

## EXECUTIVE SUMMARY

Over the past 18 months there has been wide-ranging public discussion on the potential medical uses of marijuana, particularly smoked marijuana. To contribute to the resolution of the debate, the National Institutes of Health (NIH) held a 2-day scientific meeting on February 19-20, 1997, to review the scientific data concerning the potential therapeutic uses for marijuana and the need for and feasibility of additional research.

Central to the current debate about the therapeutic uses of marijuana is the claim that smoked marijuana offers therapeutic advantages over the currently available oral form (dronabinol capsules) of its most active ingredient, delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC), for a wide variety of conditions. As the therapeutic claims surrounding marijuana are wide-ranging, 10 separate NIH Institutes (with interest in the relevant areas) selected a group of eight experts with broad experience in clinical studies and therapeutics (and none of whom had a predetermined position on the medical utility of marijuana) to examine the data from the published scientific literature presented by speakers in the various therapeutic fields. The Ad Hoc Group of Experts also considered public comments including those of patients and advocacy groups as well as written material submitted to the Group after the meeting. The Expert Group was asked to focus on four questions:

*Question 1* - What research has been done previously and what is currently known about the possible medical uses of marijuana?

*Question 2* - What are the major unanswered scientific questions?

*Question 3* - What are the diseases or conditions for which marijuana might have potential as a treatment and that merit further study?

*Question 4* - What special issues have to be considered in conducting clinical trials of the therapeutic uses of marijuana?

Each presentation of data by a speaker was followed by a question-and-answer session by the Expert Group. There was no requirement that individuals on the Group agree or express a consensus view, although they were free to do so if they so desired. A second day was provided for public comment and further discussion by the Expert Group.

This report is a compilation of the opinions of the Expert Group. Speakers reviewed the literature on the potential efficacy of cannabinoids, including smoked marijuana, in the areas of analgesia, neurological and movement disorders, nausea and vomiting associated with cancer chemotherapy, glaucoma, and appetite stimulation/cachexia. A review of selected aspects of the general clinical pharmacology of marijuana precedes the disorder-specific commentary.

The discovery of receptors in the central nervous system (CNS) for cannabinoid compounds, and the presence of an endogenous ligand for these receptors, is of importance to the debate concerning the potential therapeutic uses of marijuana. This discovery supports a recommendation for more basic research to discover the functional roles of the cannabinoid

receptors as a key underpinning for possible therapeutic applications. Such an approach allows the bridging of knowledge from molecular neurobiology to animal studies to human clinical trials.

The scientific process should be allowed to evaluate the potential therapeutic effects of marijuana for certain disorders, dissociated from the societal debate over the potential harmful effects of nonmedical marijuana use. All decisions on the ultimate usefulness of a medical intervention are based on a benefit/risk calculation, and marijuana should be no exception to this generally accepted principle.

The availability of THC in capsule form does not fully satisfy the need to evaluate the potential medical utility of marijuana. The Expert Group noted that, although delta-9-tetrahydrocannabinol (THC, dronabinol, Marinol<sup>®</sup>, or  $\Delta^9$ -THC) is the principal psychoactive component of the cannabis leaf, there may be other compounds in the leaf that have useful therapeutic properties. Furthermore, the bioavailability and pharmacokinetics of THC from smoked marijuana are substantially different than those of the oral dosage form. These are the rationales for studying the pharmacological actions of other constituents of the cannabis leaf, as well as determining whether a differential benefit occurs with smoked marijuana rather than oral dronabinol.

The Expert Group noted that even for conditions where good therapies are available, some patients develop adverse reactions or are nonresponders. The needs of this subset of nonresponders must be considered in the deliberations on testing marijuana as a possible therapeutic agent.

The Expert Group also noted that risks associated with marijuana, especially smoked marijuana, must be considered not only in terms of immediate adverse effects on the lung; e.g., bronchi and alveoli, but also long-term effects in patients with chronic diseases. Additionally, age, immune status, the development of intercurrent illnesses, and concomitant diseases should be considered in the determination of the risk calculation. The possibility that frequent and prolonged marijuana use might lead to clinically significant impairments of immune system function is great enough that relevant studies should be part of any marijuana medication development research, particularly when marijuana will be used by patients with compromised immune systems. Concerns were expressed by members of the Expert Group on the use of smoked marijuana because of the combustion byproducts, particularly when marijuana would be used for conditions requiring chronic therapy. Hence, a recommendation was made for the development of insufflation/inhalation devices or dosage forms capable of delivering purer THC or cannabinoids to the lungs free of dangerous combustion byproducts.

The major conclusions in each therapeutic area are summarized below.

## **Analgesia**

No clinical trials involving smoked marijuana have been performed in patients with naturally occurring pain. Two adequate and well-controlled studies in cancer pain compared graded doses of oral  $\Delta^9$ -THC to placebo, and one of these included graded doses of codeine as a control. Although there was evidence of analgesic efficacy, the studies indicate there is a narrow

therapeutic margin between the doses that produce useful analgesia and those producing unacceptable adverse CNS effects.

## **Neurological and Movement Disorders**

Numerous preclinical and clinical studies of the use of cannabinoids in neurological and movement disorders have been reported as accounts of animal experiments, clinical anecdotes, surveys, and clinical studies.

Evidence that marijuana relieves spasticity produced by multiple sclerosis (MS) and partial spinal cord injury is largely anecdotal. Large-scale trials or controlled studies to compare marijuana or THC with currently available therapies have not been performed. There is no published evidence that cannabinoids are superior or equivalent to available therapies.

Preclinical evidence suggests a possible role for cannabinoids in the treatment of the epilepsies, particularly generalized and partial tonic-clonic seizures. There is scant information on the use of marijuana or other cannabinoids for the actual treatment of epilepsy.

Individual case studies have reported some benefit of smoked marijuana in treatment of dystonic states. Smoked marijuana or oral THC administrations for Parkinson's disease or Huntington's chorea have not been effective.

Cannabinoids have shown efficacy as immune modulators in animal models of neurological conditions such as experimental allergic encephalomyelitis (EAE) and neuritis. These data suggest that cannabinoids might modify the presumed autoimmune cause of a disease such as MS. However, long-term risks of smoked marijuana need to be quantified when considering chronic therapy for neurological conditions.

## **Nausea and Vomiting Associated With Cancer Chemotherapy**

There is a large body of literature on the effects of cannabinoids on chemotherapy-induced nausea and vomiting. Most of the clinical trials used oral dronabinol rather than smoked marijuana. The oral THC studies showed this dosage form to be superior to placebo and generally equivalent or superior to prochlorperazine, but inferior to metoclopramide. Only one study compared smoked marijuana and dronabinol in a crossover design. Of the 20 patients studied, 9 had no preference, 7 preferred dronabinol, and 4 preferred smoked marijuana.

Since the approval of dronabinol in the mid 1980s for the relief of nausea and vomiting associated with cancer chemotherapy, more effective antiemetics have been developed, such as ondansetron, granisetron, and dolasetron, each combined with dexamethasone. The relative efficacy of cannabinoids versus these newer antiemetics has not been evaluated. Smoked marijuana was tested in one trial in patients who previously had no benefit from older antiemetic agents. Nearly one-quarter of patients who initially agreed to participate later declined citing bias against smoking, the harshness of smoke, and preference for dronabinol. Among the remaining 56 patients, 78 percent rated smoked marijuana very effective or moderately effective. Sedation was

seen in 88 percent and dry mouth in 77 percent. It is not known whether smoked marijuana would benefit patients refractory to the current generation of antiemetic therapy.

## **Glaucoma**

Smoked marijuana has been shown to lower intraocular pressure (IOP) in subjects with normal IOP and patients with glaucoma. The duration of the pressure-lowering effect is 3 to 4 hours. Single-administration studies have reported blood pressure falls concurrently with the IOP lowering, raising concern that blood flow to the optic nerve could be compromised. Mitigating this concern are data suggesting that tolerance may develop to cardiovascular effects. Efforts to avoid or reduce side effects led to the development of a topical dosage form of THC. Topically applied THC did not lower IOP.

The mechanism of all IOP-lowering drugs currently used to treat glaucoma is known with the exception of marijuana. The interactive effect of marijuana with currently available IOP-lowering agents is not known but is evaluable. Elucidation of the mechanism of action of marijuana's IOP-lowering effect is crucial to its potential utilization for treatment of glaucoma; a unique mechanism of action might provide additive benefit whereas a mechanism identical to an available medication would suggest an unfavorable benefit/risk ratio.

## **Appetite Stimulation/Cachexia**

Clinical studies and survey data in healthy populations have shown a strong relationship between marijuana use and increased eating. Marijuana is reported to increase food enjoyment and the number of times individuals eat per day. Mechanistic studies of marijuana on taste and satiety have shown that it does not affect taste or produce a collapse of normal satiety mechanisms. Food intake associated with marijuana use is influenced by the social setting.

There are no controlled studies of marijuana in the AIDS-wasting syndrome, nor have there been any systematic studies of the effects of smoked marijuana on immunological status in HIV-infected patients. Smoking (tobacco, marijuana, or crack cocaine) has been shown to increase the risk of developing bacterial pneumonia in HIV-positive immune-compromised patients. Dronabinol has been shown to increase appetite and produce weight gain in AIDS and cancer patients, although the weight gain is not in lean body mass. Dronabinol is approved for the treatment of anorexia in patients with AIDS-associated weight loss.

## **Question 3: Which Diseases or Conditions Merit Further Study?**

Concerning Question 3, there were varying degrees of enthusiasm to pursue smoked marijuana for several indications. This enthusiasm was tempered by the fact that, for many of these disorders, effective alternative treatments are already available. Given the general consensus among the experts that the number, design and documentation of studies performed to date with smoked marijuana did not provide definitive answers, it was difficult to compare marijuana with products that had received regulatory approval under more rigorous experimental conditions. This does not mean, however, that the issue should be foreclosed. It simply means that in order to evaluate various hypotheses concerning the potential utility of marijuana in various therapeutic areas, more and better studies would be needed. In the words of Dr. William Beaver, Professor of Pharmacology and Anesthesia, Georgetown University School of Medicine, who

chaired the workshop, “For at least some potential indications, marijuana looks promising enough to recommend that there be new controlled studies done.” The indications in which varying levels of interest was expressed are the following:

- Appetite stimulation/cachexia<sup>1</sup>
- Nausea and vomiting following anticancer therapy<sup>2</sup>
- Neurological and movement disorders
- Analgesia
- Glaucoma

Accordingly, the NIH should consider relevant administrative mechanisms to facilitate grant applications in each of these areas. Whether or not the NIH is the primary source of grant support for a proposed bona fide clinical research study, if that study meets U.S. regulatory standards (U.S. Food and Drug Administration (FDA) protocol approval and Drug Enforcement Administration (DEA) controlled substances registration) the study should receive marijuana and/or matching placebo supplied by the National Institute on Drug Abuse (NIDA). In this way, a new body of studies may emerge to test the various hypotheses concerning marijuana.

The last question, Question 4, concerning the special issues involved in conducting clinical trials with marijuana, was particularly difficult. There was considerable discussion and debate as to whether smoked marijuana (with the inherent health risks of smoking) would need to demonstrate clear superiority or some unique benefit compared with other medications currently available for these conditions. The Expert Group concluded that smoked marijuana should be held to standards equivalent to other medications for efficacy and safety considerations. Moreover, there might be some patient populations; e.g., cancer patients experiencing nausea and vomiting during chemotherapy, for whom the inhalation route might offer advantages over the currently available capsule formulation. This raises many issues concerning the best mode of administration. Generally accepted pharmacotherapy development schema would favor finding routes of administration under which dosing could be more tightly controlled and easily titrated. Smoking plant material poses difficulties in standardizing testing paradigms, and components of the smoke are hazardous, especially in the immunocompromised patient. Additionally, practical problems exist. Given the no-smoking policy of hospitals and public facilities, it would be difficult to imagine the utility of smoked marijuana in these settings. Therefore, the experts generally favored the development of alternative dosage forms, including an inhaler dosage form into which a controlled unit dose of THC could be placed and volatilized. Other problems noted were the difficulty in attempting to match placebo control against smoked marijuana (especially for those with previous marijuana experience), and the fact that under U.S. law, researchers will need to obtain DEA registration to handle marijuana, which is currently a Schedule I controlled substance (see Appendix).

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<sup>1</sup> Dronabinol is currently marketed in the United States for the stimulation of appetite in AIDS patients. The effects of smoked marijuana on cachexia associated with AIDS or cancer would need to be determined.

<sup>2</sup> Dronabinol is currently marketed in the United States for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. The effects of smoked marijuana for this indication merit consideration for further research.

In summary, the testing of smoked marijuana to evaluate its therapeutic effects is a difficult, but not impossible, task. Until studies are done using scientifically acceptable clinical trial design and subjected to appropriate statistical analysis, the questions concerning the therapeutic utility of marijuana will likely remain much as they have to date—largely unanswered. To the extent that the NIH can facilitate the development of a scientifically rigorous and relevant database, the NIH should do so.

## INTRODUCTION

On February 19 and 20, 1997, the National Institutes of Health (NIH) held a meeting concerning the potential medical uses of marijuana. Recent (November 1996) ballot initiatives in California and Arizona had sparked a public health and policy debate on the medical utility of marijuana and the desirability of allowing healthcare providers to prescribe, and patients to receive, marijuana for medicinal purposes.

For some years the principal psychoactive ingredient of marijuana, delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC), has been available to healthcare providers in an oral form as dronabinol (trade name Marinol) for the treatment of emesis associated with cancer chemotherapy and for appetite stimulation in the treatment of AIDS wasting syndrome. The current debate centers primarily on the potential for other treatment indications and the claims that, when smoked, marijuana offers therapeutic advantages over the currently available oral form. As the Federal Government's principal biomedical research agency, the NIH believed that the public debate could benefit from an impartial examination of all the data available to date concerning these issues. As the claims for benefits were wide ranging, 10 major components of the NIH participated in the planning for the conference.

The NIH planning group focused the meeting on the following four questions concerning marijuana as a potential therapeutic agent:

*Question 1* - What research has been done previously and what is currently known about the possible medical uses of marijuana?

*Question 2* - What are the major unanswered scientific questions?

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*Question 4* - What special issues have to be considered in conducting clinical studies of the therapeutic uses of marijuana?

The meeting was formatted as a scientific workshop. It was not an attempt to render a consensus. Therefore, it was structured so that speakers with experience in the relevant therapeutic areas would present to a group of eight expert consultants who possessed broad expertise in clinical studies and therapeutics and who had no public positions on the potential use of marijuana as a therapeutic agent. Each presentation was followed by a session for questions and answers from the Expert Group. The second day was allotted for the public to present their views and for discussion by the Expert Group. This report represents a compilation of the views of the Expert Group. Since this report was not intended as a general review of the literature on marijuana and THC, only a few selected references from among the thousands that exist are cited. Each of the members in the Expert Group chose those references relevant to their own contributions to the report.

# CLINICAL PHARMACOLOGY OF MARIJUANA

## The Pharmacology of Natural Products

It is important to keep in mind that marijuana is not a single drug. Marijuana is a mixture of the dried flowering tops and leaves from the plant *cannabis sativa* (Agurell et al. 1984; Graham 1976; Jones 1987; Mechoulam 1973). Like most plants, marijuana is a variable and complex mixture of biologically active compounds (Agurell et al. 1986; Graham 1976; Mechoulam 1973). Characterizing the clinical pharmacology of the constituents in any pharmacologically active plant is often complicated, particularly when the plant is smoked or eaten more or less in its natural form. Marijuana is not unusual in this respect. *Cannabis sativa* is a very adaptive plant, so its characteristics are even more variable than most plants (Graham 1976; Mechoulam 1973). Some of the seeming inconsistency or uncertainty in scientific reports describing the clinical pharmacology of marijuana results from the inherently variable potency of the plant material used in research studies. Inadequate control over drug dose when researching the effects of smoked and oral marijuana, together with the use of research subjects who vary greatly in their past experience with marijuana, contribute differing accounts of what marijuana does or does not do.

## The Plant

Marijuana contains more than 400 chemicals. Approximately 60 are called cannabinoids; i.e., C<sub>21</sub> terpenes found in the plant and their carboxylic acids, analogs, and transformation products (Agurell et al. 1984, 1986; Mechoulam 1973). Most of the naturally occurring cannabinoids have been identified. Cannabinoids appear in no other plant. Cannabinoids have been the subject of much research, particularly since the mid 1960s when Mechoulam and his colleagues first isolated delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) (Mechoulam 1973; Mechoulam et al. 1991). THC in the scientific literature is termed  $\Delta^9$ -THC or  $\Delta^1$ -THC depending on whether the pyran or monoterpenoid numbering system is used.

## Cannabinoids of Importance

THC, the main psychoactive cannabinoid in marijuana, is an optically active resinous substance. THC is not soluble in water but is extremely lipid soluble (Agurell et al. 1984, 1986; Mechoulam 1973). Varying proportions of other cannabinoids, mainly cannabidiol (CBD) and cannabinol (CBN), are also present in marijuana, sometimes in quantities that might modify the pharmacology of THC or cause effects of their own. CBD is not psychoactive but has significant anticonvulsant, sedative, and other pharmacologic activity likely to interact with THC (Adams and Martin 1996; Agurell et al. 1984, 1986; Hollister 1986a).

The concentration of THC and other cannabinoids in marijuana varies greatly depending on growing conditions, plant genetics, and processing after harvest (Adams and Martin 1996; Agurell et al. 1984; Graham 1976; Mechoulam 1973). In the usual mixture of leaves and stems distributed as marijuana, concentration of THC ranges from 0.3 percent to 4 percent by weight. However, specially grown and selected marijuana can contain 15 percent or more THC. Thus, a

marijuana cigarette weighing 1 gram (g) might contain as little as 3 milligrams (mg) of THC or as much as 150 mg or more.

## **Potency of Tetrahydrocannabinol**

THC is quite potent when compared to most other psychoactive drugs. An intravenous (IV) dose of only a milligram or two can produce profound mental and physiologic effects (Agurell et al. 1984, 1986; Fehr and Kalant 1983; Jones 1987). Large doses of THC delivered by marijuana or administered in the pure form can produce mental and perceptual effects similar to drugs usually termed hallucinogens or psychomimetics. However, the way marijuana is used in the United States does not commonly lead to such profound mental effects. Despite potent psychoactivity and pharmacologic actions on multiple organ systems, cannabinoids have remarkably low lethal toxicity. Lethal doses in humans are not known. Given THC's potency on some brain functions, the clinical pharmacology of marijuana containing high concentrations of THC, for example greater than 10 percent, may well differ from plant material containing only 1 or 2 percent THC simply because of the greater dose delivered.

## **Some Limitations of Previous Marijuana Research**

Unfortunately, much of what is known about the human pharmacology of smoked marijuana comes from experiments with plant material containing about 2 percent THC or less, or occasionally up to 4 percent THC. In addition, human experiments typically are done in laboratory settings where only one or two smoked doses were administered to relatively young, medically screened, healthy male volunteers well experienced with the effects of marijuana. Females rarely participated in past marijuana research because of prohibitions (now removed) against their inclusion. Thus the clinical pharmacology of single or repeated smoked marijuana doses given to older people or to people with serious diseases has hardly been researched at all in a controlled laboratory or clinic setting. Some of the very few reports of experiments that have included older or sicker people, particularly patients less experienced in using marijuana, suggest the profile of adverse effects may differ from healthy student volunteers smoking in a laboratory experiment (Hollister 1986a, 1988a).

THC administered alone in its pure form is the most thoroughly researched cannabinoid. Much of what is written about the clinical pharmacology of marijuana is actually inferred from the results of experiments using only pure THC. Generally, in experiments actually using marijuana, the assumed dose of marijuana was based only on the concentration of THC in the plant material. The amounts of cannabidiol and other cannabinoids in the plant also vary so that pharmacologic interactions modifying the effects THC may occur when marijuana is used instead of pure THC. Only rarely in human experiments using marijuana was the content of CBD or other cannabinoids specified or the possibility of interactive effects between THC and other cannabinoids or other marijuana constituents actually measured.

The result of this research strategy is that a good deal is known about the pharmacology of THC, but experimental confirmation that the pharmacology of a marijuana cigarette is indeed entirely or mainly determined by the amount of THC it contains remains to be completed. The scientific literature contains occasional hints that the pharmacology of pure THC, although similar, is not always the same as the clinical pharmacology of smoked marijuana containing the same amount of THC (Graham 1976; Harvey 1985; Institute of Medicine 1982). Proponents of therapeutic

applications of marijuana emphasize possible but not well documented or proven differences between the effects of the crude plant and pure constituents like THC (Grinspoon and Bakalar 1993).

## **Route-Dependent Pharmacokinetics**

Route of administration determines the pharmacokinetics of the cannabinoids in marijuana, particularly absorption and metabolism (Adams and Martin 1996; Agurell et al. 1984, 1986). Typically, marijuana is smoked as a cigarette (a joint) weighing between 0.5 and 1.0 g, or in a pipe in a way not unlike tobacco smoking. Marijuana can also be baked in foods and eaten, or ethanol or other extracts of plant material can be taken by mouth. Some users claim marijuana containing adequate THC can be heated without burning and the resulting vapor inhaled to produce the desired level of intoxication. This has not been studied under controlled conditions. Pure preparations of THC and other cannabinoids can be administered by mouth, by rectal suppository, by IV injection, or smoked. IV injection of crude extracts of marijuana plant material would be quite toxic, however.

## **Marijuana Smoking and Oral Administration**

Smoking plant material is a special way of delivering psychoactive drugs to the brain. Smoking has different behavioral and physiologic consequences than oral or IV administration. What is well known about tobacco (nicotine) and coca (cocaine) clinical psychopharmacology and toxicity illustrates this point all too well. When marijuana is smoked, THC in the form of an aerosol in the inhaled smoke is absorbed within seconds and delivered to the brain rapidly and efficiently as would be expected of a very lipid-soluble drug. Peak venous blood levels of 75 to 150 nanograms per milliliter (ng/mL) of plasma appear about the time smoking is finished (Agurell et al. 1984, 1986; Huestis et al. 1992*a*, 1992*b*). Arterial concentrations of THC have not been measured but would be expected to be much higher initially than venous levels, as is the case with smoked nicotine or smoked cocaine.

Oral ingestion of THC or marijuana is quite different than smoking. Maximum THC and other cannabinoid blood levels are only reached 1 to 3 hours after an oral dose (Adams and Martin 1996; Agurell et al. 1984, 1986). Onset of psychoactive and other pharmacologic effects is rapid after smoking but much slower after oral doses.

## **Marijuana Smoking Behavior and Dose Control**

As with any smoked drug (e.g., nicotine or cocaine), characterizing the pharmacokinetics of THC and other cannabinoids from smoked marijuana is a challenge (Agurell et al. 1986; Heishman et al. 1989; Herning et al. 1986; Heustis et al. 1992*a*). A person's smoking behavior during an experiment is difficult for a researcher to control. People differ. Smoking behavior is not easily quantified. An experienced marijuana smoker can titrate and regulate dose to obtain the desired acute psychological effects and to avoid overdose and/or minimize undesired effects. Each puff delivers a discrete dose of THC to the body. Puff and inhalation volume changes with phase of smoking, tending to be highest at the beginning and lowest at the end of smoking a cigarette. Some studies found frequent users to have higher puff volumes than did less frequent marijuana users. During smoking, as the cigarette length shortens, the concentration of THC in

the remaining marijuana increases; thus, each successive puff contains an increasing concentration of THC.

One consequence of this complicated process is that an experienced marijuana smoker can regulate almost on a puff-by-puff basis the dose of THC delivered to lungs and thence to brain. A less experienced smoker is more likely to overdose or underdose. Thus a marijuana researcher attempting to control or specify dose in a pharmacologic experiment with smoked marijuana has only partial control over drug dose actually delivered. Postsmoking assay of cannabinoids in blood or urine can partially quantify dose actually absorbed after smoking, but the analytic procedures are methodologically demanding, and only in recent years have they become at all practical.

After smoking, venous blood levels of THC fall precipitously within minutes, and an hour later they are about 5 to 10 percent of the peak level (Agurell et al. 1986; Huestis et al. 1992*a*, 1992*b*). Plasma clearance of THC is quite high, 950 milliliters per minute (mL/min) or greater; thus approximating hepatic blood flow. However, the rapid disappearance of THC from blood is largely due to redistribution to other tissues in the body rather than simply because of rapid cannabinoid metabolism (Agurell et al. 1984, 1986). Metabolism in most tissues is relatively slow or absent. Slow release of THC and other cannabinoids from tissues and subsequent metabolism makes for a very long elimination half-time. The terminal half-life of THC is estimated to be from about 20 hours to as long as 10 to 13 days, though reported estimates vary as expected with any slowly cleared substance and the use of assays with varied sensitivity.

Cannabinoid metabolism is extensive with at least 80 probably biologically inactive but not completely studied metabolites formed from THC alone (Agurell et al. 1986; Hollister 1988*a*). 11-hydroxy-THC is the primary active THC metabolite. Some inactive carboxy metabolites have terminal half-lives of 50 hours to 6 days or more and thus serve as long persistence markers of prior marijuana use by urine tests. Most of the absorbed THC dose is eliminated in feces and about 33 percent in urine. THC enters enterohepatic circulation and undergoes hydroxylation and oxidation to 11-nor-9-carboxy-delta-9-THC (9-COOH-<sup>9</sup>-THC). The glucuronide is excreted as the major urine metabolite along with about 18 nonconjugated metabolites. Frequent and infrequent marijuana users are similar in the way they metabolize THC (Agurell et al. 1986; Kelly and Jones 1992).

## **Route of Use Bioavailability and Dose**

THC bioavailability, i.e., the actual absorbed dose as measured in blood, from smoked marijuana varies greatly among individuals. Bioavailability can range from 1 percent to 24 percent with the fraction absorbed rarely exceeding 10 percent to 20 percent of the THC in a marijuana cigarette or pipe (Agurell et al. 1986; Hollister 1988*a*). This relatively low and quite variable bioavailability results from significant loss of THC in sidestream smoke, from variation in individual smoking behaviors, from incomplete absorption from inhaled smoke, and from metabolism in lung and cannabinoid pyrolysis. A smoker's experience is probably an important determinant of dose actually absorbed (Herning et al. 1986; Johansson et al. 1989). Much more is known about the dynamics of tobacco (nicotine) smoking. Many of the same pharmacokinetic considerations apply to marijuana smoking.

Oral bioavailability of THC, whether given in the pure form or as THC in marijuana, also is low and extremely variable, ranging between 5 percent and 20 percent (Agurell et al. 1984, 1986). Great variation can occur even when the same individual is repeatedly dosed under controlled and ideal conditions. THC's low and variable oral bioavailability is largely a consequence of large first-pass hepatic elimination of THC from blood and due to erratic absorption from stomach and bowel. Because peak effects are slow in onset and variable in intensity, typically at least an hour or two after an oral dose, it is more difficult for a user to titrate dose than with marijuana smoking. When smoked, THC's active metabolite 11-hydroxy-THC probably contributes little to the effects since relatively little is formed, but after oral doses the amounts of 11-hydroxy-THC metabolite may exceed that of THC and thus contribute to the pharmacologic effects of oral THC or marijuana.

## **Mental and Behavioral Effects**

### *Common Acute Effects*

Usually the mental and behavioral effects of marijuana consist of a sense of well-being (often termed euphoria or a high), feelings of relaxation, altered perception of time and distance, intensified sensory experiences, laughter, talkativeness, and increased sociability when taken in a social setting. Impaired memory for recent events, difficulty concentrating, dreamlike states, impaired motor coordination, impaired driving and other psychomotor skills, slowed reaction time, impaired goal-directed mental activity, and altered peripheral vision are common associated effects (Adams and Martin 1996; Fehr and Kalant 1983; Hollister 1988a; Institute of Medicine 1982; Tart 1971).

With repeated exposure, varying degrees of tolerance rapidly develops to many subjective and physiologic effects (Fehr and Kalant 1983; Jones 1987). Thus, intensity of acute effects is determined not only by THC dose but also by past experience, setting, expectations, and poorly understood individual differences in sensitivity. After a single moderate smoked dose most mental and behavioral effects are easily measurable for only a few hours and are usually no longer measurable after 4 to 6 hours (Hollister 1986a, 1988a). A few published reports describe lingering cognitive or behavioral changes 24 hours or so after a single smoked or oral dose (Fehr and Kalant 1983; Institute of Medicine 1982; Yesavage et al. 1985). Venous blood levels of THC or other cannabinoids correlate poorly with intensity of effects and character of intoxication (Agurell et al. 1986; Barnett et al. 1985; Huestis et al. 1992a).

### *Adverse Mental Effects*

Large smoked or oral marijuana doses or even ordinary doses taken by a sensitive, inexperienced, or predisposed person can produce transient anxiety, panic, feelings of depression and other dysphoric mood changes, depersonalization, bizarre behaviors, delusions, illusions, or hallucinations (Adams and Martin 1996; Fehr and Kalant 1983; Hollister 1986a, 1988a; Institute of Medicine 1982). Depending on the mix of symptoms and behaviors, the state has been termed an acute panic reaction, toxic delirium, acute paranoid state, or acute mania. The unpleasant effects are usually of sudden onset, during or shortly after smoking, or appear more gradually an hour or two after an oral dose, usually last a few hours, less often a few days, and completely clear without any specific treatment other than reassurance and a supportive environment. A subsequent marijuana dose, particularly a lower one, may be well tolerated. In a large survey of

regular marijuana users, 17 percent of young adult respondents reported experiencing at least one of the preceding symptoms during at least one occasion of marijuana use, usually early in their use (Tart 1971).

Whether marijuana can produce or trigger lasting mood disorders (depression or mania) or schizophrenia is less clearly established (Fehr and Kalant 1983; Gruber and Pope 1994; Hollister 1986a, 1988a; Institute of Medicine 1982). A psychotic state with schizophrenic-like and manic features lasting a week or more has been described. Marijuana can clearly worsen schizophrenia. Chronic marijuana use can be associated with behavior characterized by apathy and loss of motivation along with impaired educational performance even without obvious behavioral changes (Pope and Yurgelun-Todd 1996; Pope et al. 1995). The explanation and mechanisms for this association are still not well established.

### *Cardiovascular and Autonomic Effects*

A consistent, prominent, and sudden effect of marijuana is a 20 to 100 percent increase in heart rate lasting up to 2 to 3 hours (Hollister 1986a, 1988a; Jones 1985). After higher smoked or oral doses postural hypotension and associated faintness or dizziness can occur upon standing up from a supine or prone position. Tolerance to these effects appears after only a few days of two to three times per day dosing (Benowitz and Jones 1981; Jones 1985). Typical is a modest increase in supine blood pressure. Cardiac output can increase 30 percent when supine. Peripheral vascular resistance decreases with the greatest drop in resistance in skeletal muscles. Skin temperature drops are large; 4 to 6 degrees centigrade, even after a modest smoked dose and roughly parallel to plasma norepinephrine increases. With a few days of repeated exposure to frequent doses of oral THC or marijuana extract, supine blood pressure falls, the sometimes marked initial orthostatic hypotension disappears, blood volume increases, and heart rate slows (Benowitz and Jones 1981). Thus like other system effects, the intensity and character of many hemodynamic effects of single smoked doses in humans are a function of recent marijuana exposure, dose, and even body position.

The cardiovascular effects of smoked or oral marijuana have not presented any health problems for healthy and relatively young users. However, marijuana smoking by older patients, particularly those with some degree of coronary artery or cerebrovascular disease, is likely to pose greater risks because of the resulting increased cardiac work, increased catecholamines, carboxyhemoglobin, and postural hypotension (Benowitz and Jones 1981; Hollister 1988a). Such issues have not been well addressed in past marijuana research.

### *Respiratory System Effects*

Pulmonary effects associated with marijuana smoking include transient bronchodilation after acute exposure. Chronic bronchitis and pharyngitis are associated with repeated exposure with an increased frequency of pulmonary illness. With chronic marijuana smoking, large-airway obstruction is evident on pulmonary function tests, and cellular inflammatory histopathological abnormalities appear in bronchial epithelium (Adams and Martin 1996; Hollister 1986a). These effects appear to be additive to those produced by tobacco smoking.

### *Endocrine System*

Endocrine system effects include a moderate depression of spermatogenesis and sperm motility and a decrease in plasma testosterone in males. Prolactin, FSH, LH, and GH levels are decreased in females. Although suppressed ovulation and other ovulatory cycle changes occur in nonhuman primates, a study of human females smoking marijuana in a research hospital setting did not find hormone or menstrual cycle changes like those in the monkeys given THC (Mendelson and Mello 1984; Mendelson et al. 1984a). Relatively little research has been done on experimentally administered marijuana effects on human female endocrine and reproductive system function.

### *Immune System*

THC and other cannabinoids in marijuana have immunosuppressant properties producing impaired cell-mediated and humoral immune system responses. A large literature describes the results of experiments with animal and animal tissue in *in vivo* and *in vitro* model systems. THC and other cannabinoids suppress antibody formation, cytokine production, leukocyte migration and natural killer-cell activity. Cannabinoids decrease host resistance to infection from bacterial and viral infection in animals. Marijuana smokers show evidence of impaired immune function: for example, decreased leukocyte blastogenesis in response to mitogens. Marijuana smokers, when compared to nonmarijuana smokers, have more respiratory illness (Polen et al. 1993).

The cannabinoids have been characterized as immunomodulators because although they generally suppress, they occasionally enhance some immune responses (Friedman et al. 1995). Reviews of marijuana immune system effects have characterized the effects as complicated or conflicting or controversial (Adams and Martin 1996; Hollister 1988b). The clinical significance or relevance of these findings remains uncertain. Much of the complexity and controversy results from the use of mostly *in vitro* animal models, or *in vitro* animal and human cell cultures, or *in vivo* animal studies. Generally in most studies the cannabinoid doses or concentrations used have been quite high when compared to reasonable levels of exposure in human marijuana smoking.

Suppressed or impaired immune mechanisms would likely have negative effects on health by increasing susceptibility to infection or to tumors. People with compromised immune systems or existing malignancies may be at higher risk than healthy people. For example, the risk of developing AIDS may be higher with HIV infection, with a higher risk for infection by opportunistic bacteria, fungi, or viruses. On the other hand, some have suggested that the immunosuppressive effects of cannabinoids might be useful clinically; for example, in treating

multiple sclerosis, mostly reasoning from theoretical assumptions or experimental disease models in animals.

In summary, there is good evidence that THC and other cannabinoids can impair both cell-mediated and humoral immune system functioning, leading to decreased resistance to infection by viruses and bacteria. However, the health relevance of these findings to human marijuana use remains uncertain. Conclusive evidence for increased malignancy, or enhanced acquisition of HIV, or the development of AIDS, has not been associated with marijuana use.

There is a need for further research, particularly in circumstances where long-term administration of marijuana might be considered for therapeutic purposes; for example, in individuals who are HIV-positive or who have tumors, malignancies, or diseases where immune system function may be important in the genesis of the disease. Clinical studies with smoked marijuana in patients with compromised immune systems may offer a sensitive index of adverse immune system effects associated with cannabinoid exposure. Direct measures of viral load and other sensitive indices of immune system function are now more practical than in past years when most of the cannabinoid immune system research was carried out. The possibility that frequent and prolonged marijuana use might lead to clinically significant impairments of immune system function is great enough that such studies should be part of any marijuana medication development research, particularly when marijuana will be used by patients with compromised immune systems.

## **Tolerance and Physical Dependence**

After repeated smoked or oral marijuana doses, marked tolerance is rapidly acquired (after a day or two) to many marijuana effects, e.g., cardiovascular, autonomic, and many subjective effects. After exposure is stopped, tolerance is lost with similar rapidity (Jones et al. 1981). Measurable tolerance or tachyphalaxis is evident for some hours after smoking even a single marijuana cigarette.

Withdrawal symptoms and signs appearing within hours after cessation of repeated marijuana use have been occasionally reported by patients in clinical settings (Duffy and Milin 1996; Mendelson et al. 1984*b*). A withdrawal syndrome was reliably produced by as little as 5 days of modest but frequent oral doses of THC or marijuana extract in double-blind, placebo-controlled experiments (Jones et al. 1981). THC decreased or relieved the symptoms. Typical symptoms and signs were restlessness, insomnia, irritability, salivation, tearing, nausea, diarrhea, increased body temperature, anorexia, weight loss, tremor, sweating, sleep brainwave rapid eye movement rebound, and subjective sleep disturbance. Increased dreaming contributing to the sleep disturbance sometimes persisted for weeks, but the other signs and symptoms were gone or markedly diminished within 48 hours after the last oral marijuana dose.

## **Drug Interactions With Marijuana**

Tobacco, ethanol, and other psychoactive and therapeutic drugs commonly consumed together with marijuana share metabolic pathways with cannabinoids, so metabolic interactions are likely. Both THC and CBD inhibit the metabolism of drugs metabolized by hepatic mixed-function oxidase enzymes (Benowitz and Jones 1977; Benowitz et al. 1980; Hollister 1986*b*).

The absorption or clearance of other drugs taken with marijuana may be slowed or hastened depending on timing and sequence of drug ingestion and past exposure. For example, ethanol consumed just after smoking a marijuana cigarette produces a much lower peak blood level than the same dose of ethanol taken an hour before marijuana smoking because THC slows gastric emptying time, thus slowing absorption of ethanol.

THC is highly bound to plasma proteins (97 percent to 99 percent) and thus is likely to interact with other highly bound drugs because of competition for binding sites on plasma proteins.

Finally, there is experimental evidence for drug interactions at the functional (neural) adaptation level (Adams and Martin 1996).

By those and possibly by other mechanisms, recent or concurrent THC or CBD exposure measurably alters the pharmacokinetics and/or effects of ethanol, barbiturates, nicotine, amphetamines, cocaine, phencyclidine, opiates, atropine, and clomipramine (Fehr and Kalant 1983; Institute of Medicine 1982). Marijuana use is likely to alter the pharmacology of some concurrently used therapeutic drugs, e.g., cancer chemotherapeutic agents or anticonvulsants.

## **Cannabinoid Receptors**

Mechanisms of psychoactive cannabinoid action were long suspected to be through interactions of/with lipid components of cell membranes (Adams and Martin 1996; Hollister 1988*a*). The discovery of cannabinoid receptors in the human brain in the late 1980s led to renewed interest in the pharmacology and potential therapeutic uses of cannabinoids (Adams and Martin 1996; Herkenham 1992). The mechanisms of action of THC are now assumed to be mainly receptor mediated. So far, it still is a relatively simple receptor family (CB 1 and CB 2). Receptors are abundant in brain areas concerned with memory, cognition, and motor coordination. An endogenous ligand, a fatty acid derivative named anandamide, has been identified but not yet studied in humans (Thomas et al. 1996). A specific THC antagonist, SR141716A, provokes intense withdrawal signs and behaviors in rodents that have been exposed to THC for even relatively brief periods (Adams and Martin 1996). The clinical pharmacology of the antagonist has not been studied in humans.

## REFERENCES

- Adams, I.B., and Martin, B.R. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91(11):1585-1614, November 1996.
- Agurell, S., Dewey, W.L., and Willett, R.E., eds. *The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects*. New York: Academic Press, 1984.
- Agurell, S.; Halldin, M.; Lindgren, J.E.; Ohlsson, A.; Widman, M.; Gillespie, H.; and Hollister, L. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 38(1):21-43, March 1986.
- Barnett, G.; Licko, V.; and Thompson, T. Behavioral pharmacokinetics of marijuana. *Psychopharmacology* 85(1):51-56, 1985.
- Benowitz, N.L., and Jones, R.T. Effect of delta-9-tetrahydrocannabinol on drug distribution and metabolism: Antipyrine, pentobarbital and ethanol. *Clin Pharmacol Ther* 22(3):259-268, 1977.
- Benowitz, N.L., and Jones, R.T. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *J Clin Pharmacol* 21:214S-223S, 1981.
- Benowitz, N.L.; Nguyen, T.; Jones, R.T.; Herning, R.I.; and Bachman, J. Metabolic and psychophysiological studies of cannabidiol-hexobarbital interaction. *Clin Pharmacol Ther* 28:115-120, 1980.
- Duffy, A., and Milin, R. Case study: Withdrawal syndrome in adolescent chronic cannabis users. *J Am Acad Child Adolesc Psychiatry* 35(12):1618-1621, December 1996.
- Fehr, K., and Kalant, H., eds. *ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use (1981: Toronto, Canada) Cannabis and Health Hazards: Proceedings of an ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use*. Toronto, Canada: Addiction Research Foundation, 1983.
- Friedman, H.; Klein, T.W.; Newton, C.; and Daaka, Y. Marijuana, receptors and immunomodulation. *Adv Exp Med Biol* 373:103-113, 1995.
- Graham, J.D.P., ed. *Cannabis and Health*. New York: Academic Press, 1976.
- Grinspoon, L., and Bakalar, J.B. *Marihuana, the Forbidden Medicine*. New Haven: Yale University Press, 1993.
- Gruber, A.J., and Pope, H.G. Cannabis psychotic disorder: Does it exist? *Am J Addict* v3 (n1):72-83, Winter 1994.
- Harvey, D.J., ed. *Satellite Symposium on Cannabis (3rd: 1984: Oxford, England) Marihuana '84: Proceedings of the Oxford Symposium on Cannabis*. Washington, DC: IRL Press, 1985.
- Heishman, S.J.; Stitzer, M.L.; and Yingling, J.E. Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. *Pharmacol Biochem Behav* 34(1):173-179, September 1989.
- Herkenham, M. Cannabinoid receptor localization in brain: Relationship to motor and reward systems. In: Kalivas, P.W., and Samson, H.H., eds. *The neurobiology of drug and alcohol addiction*. *Ann N Y Acad Sci* 654:19-32, 1992.
- Herning, R.I.; Hooker, W.D.; and Jones, R.T. Tetrahydrocannabinol content and differences in marijuana smoking behavior. *Psychopharmacology* 90(2):160-162, 1986.
- Hollister, L.E. Health aspects of cannabis. *Pharmacol Rev* 38(1):1-20, March 1986a.
- Hollister, L.E. Interactions of cannabis with other drugs in man. In: Braude, M.C., and Ginzburg, H.M., eds. *Strategies for Research on the Interactions of Drugs of Abuse*. National Institute on Drug Abuse Research Monograph 68. DHHS Pub. No. (ADM)86-1453. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1986b. pp. 110-116.

- Hollister, L.E. Cannabis—1988. (Literature review). *Acta Psychiatr Scand* (Suppl) 78(345):108-118, 1988a.
- Hollister, L.E. Marijuana and immunity. *J Psychoactive Drugs* 20(1):3-8, January-March 1988b.
- Huestis, M.A.; Henningfield, J.E.; and Cone, E.J. Blood Cannabinoids. 1. Absorption of THC and formation of 11-OH-THC and THC COOH during and after smoking marijuana. *J Anal Toxicol* 16(5):276-282, September-October 1992a.
- Huestis, M.A.; Sampson, A.H.; Holicky, B.J.; Henningfield, J.E.; et al. Characterization of the absorption phase of marijuana smoking. *Clin Pharmacol Ther* 52 (1):31-41, July 1992b.
- Institute of Medicine. *Division of Health Sciences Policy. Marijuana and Health: Report of a Study by a Committee of the Institute of Medicine, Division of Health Sciences Policy.* Washington, DC: National Academy Press, 1982.
- Johansson, E.; Halldin, M.M.; Agurell, S.; Hollister, L.E.; and Gillespie, H.K. Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. *Eur J Clin Pharmacol* 37(3):273-277, 1989.
- Jones, R.T. Drug of abuse profile: Cannabis. *Clin Chem* 33 (11 Suppl):72B-81B, October 1987.
- Jones, R.T. Cardiovascular effects of cannabinoids. In: Harvey, D.J., ed. *Marihuana, '84: Proceedings of the Oxford Symposium on Cannabis.* Oxford: IRL Press, 1985. pp. 325-334.
- Jones, R.T.; Benowitz, N.L.; and Hering, R.I. Clinical relevance of cannabis tolerance and dependence. *J Clin Pharmacol* 21:143S-152S, 1981.
- Kelly, P., and Jones, R.T. Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users. *J Anal Toxicol* 16:228-235, 1992.
- Mechoulam, R., ed. *Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects.* New York: Academic Press, 1973.
- Mechoulam, R.; Devane, W.A.; Breuer, A.; and Zahalka, J. A random walk through a cannabis field. Special Issue: Pharmacological, chemical, biochemical and behavioral research on cannabis and the cannabinoids. *Pharmacol Biochem Behav* 40(3):461-464, November 1991.
- Mendelson, J.H., and Mello, N.K. Effects of marijuana on neuroendocrine hormones in human males and females. In: Braude, M.C., and Ludford, J.P., eds. *Marijuana Effects on the Endocrine and Reproductive Systems.* National Institute on Drug Abuse Research Monograph 44. DHHS Pub. No. (ADM)84-1278. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984. pp. 97-114.
- Mendelson, J.H.; Mello, N.K.; Cristofaro, P.; Ellingboe, J.; and Benedikt, R. Acute effects of marijuana on pituitary and gonadal hormones during the periovulatory phase of the menstrual cycle. In: Harris, L.S., ed. *Problems of Drug Dependence, 1984: Proceedings of the 46<sup>th</sup> Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc. National Institute on Drug Abuse Research Monograph 55.* DHHS Pub. No. (ADM)85-1393. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1984a. pp. 24-31.
- Mendelson, J.H.; Mello, N.K.; Lex, B.W.; and Bavli, S. Marijuana withdrawal syndrome in a woman. *Am J Psychiatry* 141(10):1289-1290, October 1984b.
- Polen, M.R.; Sidney, S.; Tekawa, I.S.; Sadler, M.; and Friedman, G.D. Health care use by frequent marijuana smokers who do not smoke tobacco. *West J Med* 158(6):596-601, June 1993.
- Pope, H.G., Jr., and Yurgelun-Todd, D. The residual cognitive effects of heavy marijuana use in college students. *JAMA* 275(7):521-527, February 21, 1996.
- Pope, H.G.; Gruber, A.J.; and Yurgelun-Todd, D. The residual neuropsychological effects of cannabis: The current status of research. *Drug Alcohol Depend* 38(1):25-34, April 1995.
- Tart, C.T. *On Being Stoned: A Psychological Study of Marijuana Intoxication.* Palo Alto, CA: Science and Behavior Books, 1971.

- Thomas, B.F.; Adams, I.B.; Mascarella, S.W.; Martin, B.R.; and Razdan, R.K. Structure-activity analysis of anandamide analogs: Relationship to a cannabinoid pharmacophore. *J Med Chem* 39(2):471-497, January 19, 1996.
- Yesavage, J.A.; Leirer, V.O.; Denari, M.; and Hollister, L.E. Carry-over effects of marijuana intoxication on aircraft pilot performance: A preliminary report. *Am J Psychiatry* 142(11):1325-1329, November 1985.

## ANALGESIA

### *1. What research has been done and what is known about the possible medical uses of marijuana?*

A number of studies have been conducted on the antinociceptive or analgesic effect of tetrahydrocannabinol (THC) or marijuana in both animals and human subjects; the results have been conflicting. Of interest is the recent identification of cannabinoid receptors as well as an endogenous ligand, anandamide. There is some evidence that they are part of a natural pain control system distinct from the endogenous opioid system. Recognizing that some studies have demonstrated an antinociceptive (analgesic) effect of THC and related compounds in rodents, it may be useful to identify what specific kinds of pain may be relieved by marijuana or THC.

Animal studies on the analgesic effect of marijuana have produced inconsistent results. Whereas one study shows that delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) is equipotent to morphine in rats (tailflick test), and more potent than morphine in mice (hotplate test), other studies showed that  $\Delta^9$ -THC was less potent than morphine in both mice and rats. Cannabinoids have been shown to be possibly analgesic in animal models of neuropathic pain.

There have been a few studies of marijuana/ $\Delta^9$ -THC employing different models of experimentally induced pain in volunteer subjects, and these studies have also yielded conflicting results. Raft and colleagues (1977) found that, in oral surgery patients, premedication with intravenous  $\Delta^9$ -THC was less effective than diazepam or placebo in reducing two kinds of experimentally induced pain. Another study showed that smoked marijuana increased pain tolerance, while others showed either no effect or a lowering of pain threshold after oral or intravenous dosing with  $\Delta^9$ -THC or smoking marijuana. The current "FDA Guideline for the Clinical Evaluation of Analgesic Drugs" (FDA 1992) notes that "Evidence is still inadequate to establish that any experimental pain model will consistently and accurately predict the clinical efficacy of new analgesics, . . . [and] they cannot substitute for controlled trials in patients with pathologic pain [naturally occurring pain caused by disease or tissue injury] in producing substantial evidence of analgesia . . ." This is also the overwhelming consensus of investigators who conduct controlled clinical trials of analgesic efficacy. Therefore, the above studies contribute little information about the analgesic efficacy of marijuana/ $\Delta^9$ -THC in patients with pain.

There appear to be no controlled analgesic studies of smoked marijuana in patients with naturally occurring pain. However, Noyes and his colleagues conducted two studies of oral  $\Delta^9$ -THC in inpatients with cancer pain. Both of these studies used the same standard single-dose analgesic study methodology and met the criteria for well-controlled clinical trials of analgesic efficacy, but with small sample sizes. Both were randomized, double-blind, crossover comparisons employing a full-time nurse-observer, who collected hourly subjective ratings of pain intensity and pain relief. Observed and reported side effects were recorded, as were the responses to an 11-item subjective effects questionnaire.

The first study in 10 cancer patients compared a placebo and 5, 10, 15, and 20 mg doses of  $\Delta^9$ -THC over a 6-hour observation period (Noyes et al. 1975a). The slope of the dose-response curve for pain relief was significant, as was a pairwise comparison of pain relief after the two

lower doses combined versus the two higher doses combined. There was also a clear dose-response relationship for sedation, mental clouding, and other central nervous system (CNS) related side effects. Because of sedation, the 20-mg dose was judged to be “of limited value for most patients.”

The second study in 36 cancer patients compared placebo, 10, and 20 mg of  $\Delta^9$ -THC and 60 and 120 mg of codeine over a 7-hour observation period (Noyes et al. 1975b). Codeine 120 mg and  $\Delta^9$ -THC 20 mg were similar to each other and significantly superior to placebo for the sum of the pain intensity differences and total pain relief, while other pairwise contrasts were not significant. Relative potency analysis was not performed.

The time-effect curves for both doses of codeine and for  $\Delta^9$ -THC, 10 mg, peaked at the third hour. As in the first study, the 20 mg dose of  $\Delta^9$ -THC peaked at the fifth hour, which probably reflects the delayed absorption of oral THC. “Patients receiving 20 mg of THC were heavily sedated and even at 10 mg reported considerable drowsiness. Other dose limiting side effects included dizziness, ataxia and blurred vision” (Noyes et al. 1975b). Mental clouding, thinking impairment, disconnected thought, disorientation, slurred speech, and impaired memory were much more prominent after both doses of  $\Delta^9$ -THC than after codeine administration, and patients expressed particular concern over their “loss of control” over thought and action. Five patients experienced very unpleasant psychic effects after  $\Delta^9$ -THC; three patients said they felt as if they were dying, one patient experienced depressed mood, and one patient suffered paranoid ideation. In two patients, the adverse mood effects persisted 3 or 4 days.

These studies indicate that  $\Delta^9$ -THC has some analgesic activity in humans. They also indicate that there is, at best, a very narrow therapeutic window between doses that produce useful analgesia and those that produce unacceptable adverse CNS effects.

## 2. *What are the major unanswered scientific questions?*

Since oral  $\Delta^9$ -THC has some analgesic activity, it is highly likely that smoked marijuana has some analgesic activity in some kinds of clinical pain. Because  $\Delta^9$ -THC from smoked marijuana is absorbed directly into the pulmonary circulation, this route of administration results in a  $\Delta^9$ -THC blood level curve much more like that produced by an intravenous injection than that after oral administration. It is therefore likely that smoked marijuana potentially allows a more precise titration to effect than oral administration of  $\Delta^9$ -THC with its delayed, poor, and erratic bioavailability. Theoretically, smoked marijuana or inhaled THC potentially has some of the characteristics of a patient-controlled analgesia (PCA) pump. It is therefore possible that some pain patients could use smoked marijuana to titrate themselves into the therapeutic window of adequate pain relief while avoiding unacceptable adverse effects. Although the above scenario is pharmacologically reasonable, only properly designed controlled clinical analgesic studies can determine if it actually works and is practically useful. For example, it is also possible that the minimum blood level of  $\Delta^9$ -THC that produces useful analgesia also usually produces a level of sedation, mental clouding, and thinking impairment that is unacceptable to most patients.

There are currently available a great variety of both opioid and nonsteroidal anti-inflammatory drug (NSAID) analgesics in various dosage formulations suitable for many routes of administration. Adroit use of these can manage most acute pain and even chronic cancer pain satisfactorily. If marijuana is to be a useful analgesic, healthcare providers need to know how it

compares in efficacy and safety to at least a few of the standard analgesics that would be used in managing a particular kind of pain.

3. *What are the diseases or conditions for which marijuana might have potential as a treatment and which merit further study?*

Neuropathic pain represents a treatment problem for which currently available analgesics are, at best, marginally effective. Since  $\Delta^9$ -THC is not acting by the same mechanism as either opioids or NSAIDs, it may be useful in this inadequately treated type of pain. Evaluation of cannabinoids in the management of neuropathic pain, including HIV-associated neuropathy, should be undertaken. A few animal studies support this idea. Another potentially useful role for marijuana/ $\Delta^9$ -THC might be as an adjuvant when added to a regimen of standard analgesics.

## REFERENCES

- FDA Guideline for the Clinical Evaluation of Analgesic Drugs*. DHHS Pub. No. 93-3093. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, 1992.
- Noyes, R., Jr.; Brunk, S.F.; Baram, D.A.; and Canter, A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol* 15(2-3):139-143, February-March, 1975*a*.
- Noyes, R., Jr.; Brunk, S.F.; Avery, D.A.H.; and Canter, A.C. The analgesic properties of delta-9-tetrahydrocannabinol. *Clin Pharmacol Ther* 18(1):84-89, July, 1975*b*.
- Raft, D.; Gregg, J.; Ghia, J.; and Harris, L. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. *Clin Pharmacol Ther* 21(1):26-33, 1977.

## USE OF MARIJUANA IN NEUROLOGICAL AND MOVEMENT DISORDERS

### *1. What research has been done and what is known about the possible medical uses of marijuana?*

There have been numerous studies both in animals and in various clinical states on the use of cannabinoids on neurological and various movement disorders. These results range from anecdotal reports to surveys and clinical trials. Marijuana or tetrahydrocannabinol (THC) is reported to have some antispasticity, analgesic, antitremor, and antiataxia actions, as well as some activity in multiple sclerosis (MS) and in spinal cord injury patients.

The spasticity and nocturnal spasms produced by MS and partial spinal cord injury have been reported to be relieved by smoked marijuana and to some extent by oral THC in numerous anecdotal reports. The effect seems to appear rapidly with smoked marijuana; patients are able to titrate the dose by the amount they smoke. No large-scale controlled studies or studies to compare either smoked or oral THC with other available therapies have been reported. Several relatively good therapeutic alternatives exist. There is no published evidence that the cannabinoid drugs are superior or even equivalent.

Substantial experimental animal literature exists showing that various cannabinoids, given primarily by parenteral routes, have a substantial anticonvulsant effect in the control of various models of epilepsy, especially generalized and partial tonic-clonic seizures. Scant information is available about the human experience with the use of marijuana or cannabinoids for the treatment of epilepsy. This is an area of potential value, especially for cannabis therapies by other than the smoked route.

Several single case histories have been reported indicating some benefit of smoked marijuana for dystonic states. It must be remembered that dystonia is a clinical syndrome with numerous potential causes, and the information available now does not differentiate which causes are most likely to be improved. Smoked marijuana and oral THC have been tested in the treatment of Parkinson's disease and Huntington's chorea without success.

The cannabinoids also have been used as experimental immunologic modifiers to treat such conditions as the animal models of experimental allergic encephalomyelitis (EAE) and neuritis. Parenteral cannabinoids have been successful in modifying EAE in animals, suggesting that cannabinoids may be of value in a more fundamental way by altering the root cause of a disease such as MS rather than simply treating its symptoms. Smoked marijuana would not be acceptable for such a role because of the variability of dose with the smoked route.

### *2. What are the major unanswered scientific questions?*

The discovery of dedicated systems of central nervous system (CNS) neurons approximately 8 years ago, which express receptors specific for the cannabinoids, is of major scientific interest and importance. The distribution of these cannabinoid receptor-bearing neurons corresponds well with the clinical effects of smoked marijuana; for instance, their presence in the forebrain may relate to adverse changes in short-term memory, but perhaps positively in the control of epilepsy. Cannabinoid receptors in the brainstem and cerebellum may relate to the recognized

incoordination that accompanies smoked marijuana use. The discovery of intrinsic ligands for these receptors in the mammalian brain is also of great importance. This system of cannabinoid receptors and ligands may be analogous to the discovery of opiate receptors and endorphins, which linked various opium derivatives (heroin and morphine) to an intrinsic system of neurons in the CNS. That discovery was of major importance for pain research.

The major unanswered scientific questions are:

- How useful is smoked marijuana of known specific potency in controlling various neurologic conditions?
  - In comparative studies, how useful is smoked marijuana in altering objective abnormalities such as spasticity versus current standard therapies that have already been approved for human use?
  - Can alternative delivery systems (other than the oral route) be developed to provide rapidity of action with more safety than smoked marijuana?
  - Can available or newly developed synthetic cannabinoids be used more effectively to stimulate or block receptor activity in the cannabinoid system of the CNS?
  - What are the immune-modulating characteristics of the cannabinoids and can they be used for therapeutic human benefit?
  - Can the long-term risks of daily smoked marijuana be quantified so that useful risk versus benefit ratios can be determined, especially when considering treatment of long-term conditions such as spasticity or epilepsy?
3. *What are the diseases or conditions for which marijuana might have potential as a treatment and which merit further study?*

Marijuana or the use of other cannabinoids as human therapies might be considered for treating spasticity and nocturnal spasms complicating MS and spinal cord injury, for various active epilepsy states, for some forms of dystonia, and perhaps most interestingly, for treating neuropathic pain (Zeltser et al. 1991). (Also see the chapter titled ANALGESIA.) Neuropathic pain complicates many CNS diseases. Few available therapies provide even partial relief.

## REFERENCE

Zeltser, R.; Seltzer, Z.; Eisen, A.; Feigenbaum, J.J.; and Mechoulam, R. Suppression of neuropathic pain behavior in rats by a non-psychotropic synthetic cannabinoid with NMDA receptor-blocking properties. *Pain* 47(1):95-103, October 1991.

## NAUSEA AND VOMITING

### *1. What research has been done and what is known about the possible medical uses of marijuana?*

There is a large body of clinical research on the use of cannabinoids for chemotherapy-related nausea and vomiting. Most of this work was conducted during the early 1980s. The majority of reports deal with oral dronabinol rather than smoked marijuana. These studies demonstrated that dronabinol was superior to placebo in controlling nausea and vomiting caused by chemotherapy that induces a moderate amount of emesis (Sallan et al. 1975). Several studies compared oral dronabinol with prochlorperazine (Sallan et al. 1980). Mixed results were reported from these studies, but generally dronabinol was found equivalent.

Gralla and colleagues (1984) examined metoclopramide versus dronabinol in patients given cisplatin in a randomized double-blind trial. These investigators reported poorer antiemetic control and more side effects with dronabinol than with the metoclopramide.

None of these studies compared oral dronabinol or smoked marijuana with what are now considered the most effective antiemetic regimens, the combination of a specific serotonin antagonist (like ondansetron, granisetron, or dolasetron) plus dexamethasone, which were introduced in the early 1990s. This combination has demonstrated complete protection from vomiting during the initial 24 hours after cisplatin (the most potent emetic stimulus) in 79 percent of patients treated (Italian Group for Antiemetic Research 1995). Without antiemetic protection, 98 percent of similar patients vomit a median of six times within the first 24 hours alone after cisplatin (Kris 1996). Side effects of these newer antiemetic regimens are negligible and would permit a patient to drive or return to his or her job immediately after receiving chemotherapy.

Only two clinical trials have formally addressed the effectiveness of smoked marijuana. Levitt and colleagues (1984) conducted a random-order assignment crossover study comparing smoked marijuana and dronabinol in 20 subjects, 15 men and 5 women. Twenty-five percent of the subjects were free of vomiting and 15 percent were free of nausea. As to individual preference for the route of administration, 45 percent of the patients had no preference, 35 percent preferred oral dronabinol, and 20 percent preferred smoked marijuana.

Vinciguerra and colleagues (1988) studied smoked marijuana in an open trial in 74 patients who previously had no improvement with standard antiemetic agents. Nearly 25 percent of patients who initially consented to participate later refused treatment citing bias against smoking, harshness of smoke, and preference for oral dronabinol. Of the remaining 56 patients, 18 (34 percent) rated it very effective and 26 (44 percent) moderately effective. Twelve (22 percent) noted no benefit. Sedation occurred in 88 percent, dry mouth in 77 percent, and dizziness in 39 percent. Only 13 percent were free of adverse effects.

2. *What are the major unanswered scientific questions?*

No scientific questions have been definitively answered about the efficacy of smoked marijuana in chemotherapy-related nausea and vomiting. A comparison of the efficacy of smoked marijuana versus oral dronabinol would also be of interest. In addition, further information on appropriate dosage and frequency, side effects, tolerability, and patient acceptability for smoked marijuana would need to be established.

3. *What are the diseases or conditions for which marijuana might have potential as a treatment and which merit further study?*

Inhaled marijuana has the potential to improve chemotherapy-related nausea and vomiting. Because the combination of a serotonin antagonist plus dexamethasone prevents chemotherapy-related nausea and vomiting in the majority of patients, investigation of smoked marijuana as a treatment for the minority of patients who vomit despite receiving the current best regimens (i.e., rescue therapy in refractory patients) might be an initial focus. Another line of investigation could be the efficacy of inhaled marijuana in delayed nausea and vomiting due to chemotherapy.

An add-on design in which smoked marijuana or placebo would be administered to incomplete responders to standard combination therapy would be appropriate. A dronabinol capsule group should also be included. Stratification should be done for naive versus experienced marijuana smokers. Nausea severity, vomiting prevention, and CNS effects assessments should be primary endpoints.

Inhaled marijuana merits testing in controlled, double-blind, randomized trials for the above indications.

## REFERENCES

- Gralla, R.J.; Tyson, L.B.; Bordin, L.A.; Clark, R.A.; Kelsen, D.P.; Kris, M.G.; Kalman, L.B.; and Groshen, S. Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treat Rep* 68(1):163-172, January 1984.
- Italian Group for Antiemetic Research. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. *Ann Oncol* 6:805-810, 1995.
- Kris, M.G.; Cubeddu, L.X.; Gralla, R.J.; Cupissol, D.; Tyson, L.B.; Venkatraman, E., and Homesley, H.D. Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. *Cancer* 78:2193-2198, 1996.
- Levitt, M.; Faiman, C.; Hawks, R.; and Wilson, A. Randomized double-blind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. *Proc Am Soc Clin Oncol* 3:91, 1984.
- Sallan, S.E.; Zinberg, N.E.; and Frei, III, E. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med* 293:795-797, 1975.
- Sallan, S.E.; Cronin, C.; Zelen, M.; and Zinberg, N.E. Antiemetics in patients receiving chemotherapy for cancer—a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 302:135-138, 1980.
- Vinciguerra, V.; Moore, T.; and Brennan, E. Inhalation marijuana as an antiemetic for cancer chemotherapy. *NY State Med J* 88(10):525-527, October 1988.

## GLAUCOMA

### *1. What research has been done and what is known about the possible medical uses of marijuana?*

Marijuana is not generally accepted as a safe and effective treatment for glaucoma. The American Academy of Ophthalmology (1992) stated: “There is evidence that marijuana (or its components), taken orally or by inhalation can lower intraocular pressure. However, there are no conclusive studies to date to indicate that marijuana (or its components) can safely and effectively lower intraocular pressure enough to prevent optic nerve damage. . . . The dose of marijuana necessary to produce a clinically relevant effect in the short term appears to produce an unacceptable level of undesirable side effects such as euphoria, systemic hypotension, and/or dry eye and conjunctival hyperemia in the majority of glaucoma patients in whom the drug has been carefully studied. No data have been published on studies of long-term ocular and systemic effects of the use of marijuana by glaucoma patients.

“ . . . Because the possibility exists that marijuana (or its components) may be useful in treating glaucoma, the American Academy on Ophthalmology Committee on Drugs believes that a long term clinical study, designed to test the safety and efficacy of marijuana in the prevention of progressive optic nerve damage and consequent visual field loss, appears appropriate.”

The National Eye Institute (1997) has recently stated much the same thing. “Studies in the early 1970s showed that marijuana, when smoked, lowers intraocular pressure in people with normal pressure and those with glaucoma. . . . However, none of those studies demonstrated that marijuana—or any of its components—could safely and effectively lower intraocular pressure any more than a variety of drugs then on the market. . . . [and] some potentially serious side effects were noted. . . . Research to date has not investigated whether marijuana use offers any advantages over currently available glaucoma treatments or if it is useful when used in combination with standard therapies. . . . [t]he National Eye Institute stands ready to evaluate any well-designed studies for treatment of eye diseases, including those involving marijuana for treatment of glaucoma.”

The initial observation that smoked marijuana lowered intraocular pressure (IOP) in humans in acute experiments was made by Hepler and Frank in 1971. Hepler and Petrus (1976) later reported in greater detail that 4 percent (tetrahydrocannabinol (THC)) marijuana cigarettes lowered the IOP about 27 percent more than did a placebo at 30 minutes in normal volunteers, and that 20 mg of oral THC lowered the IOP about 17 percent more than placebo at 30 minutes. They also reported that smoked marijuana lowered IOP much more dramatically in patients with poorly controlled glaucoma, with 10 of 12 responding, and presented graphs showing the timecourse. One patient demonstrated a reduction from 40 mm Hg to 10 mm Hg in one eye and from 35 mm Hg to 15 mm Hg in the other. Since patients with severe glaucoma did not discontinue their current therapy (pilocarpine - 4 percent, epinephrine - 2 percent, or oral acetazolamide) Hepler and Petrus concluded that smoked marijuana or oral THC were additive to the then-known classes of therapeutic agents, and presumably worked by an independent mechanism (Hepler and Petrus 1976). In these short-term studies, lasting up to 4 hours, 2 cigarettes were as effective as 20 cigarettes, and intoxication occurred. Others confirmed that the marijuana could have a significant adjunctive effect in glaucoma patients, with Cuendet and

colleagues reporting that 12/16 eyes of 10 patients had a reduction of 15 percent or more (Cuendet et al. 1976).

Flom and colleagues (1975) concluded that in normal volunteers in acute studies the lowering of IOP was proportional to the “high,” and that experienced users who did not experience a “high” did not have a lowering of IOP. Merritt and colleagues (1980) studied the blood pressure (BP) and IOP of 18 glaucoma patients in short-term studies, which compared smoking a single 2 percent THC cigarette versus a placebo cigarette of the same smell and taste and concluded that the IOP was reduced by 4 mm Hg at 30 minutes and by 6 mm Hg at 90 minutes (in patients with either open-angle or synechial angle-closure glaucoma), returning to baseline by 4 hours with THC, while there was no change with the placebo, but that the pulse rose from 82 beats per minute (bpm) to 123 bpm at 15 minutes, and the systolic BP fell 11 mm Hg and diastolic BP fell 5 mm Hg, suggesting that reduced perfusion of the ciliary body accounted for the reduction in IOP and that the adverse systemic effects, including postural hypotension, would limit the potential usefulness of marijuana. Indeed, Merritt concluded in an editorial in the *Journal of the National Medical Association* (1982) that “Systemic delta-9 THC therapies invariably produce a decreased perfusion pressure to the eye. This decreased perfusion to an already damaged optic nerve may not be of long-term benefit to glaucoma victims.” However, there are several anecdotal reports that, on continued use, tolerance develops to the undesirable cardiovascular and mood effects of marijuana, while tolerance does not develop to the beneficial effects on IOP in patients with glaucoma (Palmberg 1997).

Efforts to avoid systemic effects of THC in glaucoma treatment led to studies of topical preparations, such as 1 percent THC in peanut oil. However, no effect of the preparation on IOP was found by Jay and Green (1983).

Animal studies have yielded conflicting results about the mechanism of action of THC on the IOP. The studies by Green in rabbits suggested central effects mediated through the adrenergic nervous system (Green 1979), but the studies of Colasanti (1990) in cats indicated no effect of either sympathetic or parasympathetic denervation on the action of THC. She also found that THC has no effect on aqueous production in anesthetized cats, but rather increased aqueous outflow facility threefold.

The mechanism in humans has never been investigated by modern means, including fluorophotometry, coupled with the older method of tonography, which could yield clear information about the mechanism of action, whether on inflow, conventional outflow, or uveo-scleral outflow. In addition, it would now be possible to test the additivity of marijuana to a wide variety of agents now available, including beta-1 and beta-2 agonists and antagonists, alpha-2 agonists, dorzolamide, and latanoprost, to see whether or not THC works by a separate mechanism.

## 2. *What are the major unanswered scientific questions?*

Researchers do not know the mechanism of action of cannabis on IOP, given either as smoked marijuana or as oral THC.

Additional studies of long-term marijuana use are needed to determine if there are or are not important adverse pulmonary, central nervous system (CNS), or immune system problems.

It needs to be determined if smoked or eaten marijuana is more effective in lowering IOP on a chronic basis than THC alone, as marijuana advocates maintain on the basis of anecdotal experience, or if pure THC, without the particulates and carcinogens of marijuana smoke, could be inhaled by means other than smoking, or taken orally, with equal long-term effect on IOP.

Researchers do not know if marijuana would be additive to the new, very potent types of eyedrops now available to treat glaucoma, including alpha-2 agonists, dorzolamide and latanoprost (a prostaglandin that increases uveoscleral outflow and, like THC, causes conjunctival hyperemia). If marijuana were not to be additive to one of these agents, marijuana would be obsolete, since these agents have no systemic side effects (other than slightly dry mouth in some patients with apraclonidine and bromonidine), and they have a duration of action of 12 to 24 hours.

*1. What are the diseases or conditions for which marijuana might have potential as a treatment and which merit further study?*

Further studies to define the mechanism of action and to determine the efficacy of delta-9-tetrahydrocannabinol and marijuana in the treatment of glaucoma are justified.

In glaucoma, there does not appear to be any obvious reason to use smoked marijuana as a primary “stand alone” investigational therapy, as there are many available agents for treatment, and these topical preparations seem to be potentially ideal. An approach that may be useful is to study smoked marijuana in incomplete responders to standard therapies. The suggested design for clinical studies is to add marijuana, oral THC, or placebo to standard therapy under double-blind conditions. Studies proposed should consider the following measures:

- Establish dose-response and dose-duration relationships for IOP and CNS effects.
- Relate IOP and blood pressure measurements longitudinally to evaluate potential tolerance development to cardiovascular effects.
- Evaluate CNS effects longitudinally for tolerance development.

## REFERENCES

- American Academy of Ophthalmology. "The Use of Marijuana in the Treatment of Glaucoma." Statement by the Board of Directors of the American Academy of Ophthalmology, PO Box 7424, San Francisco, CA, June 1992.
- Colasanti, B.K. Review: Ocular hypotensive effect of marijuana cannabinoids: Correlate of central action or separate phenomenon? *J Ocular Pharmacol* 6(4):259-269, 1990.
- Cuendet, J.F.; Sapiro, D.; Calanca, A.; Faggioni, R.; and Ducrey, N. Action of delta-9-tetrahydrocannabinol on ophthalmotonus. *Ophthalmologica* 172:122-127, 1976.
- Flom, M.C.; Adams, A.J.; and Jones, R.T. Marijuana smoking and reduced pressure in human eyes: Drug action or epiphenomenon? *Invest Ophthalmol* 14(1):52-55, 1975.
- Green, K. Marihuana in ophthalmology—past, present and future. (Editorial). *Ann Ophthalmol* 11(2):203-205, 1979.
- Hepler, R.S., and Frank, I.R. Marijuana smoking and intraocular pressure. (Letter). *JAMA* 217:1392, 1971.
- Hepler, R.S., and Petrus, R.J. Experiences with administration of marihuana to glaucoma patients. In: Cohen, S., and Stillman, R.C., eds. *The Therapeutic Potential of Marihuana*. New York: Plenum Medical Books, 1976. pp. 63-75.
- Jay, W.M., and Green, K. Multiple-drop study of topically applied 1% delta 9-tetrahydrocannabinol in human eyes. *Arch Ophthalmol* 101(4):591-593, 1983.
- Merritt, J.C. Glaucoma, hypertension, and marijuana. (Editorial). *J Natl Med Assn* 74(8):715-716, 1982.
- Merritt, J.C.; Crawford, W.J.; Alexander, P.C.; Anduze, A.L.; and Gelbart, S.S. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology* 87(3):222-228, 1980.
- National Eye Institute. "The Use of Marijuana for Glaucoma." Statement of the National Eye Institute of the National Institutes of Health, February 18, 1997.
- Palmberg, P. Unpublished observations presented at the Workshop on the Medical Utility of Marijuana, National Institutes of Health, Bethesda, MD, February 20, 1997.

## APPETITE STIMULATION/CACHEXIA

### 2. *What research has been done and what is known about the possible medical uses of marijuana?*

It has been shown that there is a strong relationship between smoking marijuana and increased frequency and amount of eating.

Survey data on appetite stimulation (Haines and Green 1970) (N = 131) showed that 91 percent of marijuana users eat every time they smoke. Tart (1970) found that 93 percent of marijuana users (131) reported that marijuana made them enjoy eating very much and that they consequently ate a lot more. Foltin and colleagues (1986) reported that marijuana users eat more often. A study by Farrow and associates (1987) reported no hematologic changes or signs of nutrient deficiencies in marijuana users.

Marijuana is reported to enhance the sensory appeal of foods. Taste does not seem to be altered as measured by indexes of sourness (citric acid in lemonade), saltiness (NaCl in tomato juice), sweetness (sucrose in cherry-flavored drink), and bitterness (urea in tonic water). There does not appear to be impairment in the normal satiety mechanisms following marijuana ingestion.

Foltin and colleagues (1988) saw signs of a general increase in food intake on smoked marijuana days versus placebo days. The effect may not persist over an extended period of time, but long-term studies have not been done. Setting is important in appetite enhancement and social settings contribute heavily. Williams and associates (1946) did a chronic dosing study. They found that body weight went up and stayed up, possibly due to an effect of marijuana on fluid retention. Greenberg and colleagues (1976) saw a sharp increase in food intake followed by a leveling off. The increase in body weight may reflect a reduction in energy expenditure.

Food intake was greater after smoking, compared to oral and sublingual administration, but there was much individual variability. Marijuana seems to enhance appetite in the evening, whereas many cancer patients report having most of their appetite in morning. This would suggest a potential complementary use of marijuana.

Cachexia or wasting due to HIV infection is increasingly prevalent in the era of effective prophylaxis for *Pneumocystis carinii* pneumonia (Hoover et al. 1993). Significant weight loss, more than 20 percent of ideal body weight, is associated with shortened survival of HIV-infected patients (Kotler et al. 1989). The major causes of weight loss in HIV-infected patients are opportunistic infections, enteric infections associated with malabsorption, and reduced caloric intake. The latter is the most important cause of wasting in the absence of opportunistic infections and malabsorption (MacCallan et al. 1995).

Administration of the appetite stimulants megestrol acetate (VonRoenn et al. 1994) and dronabinol (Gorter et al. 1992) is associated with weight gain in HIV-infected patients. Anabolic steroids and recombinant human growth hormone produce an increase in lean body mass (Mulligan et al. 1993). In published studies, the weight gain produced by appetite stimulants or hormonal therapy has not been shown to be associated with an improved immunologic status or clinical outcome. All investigations, however, have been relatively short, 12 to 24 weeks in

length. Although there is much anecdotal evidence of weight gain produced by use of smoked marijuana, no objective data relative to body composition alterations, HIV replication, or immunologic function in HIV-infected patients are available. An epidemiologic study demonstrated no alteration in the natural history of HIV infection with use of smoked marijuana (Kaslow et al. 1989), although other investigations in uninfected volunteers and animal models indicated that there are effects on components of the immune system. There have been no recent published studies of the impact of smoked marijuana on the immune system in HIV-infected patients using state-of-the-art immunologic assays.

Megestrol acetate (Oster et al. 1994, VonRoenn et al. 1994) produces weight gain that is predominantly fat, with very little increase in lean body mass. Dronabinol ( $\Delta^9$ -THC) has been studied in patients with cancer (Nelson et al. 1994; Plasse et al. 1991) and AIDS (Gorter et al. 1992), who showed increased weight gain.

Beal and colleagues (1995) studied dronabinol as treatment for anorexia associated with weight loss in patients with AIDS. A significant increase in appetite was seen with a decrease in nausea, and a mood increase that was not significant. The 6-week study may have been too short to fully capture the effects of dronabinol.

In a survey looking at physicians' choice of drugs to treat wasting, the first line choice of 80 percent of the care providers was megestrol with dronabinol being used by 54 percent. Dronabinol was also the second line choice of most providers.

Problems that have been identified with dronabinol are that patients feel "too stoned"; are unable to titrate their dose properly; note delayed onset of effect, prolonged duration of effect, or problems with malabsorption; and "not the same feeling as smoked marijuana."

Several panelists pointed out that the weight gain is primarily an accumulation of water (sometimes of fat), but not of lean body mass. On the other hand, oncologists heard from patients with advanced cancer that increased appetite and weight gain are psychologically helpful, regardless of the nature of the added weight, and regardless of the impact (if any) on survival. Panelists also commented that very likely weight loss is an indicator rather than a cause of impending death.

## *2. What are the major unanswered scientific questions?*

Some questions that need to be answered in future studies are:

3. Does smoking marijuana increase total energy intake in patients with catabolic illness?
4. Does marijuana use alter energy expenditure?
5. Does marijuana use alter body weight, and to what extent?
6. Does marijuana use alter body composition, and to what extent?

So far, it has not been shown that reversing wasting changes mortality risk. Another question is whether weight gain is associated with positive changes in psychological status. It seems related but has not been systematically addressed.

3. *What are the diseases or conditions for which marijuana might have potential as a treatment and which merit further study?*

Areas of study for the potential appetite-stimulating properties of marijuana include the cachexia of cancer, HIV/AIDS symptomatology, and other wasting syndromes. With an appropriate delivery system designed to minimize the health risks of smoking, studies of the appetite-stimulating potential of cannabinoids are justified. Such investigations should be designed to assess long-term effects on immunologic status, the rate of viral replication, and clinical outcomes in participants as well as weight gain.

In therapeutic trials for cachexia, research should attempt to separate out the effect of marijuana on mood versus appetite. Complex interactions likely are involved.

## REFERENCES

- Beal, J.E.; Olson, D.O.; Laubenstein, L.; et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 10:89-97, 1995.
- Farrow, J.A.; Rees, J.M.; and Worthington-Roberts, B.S. Health, developmental, and nutritional status of adolescent alcohol and marijuana abusers. *Pediatrics* 79:218, 1987.
- Foltin, R.W.; Brady, J.V.; and Fischman, M.W. *Pharmacol Biochem Behav* 25:577-582, 1986.
- Foltin, R.W.; Fischman, M.W.; and Byrne, M.F. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11:1-14, 1988.
- Gorter, R.; Seifried, M.; and Volberding, P. Dronabinol effects on weight in patients with HIV infection. *AIDS* 6:127, 1992.
- Greenberg, I.; Kuehnle, J.; Mendelson, J.H.; and Bernstein, J.G. Effects of marijuana use on body weight and caloric intake in humans. *Psychopharmacology* 49:79-84, 1976.
- Haines, L., and Green, W. Marijuana use patterns. *Br J Addict* 65:347, 1970.
- Hoover, D.R.; Saah, A.J.; Bacellar, H.; et al. Clinical manifestations of AIDS in the era of Pneumocystis prophylaxis. Multicenter AIDS Cohort Study. *N Engl J Med* 329:1922-1929, 1993.
- Kaslow, R.A.; Blackwelder, W.C.; Ostrow, D.G.; et al. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1-positive individuals: A report from the Multicenter AIDS Cohort Study. *JAMA* 26:3424-3429, 1989.
- Kotler, D.P.; Tierney, P.R.; Wang, J.; and Pierson, R.N., Jr. The magnitude of body cell mass depletion determines the timing of death from wasting in AIDS. *Am J Clin Nutr* 50:444-447, 1989.
- MacCallan, D.C.; Noble, C.; Baldwin, C.; et al. Energy expenditure and wasting in human immunodeficiency virus infection. *N Engl J Med* 333:83-88, 1995.
- Mulligan, K.; Grunfeld, C.; Hellerstein, M.K.; et al. Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab* 77:956-962, 1993.
- Nelson, K.; Walsh, D.; Deeter, P.; and Sheehan, F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia (Review). *J Palliat Care* 10(1):14-18, Spring 1994.
- Oster, M.H.; Enders, S.R.; Samuels, S.J.; Cone, L.A.; et al. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med* 121:400-408, 1994.
- Plasse, T.F.; Gorter, R.W.; Krasnow, S.H.; Lane, M.; Shepard, K.V.; and Wadleigh, R.G. Recent clinical experience with dronabinol. *Pharmacol Biochem Behav* 40:695-700, 1991.
- Tart, C.T. Marijuana intoxication: Common experiences. *Nature* 226:701, 1970.
- VonRoenn, J.; Armstrong, D.A.; Kotler, D.P.; et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 121:393-399, 1994.
- Williams, E.G.; Himmelsbach, C.K.; Wikler, A.; and Rudle, D.C. Studies on marijuana and pyrahexyl compound. *Publ Health Rep* 61(29):1059, July 19, 1946.

## **QUESTION 4. WHAT SPECIAL ISSUES HAVE TO BE CONSIDERED IN CONDUCTING CLINICAL TRIALS OF THE THERAPEUTIC USES OF MARIJUANA?**

### **Benefit and Risk Considerations**

There are a number of guidelines and specific issues related to smoked marijuana that are important in planning trial designs and carrying out clinical studies. The current state of knowledge regarding the efficacy of smoked marijuana for a given disease/condition should be taken into account in designing clinical protocols. Investigators should give consideration to the range of potential questions that could be addressed and propose to address the most pertinent question(s) with the most appropriate study designs. This strategy should enhance the possibility of National Institutes of Health (NIH) funding support. In some instances, the initial question to be addressed may be whether smoked marijuana is efficacious in the treatment/management of a clinical condition. Such a proposed study may be a validation of clinical anecdotes or be proposed from basic research findings that suggest a potential benefit. In either case, the question should be formulated as a testable hypothesis. In other instances, the more germane question may be whether smoked marijuana possesses specific advantages over dronabinol capsules or other pharmacological therapies, has additional therapeutic effects in combination with standard therapies, has benefit in patients refractory to standard medications, or has benefit primarily in marijuana-experienced patients.

The risks of concern associated with the investigational use of marijuana differ depending on the patient populations being studied and with the proposed duration of administration. For example, there is a different level of risk of developing bacterial pneumonia associated with marijuana administration to immune-compromised patients compared with nonimmune-compromised subjects. On the other hand, some risks may decrease with continued use due to the rapid tolerance development to certain central nervous system (CNS) and cardiovascular effects of marijuana. Marijuana-experienced subjects may already have some level of tolerance to certain effects. Hence, it is critical to consider the side effects of marijuana, the proposed duration of administration, the previous and current level of marijuana use in the proposed study population, and any additional risks that may be conferred by the disease status of the population in the assessment of risks and the appropriate type and frequency of safety monitoring. Concerns regarding the long-term risks associated with smoking are less important in conditions where short-term use is being proposed or patients are terminally ill. However, such risks are of concern for conditions where chronic administration of smoked marijuana is likely. Regardless of whether short-term or long-term use is being studied, all clinical trials must monitor side effects.

### **Study Design Considerations**

Beyond the benefit and risk considerations, there are some general and specific study design issues regarding the evaluation of the therapeutic effects of smoked marijuana.

There are two basic types of control groups to be considered in designing studies of the medical use of smoked marijuana: placebo control and active control groups. A placebo control is

important in studying clinical conditions where there is no known effective therapy. Placebo controls are also desirable in studies where the question is whether smoked marijuana is effective or whether it is equivalent to another drug, and many study designs utilize both placebo and active control groups. This allows a determination as to whether a valid conclusion can be drawn about the efficacy of the test drug by providing a measure of assay sensitivity for the study; i.e., did any treatment show superiority to placebo. This design also allows comparison of marijuana with a standard therapy. If an effective standard treatment exists, there are conditions such as chemotherapy-related nausea and vomiting in which it would be unethical to include a placebo control group. On the other hand, in single-dose analgesic studies a placebo group can be incorporated in the design if appropriate provision is made for administration of a “rescue” analgesic if the study medication proves ineffective. Adding a placebo group increases the complexity of the study design and the number of subjects required and presents ethical questions that must be confronted and answered on a study-by-study basis, but a study without a placebo group may yield uninterpretable results unless some other measure of assay sensitivity is incorporated in the study.

If smoked marijuana is being compared to a standard of care, placebo may not be needed if objective endpoints are being measured; e.g., number of vomiting episodes per day. Since many of the potential therapeutic uses of marijuana involve the use of the drug as an “add on” or adjunctive therapy administered concomitantly with a standard therapeutic regimen, a practical strategy for avoiding a placebo group is to administer the standard therapy to all patients in the study, and **in addition** administer marijuana to half the patients and a placebo marijuana to the other half. In that way, no patient would be deprived of standard effective therapy.

Some investigations address whether an effect is dose related. This type of design allows for the assessment of the dose range that produces therapeutic effects and the relationship between these effects and dose-related side effects. Although these designs do not exclude the addition of placebo groups, a placebo is often not used because the determination of a positive dose-response curve for an effect provides an internal measure of assay sensitivity. An obvious difficulty with this type of design for smoked marijuana is the inability to standardize dose delivery due to the inherent variability associated with pulmonary administration. One possible design is to compare self-titrated smoking with several fixed doses of THC capsules.

## **Selection of Patient Population**

The selection of the patient population to be studied, and the inclusion /exclusion criteria for the defined population, are another critical set of decisions. Design choices include patients who are the general population of patients with the disorder, or one of the following groups: nonresponders or incomplete responders to other therapies, patients selected in open-trial designs who responded to marijuana, and naive versus experienced marijuana smokers.

One proposed strategy, selecting subsets responsive to marijuana in an open manner (i.e., “enrichment design”), assumes that there may be subpopulations that are difficult to recognize, except on the basis of their prior putative response to marijuana. Once identified, such patients are randomly assigned to a study drug or control group and are evaluated in a prospective manner. This approach is useful in situations where responses are variable and/or modest, making it difficult to demonstrate an effect, and where it would be of interest to know if a drug

was useful even in a subset of the patient population. However, the limitation of this approach is the difficulty of estimating the size of the population to which study results can be generalized.

Single-patient (N = 1) studies utilize multiple periods of a study drug-control, within-subject, crossover design. Evidence of efficacy in single patients can be determined in such designs, although carryover effects from the long plasma half-life of cannabinoids may confound interpretation of results.

## **Blinding or Masking Treatment Assignments**

The issue of “blinding” or “masking” marijuana cigarettes was discussed at some length. Blinding may be difficult, even with identical-looking placebo cigarettes. Experienced marijuana users may be able to discern from the subjective effects whether they received active or placebo cigarettes. Nonetheless, there should be an effort to mask treatment assignment from both the patient and investigator, i.e., the double-blind technique. The effectiveness of blinding can be evaluated to some extent by querying patients after the study about their guess as to the identity of their treatment. In order to maintain double-blind conditions when comparing smoked marijuana with a control treatment in tablet or capsule form, a double-dummy technique is used. The marijuana treatment group would receive active marijuana plus dummy tablets or capsules, while the control group would receive dummy marijuana (i.e., with little or no THC) plus active tablets or capsules.

## **Selection of Clinical Endpoints**

The choice of clinical endpoints for evaluation of potential efficacy should be guided by the desire to obtain objective data, if such endpoints can be obtained and are clinically relevant. Examples of such endpoints would be the number of vomiting episodes associated with a particular chemotherapy, intraocular pressure (IOP) measurements in glaucoma trials, and weight gain and percent changes in body composition in AIDS-wasting syndrome studies. The frequency of measurements should be dictated by the clinical condition being studied.

While blinding may not be as important in studies with clear objective endpoints, some potential indications for marijuana are in conditions that involve subjective responses, e.g., treating the symptoms and improving the quality of life in very sick or dying patients. Scientific evidence can be generated on the basis of subjective responses. These therapeutic areas should not be avoided on the grounds that studies involving objective endpoints would be easier to quantitate or would be more immune to bias.

Because of the importance of the questions of the medical utility of marijuana and the inherent difficulties in designing a definitive study with clinically important endpoints, a mechanism could be considered, such as a forum where experts in the subject areas and experts in clinical trial methodology, Government scientists, and applicable physicians and patients could engage in dialog regarding appropriate study designs prior to their adoption.

## **Possible Role of the NIH in Facilitating Clinical Evaluation of the Medical Utility of Marijuana**

There are several mechanisms whereby the NIH can facilitate clinical trials with marijuana.

Adequate supplies of marijuana of various and consistent strengths and placebos should be made available to investigators. The NIH should consider using its facilities and influence to assure the availability of comparator compounds and appropriate placebos (e.g., active and identical placebo amitriptyline tablets to permit a randomized trial versus smoked marijuana/smoked marijuana placebo for the control of neuropathic pain).

Because of the broad range of potential uses of marijuana cutting across many NIH Institutes, a centralized mechanism should be considered to facilitate the design, approval, and conduct of trials supported by the NIH. Consideration should be given to supporting mechanisms whereby experts in multiple areas and physicians and patients could engage in dialog regarding study designs prior to their commencement. In addition, to permit the most rapid and accurate determination of marijuana's medical utility, the NIH should coordinate with efforts in individual States and by research organizations also conducting peer-reviewed research studying marijuana (e.g., American Cancer Society, Multiple Sclerosis Society). The NIH should also work closely with the Drug Enforcement Administration (DEA) and the U.S. Food and Drug Administration (FDA) to ensure that FDA regulations are followed and that clinical trials supported are adequate for submission as part of an FDA approval package should marijuana prove effective for a particular indication.

The NIH should use its resources and influence to rapidly develop a smoke-free inhaled delivery system for marijuana or THC. This effort will remove a significant health hazard during clinical testing and future potential use. This will also bring this research effort in line with other Government initiatives to curtail cigarette smoking, the number-one preventable cause of premature death and disability in America. Until this is done, the testing of smoked marijuana would be difficult in smoke-free healthcare and municipal facilities. In addition, study of smoked marijuana in private facilities such as community medical offices or patients' homes, where smoking is not prohibited, would still present an environmental hazard of secondhand smoke for healthcare workers and family members. "Taking the smoke" out of an inhaled dosage form of marijuana or THC would remove an important obstacle to the accurate determination of inhaled marijuana's beneficial and deleterious effects.

## **APPENDIX: THE EFFECT OF CONTROLLED SUBSTANCES SCHEDULING ON MARIJUANA RESEARCH**

*(Although not discussed at the meeting, this section is provided as background regarding research with Schedule I substances.)*

In addition to the requirements of the U.S. Food and Drug Administration (FDA) and sponsoring organizations such as the National Institutes of Health (NIH) concerning the conduct of clinical research, U.S. investigators are subject to specific FDA and Drug Enforcement Agency (DEA) regulations concerning research with controlled substances. Under the Controlled Substances Act (21 USC 822 (a)(1)) and implementing DEA regulations, persons conducting clinical research with any controlled substance must register with the DEA, keep specific types of records, and periodically report to the DEA. Marijuana is currently classified at the highest (most restrictive) level as a Schedule I drug (no accepted medical use, high potential for abuse). Attempts by various petitioners to have marijuana rescheduled have not been successful.

Therefore, there is at least one extra layer (many States have their own laws modeled after the Controlled Substances Act (CSA), which add further complexity) for any investigator undertaking clinical trials with controlled substances. In the case of research conducted under an Investigational New Drug Application (IND), recordkeeping requirements are exempt from the CSA but must be kept in accordance with the Food, Drug and Cosmetic Act (FDCA). Under the FDCA, a sponsor or investigator must make its records concerning shipment, delivery, receipt, and disposition available for inspection and copying at DEA's request. Additionally, FDA regulations require that sponsors and investigators conducting clinical trials take special precautions to prevent diversion, including storage in a secure place with limited access. In the case of some investigator sites, this may require acquisition of a safe and/or other physical space changes and/or procedures to insure security and accountability of the substance.

The CSA also mandates reporting procedures when conducting research with controlled substances. A DEA registration for controlled substances also authorizes (within specified limits) the manufacture and distribution of the substances. If a researcher engages in manufacture or distribution, then he or she is held to the reporting standard of manufacturers and distributors. Presumably, the manufacturer/distributor reporting requirements would not apply in most studies, as the source of marijuana would be the National Institute on Drug Abuse (NIDA) and most studies would not be using the plant material to manufacture other forms or products.

Where research studies of Schedule I substances are not conducted under an IND, the DEA requires a copy of the research protocol be submitted for approval and identify in the registration applications the extent to which the research will involve manufacture or importation. Where research is conducted under an IND, however, the sponsor need only provide the DEA with a copy of the IND and a statement of security precautions. The FDA has ultimate authority to decide whether the research may proceed either under its jurisdiction over INDs (FDCA) or in the case of non-IND research, under the CSA (21CFR1301.42). Where non-IND research is undertaken, the FDA must consult with the DEA concerning the adequacy of the applicant's diversion control procedures. If a researcher desires to increase the amount of Schedule I material it has previously received permission to use, it must apply to the DEA for the increase,

and the DEA will forward the request to the FDA for approval/denial, taking into account DEA comments on the adequacy of the researcher's security against diversion control.

Some States may have their own registration requirements for Schedule I substances above and beyond the Federal requirements. Each researcher must check his or her own State authorities to see if other regulatory requirements need to be met. Given the small amounts of research material used by researchers in comparison to the additional regulatory burden and time delays, many researchers have been discouraged from pursuing research with these substances. Indeed, one of the recommendations of the Institute of Medicine Report entitled *The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector* (National Academy Press, Washington, DC 1995, pp. 168-171) was that the current regulatory system be modified to remove barriers to undertaking clinical research with controlled substances.

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