizens, the U.S. government should state clearly that marijuana is dangerous and a threat to the American population; that it is an unfriendly act for any government to condone it and that policies will be adopted to dissuade such tacit support. The idea that Jamaica can only survive if marijuana cultivation is allowed continue is ridiculous. The reason that the industry is now so important to Jamaica is that it is highly profitable. If the incentives were altered, other industries would develop. It should therefore be the goal of U.S. policy to apply penalties against Jamaica and similar countries if they continue to allow the trade to flourish, while offering American assistance to develop other industries. Tolerating the present state of affairs is an abrogration of responsibility by Washington. How can we justify putting our citizens in jail for using marijuana when we refuse to deal effectively with the chief suppliers of the drug?

EDUCATION

While effective action must be taken to deal with the flow of marijuana into this country, the other weapon in the battle to control the marijuana epidemic is education. People simply do not know the damage that the drug may do to them, and this misunderstanding of its consequences is at the root of the growing disrespect for the law dealing with it. We spend enormous sums of money teaching children how to use birth control devices but very little educating them about the effects of a drug which large numbers of them use during the school break. The scale of the problem is so great that a major drug education program in the schools should be a priority.

But education should not be confined to the schoolroom. Most adult users know little of the drug's effects, and parents usually have no idea how to recognize the symptoms of use -- or how to deal with the situation if they do recognize them. There are a number of organizations that do seek to educate parents, such as the <u>Citizens for Informed Choices on Marijuana</u>, based in Stamford, Connecticut. The work of groups such as this is crucial and should be encouraged. In addition, groups such as the <u>American Council on Marijuana</u>, in New York City, have taken the lead in providing succinct, readable scientific information for the layman. But a great deal more needs to be done, and both private and public resources should be made available.

CONCLUSIONS

1. Marijuana is a dangerous drug. It is quite unlike alcohol and tobacco in the way in which it remains in the system and the lasting damage it can cause with only moderate use.

2. While it may seem unjust to impose penalties on users, legalization -- and possibly decriminalization -- would be taken as an official declaration that the drug was safe. This could lead to the acceleration of an already rapid growth in use.

3. The thrust of public policy should be a combination of active discouragement and restriction of supply, rather than increasing penalties for use.

4. The public should be made aware of the effect of marijuana on the ability to drive. Firmer penalties for driving under the influence of the drug should be enacted at the state level, and drivers should be made aware of the dangers and the penalties involved -- as they are regarding alcohol.

5. For medical purposes, marijuana should be treated like any other drug that appears to have some benefits for certain patients. Research should not be discouraged because the drug is used illegally for non-therapeutic purposes.

6. The government and private institutions should take the lead in discouraging use of the drug, through a greatly expanded program of education in the schools, and among the general population.

7. Measures should be taken to interrupt the flow of marijuana into the country. Resources should be made available to enable the seizure rate to be increased substantially. In addition, tougher steps should be taken to interrupt domestic production.

8. Sanctions or other pressures should be adopted against countries which allow the cultivation of marijuana for the American market. Damaging the health of U.S. citizens should no longer be considered acceptable as a means of relieving the economic plight of other nations.

Stuart M. Butler, Ph.D.
Policy Analyst

Report

OF AN ARF/WHO SCIENTIFIC MEETING ON ADVERSE HEALTH AND BEHAVIORAL CONSEQUENCES OF

Cannabis Use

Toronto, Ontario
30 March – 3 April, 1981

WORLD HEALTH ORGANIZATION • ADDICTION RESEARCH FOUNDATION

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CONTENTS

REPORT OF AN ARF/WHO SCIENTIFIC MEETING ON ADVERSE HEALTH AND BEHAVIORAL CONSEQUENCES OF CANNABIS USE

TORONTO, CANADA, 30 MARCH - 3 APRIL, 1981

1. INTRODUCTION

1.1. Background and Objectives

The report of a WHO Scientific Group on the Use of Cannabis,[1] which was published in 1971, brought together all the available information on the behavioral effects of cannabis use and other useful material. However, despite the existence of a substantial number of clinical case reports, not much accurate quantitative knowledge was available concerning the possible adverse effects of heavy use of cannabis on the health of users. Since that time, the extent of cannabis use in many countries has increased greatly, and a large body of experimental and clinical observations is now available. At the same time, a number of countries are reexamining their legal policies with respect to cannabis control, and require accurate knowledge on cannabis-related health hazards, as one element in their policy discussions.

In 1980-81, a joint study was undertaken by the Addiction Research Foundation (WHO Collaborating Center) and the World Health Organization on "Adverse Health and Behavioral Consequences of Cannabis Use." A meeting of experts on various aspects of cannabis and health was convened in Toronto, Canada, from 30 March to 3 April, 1981,[2] under the joint auspices of the Addiction Research Foundation (ARF) of Ontario (Canada) and the World Health Organization, to undertake a critical assessment of current knowledge concerning the possible health hazards related to the use of this drug. The mandate extended to the participants was to consider only the scientific, clinical, and epidemiological information concerning potential and actual hazards to health resulting from the non-medical use of cannabis and its various psychoactive constituents. The objectives were to review the evidence, assess its completeness and validity, identify significant points of disagreement or gaps in knowledge, and make recommendations with respect to research policy and specific matters requiring further research.

[1] In this report, the term "cannabis" refers to all preparations derived from the leaves, bracts, flowers, or resin of the plant *Cannabis sativa* L.

[2] See Appendix A for the list of the participants

See Appendix B for the list of the members of the planning committee

The present report is to be submitted jointly by the Addiction Research Foundation and WHO to the United Nations and other international bodies and agencies, national bodies, professional and educational groups, and others interested in the prevention and treatment of health problems related to the use of cannabis and other psychoactive drugs. It is anticipated that this information will constitute an important element in the deliberations of national bodies responsible for decisions on social and political policy with respect to drug use. However, such policy decisions are based on many other considerations — legal, political, social, ethical, and others — in addition to health concerns. Therefore, in the interests of effective and objective scientific discussion, the subject of control policies and policy recommendations was specifically excluded from the scope of this meeting.

In addition, it was decided not to consider the therapeutic uses or other beneficial effects of cannabis. This decision is in no way due to a rejection of the possibility of any beneficial or therapeutic effects, but arises from simple recognition of the fact that the evaluation of these effects is not directly related to the evaluation of the health hazards. Inclusion of the former would have enlarged the scope of the meeting beyond the limits of feasibility for the available time and the number of participants. An independent review, now being conducted by the National Academy of Sciences, Institute of Medicine, Washington, DC, USA (1981), draws attention to the question of therapeutic uses and of other matters outside the scope of the present report.

Also in the interests of feasibility, this report does not deal with many basic scientific aspects of the mechanisms of action of cannabis. Such matters as the details of biotransformation, effects on cell membranes, neurotransmitter biosynthesis and turnover, electrophysiological processes, and experimental analysis of behavior are covered only to a very limited extent. The emphasis is on those basic processes and functional alterations which, on the basis of present knowledge, can be related directly to significant malfunction or disease in experimental animals or humans.

1.2. Definitions

Certain terms in this report have been used in the past in various ways. For the present purposes, the following explanatory comments are given.

1.2.1. *"Adverse Effect"*

An adverse effect of cannabis use may be considered to occur when such use produces impairment of an individual's biological, behavioral, or social function. Some effects (such as severe respiratory complications) would certainly be considered adverse in or by all users. However, it is clear that others (such as alterations of time sense), may be regarded as pleasurable or unpleasant, or as wanted or unwanted, according to circumstances and factors such as age, expectations, setting, or the perceptions and value systems of subjects or observers. Mental effects that are enjoyed by a young user at a party might be considered adverse by a middle-aged patient receiving a cannabis preparation in combination with cancer chemotherapy. A state which a student may describe as "agreeable relaxation" might be considered by the teacher as "impaired concentration." Reduction of blood pressure has been regarded both as a desirable therapeutic goal and as potentially dangerous. From this it is obvious that often no sharp classifications can be made, and the implications of such a phrase as "adverse effect" must be drawn from the context of its use.

1.2.2. *"Intoxication" versus "Toxicity"*

A similar situation applies to the judgment of toxicity. One person's "intoxication" is another person's "toxic reaction." There is a continuous spectrum, which exists also with alcohol and other drugs, and to draw any sharp line is necessarily arbitrary. The decision as to when to draw such a line is shaped by the user's own perceptions as well as by the observer's concern.

1.2.3. *"Acute" versus "Chronic"*

"Acute" is used to refer to single doses and their effects, or to reactions or responses on single occasions of brief duration. At the other extreme, "chronic" assumes various meanings. One of these refers to that duration of exposure beyond which further use reveals no new phenomena. Another meaning refers to a period of time that is a substantial fraction of the lifetime of a human or animal. It is worth noting that the pattern of dosage is important, and "chronic" effects may be evoked earlier with high than with low dose rates. Even when amount and pattern of alcohol consumption are allowed for, the latency of onset of Laennec's cirrhosis may range from 5 to 20 years (Lelbach, 1974). Lung cancer from cigarette smoking, and carcinoma of the vagina following *in utero* exposure to diethylstilbestrol, also show long and variable latencies of onset. Therefore the production — and also the recognition — of some adverse effects of cannabis may require similarly long and variable periods of exposure.

1.2.4. *Rates of Use*

Words describing rates of use are particularly difficult to define. For example, the word "heavy" has been employed to describe use ranging from 1 gram of marihuana (or its equivalent) per week to more than 10 marihuana cigarettes (approximately 2-10 grams) a day. Heavy use in one society may be perceived as light in another. The only satisfactory solution is to specify the use rates quantitatively, highlighting patterns of consumption, route of administration, and the potency of the material, as well as total amount used in unit time. Description of use as more or less "frequent" may sometimes be more appropriate than "heavy" or "light." Significant, too, may be particular details of self-administration; for instance, just as morning drinking of alcohol, or smoking immediately on rising in the morning, are signs of heavy consumption of alcohol and tobacco, so use of cannabis early in the day may be indicative of heavy consumption.

2. GENERAL TOXICITY

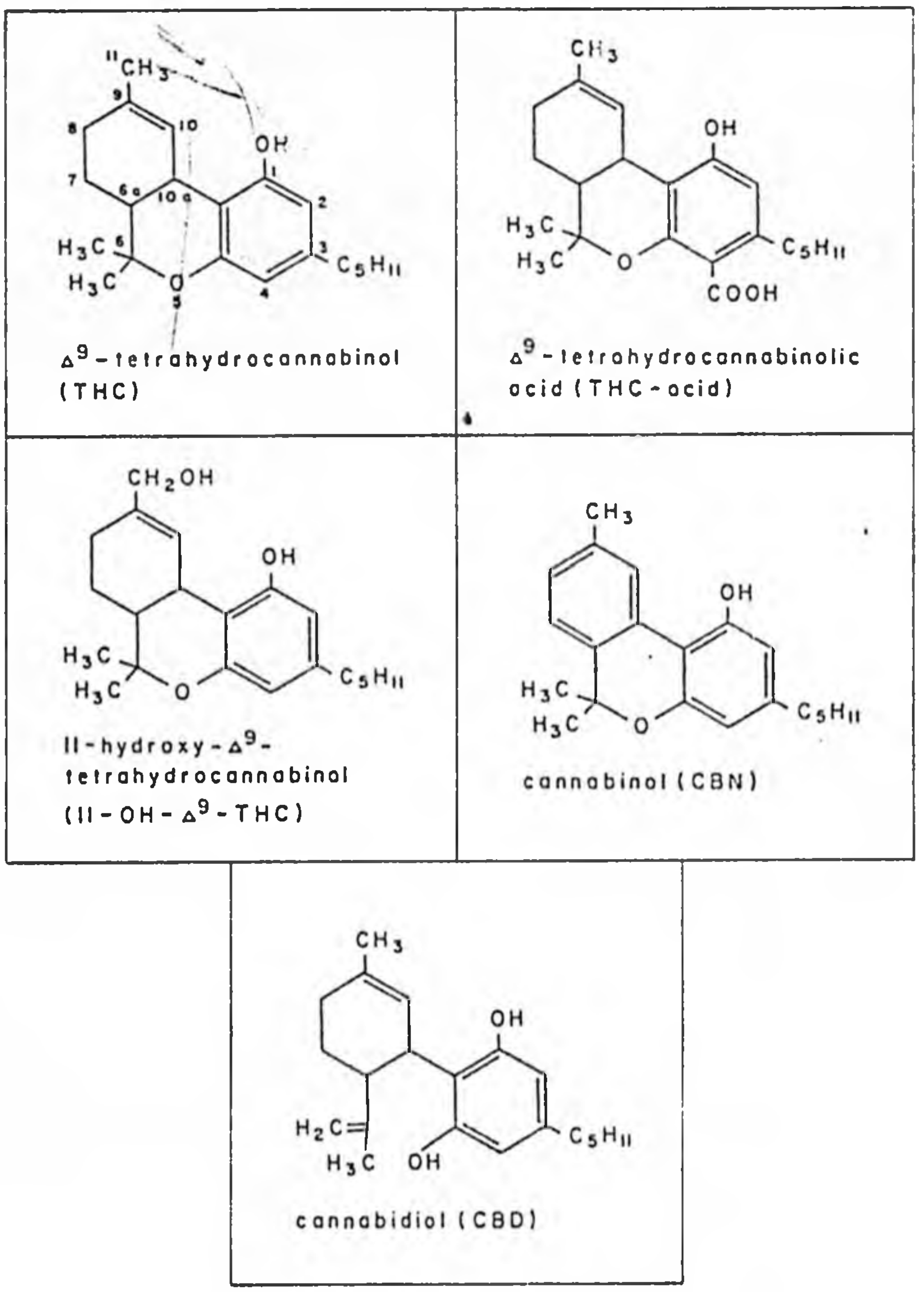
2.1. Cannabis Preparations

Among the 421 compounds thus far identified in the cannabis plant are approximately 61 with the cannabinoid structure (Turner *et al.*, 1980). Of the latter, (-) -Δ^9 -tetrahydrocannabinol (THC) (Figure 1) is of greatest interest in the context of this report, since only structures closely related to THC elicit, at low doses, the characteristic mental effects that constitute the main reason for use of cannabis by humans (Mechoulam *et al.*, 1980). Several other cannabinoids including cannabidiol (CBD) and cannabinol (CBN) (Figure 1), as well as various non-cannabinoid constituents of unpyrolyzed cannabis, may also have biological activities of other types. Dependent on the geographical origin of the plant, the relative and absolute contents of individual cannabinoids vary widely (Turner *et al.*, 1980).

Various preparations derived from the cannabis plant have a wide range of potencies. *Marihuana* or *bhang* consists mainly of dried leaves and stems and can range in content from less than 1% to greater than 8% THC. The content of THC steadily decreases at a rate of approximately 5% per year in refrigerated plant material (Turner *et al.*, 1973). Other preparations *(hashish, ganja, charas)* made from the resin and flowering tops of the plant can contain up to 15% THC. Recently, solvent extracts of leaf material, flowers, or resin have appeared on the illicit markets. The potency of this so-called "hashish oil," "honey oil," or "weed oil" is extremely variable; the THC content can range up to 60%. The toxicity of these preparations appears to be related to their THC content, although other cannabinoids or non-cannabinoids may contribute significantly. The biological effects of the remaining chemical constituents of these extracts are largely unknown at present. The existence of these high potency preparations facilitates the self-administration of large doses of THC.

The pyrolysis of cannabis products produces hundreds of compounds that make up the vapor and particulate phases of the smoke. The vapor phase consists of nitrogen oxides, carbon monoxide, hydrogen cyanide,

FIGURE 1
Structures of Major Cannabinoids



and nitrosamines, together with other known toxic chemicals (Leuchtenberger. 1982). Along with the cannabinoids, the particulate phase contains many known carcinogens including phenols, cresols, and polynuclear aromatic hydrocarbons (Lee *et al.*, 1976). During pyrolysis at usual burning temperatures, tetrahydrocannabinolic acid (Figure 1) is activated by conversion to THC, but there appear to be few other significant cannabinoid interconversions. CBD can be converted to THC, especially when cannabis is pyrolyzed together with tobacco. About 50% of the total available THC is delivered in the mainstream smoke from a marihuana cigarette during the burning procedure (Rosenkrantz, 1982).

2.2. Lethality

2.2.1. *Acute Studies in Experimental Animals*

In acute studies, pure THC appears to be the most toxic cannabinoid of cannabis smoke. The LD_{50} values by inhalation and by i.v. administration are similar in rodents, and the LD_{50} for THC is smaller than those for CBD, cannabichromene, or crude marihuana extract. Intravenous LD_{50} values for THC range from about 40 mg/kg in the rat to 128 mg/kg in the monkey. In mammals, an interesting finding is that the potency of THC in lethality tests decreases as one ascends the phylogenetic tree. For most other effects, the potency is inversely related to the body size of the species, rats and mice being much more resistant than the Rhesus monkey or man (Rosenkrantz, 1982).

Species differences in pharmacokinetics must exist, since the ratio of the intravenous to the oral acute lethal dosages ranges from about 1:30 to 1:40 for rodents but is closer to 1:100 for monkeys and probably dogs (Rosenkrantz, 1982).

In experimental animals, death usually results from cardiac arrest or respiratory failure. Since, at acute lethal doses, artificial respiration is only temporarily effective in preventing death, it appears that cardiac dysfunction rather than the profound hypopnea is the major cause of death (Rosenkrantz, 1982).

2.2.2. *Chronic Studies in Experimental Animals*

Chronic animal studies have indicated a significant degree of unexplained *delayed lethality.* In one experiment, approximately 12% of rats, mainly males, survived the initial dose but died suddenly after 2-3 weeks of continued treatment (Rosenkrantz and Fleischman, 1979). Though the mechanism is not yet clear, it is possible that this delayed lethality may be related to accumulation of THC or its metabolites in the body during prolonged administration (see Section 9.1.1.2.).

2.2.3. *Humans*

No LD_{50} values can be reliably estimated for humans, since only a very small number of fatalities have been reported, and the role of cannabis in these cases is questionable (Rosenkrantz, 1982).

2.3. Clinical and Experimental Toxicity

The past decade has witnessed the clinical documentation of many toxic effects that were previously described anecdotally or superficially. Systematic evaluations of clinical populations, closed-ward drug administration studies, controlled field studies, and accumulated self-reports by users have all been remarkably consistent in their findings. The more prominent effects are summarized below by organ system.

2.3.1. *Respiratory Toxicity*

2.3.1.1. Experimental animals. Single doses of cannabis or THC in animals affect respiration mainly by depression of respiratory rate. This effect is synergistic with that of general anesthetics and other central depressants. Though compliance (elasticity of lung and bronchioles) may be diminished, lung tissue damage has not been observed histologically in acute studies. However, prolonged and repeated exposure to cannabis smoke results in bronchiolar inflammation and morphologic alteration of the lung in rats and dogs (Rosenkrantz, 1982).

2.3.1.2. Humans. Given acutely, THC or cannabis smoke produces a small transient respiratory depression (Bellville *et al.*, 1975) and bronchodilatation (Tashkin *et al.*, 1973).

Respiratory and pulmonary toxicity have emerged as major clinical complications of chronic cannabis smoking. Cannabis smoke appears to be more injurious to the lung than cigarette smoke, as judged by the use of sophisticated pulmonary function testing in well-controlled studies (Rosenkrantz, 1982). Possibly because of its high combustion temperature, hashish appears to yield a particularly irritating smoke. In addition to the ability of cannabis to produce bronchitis, and obstructive pulmonary disease, it might after sufficient exposure produce cancer (see Section 3.2.). In the light of increased frequency of cannabis use, knowledge of the natural course of pulmonary disease suggests that the next three decades may demonstrate an increased prevalence of severe pulmonary disease and possibly of lung cancer. This risk is probably greater in those users (now a majority) who smoke cannabis and tobacco concurrently (Tennant, 1982). In present-day clinical settings the most commonly encountered toxic effects will be the respiratory problems of rhinitis, sinusitis, pharyngitis, and bronchitis (Tennant, 1982).

2.3.2. *Cardiovascular Toxicity*

2.3.2.1. Experimental animals. The major cardiovascular effects of a single dose of THC in most animal species are bradycardia, decreased cardiac reflexes, and hypotension. As a result, cardiac output and cerebral blood flow are usually decreased. Chronic administration may lead to some degree of tolerance to these effects (Rosenkrantz, 1982).

2.3.2.2. Humans. In humans, in contrast, the major effect of a single dose is tachycardia; the heart rate may reach 160 beats per minute or more (Hardman and Hosko, 1976). Acute effects on blood pressure, organ blood flow, and the electrocardiogram are variable and transient (Rosenkrantz, 1982; Tennant, 1982) and are probably due to varying degrees of effect on vasomotor tone (degree of constriction of blood vessels) and vasomotor reflexes (automatic responses to changes in body position, blood volume, etc.). In general, effects on supine blood pressure are relatively slight but postural hypotension has been repeatedly reported. There is little evidence of direct toxic effect on the heart muscle. Chronic use has not resulted in any detectable permanent alterations of cardiovascular function (Tennant, 1982). However, patients with preexisting heart disease due to a relative decrease in coronary blood flow may experience greater risk of angina pectoris and possible infarction because of the extra demand placed on the compromised heart by the drug-induced tachycardia (Tennant, 1982). Cannabis and tobacco smoke contain similar amounts of carbon monoxide. Therefore, the formation of carboxyhemoglobin, which would also contribute to impaired oxygenation of the myocardium, also needs to be considered in cannabis smokers.

2.3.3. *Growth and Body Weight*

2.3.3.1. Experimental animals. Many studies have indicated that either single or repeated exposures to cannabis cause loss, or reduced rate of gain, of body weight (Rosenkrantz, 1982). This is probably due to both decreased food intake and altered endocrine function (see Sections 5 and 6). The long-term health consequences of growth impairment by these factors are unknown but may be most important in relation to the development of the fetus, neonate, or adolescent (see Section 6).

2.3.3.2. Humans. No data on body weight and growth rates before and during periods of cannabis use, comparable to those from controlled animal studies, are available for humans. Numerous clinical case reports from India and North Africa describe regular heavy cannabis smokers as emaciated or malnourished (Bouquet, 1951), and the observations of some modern field studies have suggested that regular users are lighter in weight than non-users (Rubin and Comitas, 1975; Coggins *et al.*, 1980). Social factors such as marital status or other differences in lifestyle may have contributed to this finding (Coggins *et al.*, 1980). In short-term laboratory studies, a weight increase attributable to increases in body water and caloric intake has been observed (Jones and Benowitz, 1976; Greenberg *et al.*, 1976). There is little or no information on possible long-term effects of cannabis on growth, development, and maturation of humans.

2.3.4. *Gastrointestinal*

2.3.4.1. Experimental animals. In dogs and monkeys exposed to high oral doses of cannabis acutely, vomiting and diarrhea may occur (Thompson *et al.*, 1973). Chronic administration does not appear to be associated with significant gastrointestinal toxicity in animals (Rosenkrantz *et al.*, 1975), but may decrease gut motility.

2.3.4.2. Humans. In humans, acute or sub-acute use may produce vomiting, diarrhea, and abdominal distress (Halikas *et al.*, 1971; Tennant, 1974). Chronic cannabis use may decrease gastric acid secretion and possibly make the intestine more susceptible to *Vibrio cholerae* and *Escherichia coli* infections (Nalin *et al.*, 1978), which may pose a particular threat to travelers. Liver toxicity has been observed occasionally in cannabis users (Tennant, 1982). Concurrent alcohol abuse appears to be a factor in these cases. The mechanism by which cannabis could enhance alcohol-induced hepatotoxicity is unknown. The observation of abnormal liver function tests in users who had developed antibodies to marihuana (Shapiro *et al.*, 1976) suggests a possible antigenic response. Lysosomal damage, observed in animals treated chronically with THC (Mellors, 1976), may also play a role.. The sharing of cannabis products or paraphernalia with other smokers has led to the spread of hepatitis in some groups (Drachler, 1975). Possible decreased immunity to viral infections is discussed in Section 4.3.

2.3.5. *Miscellaneous Toxic Manifestations*

Individual case reports have also described a variety of apparent toxic reactions to cannabis in humans, of relative rarity and possibly dependent on unusual individual sensitivity (Tennant, 1982). For example, cannabis products often contain pathogenic fungi such as aspergillus, and aspergillosis has been reported to occur in cannabis-using persons who had preexisting pulmonary disease or asthma (Kagen, 1981). Other allergic phenomena are often aggravated by cannabis use and one case of anaphylatic shock has occurred in an allergic person after cannabis use (Liskow *et al.*, 1971). Some clinical reports suggest that cannabis possibly aggravates some dermatologic conditions (Tennant, 1982).

2.3.6. *Toxicity Related to Unusual Methods of Cannabis Exposure*

Unusual exposure to cannabis includes intravenous injection of plant extracts, oral ingestion of large amounts of the raw or cooked plant, swallowing of cannabis-filled balloons to escape police detection, and use of high-potency butter-paste preparations. The use of cannabis by the above routes has led to highly toxic reactions (Tennant, 1982). These reactions are either consequences of gross overdose (e.g., from intra-intestinal rupture of a balloon filled with "hash oil"), or complications produced by the physical rather than the pharmacological properties of the material (e.g., microembolism due to intravenous injection of a particulate suspension).

3. CELLULAR TOXICITY

Cytotoxic effects of cannabinoids have been studied by a number of different techniques, reflecting different research interests. The principal questions addressed include the possibility of cannabis mutagenicity, carcinogenicity, and impairment of biosynthesis of nucleic acids and proteins. These have involved both *in vivo* and *in vitro* approaches.

3.1. Chromosomal Aberrations and Mutagenicity

During the past 11 years, about two dozen publications on the possible cytogenetic effects of cannabinoids have appeared (Bloch, 1982). Two-thirds have dealt with examination of human chromosomes, and the remainder with rodent chromosomes.

Cytogenetic analyses of lymphocyte cultures from chronic marihuana smokers have yielded contradictory results (Bloch, 1982). Four controlled prospective studies (Nichols *et al.*, 1974; Matsuyama *et al.*, 1976; 1977; Morishima *et al.*, 1979) involving experimental administration of 1 to 15 marihuana cigarettes a day for 5 to 13 days, gave no evidence of increased chromosomal breaks or gaps, though heavy doses gave rise to a higher proportion of hypoploid cells (i.e., cells containing a smaller than normal number of chromosomes) (Morishima *et al.*, 1979). This anomaly disappeared after cessation of smoking.

Rodent and human lung cells in tissue culture exposed to marihuana smoke *in vitro* also tended to show reduced chromosome complements, but not increased incidence of chromosome breaks or gaps (Leuchtenberger, 1982). Diverse studies with rodent cells also indicate little interference with chromosomal replication by cannabinoids (Bloch, 1982).

However, in contrast to purified cannabinoids, marihuana smoke has been reported to produce chromosomal aberrations (Leuchtenberger, 1982), hypoploidy (Leuchtenberger, 1982), mutagenicity in bacteria as demonstrated by the Ames test (Busch *et al.*, 1979; Wehner *et al.*, 1980), and impaired development in the F_2 generation (the second generation of offspring) of treated animals (Fried and Charlebois, 1979). Studies to date have not shown cytogenetic abnormalities or mutagenic effects which are definitely attributable to cannabinoids, or unambiguously identifiable in the human population.

3.2. Carcinogenicity

Analysis of cannabis smoke, animal studies, and one clinical report suggest that cannabis may have significant carcinogenic potential. Cannabis smoke condensate ("tar") is a mutagen (Section 3.1.) and when painted on animal skin has resulted in alterations of cell development (metaplasia) in the sebaceous glands (Magus and Harris, 1971) and tumor formation (Hoffmann *et al.*, 1975). Certain naphthalenes, particularly benzopyrene, are known to be as much as 70% more abundant in cannabis "tar" than in tobacco "tar" (Novotny *et al.*, 1976). Rodents made to inhale cannabis smoke for several months show changes in bronchial epithelium that are compatible with precancerous alteration (Rosenkrantz and Fleischman, 1979).

One study of bronchial biopsies in young men who were heavy users showed histopathological changes similar to those observed in much older smokers of tobacco cigarettes who may develop lung cancer (Tennant, 1980). The combination of tobacco plus hashish smoking may have enhanced the development of precancerous lesions.

One team of investigators has studied the effects of chronic exposure to fresh whole cannabis smoke and to its gas vapor phase on human lung tissue cultures (Leuchtenberger, 1982). Cellular abnormalities developed in essentially the same sequence which occurs with tobacco smoke, and appeared to be related to component(s) of the gas vapor phase of the fresh cannabis smoke. Abnormalities in mitosis, DNA complement and chromosomal number, as well as cellular proliferation, were observed. All these changes were more severe after exposure to cannabis smoke than to tobacco smoke. In hamster lung cultures, both cannabis and tobacco smoke led to malignant transformation; both types of smoke appeared to promote rather than to initiate malignant transformation. When the malignant cells were injected into immunoresistant nude mice, fibrosarcomas developed. It has been reported that ascorbic acid protects human and hamster lung cell cultures from malignant transformation induced by cannabis smoke, but may enhance cancerous cell growth and dedifferentiation (conversion to more primitive cell forms) in human breast cancer cultures exposed to cannabis smoke. The significance of these findings is not yet clear.

At this time there is no confirmed evidence that cannabis has produced cancer in humans. Available information, however, indicates that cannabis has carcinogenic potential, and human users should be carefully surveyed and monitored for evidence of cancer development.

3.3. Impairment of Macromolecule Synthesis

Marihuana smoke (whole smoke) evoked a decrease in DNA content in spermatids (immature sperm) of cultured animal testis (Leuchtenberger, 1982). This alteration was not found in spermatids after exposure to the gas vapor phase of marihuana smoke, or after exposure to tobacco smoke (whole smoke or the gas vapor phase). Therefore the cannabinoids of marihuana smoke were probably mainly responsible for the alterations in DNA synthesis. Similar inhibition of DNA synthesis (decreased incorporation of ^{3}H-thymidine) has also been reported in cultured lymphocytes from human users of cannabis and from THC-treated monkeys, rats, guinea pigs, and mice, as well as in various unicellular organisms and cultured malignant cells exposed to THC *in vitro* (Munson and Fehr, 1982). Inhibition of RNA synthesis (decreased incorporation of ^{3}H-uridine) and of protein synthesis has also been reported in a similar range of preparations (Munson and Fehr, 1982).

In most of these studies, the concentration of THC added *in vitro* was 10^{-4} - 10^{-6} mol/1 which is probably well above the range of THC concentrations found in the plasma or tissue fluids of human users of cannabis. But there is some difficulty in specifying concentration of THC since its maximum solubility in water is of the order of 10^{-6} mol/1 or less (Banerjee *et al.*, 1975), so that one must suppose the "free" concentration cannot rise much above this. In plasma, THC and its first metabolite, (11-hydroxy-THC) are strongly bound (up to 99%) *in vivo* to lipoprotein or albumen. *In vitro*, the nominal concentration will be reduced by adsorption to glass and by uptake into the tissue or test material, and some of it may be bound either by protein in the culture medium, or by protein released by the tissue into the medium. The nominal concentration in such experiments must therefore be regarded as representing not "free" concentration, but the amount of THC available to be taken up by the test system. In the few studies in which tissue/medium ratios have been reported, the latter have been in the order of 100-600. The correlation of *in vitro* with *in vivo* work would be greatly aided by further study of these factors.

3.4. Possible Biochemical Mechanisms

Interference with macromolecule synthesis might result from various mechanisms; examples are failure of cellular uptake of the precursor substances, inhibition of the synthesizing enzymes, perturbation of the cellular membranes in which the enzymes are located, blockade of receptors for hormones which modulate the syntheses, and so forth. The evidence on these points is not reviewed here for reasons outlined in Section 1.1.

Only one hypothesis is mentioned here in some detail, because it is recent and imaginative, and because it proposes a single explanation both for the deficiency in nuclear histone synthesis and for the ultrastructural alterations encountered in the leukocytes and spermatozoa of chronic human users of hashish (Issidorides, 1982). These cells are characterized by a depletion of the amino acid arginine and by abnormal chromatin condensation. According to this hypothesis, the biological effects observed in chronic cannabis users may be explained by arginine depletion which, in itself, can cause chromosomal aberrations, decreased sperm maturity and motility, defective ovulation, growth retardation, immunosuppression and the reactivation of latent viral infections, and CNS effects such as anorexia, motor incoordination, and lethargy. Furthermore, the enzymes reported to be affected by cannabis possess essential arginine residues at their active sites, which would permit a THC/arginine interaction.

4. IMMUNE SYSTEM

The immune system in humans and other higher animals plays a major role in protecting the body against bacterial, viral, and other infections against the growth and spread of body cells which have undergone transformation to a cancerous state, and against foreign proteins and many other substances. A considerable number of scientific reports deal with the effects of cannabinoids on the various main components of the immune system in humans and experimental animals. These principal components are the T-lymphocytes, the B-lymphocytes (which form antibodies or immunoglobulins), and the macrophages.

4.1. Experimental Animals

In contrast to the conflicting findings so far available in humans, there is consistent evidence that THC and marihuana administered parenterally or by inhalation induce immunological defects in mice and rats, and that rats are more sensitive than mice (Munson and Fel r, 1982). The immunological responses that have been shown to be perturbed include:

a) humoral immune suppression in mice and rats, as measured by decreased antibody responses to T-dependent and T-independent antigens, and decreased lymphocyte response to a B-cell mitogen;

b) cell-mediated immune suppression in mice as measured by a reduction of the delayed hypersensitivity response to *corynebacterium parvum*, sheep red blood cells, oxazolone and skin allografts, and decreased lymphocyte response to the T-cell mitogen, phytohemagglutinin (PHA). The depression of PHA-induced lymphocyte response was also seen in rats and monkeys.

These effects were obtained with doses of THC which produced very little behavioral effect in the mice. However, the molecular structural requirements for immunosuppressant action are different from those for psychoactivity (Smith *et al.*, 1978), so that cannabinoids other than THC may contribute to the suppressant effect of cannabis.

The evidence that marihuana or THC can perturb monocyte or macrophage function is mixed (Munson and Fehr, 1982). Overall there appears to be a reduction in the staphylococcus-killing ability of cells obtained by bronchopulmonary lavage from animals exposed to cannabis smoke, along with a reduction in the release of lysosomal enzymes, in superoxide formation and in oxygen consumption. Decreased phagocytic activity has also been observed after exposure of lung macrophages to cannabinoids or cannabis smoke *in vitro*.

The degree of immunosuppression produced by THC is a function of the temporal relationship between the administration of the cannabinoid and the antigen. The effects are more pronounced if the cannabinoids are administered during the early phase of antibody formation (Luthra *et al.*, 1980) and are more evident in young animals (Pruess and Lefkowitz, 1978). The degree of tolerance that can develop to these effects is not yet clear.

The role of adrenal steroids in the immunosuppressive action of the cannabinoids is not clear. One study (Smith and Munson, 1976) suggests that a cannabinoid-induced increase in corticosteroid release may mediate certain aspects of the immune suppression (e.g., splenic atrophy), but not others (e.g., the inhibition of antibody formation).

4.2. Humans

At present, there is only suggestive but not conclusive evidence that consumption of cannabis or THC may produce immune dysfunction in humans as measured by the following immunological indicators (Munson and Fehr, 1982):

a) the numbers of T-lymphocytes, B-lymphocytes or macrophages
b) the functioning of T-lymphocytes, B-lymphocytes or macrophages
c) serum immunoglobulin levels.

The numerous studies in which these indicators have been used have yielded roughly similar numbers of reports of increased, decreased, or unaltered immune responses in cells from cannabis users compared to non-users.

There is suggestive evidence that T-lymphocyte function may be impaired, as measured by a reduced responsiveness to mixed lymphocyte cultures or to PHA, and reduction in the number that can form rosettes with sheep red blood cells.

There is one report that the phagocytic ability of polymorphonuclear leukocytes is impaired in subjects smoking marihuana (Petersen *et al.*, 1975). There is also one report of biochemical and ultrastructural changes in the leukocytes of chronic hashish smokers (Section 3.4.) (Stefanis and Issidorides, 1976; Issidorides, 1979).

4.3. Biological Significance

If the effects of cannabis on the immune system, as examined *in vitro*, are of biological importance, it should be possible to demonstrate that they reduce the resistance of the living organism to infection or to cancer although the latter effects might be altered by an inhibitory effect of THC on the cancer cells directly. Decreased resistance to infection by *Listeria monocytogenes* and to herpes simplex virus has been found in cannabis-treated mice (Morahan *et al.*, 1979). Since other drugs which suppress immune responses in mice also do so in humans, the apparent differences between the findings with cannabis in humans and rodents may depend merely on relative doses used. In humans, it has been reported that dormant genital herpes infections have been reactivated shortly after the smoking of cannabis (Juel-Jensen, 1972).

It can be expected that the immunosuppressant efficacy of cannabis, like that of any other immunosuppressant drug, will vary along a continuum, ranging from little or no effect against immunity to common viral infections such as influenza, up to marked suppression of resistance to unusual infections such as Listeria pneumonia in the mouse. Since immunological function is normally less effective in older persons than in younger ones (Hallgren *et al.*, 1973; Burnet, 1976), it is also possible (though not yet studied) that the immunosuppressant effect of cannabis would be appreciably greater in the elderly. The magnitude of public health consequences of such a drug effect is therefore difficult to assess. One of the problems of interpretation of these findings is the relative crudeness and high variability of the tests of immune function *in vivo* compared to those *in vitro*. It is necessary to have a high degree of immunosuppression *in vitro* before a statistically significant *in vivo* effect can be demonstrated in a small number of experimental animals. Therefore some immunologists consider the *in vitro* effects of cannabis to be without functional significance for health.

However, epidemiological observations on large populations of users should permit a clearer assessment of the biological significance of small degrees of impairment of immune function. A minor degree of immunosuppression in a substantial number of cannabis users might result not in any sudden and dramatic increase in incidence of unusual infections, but rather in a slight increase in incidence, severity, and duration of common ones. Cumulatively, this could have considerable significance for public health and health care delivery systems.

4.4. Cannabis As an Allergen

Cannabinoids have some allergic potential. From the few data available, it appears that allergic reactions in humans are uncommon, although cannabis use has been reported to worsen allergic symptoms in atopic persons (Tennant *et al.*, 1971). Skin tests in cannabis smokers have usually shown little or no reaction to cannabis or its constituents (Tennant *et al.*, 1971; Lewis and Slavin, 1975), although some cannabis users have demonstrated serum antibody responses to THC and other cannabinoids, suggesting that these compounds can act as haptens (Liskow *et al.*, 1971; Shapiro *et al.*, 1976). Antibodies have also been made against THC in experimental animals (e.g., Lecorsier *et al.*, 1977).

5. EFFECTS ON ENDOCRINE FUNCTION

As with the work on the immune system, fairly impressive and consistent effects of cannabis have been observed in endocrine functions in experimental animals, while only weak and inconsistent effects have been reported in humans (Bloch, 1982). It is not clear whether this represents a species difference or a consequence of differences in dosage and pattern of administration, or of clinical variation. The endocrine responses of experimental animals to most other drugs are at least qualitatively similar to those of humans, although there are exceptions to this statement. Therefore, when a particular endpoint or system reacts uniformly to cannabinoid exposure in several species of several classes, including monkeys, a qualitatively similar response in humans may be anticipated.

5.1. Methodological Considerations

A number of the hormones studied, such as testosterone and luteinizing hormone (LH), show very large, short-lived, and quite irregular variations in blood levels, independent of any regular diurnal rhythms (De Lacerda *et al.*, 1973). Therefore occasional measurements at single points in time show very wide scatter and large standard deviations in small groups of normal subjects. In order to demonstrate reliable though small differences between groups submitted to different treatments, it is necessary to use either:

a) very large numbers of subjects, so that the standard error of the mean for the group is decreased in correspondence with the sample size, or
b) frequent or continuous sampling (e.g., by indwelling venous cannula), to estimate the true mean for each subject.

In human studies, (a) is probably not feasible for financial reasons, but (b) has been employed in the best recent investigations (e.g., Mendelson *et al.*, 1978).

In animal studies, published work has been deficient in a variety of important ways:

a) often only single doses of cannabinoids have been used, rather than full log-dose/response curves, so that the biological significance of the findings is difficult to determine;
b) *in vitro* drug concentrations may often be too high to be relevant to *in vivo* levels of cannabinoids (see Section 3.3.);
c) the duration of cannabis treatment is often variable and arbitrary;
d) the time between drug administration and hormone measurement is variable and often not stated;
e) animal strains are occasionally not specified;
f) data variance within the same study often differ widely;
g) in most experiments, cannabis-treated animals are compared with vehicle-treated controls, but for explanation of mechanisms there should also be comparisons with analogs, homologs, and derivatives of THC.

Despite these shortcomings, a good measure of agreement has been found in relation to the effects of cannabinoids on male and female gonadal and adrenal hormone production and on hypothalamic-pituitary regulation. Much less is known about the effects on other hormones.

5.2. Male Reproductive Hormones

5.2.1. *Experimental Animals*

In rats and mice, cannabinoids disrupt normal *male reproductive* physiology (Bloch, 1982). Testicular metabolic activity and *in vitro* testosterone synthesis are decreased; plasma levels of both testosterone and LH fall, and, upon chronic intake, androgenic target tissues show varying degrees of functional and morphological involution. Prolonged cannabinoid intake leads to diminished spermatogenesis. The effects of marihuana and cannabinoids on male reproductive endocrinology and on spermatogenesis are apparently reversible, since no permanent changes have been described following cessation of cannabinoid intake. These effects have been studied mainly in immature and pubertal rats. There is a need for corresponding studies in mature male rats.

5.2.2. *Humans*

Only a few studies have been carried out with modern methods of hormone measurement. These have involved young healthy users of cannabis, either with or without controlled experimental administration of cannabis as part of the study design. A few groups of investigators have reported reduced plasma levels of LH and/or testosterone and reduced sperm counts in the users, while other groups have found no changes (Bloch, 1982). To date the difference has not been satisfactorily explained, but in view of the findings in the animal studies, it is possible that the cannabis doses in the humans have been just at or below the lower margin of the effective range.

5.3. Female Reproductive Hormones

5.3.1. *Experimental Animals*

As in the male, the acute or single administration of THC to *non-pregnant female rats* transiently inhibits functioning of the hypothalamic-pituitary-gonadal axis (Bloch, 1982). Plasma LH and prolactin levels are decreased; the pre-ovulatory LH surge is suppressed, and estrus is delayed. Chronic THC or crude marihuana extract intake seems to impair reproductive function reversibly. The uteri and the vagina show signs of morphological and functional involution, and ovarian function may be affected. Estrous cycles are inconsistently interrupted or abolished.

The few studies on monkey and other non-human primates tend to confirm a suppressive effect of cannabinoids on pituitary gonadotropin release, and the blocking of ovulation (Bloch, 1982). Too few studies evaluating other parameters have been carried out to permit even tentative inferences.

In experimental animals, THC exerts few effects unique to pregnancy (Bloch, 1982). High doses suppress or diminish the maternal weight gain normally occurring during pregnancy. THC also decreases prolactin levels, which may explain the reduced and inadequate lactation seen in the post-partum, cannabinoid-ingesting rat.

5.3.2. *Humans*

There is one preliminary report of an increased proportion of menstrual cycles that were either anovulatory or marked by an inadequate luteal phase in marihuana smoking women as compared with a group of non-users (Bauman *et al.*, 1980). Otherwise, this subject has been virtually unexplored in human females.

5.4. Adrenal Cortex

5.4.1. *Experimental Animals*

Pure cannabinoids and crude marihuana extract stimulate adrenal cortical function in rats (Bloch, 1982). Acute administration results in increased plasma corticosterone concentrations; long-term and short-term exposure lead to adrenal weight increase and thymus weight decrease.

5.4.2. *Humans*

Several studies in humans, however, have failed to show changes in adrenocortical function as a result of cannabis use or experimental administration (Bloch, 1982). Only one group (Benowitz *et al.*, 1976) has reported a decreased plasma cortisol response to insulin-induced hypoglycemia in THC-treated males. Again, the difference between the results in humans and animals may reflect differences in relative doses of cannabinoids. In the animal studies, adrenal activation was observed only after rather large doses of THC, and not proportionately at all doses. Therefore, it may reflect a non-specific stress response, above a certain threshold dose, as has been reported with alcohol (Stokes, 1971; Kakihana and Butte, 1979). In the human studies, the doses used may not have been high enough to produce this.

5.5. Other Hormones

Very little information exists on the effects of cannabis on other endocrine secretions. Several animal studies have shown reduction of circulating thyroxine or triiodothyronine levels after acute or chronic administration of THC, but this has not been confirmed in humans (Bloch, 1982). Plasma growth hormone levels have shown variable responses to THC, according to the age of the rat and route of administration (Bloch, 1982). There is one report of decreased growth hormone response to insulin injection in humans taking THC by mouth (Benowitz *et al.*, 1976).

5.6. Locus and Mechanisms of Action

Experimental animal studies have revealed the primary locus of cannabinoid action in the brain, probably in the hypothalamus (Bloch, 1982). Cannabinoid stimulation of the adrenal cortex can be abolished by agents and procedures which block pituitary ACTH production, while LH-releasing hormone will stimulate pituitary LH release in the THC-blocked rat.

Crude marihuana extract and THC probably also exert a direct inhibitory effect on gonadal and adrenal cortical function. This is especially true for the testes, where *in vivo* and *in vitro* experiments have demonstrated an inhibition of testosterone synthesis, perhaps via reduced cholesterol esterase activity. Another possible mechanism is inhibition of testicular synthesis of prostaglandin E which is involved in mediating trophic hormone effects Diminished metabolic activity and decreased macromolecule synthesis in testes following exposure to cannabinoids may explain the reduced spermatogenesis observed after cannabis intake.

Repeated administration of cannabinoids may result in a direct effect on the uterus, and possibly also on prostate and mammary gland tissue (Bloch, 1982). Interpretation of the data is made difficult by the fact that some investigators have used cannabis extracts while others have used THC. These preparations differ with respect to their respective dose-response relations for each effect. If direct effects exist, they occur at larger doses than are needed to produce indirect effects (e.g., via actions on the hypothalamus and the pituitary), and may reflect a more general toxicity.

The molecular mechanism of cannabinoid action remains to be elucidated. It must also be remembered that marihuana contains other components which may have activity with quite different loci of action.

6. REPRODUCTION AND DEVELOPMENT

The effects of cannabinoids have been investigated to a very limited extent on aspects of reproduction and development other than the endocrine aspects mentioned in Section 5.

6.1. Sexual Behavior

Although there are descriptive references to decreased potency, sexual activity, and fertility of males in India, North Africa, and other regions of the world (e.g., Chopra and Chopra, 1939; Bouquet, 1951), attributed to heavy use of cannabis, these observations are not accompanied by any investigation adequate to support a causal link. In more recent field studies, both the users and their spouses indicated that sexual behavior was normal, but the users stated that they often smoked cannabis in order to prolong or be able to enjoy coitus (Page and Carter, 1980). A few experimental studies have reported decreased sexual reflexes and increased latency to mount in male rats (e.g., Corcoran *et al.*, 1974).

Clearly, the effects of cannabis on sexual behavior require considerably more systematic research.

6.2. Fertility

In animals, fertility in males and females has not been significantly altered by sub-chronic or chronic treatment with THC or cannabis extracts (Grilly *et al.*, 1974; Wright *et al.*, 1976).

In one study in humans, it was claimed that sterility was twice as common among chronic cannibis users as among the general population (Chopra and Chopra, 1939). However, there is no consistent evidence of decreased fertility, as indicated by the number of offspring of males who are chronic cannabis users (True *et al.*, 1980). Fertility has hardly been studied in female users of cannabis. If, as preliminary studies suggest, ovulation is suppressed by THC treatment, fertility would be adversely affected.

6.3. Teratogenesis

Any drug could potentially affect fetal development in two ways. First, exposure to a mutagenic agent prior to conception could alter the germ cells of the male or the female and thus influence the expression of the genes in the offspring. Cytogenetic effects of cannabis have been reviewed in Section 3.1. As noted there, it seems doubtful that crude cannabis extracts or THC are mutagenic in humans, although pyrolysis products present in cannabis smoke may have mutagenic activity.

Secondly, if exposure occurs during pregnancy, drugs can produce direct toxic effects on the fetus. THC administered to pregnant rodents results in a concentration gradient of mother > placenta > fetus (Bloch, 1982). The placenta takes up THC more avidly than the fetal tissues do, but releases it only slowly. This makes the placenta potentially a barrier against, but also a reservoir for, THC transfer into the fetus. A THC-induced disruption of placental development or function as suggested by preliminary observations of Sassenrath *et al.* (1979) may be significant, and could contribute to abnormalities in the fetus.

Cannabinoid administration during the first two-thirds of gestation is associated with increased frequency of fetal resorption and decreased birth weights in mice, rats, rabbits, and hamsters (Bloch, 1982).

There are three reports that the administration of large doses of THC to mice during the critical periods of palate and brain development correlates with increased frequency of cleft palate and exencephaly respectively (Mantilla-Plata *et al.*, 1975; Joneja, 1976; Bloch *et al.*, 1979). Cannabinoid-exposed hamsters also had an increased incidence of malformations (Geber and Schramm, 1969). Other reports of cannabinoid-induced malformations cannot be considered as definitive, and the majority of studies in these species have demonstrated no significant teratogenicity. Cannabis extracts may contain constituents other than THC which are teratogenic. The few reports of teratogenicity in rodents and rabbits (Bloch, 1982) indicate cannabinoids to be, at most, weakly teratogenic in these species, and the activity, if any, may reside in cannabinoids other than THC, or in non-cannabinoid constituents of cannabis or cannabis smoke.

The teratogenic potential, however, has never been accurately assessed in humans. A major prospective study (Zuckerman *et al.*, 1981) now in progress, should provide valuable information in this area.

6.4. Post-Natal Development

Drug effects on post-natal development may be exerted through alterations in ability of the lactating mother to feed the young adequately, through alterations in other maternal behavior towards the young both during lactation and after weaning, and through tissue alterations in the offspring themselves as a result of drug exposure *in utero* and/or via the milk. In animals, and presumably in humans, cannabinoids can cross the placenta, and are also secreted in the milk (Chao *et al.*, 1976).

There has been very little systematic study of cannabis effects on general maternal behavior toward the offspring. However, animal studies have shown repeatedly that cannabis can impair lactation, probably by central actions leading to reduced prolactin output. This results in neonatal malnourishment, unless cross-fostering procedures (i.e., allowing untreated mothers to rear drug-exposed offspring) are used; consequently there is retardation of weight gain and skeletal growth, and increased neonatal mortality. A clear-cut maldevelopment of any other type such as delayed eye opening or incisor eruption is less often reported (Bloch, 1982). Follow-up observations, now in progress, of babies born of mothers who have smoked cannabis during pregnancy will be informative in this regard (Fried, 1980).

A major concern is the possibility of retardation of later juvenile maturation and development as a result of either *in utero* exposure or early commencement of cannabis use by children and adolescents. This has been until now an almost totally neglected research field and requires specific attention.

7. EFFECTS ON NERVOUS SYSTEM FUNCTION

7.1. Effects of Cannabis on Behavior

7.1.1. *Acute Effects on Intellectual Functions*

The effects of any drug on behavior are markedly influenced by a wide variety of factors, both within the individual user and derived from the environment at the time of testing. This is just as true of cannabis as of any other psychoactive drug. Consequently the picture of effects seen in any given instance depends on the relative contributions of the drug-specific effects (which are relatively predictable and reproducible) and of the individual and environmental influences (which are much more variable and less predictable). As a result, the behavioral effects of low doses of cannabis are relatively non-specific and can show extensive overlap with those of amphetamines, opiates, hypnosedatives, and alcohol. In contrast, at high doses the cannabis effects are much more characteristic and identifiable. This is true not only for behavioral effects, but also for neurotoxicity and psychiatric effects, which are discussed in the following sections of this report.

In studies with rodents, dogs, and monkeys, behavioral profiles reveal a biphasic dose-effect and time-effect relation of cannabis and of THC. At low doses, hyperactivity and hypersensitivity (particularly to auditory and tactile stimuli) are evident, and there is synergism (mutual enhancement) with the corresponding effects of amphetamines and of low doses of opiates. At higher doses, ataxia, hypomotility, stupor, or coma are encountered, and the corresponding effects of other central depressant drugs are enhanced (Rosenkrantz, 1982). Biphasic patterns of changes in spontaneous activity related to both time and dose have also been described repeatedly in humans (Jones, 1980).

These changes do not, in themselves, constitute adverse effects; rather, they are the characteristic features of intoxication with cannabis. They are adverse effects only when they compromise the health or safety of the user or of others, by impairing the user's ability to carry out necessary cognitive-perceptual or psychomotor functions. The main conclusions concerning the effects of cannabis on these functions can be summarized as follows (Klonoff, 1982):

a) A host of studies have demonstrated impaired functioning on a variety of cognitive and performance tasks during marihuana intoxication;
b) impaired memory, altered time sense, and decrements in performance on a number of tasks — such as those involving reaction time, concept formation, learning, perception, motor coordination, attention and signal detection — are commonly described in the literature;
c) in most laboratory studies, the duration of measurable memory alterations is a few hours after a smoked marihuana cigarette. However, for some marihuana smokers, there may be more lasting problems with transfer of new information into long-term memory storage;
d) greater appreciation has developed for the need to study a range of doses on a variety of cognitive tasks before trying to describe the effects of marihuana. For the most part, impairments are dose-related but there are apt to be multiple marihuana effects depending on the exact demands of the task; for example, performance on some cognitive tasks might even improve when low doses are used;

e) high motivation to perform well can be enhanced by incentives (e.g., more money for correct responses) and this enhancement can decrease some marihuana effects.

7.1.2. *Acute Effects on Driving Skills and Driving Performance*

Retrospective sources of information concerning the effects of cannabis on driving include:

a) self-reported experiences and perceptions of users
b) anecdotal reports by investigators
c) data collected after accidents or traffic violations.

On the basis of such accounts, there appears to be a consensus that marihuana can, and often does, impair driving ability and actual driving performance (Klonoff, 1982). There has been growing evidence that marihuana, used alone or in combination with alcohol and other drugs, is implicated in traffic accidents and fatalities (Woodhouse, 1974; Sterling-Smith, 1974; Cimbura *et al.*, 1980). The nature of this implication, however, is less than clear. Toxicological data, including measurement of cannabinoid metabolites in the urine, may mean only that the person has used cannabis at some relatively recent time (hours to days) before the time of sampling (Rubenstein, 1979). Such information obviously provides no causal link between the drug use and occurrence of an accident. Much greater attention must therefore be given to prospective studies of cannabis effects.

Prospective methods of investigation include:

a) psychomotor tasks that are presumed or known to be related to driving skills
b) driving simulators
c) traffic-free driving test courses
d) road tests under actual traffic conditions.

Psychomotor tasks can test only specific subsets of the complex behavioral demands for driving. While many such studies have reported dose-related impairment of driving skills by cannabis, there is a real question about generalizability to actual driving situations.

Driving simulators have the advantage of permitting control of many variables, but are nevertheless subject to experimental artifacts. The studies to date have operationally defined variables such as speed errors, accelerator errors, brake errors, risk-taking in terms of passing, passing-time judgments, and visual signal detection (Klonoff, 1982). Dose-related effects of cannabis on most of the measures employed have been reported, but again there is a question about generalizing to real-life driving since most of the emotional and motivational factors in real-life driving performance are missing from the simulator tests. Three published studies (LeDain, 1972; Smiley *et al.*, 1974; Hansteen *et al.*, 1976) have reported cannabis dose-related impairment of driving performance. Skilled drivers, on traffic-free test courses, have reiterated errors similar to those observed in driving simulators.

The most sophisticated study (Klonoff, 1974), and probably the most relevant, is an investigation of actual driving in downtown rush-hour traffic, in cars with dual controls to permit the observer to make the corrections required for safety. Experienced drivers were tested under placebo, small and moderate doses of marihuana, in a double-blind crossover design. Composite driving performance was improved in some cases, unchanged in others, and worse in the majority, compared to the pre-dose control period. However, the number of those who improved or remained unchanged under marihuana was smaller than under placebo, while the number who deteriorated under marihuana was larger than under placebo, and the shift was significantly greater with the higher dose of marihuana.

These findings provide a striking demonstration of the ability of even small doses of marihuana to impair driving ability. Whether or not this is translatable into the production of automobile or airplane accidents will obviously depend upon the degree of impairment relative to the margin of safety between the situational demands and the operator's remaining skills under the drug. There is a need for independent replication of this work, preferably with inclusion of higher test doses, and combinations of cannabis with alcohol and other drugs. Night driving studies should be included, if possible. It is also not known to what extent the degree of impairment observed in these studies might be modified by cannabis tolerance, and by the age and experience of the driver.

7.1.3. *Chronic Effects on Behavior*

7.1.3.1. Experimental animals. Animal studies have indicated that chronic exposure to cannabis can modify the acute behavioral effects not only by the development of tolerance (see Section 9.2.2.) (Jones, 1982), but also by the sudden appearance of new manifestations of behavioral change after several months of administration (Rosenkrantz, 1982). Prominent among these in rats and monkeys are irritability on handling, and increased aggressiveness between animals of the same or other species. Not all investigators have observed these changes, and in some species (e.g., dog) weakness and lethargy have predominated. Therefore it might be questioned whether the aggressiveness is a specific effect of cannabis inhalation or a non-specific result of repeated exposure to noxious stimuli. The relative lack of aggressiveness in control rats exposed to the noxious stimulus of smoke from cannabinoid-free marihuana tends to support the view that there is a specific drug effect (Luthra *et al.*, 1976).

7.1.3.2. Humans. In humans, a number of studies have indicated cannabis-induced impairment of short-term memory by interference with the acquisition and storage phases rather than with initiation and recall (Ferraro, 1980; Klonoff, 1982; Mendelson, 1982). This appears to involve lack of concentration on the task, and may be modified by specific motivational factors. These effects on memory appear to persist undiminished through a three-week period of daily smoking of marihuana under experimental closed-ward conditions (Rossi *et al.*, 1977). Speech and interpersonal behavior have shown only slight and subtle changes under marihuana (Mendelson, 1982), but the observations have been made only during single sessions or relatively short-term repeated observations. The field studies of long-term heavy users so far conducted have shown no major changes in social behavior (Rubin and Comitas, 1975; Fink, 1977; True *et al.*, 1980), but there are deficiencies of design in these studies, as described in Section 9.3.3.

7.2. Neurotoxicity

It is difficult to avoid arbitrariness in distinctions between behavioral effects of a drug, and drug-induced neurotoxicity. For the purposes of this report, "neurotoxicity" is used to refer to functional aberrations that appear to be qualitatively distinct from those which are characteristic of the usual pattern of reversible acute and chronic effects, and that might be caused by identified or identifiable neuronal damage.

7.2.1. *Experimental Animals*

7.2.1.1. Chronic exposure. In animal studies, two alterations of behavior have been noted to appear during the course of prolonged periods of cannabis treatment (Rosenkrantz, 1982). Sixty percent of rats exposed repeatedly to cannabis smoke for five weeks or longer develop a pattern of sudden vertical jumping which has been labelled the "popcorn reaction" (Luthra *et al.*, 1976). This is also seen in young animals exposed chronically to cannabis *in utero*, and then challenged with a single small dose of THC at 30 days of age (Rosenkrantz, 1979). Electrical and motor seizure activity have also been noted in several studies (Rosenkrantz, 1982), but the definition of abnormal spike-like wave forms reported in the EEG of the cannabis-treated animals have not been defined according to rigorous criteria, and the frequency has not been assessed quantitatively. Nevertheless, the claims of neurotoxicity during chronic cannabis exposure raise the possibility that long-lasting residual changes might be found.

7.2.1.2. Residual changes. Animal studies have shown no effect of chronic cannabis administration on brain weight or histology as evident under the light microscope (Fehr and Kalant, 1982). There has been one claim (Heath *et al.*, 1980) of residual alteration of synapses in the septum, hippocampus, and amygdala, as revealed by electron microscopy, but technical objections have been raised to this work (National Academy of Sciences, 1981) and the reported alterations are not easily quantifiable in statistical terms. EEG observations in animal studies have shown the possible occurrence of withdrawal effects (Fehr and Kalant, 1982), and three reports suggest the occurrence of long-term residual abnormalities in EEG tracings from the cortex and hippocampus of cats (Barratt and Adams, 1972), rats (Fehr *et al.*, 1976; 1979), and monkeys (Heath, 1976) exposed to long-term treatment. However, these also lack critical quantitative analysis. There is only one group reporting diverse residual neurochemical changes after long-term cannabis treatment (Luthra *et al.*, 1975a; 1975b; 1976) and the functional significance of the findings is not at all clear.

Most studies of post-drug behavioral changes in chronically treated rats have been carried out too soon after the last drug administration to prove whether any residual effects are long-term ones or merely the slow disappearance of intoxication. However, two laboratories have reported decreased learning ability months after the end of long-term treatment (Radouco-Thomas *et al.*, 1976; Fehr *et al.*, 1976; 1979; Stiglick and Kalant, 1982a; 1982b).The alterations found raise the possibility of changes in the hippocampus, since the tests used include conventional and radial maze learning, operant behavior involving time discriminations (DRL schedules or differential reinforcement of low rates of responding), open-field exploration, and two-way shuttle box avoidance learning; correct performance of these tests is dependent on spatial orientation or on response inhibition, both of which are believed to depend heavily on intact hippocampal functions.

7.2.1.3. Prenatal exposure. Several studies of prenatal exposure have indicated that the offspring of cannabis-treated animals show small delays in various stages of post-natal development, such as eye-opening, reflexes of several types, and open-field exploration (Fehr and Kalant, 1982). However, the development appears to be back to normal by several weeks or months after birth. This could mean either that no residual damage was present, that remaining damage was too slight to be detected by available measures, or that plasticity of nervous system organization in the newborn permitted adequate compensation for the loss of function of any damaged cells. Charlebois and Fried (1980) reported that the retarded development did not occur in groups of cannabis-exposed rats that were fed an enriched protein diet during pregnancy. This suggests that prenatal nutrition (possibly mediated by cannabis-induced anorexia) is a factor in the development of post-natal deficits.

7.2.2. *Humans*

7.2.2.1. Amotivational syndrome. Numerous clinical reports from several countries have described heavy, chronic cannabis users who exhibit behaviors that some observers have labelled "amotivational syndrome"

(Fehr and Kalant, 1982). Included in the various descriptions of this syndrome are the following characteristics: apathy; reduced drive and ambition; impaired ability to carry out complex tasks; failure to pursue long-term plans; reduced tolerance to frustration; diminished communication skills; neglect of personal appearance; and sluggish mental responses. The syndrome takes several weeks to clear after the termination of drug administration. This fact suggests that the symptoms are related to CNS changes rather than to the continued presence of THC. Since no estimations of plasma or tissue THC levels in chronic users are available, the actual mechanism cannot be resolved. A variety of clinical studies and reports in the past decade clearly reveal, however, that the "amotivational syndrome" is neither diagnostic of, nor specific to, chronic cannabis use. The signs and symptoms of the "amotivational syndrome" are essentially those found with chronic intoxication with a number of psychoactive drugs, particularly those that are sedative-hypnotic in nature. It may, therefore, be more appropriate to refer to "chronic cannabis intoxication" and discard the non-specific term "amotivational syndrome."

At this time the dosage of cannabis or the frequency and duration of cannabis exposure required to produce chronic intoxication are not precisely known. Well-controlled clinical studies and close clinical observations (Mendelson, 1982), however, indicate that this picture is not particularly common. In addition, personality and concomitant drug-use factors make it difficult to diagnose this state, or to specify that cannabis, per se, may produce alterations in motivation.

7.2.2.2. Residual brain damage. Human studies after the end of a period of chronic intoxication with cannabis have generally yielded no evidence of residual brain damage. There has been one report of cerebral atrophy, as indicated by air encephalography, in young cannabis users complaining of a variety of neurological symptoms, including memory and cognitive dysfunction (Campbell *et al.*, 1971). However, no atrophy was found in later studies in which computer-assisted tomographic (CAT) scans were performed in young cannabis users who were not also regular users of other drugs, and who were totally asymptomatic (Kuehnle *et al.*, 1977; Co *et al.*, 1977). CAT scans also failed to demonstrate cortical atrophy in monkeys treated chronically with cannabis extract by mouth (Rumbaugh *et al.*, 1980).

Most studies which have compared the performances of chronic users and controls in neuro-psychological tests have failed to elicit significant differences. Significant cognitive deficit is not a commonly demonstrated effect of chronic use of cannabis in clinically healthy subjects. However, to provide an appropriate comparison, most daily users of alcohol are healthy and do not show cognitive deficits, even though such abnormalities are common in clinically diagnosed alcoholics (Parsons and Farr, 1981; Wilkinson and Carlen, 1981). Therefore, it is clear that studies on relatively small samples, such as are at the moment available for cannabis, cannot be expected to rule them out.

The overall conclusions from a review of this literature are hampered by a general inadequacy of reported data, especially in the clinical studies, which have often been characterized in the past by poor sample size and selection; poor or no differentiation between intoxication, withdrawal, and residual change; and an absence of before-and-after longitudinal studies of regular users. The animal studies which revealed long-lasting impairment of learning ability after a period of chronic cannabis treatment raise the clear possibility that residual long-lasting damage can be caused by cannabis, but a decision as to whether or not it does occur in humans will probably have to await the performance of adequate confirmatory studies on brains from long-term users.

7.2.2.3. *Prenatal exposure.* In a follow-up study of a small number of babies exposed daily or less frequently to marihuana *in utero*, Fried (1980) observed dose-related abnormalities in responses to visual stimuli and an increased prevalence of irritability, tremor, and startles as compared to a group of non-exposed controls. Since the babies were observed only at two or three days post-partum, the described symptoms may have been the manifestation of a neonatal abstinence syndrome of the type described for a variety of CNS depressant drugs (Finnegan and Fehr, 1980). Ongoing assessments of these, and additional children, should yield information on the persistence and significance of these symptoms.

7.3. Psychiatric Effects of Cannabis Use

7.3.1. *Acute Consequences*

Acute panic and paranoid states are the most commonly observed short-term adverse psychological effects of cannabis use (Negrete, 1982). The validity of these conditions is no longer questioned, as they have been seen both in clinical settings and in laboratory experiments. The marked difference in frequency with which such problems are reported in different countries, and the diminishing frequency of clinical reports on this type of reaction in Europe and North America, tend to support early contentions that they may be due mainly to adverse social conditions and the user's lack of experience. Alternatively, the decreased frequency of such reports might be due to loss of novelty, and therefore decreased incentive for physicians to describe additional cases in the clinical literature. Nevertheless, it has now been satisfactorily demonstrated that setting alone does not explain their occurrence. Additional work is needed to identify the intervening pharmacological, neuro-physiological, and psychopathological factors.

Other acute reactions of increasing clinical relevance are severe dysphoric states which have been observed in the course of THC therapy (e.g., Shiling *et al.*, 1980). Such reactions were described frequently in the clinical literature at the turn of the century when therapeutic use of cannabis extract was common. A concerted effort must be made to develop specific treatment procedures with a view to preventing or minimizing these untoward psychiatric side-effects, especially in older subjects.

7.3.2. *Problems Related to Chronic Use*

These are seen mainly in younger users, principally males. This may be more a reflection of the criteria for defining "problems" or "cases" than of real differences in frequency of occurrence in different groups of users. The problem of "amotivational syndrome" has been covered in Section 7.2.3. The most important other chronic psychiatric complication is that of cannabis-related psychosis.

The only cannabis-induced psychosis picture which is supported by sufficient evidence to this moment is a short-lasting condition — from a few days to four weeks — with symptoms of mental confusion, memory impairment, regressive and impulsive behavior, delusional formations, and sensory-perceptive distortions (Negrete, 1982). The frequency of occurrence in Western societies is quite low, and it seems to affect mainly very heavy users. A commonly found predisposing factor is a high degree of premorbid personality disturbance. This condition can be expected to show a rising incidence as the numbers of daily and heavier users in the population increase. More research is needed to identify risk factors other than excessive use.

A highly relevant area of research where current data are clearly too limited, is the problem of cannabis influence on independently occurring psychiatric illness. The evidence already available, however, is sufficient to warrant large-scale prospective studies on the effects of cannabis on the phenomenology of some of the most prevalent psychiatric disorders, in terms of both symptomatology and evolution (Negrete, 1982). Also, specific research is urgently needed on the interaction between cannabis and chemical agents commonly used in psychiatric pharmacotherapy, including its possible influence on therapeutic response.

7.3.3. *Flashback*

Most of the evidence available on the recurrence of drug-related symptoms during abstinence (flashbacks) originates from self-report answers to rather imprecise questionnaire surveys, and from subjective descriptions given by individuals who believe they have experienced flashbacks (Negrete, 1982). The systematic phenomenological analysis of this clinical condition has been largely neglected, and controlled studies of the intervening etiopathogenic factors do not appear to have been carried out up to the present.

7.3.4 *Cultural Influences on Cannabis Use and Its Consequences*

7.3.4.1. Social role of cannabis and social control of its use. The most prevalent purpose of cannabis use in most cultures appears to be the recreational one, both in societies where it has been practised in a traditional manner and in those which have only recently adopted it. Medicinal and ceremonial/ritual patterns of use have also been observed, but clearly more in non-industrial than in industrialized societies (Mohan, 1982).

There appear to be major cross-cultural differences in the type of population involved in cannabis use at this time. Poorer, older, and more predominantly male sectors are typical in non-industrialized societies (Mohan, 1982). In industrial countries sex differences are relatively minor and the use tends to be confined to adolescents and young adults (Smart, 1982).

However, as is the case with other drugs of abuse, there seems to be an incipient trend towards universalization and homogenization of cannabis use patterns. Patterns in other countries are tending toward the North American picture, particularly in larger urban populations around the world (Mohan, 1982).

There are cross-cultural differences in setting of use, type of cannabis preparations preferred, route of intake, dose levels, and the concomitant use of other psychoactive agents. Oral ingestion, for instance, is more prevalent in societies in which cannabis use is traditional. Such societies appear to attribute great importance to the variations in the psychoactive potency of the different cannabis preparations in use. Social reaction towards use may vary in accordance with the type of product involved. In India, for example, there is considerably more social lenience towards the use of cannabis leaf material than to that of resin. In the past, social control mechanisms have varied cross-culturally in accordance with local social perception of use. To the extent that legal controls come to be determined by national and international perceptions and agreements, such variations tend to disappear. It is conceivable that the repeated use of cannabis would be perceived as a greater threat in the more industrialized societies, where individuals are under higher pressure in regard to productivity and mental performance.

These differences in patterns of use and level of social acceptance probably infuence the levels of use and the expectations of drug effect. Therefore they may also be expected to affect the types and incidence of various behavioral and health consequences of cannabis use.

7.3.4.2. Behavioral effects. The available literature includes reports of cultural variations in the behavior of individuals under the effects of cannabis (Rubin, 1975). Attitudes varying from aggression, psychomotor agitation, and delinquent tendencies, to passivity and easier conviviality have been recorded as typical of cannabis effects in different parts of the world. Most such differences are likely to be determined by factors other than the pharmacological action of the drug and should be scientifically re-examined. Another item that requires exploration is the possibility of ethnic variation in drug response, which has not yet been studied systematically with respect to cannabis.

7.3.4.3. Psychiatric consequences. It is quite possible that there is less cross-cultural variation in the psychiatric consequences of cannabis use than was previously believed. The higher frequency of "cannabis psychosis" observed in North Africa and India, for example, may soon disappear as the validity of this diagnosis is being questioned and the use of this term is being abandoned in that region. However, the difference in prevalence of dose-related acute reactions is likely to remain as long as there are major cross-cultural differences in the potency of cannabis preparations used.

7.3.4.4. Neuropsychological testing. At present, there is no satisfactory evidence that culture in itself may explain variations in neuropsychological test performance, provided that the tests have been properly validated in each population where they have been used.

8. EPIDEMIOLOGY

8.1. Sources of Information

A large number of studies mainly in developed countries have produced a variety of data about cannabis use. Among the most common epidemiologic sources are those listed below:

Self-report surveys of users
Observations of users
Official registration and notification records
Studies of special populations of high risk groups
Hospital, clinic, and emergency service admissions
Arrest and conviction records
Social and welfare agency records
Production and seizure records.

All of these sources of information are potentially able to give relevant and good information, although each has certain clear limitations with respect to the specific groups studied, which do not always allow generalized interpretations.

Various methodological defects impair the accuracy and uniformity of data collection, especially from self-report studies and from routine statistics of health care delivery systems. Clinical patients represent a self-selected population. Where cannabis use is illegal, it may not be reported by the user with a health problem for fear of self-incrimination, unless confidentiality of medical records is guaranteed. In emergency treatment services, the need for prompt treatment often interferes with thorough collection and recording of information on drug use, especially when the ratio of treatment staff to case load is low. High turn-over of staff may create major difficulties for systematic data collection, unless there is continuous training of new personnel and use of specific incentives for accurate recording of histories. Nevertheless, information from such sources may give useful indices of the relative magnitudes of problems related to different drugs. More detailed discussion of these questions, and specific recommendations for steps to solve them, are contained in a recent report of the WHO Expert Committee on Implementation of the Convention on Psychotropic Substances, 1971 (1981).

Despite the shortcomings in the accuracy and uniformity of data collection, and the low quantity and quality of data in some countries, much is known about incidence and prevalence of cannabis use (Smart, 1982). However, there is less epidemiological knowledge about the adverse health consequences of cannabis use. This is not surprising, since the effects described in Sections 2 to 7 of this report are not specific to cannabis in the sense that Laennec's cirrhosis is fairly specific to alcohol (Schmidt, 1977). Therefore the diagnostic entities themselves cannot be used retrospectively as indicators of hazardous levels of cannabis use in a large population.

For this reason, assessment of the contribution of cannabis to the production of public health problems will require (a) long-term prospective studies of sufficiently large groups of users and non-users to measure the comparative incidence and prevalence of various adverse effects, and (b) large-scale retrospective correlational studies, similar to those on tobacco cigarette use, when details of cannabis use have been recorded accurately in hospital case records for long enough to provide a suitable body of statistical data. Until such studies are carried out, we can have only rough impressions, at best, concerning the real magnitude of cannabis-related health problems.

The value of individual case reports (which are sometimes dismissed as "anecdotal" evidence) should not be overlooked. With cannabis as with any other drug, relatively uncommon but potentially serious untoward effects are usually identified first by astute clinicians and published as case reports. When attention has thus been drawn to a possible problem, it may then be possible to devise experimental studies of causal mechanisms, and large-scale statistical analyses.

8.2. Epidemiological Findings

8.2.1. *Studies on Distribution of Cannabis Use*

In general, recent epidemiological studies in developed countries

(Smart, 1982) indicate that:

a) In most countries that have been surveyed, cannabis has been used by about 17-19% of the general population. Among the student populations, rates of "ever used" vary from less than 1% (Belgium) to more than 60% (USA), with most countries falling in the range of 23-32%. In both student and general populations, the proportion of daily users ranges from less than 1% to more than 11%, with the student groups tending toward the upper end of the range. The apparent average for the countries surveyed was 3-4%.

b) In most countries with good trend studies (Canada, USA, Australia) cannabis use has increased greatly since the late 1960s, i.e., the proportion of users has increased by a factor of 3 to 5. There are some recent signs of stabilization in use over the past few years in Mexico, the USA, and Norway.

In developing countries (Mohan, 1982) the picture is much less clear. Use of cannabis is widespread in Africa, the Middle East, southern and southeastern Asia, Hong Kong, and the Philippines, both among lower socio-economic groups (agricultural and urban laborers, taxi and lorry drivers) and in affluent upper-class groups (adults as well as students). However, there is a scarcity of sound epidemiological studies of general populations, hospital/clinic patients, and selected population groups.

The main reasons for the scarcity of studies appear to be lack of finances and trained people to carry out the surveys, and the relatively low priority allotted to cannabis in the health sector, both nationally and internationally. Nationally, more urgent health problems, such as communicable diseases, nutrition, and sanitation, make stronger demands on scarce resources. Internationally, the Geneva Single Convention laid greatest emphasis on control and movement of opiates across national boundaries rather than of drugs such as cannabis.

One important aspect of use in some developing countries is the difference between socially sanctioned limited use of cannabis for ceremonial purposes, and socially unsanctioned regular use. In India, for example, the great majority of the Hindu population participates in ceremonial use, as in the festival of Shiva (Hasan, 1975), but regular self-administration is carried on by only a small fraction of the population (Mohan, 1982). If the unimodal distribution-of-consumption curve holds for cannabis in the same way as for alcohol, India would be expected to have a very low modal *per capita* mean daily consumption and a very low percentage of users employing large amounts, despite the availability of potent preparations. In contrast, in North America and Europe the absence of a prescribed social role for cannabis, and of traditional social controls of use, might pose a much greater risk of hazardous consumption as potent preparations become more widely accessible.

8.2.2. *Epidemiology of Adverse Effects of Cannabis*

Knowledge about the frequency of various adverse reactions to cannabis is difficult to assemble. The epidemiologist would like to know how often adverse reactions occur, in what types of users, and to identify the explanatory variables such as cannabis dose, previous drug use, and psycho-social characteristics (Smart, 1982). The epidemiologist would also like to know if there is a "safe" (non-harmful) dose of cannabis, and whether some users are *not* at risk for adverse consequences. Answers (such as they are) to these questions typically come from studies not ideally designed to answer them. Nevertheless we might be able to accept the following tentative conclusions about adverse reactions (Smart, 1982):

a) No studies of general populations have determined the rate of adverse reactions serious enough to require treatment or hospitalization. So far, no studies have been made of adverse reactions, whether of a serious or non-serious nature, in general *adult* populations of cannabis users.
b) Usually, studies of cannabis effects on biochemical and neurological functions give very little information on the frequency of adverse reactions to be expected in large populations of users (and, of course, were not designed specifically to do so). Typically, such studies use a selected and narrow range of the cannabis-using population as subjects, mainly young males experienced with cannabis. The sample sizes are usually small (less than 100), and hence the chances to detect uncommon forms of adverse consequences could be quite small.
c) The total number of patients with psychological adverse reactions reported from treatment facilities is not great for a drug used as extensively as cannabis. Unfortunately, this information does not permit calculation of a rate of incidence of such reactions. However, the low number reported suggests either that *serious* psychological disturbances from cannabis use are not common among users in general, without telling us just how uncommon, or that a large proportion of such cases is not reported in the literature.
d) Most of the reported adverse cases come from the USA; cases from outside the USA represent only about 42% of the total. That cases from the USA are over-represented should be expected, because rates of cannabis use and heavy use are higher there than in other Western countries.
e) More cannabis-related psychological problems have been reported for males than females, and for persons under than over 21. The ratio is about 3 males for 1 female, even when the survey studies with all-male military samples are deleted. The ratio of overall and daily use for males and females in the USA, at least among young persons (from which most clinical cases of adverse reactions come), is about 1.5:1. There is a clear suggestion that female users and older persons are at lower risk than young male users for serious psychological conse-

9.1. Dose-Response Relationships

9.1.1. *Pharmacokinetics of THC*

When inhaled in smoke, THC is absorbed rapidly from the lungs. Peak blood levels are reached within minutes of the beginning of smoking, and decline very rapidly to about 5-10% of their initial level within one hour, even though the subjective symptoms of intoxication may persist for 2-3 hours and the objective signs, even longer (Jones, 1980). After oral administration, an equivalent dose of THC is absorbed more slowly, producing a less intense intoxication with a longer latency of onset and a longer duration than after smoking. The decline of blood levels of THC is due to rapid conversion of THC (mainly in the liver) to the psychoactive metabolite 11-hydroxy-THC and numerous other metabolic products of little or unknown biological activity (Gudzinowicz *et al.*, 1980). THC and its metabolites are also rapidly sequestered by the fatty tissues. These compounds are then released back into the bloodstream over a period of several days; this phenomenon slows the elimination of cannabinoids from the body. In experienced users, the terminal half-life of THC (a measure of the rate of biotransformation and elimination) is 19 hours, and of its metabolites about 50 hours (Hunt and Jones, 1980). In the human, elimination of the metabolites occurs mainly through the feces, although detectable amounts are also present in urine.

9.1.1.1. Correlation of cannabis-induced effects with blood levels of THC. Because of the rapid sequestration of cannabinoids into fatty tissues, the tissue:blood ratio of these compounds is not constant. Unlike the situation with alcohol, one cannot expect the blood levels of THC to be a good predictor of biological effects (Jones, 1980). In the absence of tolerance, brain levels of psychoactive cannabinoids in the appropriate but as yet unknown subcellular fraction would provide the only estimate that could be expected to correlate with behavior. Measures of blood levels of THC may have some value, however. If, for example, the relevance of different routes of administration, or patterns of use, to peak or average blood levels can be established, blood level determinations may be more reliable than estimates of administered dose for the cross-cultural comparison of adverse effects in heavy users (Petersen, 1979).

9.1.1.2. Relevance of tissue sequestration to toxicity. Because of the sequestration of cannabinoids. THC or its biologically active metabolites could theoretically accumulate in fatty tissues during chronic or intermittent administration (Jones, 1980). This accumulation would not be measurable by determinations of blood levels of cannabinoids, and has not, as yet, been demonstrated in human tissue samples.

Although a slowly cleared drug is not necessarily more toxic than one rapidly eliminated, the slow clearance will have the effect of prolonging drug exposure, thus enhancing any toxicity that the drug may inherently possess. The irregular dose and administration schedules employed by most cannabis users make accurate determination of actual drug exposure almost impossible.

In humans, cumulative behavioral or physiological effects have not been demonstrated under conditions of controlled administration of up to three months duration, although the simultaneous development of tolerance may have masked this phenomenon (Jones, 1980). In animals, cumulative toxicity, as manifested by delayed lethality and the sudden appearance of neurotoxicity after several weeks of treatment (Luthra *et al.*, 1976), has been observed at doses relevant to those consumed by chronic human users. The possible occurrence of cumulative toxicity in humans, therefore, is a question that should be examined.

9.1.2. *Structure-Activity Relationships*

There has been considerable research into the biological activity of naturally occurring cannabinoids and their synthetic analogs (Mechoulam *et al.*, 1980). Many studies were designed to assess the potential therapeutic efficacy of these substances (Cohen, 1980). Of the major cannabinoids, only THC has significant psychoactivity. Several other cannabinoids, however, demonstrate immunosuppressant activity in the mouse (Munson and Fehr, 1982), cause endocrinological and testicular disturbances in the rat (Bloch, 1982), and inhibit the synthesis of macromolecules *in vitro* (Munson and Fehr, 1982). Thus it appears that the mechanism of the psychoactive effect of THC can be separated from those of some of its other pharmacological effects. Also, if the other major cannabinoids are present in high concentrations in plant material with a low THC content, they may contribute significantly to the spectrum of cannabis-induced immunological and endocrinological toxicity.

9.1.3. *Drug Interactions*

A third major consideration in the relationship of dose to effects is that of drug interactions. The latter, like tolerance, can be explained by dispositional mechanisms (i.e., related to the metabolic fate of the drug in the body) or by functional mechanisms (i.e., related to the manner in which drugs produce their effects), or by a combination of both.

Interactions between cannabis and other drugs and chemicals in the environment should be expected, but their magnitude and health consequences cannot, in most cases, be specified now. Our understanding of the pharmacology of cannabis is only sufficient to say that interactions with a wide variety of licit, illicit, and therapeutic drugs, and probably with almost all chemicals, can occur in principle, and often do occur in fact.

We know that it is unusual for someone to use cannabis regularly without using other drugs concurrently. For example, in North America, cannabis is commonly combined with tobacco and alcohol, and less frequently with cocaine, phencyclidine, and many other drugs (Smart, 1982). In some other parts of the world opium is often used concurrently with cannabis (Mohan, 1982). The drugs which are combined, and their doses, vary with age, culture, country, socio-economic status, availability, and many other factors not well characterized in controlled surveys.

We know from a small number of studies that cannabis alters the effects of a number of other drugs (for example, alcohol, barbiturates, nicotine, amphetamines, cocaine, phencyclidine, and opiates) (Siemens, 1980). Similarly, the other drugs can alter cannabis effects. However, the precise nature of the alterations is difficult to predict. This is probably because of the complexity of the interactions. Cannabis is a mixture of many chemicals with varied pharmacology (Turner *et al.*, 1980). THC administered orally probably has different effects on the metabolism of other drugs than does smoked cannabis. This is because a cannabis smoker would be exposed to chemicals (i.e., enzyme inducers in smoke) capable of interacting with other drugs different from those that an oral user would be exposed to. CBD has more marked effects on metabolism of certain other drugs than does THC (Siemens, 1980). Simultaneous exposure to unrecognized environmental chemicals can confound the situation even further. Since cannabis, THC, or CBD can alter the bioavailability, metabolism, clearance, and distribution of other drugs or chemicals (Benowitz and Jones, 1977), interactions could occur by means of various mechanisms. Other drugs may similarly modify the fate of cannabinoids in the body.

Cross-tolerance and cross-dependence between cannabis and other drugs can theoretically also occur by functional (non-dispositional) mechanisms. This might lead, for example, to a situation in which, because of metabolic interactions, blood barbiturate levels are elevated in a cannabis user; yet, despite this elevation, the effects of the barbiturate might be lessened because of cross-tolerance probably determined by functional interactions. Hence the prediction of behavioral consequences would be difficult.

In addition to producing drug interactions by altering shared hepatic enzyme systems important in metabolism, THC could potentially interact with other drugs because of competition for available binding sites on plasma and tissue proteins. The quantitative significance of such an interaction, if it occurs, is unknown.

In summary, one can only conclude that cannabis is likely to interact with many drugs so as to enhance, diminish, prolong, or shorten the effects of both cannabis and the other drugs. Thus the complexity of cannabis pharmacology and the paucity of adequate research studies in animals or humans makes precise predictions of health significance of drug interactions impossible. Some interactions may be mainly of interest to scientists trying to understand mechanisms of drug action; others (e.g., the delayed absorption of alcohol or slowed metabolism of anticonvulsants observed in cannabis users) (Benowitz and Jones, 1977) will without question have health significance. The well documented cross-tolerance and the possible occurrence of cross-dependence with many licit and illicit drugs make the prediction of health consequences even less precise.

Marked and serious drug interactions are often not recognized or appreciated by clinicians until a number of patients have been harmed. Although clinical data are hard to obtain from cannabis users, we know enough already to predict that such interactions *could* occur. Both laboratory experiments (human and animal) and adequate epidemiological and field studies are needed to define properly the nature and consequences of these interactions.

9.1.4. *Tolerance*

A final factor in the discussion of dose-response relationships is tolerance. The occurrence of this phenomenon, characterized by a loss of sensitivity to the effects of a drug, must be considered whenever a drug is given more than once, and thus is relevant to any study of chronic toxicity. Tolerance to most THC effects has been demonstrated repeatedly, both in animals and in humans (Jones, 1982). It will occur after administration by any route, but the rate of its development is increased if an attempt is made to maintain the blood level relatively constant (as by giving the drug orally or in frequent parenteral doses). The differential development of tolerance to various effects, together with the available pharmacokinetic data, suggest that the mechanism is more functional than dispositional (Jones, 1982).

Tolerance to some effects develops rapidly after administration of doses that many would consider surprisingly small. For many effects, tolerance disappears equally rapidly (Jones, 1982). There is a little more uncertainty as to the precise rate of disappearance of tolerance in different organ systems and in different species, since systematic studies on tolerance loss have rarely been done. The degree of tolerance that can develop is similar to that produced by some opiates. Many characteristics of tolerance to THC are similar to those of tolerance to opiates, nicotine, and alcohol (Jones, 1982).

The so-called "reverse tolerance" (an apparent increase in drug sensitivity after a few exposures to low potency cannabis), if it occurs at all, is likely due to conditioned responses linked to familiar cues, such as those related to smoking or to other environmental factors, which facilitate the production of drug effects as the user gains experience with the drug (Jones, 1982).

The significance of tolerance as a potential adverse effect is unknown. However, various dramatic and fundamental neurochemical and physiological changes occur along with the development of tolerance. Many of these can possibly be assumed to have implications for long-term health (Jones, 1982).

9.2. Some Parameters Affecting Self-Administration

9.2.1. *Titration*

There is some evidence that adverse reactions to cannabis are fairly infrequent in experienced users, in part because these individuals have learned to "titrate" their dose (Negrete, 1982). This means that they adjust their rate of smoking according to their subjective feeling of the degree of intoxication. This phenomenon is by no means unique to cannabis; it is common practice among users of alcohol, tobacco, cocaine, and other psychoactive drugs. Titration is not fully effective in preventing dysphoria, however, since even experienced users can suffer adverse effects after smoking cannabis, particularly when it is unexpectedly more potent than usual or differently constituted. Adverse reactions also appear to be more common after oral ingestion of cannabis than after smoking (Weil, 1970). This observation probably results from the user's inability to titrate an oral dose because of the long latency of onset of effects.

9.2.2. *Tolerance and Physical Dependence: Their Relationship to Drug-Seeking Behavior*

Dependence, both physical and psychological, can develop rapidly in animals and in humans who are exposed to cannabis at doses and frequencies that produce sustained THC blood levels for a significant period of time (Jones, 1982). Some components of the withdrawal syndrome are similar to those produced by opiates, and by alcohol and other sedatives, when they have been given for relatively short periods of time. Controlled clinical studies (Jones and Benowitz, 1976; Nowlan and Cohen, 1977; Georgotas and Zeidenberg, 1979) have shown a picture that includes disturbed sleep, anorexia, restlessness, irritability, sweating, chills, slight hyperthermia, nausea, muscle spasms, tremor, diarrhea, and intestinal cramps. In controlled experiments, subjects first experienced symptoms about four hours after their last oral drug administration. The reactions peaked at about eight hours and had largely dissipated by the third post-drug day. The onset of symptoms corresponded closely to the period when THC blood levels were dropping rapidly.

Other studies (Miles *et al.*, 1974; Rossi *et al.*, 1974) using different designs have failed to confirm all of these findings although some post-drug irritability was reported. The prevalence of these symptoms among populations of cannabis users is unknown. Although some symptoms of cannabis withdrawal resemble those associated with withdrawal from other central depressants, no conclusions can be made with respect to common mechanisms at this point.

On theoretical grounds, tolerance and dependence could increase drug-seeking behavior in several ways:

a) Selective tolerance to the aversive effects of a drug might unmask the rewarding effects and thus increase the probability of use;
b) tolerance, by leading to more frequent use and larger doses, might strengthen the cycle of reward and repetition;
c) the progressive narrowing of interests and activities in dependent users (particularly in urban industrial societies) might make the drug occupy a steadily more significant role in everyday life, and give rise to secondary and conditioned mechanisms that would have the effect of increasing drug use (reinforcement);
d) abstinence symptoms, occurring during drug withdrawal, could generate a new reinforcement for use to alleviate the discomfort.

For the first three ways there is no information available specifically on cannabis, though the general principles derived from the study of other drugs (Cappell and LeBlanc, 1979) would be expected to apply equally to it. With respect to the fourth point, the observations cited above suggest strongly that mild to moderate withdrawal reactions can and do occur in some regular users, especially frequent users of high doses.

9.3. Principles of Experimental Design

9.3.1. *Relevance of Animal Models for Predicting Toxicity in Man*

Although some pharmacological effects can be measured directly in humans, it is evident that experimental assessment of all risk potential of cannabis use cannot be performed safely in humans. Therefore, animal models must be utilized. The resulting problems of extrapolating from animals to humans should be minimized by selecting those *in vivo* paradigms that are relevant to human physiological and pharmacological responses. It is also important that administration of cannabis products extend over a sufficiently long fraction of the animal's life-span to simulate use of cannabis for a period of years by humans. On the other hand, some animal life-spans (e.g., dog and monkey, 15-25 years) are long enough that the investigator who wishes to use these species must have high motivation and longevity, and reliable long-term funding. If possible, the experimental designs should be comparable to current human practices such as the smoking of high potency cannabis preparations mixed with tobacco, or the combination with other drugs, and the use of oral and other routes of administration.

Advantages and disadvantages are inherent in each potential animal model. For example, several rodents can be exposed simultaneously to the smoke of the same marihuana cigarette(s). Larger animals must be exposed to the smoke of individual samples of a batch of cigarettes that may differ considerably from each other in physicochemical properties. Physiological disposition of drugs also varies among species but sufficient basic data exist on these differences to permit appropriate interpretation of differences in time of appearance, intensity, and duration of responses in laboratory animal species and in humans. It must be noted, however, that the results from some animal models (such as immunosuppression in the mouse) may be extrapolated to humans more reliably than from others (such as placental transfer of drugs in rodents).

In cannabis research, the strongest evidence supporting the relevance of animal models is the consistent dose range over which similar pharmacological events, including certain behavioral changes, can be observed and measured in rodents and non-human primates after administration of the drug by several different routes (see, for example, Rosenkrantz and Braude, 1976). These drug-related aberrations observed in animals have been produced by inhalation or oral doses that are relevant to those used by man. Indeed, circulating blood levels of THC associated with these effects have been similar in animal models and humans. Even such a phenomenon as the characteristic biphasic response to cannabinoids (CNS-stimulation/inhibition) has been observed in both animals and man (Rosenkrantz, 1982).

9.3.2. *Optimal Design of Toxicological Studies*

Apparent contradictions in the experimental literature are often difficult to interpret because of differences in experimental design. For this reason, it seems desirable to specify some basic requirements for soundness of toxicological studies. This section is not intended to be comprehensive or definitive, but identifies a few areas of special concern.

The design of toxicology studies should be such as to permit clear identification of the organs which undergo dose-dependent morphological, physiological, or biochemical disturbances. For this purpose, the ideal study would evaluate the drug effects on *all* organ systems at several dose levels. Subchronic and chronic toxicological studies should be performed in both sexes of several species of experimental animals including rodents and non-human primates. The subchronic study should be long enough to identify appropriate dose ranges and to point to specific target organs or systems that would be investigated in greater detail in the chronic study. The chronic study must be of reasonable length as discussed in Section 9.3.1., especially to provide sufficient time to determine the potential for carcinogenicity. Both inhalation and oral routes of administration should be used. Inhalation studies should use a standardized smoking system to assure direct inhalation of smoke. For inhalation studies, the cannabis preparation should be derived from standard marihuana cigarettes with sufficiently high concentration of cannabinoids to deliver the desired dose of active substance with a minimum amount of carbon monoxide. Control cigarettes should consist of the same marihuana extracted in a manner designed to maximize the difference in cannabinoid content while minimizing the loss of other constituents. A group of animals receiving the smoke from an appropriately standardized tobacco should be included so as to facilitate comparisons between the results from different laboratories.

Oral administration should be accomplished by feeding unless the drug preparation reduces food intake, in which case gavage should be used. The cannabis preparation used for oral administration should simulate as closely as possible those which are in widest use throughout the world. Adequate dose/response data must be provided, over a range extending up to the estimated maximum tolerated dose.

The toxicological study should not only assess the standard parameters such as growth rate, food and water consumption, hematology, clinical chemistry, urinalysis, and histopathology but should make every attempt to evaluate the functional aspects of the major organs and body systems. The pulmonary system should be evaluated at regular intervals in the larger animals by measuring respiratory parameters such as rate, volume, and blood gases. Behavioral effects should be monitored at regular intervals by accepted operant and non-operant methods. The cardiovascular system should be monitored regularly, primarily by electrocardiograms. Liver and kidney function tests should be followed at regular intervals. In the larger animals, simple immunological assays should be carried out during the study but detailed humoral and cell-mediated immune responses need to be tested only at the end of the sub-chronic (90 day) study. Evaluation of the endocrine system should be carried out at regular intervals and should include measurement of plasma levels of appropriate hormones.

Animals should be set aside for use in three-generation reproductive and teratogenicity studies.

Carcinogenicity should be determined by appropriate histopathological studies of tumors and tissues at time of necropsy.

9.3.3 *Selection of Subjects and Designs for Clinical Experiments*

Most individuals who have participated as subjects in cannabis-related research in North America and Western Europe have been healthy young adult males who generally have used cannabis for five years or less. Most were students from middle to upper-class socio-economic backgrounds. Therefore some data obtained in these studies may have limited generalizability to females and to individuals who use cannabis in other social, economic, and cultural environments. Cross-cultural generalization of the findings appears to be very limited, since studies of cannabis use and effects in countries such as Egypt, Jamaica, India, and Greece involved subjects who were older, less affluent, and who used higher dosages and for longer periods of time than research subjects in North America. Since patterns of dosage (both amount of drug and frequency of administration) are, in part, culturally dependent, comparisons between cultures are especially difficult (see Section 9.1.).

Many problems in design of cannabis studies are similar to those encountered in research with other psychoactive drugs. Many studies of experimental administration of cannabis have not employed placebo controls, although it should be emphasized that effective placebo control in chronic studies with highly discriminable psychoactive compounds such as cannabis, especially with experienced users, is difficult. Interpretation of results has often been rendered difficult by factors such as variable and unstated expectations or biases of subjects and experimenters, variations in criteria for defining chronicity and dosage, and variables associated with set and setting. Important controls for basic variables (e.g., drug use other than, or in addition to, cannabis) have been difficult to achieve in research on humans, except in experimental studies in monitored research ward environments. Only a few studies have provided subjects with specific incentives for cooperation, or special compensation for achieving best performance during the assessment of cannabis effects on behavior (see, for example, Cappell and Pliner, 1973). In some studies, subjects (all cannabis users) were apparently self-motivated to perform well, in order to establish the absence of cannabis-related adverse effects (Kalant, 1969). Since virtually all studies have employed volunteer subjects, there remains some question as to whether these healthy individuals are truly representative of the general population of cannabis users.

9.3.4 *Sex Differences*

There have been very few controlled administration studies in human females, or examinations of sex differences in response to cannabis in animals. Male animals demonstrated a different pattern of behavioral toxicity, and were more susceptible to delayed lethality than the females (Luthra *et al.*, 1976). Otherwise the results have revealed no overall pattern. In the past, for reasons related to U.S. Food and Drug Administration policy, or equivalent policies in other countries, there have been practically no studies of the effects of cannabis administered experimentally to human females, and none involving chronic administration.

9.4. Discussion of the Nature of Proof Required to Establish a Drug Effect

The question often arises as to the rigor of evidence or standard of proof required to substantiate statements about the effects of cannabis use. Under more readily controlled circumstances, namely, *in vitro* and in