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War Against Marijuana Consumers

Our country's war on drugs places great emphasis on arresting people for smoking marijuana. In the last decade, 6.5 million Americans have been arrested on marijuana charges, a greater number than the entire populations of Alaska, Delaware, the District of Columbia, Montana, North Dakota, South Dakota, Vermont and Wyoming combined. In 2006, state and local law enforcement arrested 829,625 people for marijuana violations. Annual marijuana arrests have nearly tripled since the early 1990s, and is the highest number ever recorded by the FBI.

As has been the case throughout the 1990s, the overwhelming majority of those charged with marijuana violations in 2006 -- **738,915** Americans (89 %) -- were for simple possession. The remaining **90,710** individuals were for "sale/manufacture", an FBI category which includes marijuana grown for personal use or purely medical purposes. These new FBI statistics indicate that **one marijuana smoker is arrested every 38 seconds in America.** Taken together, the total number of marijuana arrests for 2006 far exceeded the combined number of arrests for violent crimes, including murder, manslaughter, forcible rape, robbery and aggravated assault.

Like most Americans, people who smoke marijuana also pay taxes, love and support their families, and work hard to make a better life for their children. Suddenly they are arrested, jailed and treated like criminals solely because of their recreational drug of choice. State agencies frequently step in and declare children of marijuana smokers to be "in danger", and many children are placed into foster homes as a result. This causes enormous pain, suffering and financial hardship for millions of American families. It also engenders distrust and disrespect for the law and for the criminal justice system overall. Responsible marijuana smokers present no threat or danger to America or its children, and there is no reason to treat them as criminals, or to take their children away. As a society we need to find ways to discourage personal conduct of all kinds that is abusive or harmful to others. Responsible marijuana smokers are not the problem and it is time to stop arresting them.

The ultimate goal of NORML and The NORML Foundation is to end the criminal prohibition of marijuana. We do not believe otherwise law-abiding citizens who smoke marijuana should be arrested and treated like criminals. Adults should be permitted to smoke marijuana in private. Federal prohibition of marijuana should be abolished and the states should be encouraged to experiment with different models of decriminalization.

Please read further so that you may know and exercise your rights.

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Basics

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Cannabis and Driving: A Scientifc and Rational Review

Enforcement
Read NORML's response to the Drug Czar's letter to prosecutors.

NORML's Testimony Before State and Federal Legislatures
See what NORML has been telling elected officials and be sure to make your own voice heard.

- **Recent Additions:**

Testimony in Favor of SJR 14[PDF] (CA)
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Resources

Medical Marijuana
Marijuana's therapeutic uses are well-documented in modern scientific literature. Find information regarding nausea, appetite stiumulation, weight gain, glaucoma, spinal cord injuries, multiple sclerosis, migraine headaches, depression, seizures, insomnia, chronic pain and more. Also see NORML's Medical Use section.

Hemp
Access studies and information on the Industrial Use of marijuana.

European Drug Laws
Get a comprehensive overview of Europe's approach to marijuana use as a health issue.

NORML Freedom of Information Act Requests
See how NORML is keeping an eye on the government's drug enforcement activities.

Legal Brief Bank
Research marijuana-related decisions on a variety of subjects.

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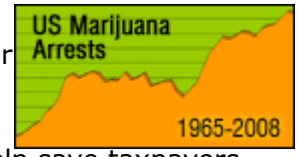
Marijuana Decriminalization
Since the 1970s, more than a dozen government-appointed commissions have examined the effects of marijuana, and made public policy recommendations regarding its use.

Marijuana and Health
Learn the health impacts of marijuana.

Marijuana Arrests
See who's getting busted and who's not. Get arrest data on your state or county.



The Economics of Marijuana and Marijuana Prohibition
"Follow the money," and find out how loosening marijuana laws could help save taxpayers money.

Driving and Marijuana
Read NORML's position on marijuana and driving, and research the effect of marijuana usage on psychomotor skills.

Marijuana as a Cash Crop
Remarkably, despite being illegal for nearly 65 years, domestically grown marijuana is one of the top cash crops in the U.S. Check your state's estimated crop output.

Drug Testing
Read reports on testing. For further information see NORML's Drug Testing section.

Marijuana Related Surveys and Polling Information
Check the state of public awareness on marijuana law reform.

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- Marijuana May Extend Life Expectancy Of Lou Gehrig's Disease Patients, Study Says
- Patients With Schizophrenia Report Subjective Benefits From Marijuana, Study Says
- Marijuana Compound Halts Spread Of Biliary Tract Cancers, Study Says
- Urine Testing Unlikely To Identify Drugged Employees Or Reduce Workplace Accidents, Study Says
- CBS Polls Finds Majority Of Western Voters, Californians, Back Legalization

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- US CA: Column: Marijuana's Future Has An Upscale Look
- CN ON: PUB LTE: Opposition To Marijuana Study An Example Of Warped Logic
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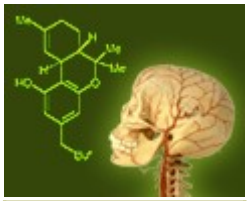
Medical Marijuana Reports



Health Reports

Marijuana's therapeutic uses are well-documented in modern scientific literature. The studies indicate that marijuana provides symptomatic relief for a number of medical conditions, including nausea and vomiting, stimulating appetite, promoting weight gain, and diminishing intraocular pressure from glaucoma. There is also evidence that smoked marijuana and/or THC reduces muscle spasticity from spinal cord injuries and multiple sclerosis, and diminishes tremors in multiple sclerosis patients. Patients and physicians have also reported that smoked marijuana provides relief from migraine headaches, depression, seizures, insomnia and chronic pain, among other conditions.

Reference materials on marijuana as medicine:

- Marinol vs. Natural Cannabis - Pros, Cons and Options for Patients PDF
- NORML's Statement on the Medical Use of Marijuana - Science Supports Amending Federal Law PDF
- National Institute of Health's Workshop on the Utility of Medical Marijuana (1998)
- Drug Sense's Review of Medical Marijuana Studies and Reports (1997)
- Institute of Medicine's "Marijuana and Medicine: Assessing the Science Base" (1999) (book no. 0309071550)
- NORML's Review of Human Studies and Medical Marijuana (1996) PDF
- Landmark Legal Case: NORML v. DEA
- Guest Editorial in the Journal of American Medical Association, by L. Grinspoon, M.D. "Marijuana as Medicine -- A Plea for Reconsideration" (June 21, 1995) PDF
- News magazine article, "The more things change, the more they stay the same..." PDF
- Newt Gingrich's Letter Supporting Medical Marijuana, published in the Journal of American Medicine (JAMA, 1982) PDF
- Institute of Medicine Report Endorsing Medical Marijuana (1982) PDF
- New England Journal of Medicine's Endorsement of Medical Marijuana

National Institute of Health's Workshop on the Utility of Medical Marijuana (1998)

Report to the Director,
National Institutes of Health,
by the Ad Hoc Group of Experts

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 Download **WordPerfect 6.1** version of "Workshop on the Medical Utility of Marijuana."

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 ( ^{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?

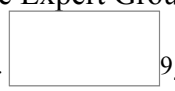
Question 4 - What special issues have to be considered in conducting clinical trials of the therapeutic uses of marijuana?

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®, or  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.

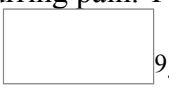
The Expert Group noted that even for conditions where good therapies are available, some patients develop adverse reactions or are nonresponders. The needs of this subset of nonresponders must be considered in the deliberations on testing marijuana as a possible therapeutic agent.

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  ^{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[(1)]
- Nausea and vomiting following anticancer therapy[(2)]
- 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).

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.

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1. 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.

2. 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.

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 ( ^{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?

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 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_{21} 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 (^{9}-THC) (Mechoulam 1973; Mechoulam et al. 1991). THC in the scientific literature is termed ^{9}-THC or ^{1}-THC depending on whether the pyran or monoterpinoid 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 1986*a)*.

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 1986*a*, 1988*a*).

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-  ^{9}-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 1988*a*; 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 1986*a*, 1988*a*). 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. 1992*a*).

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 1986*a*, 1988*a*; 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 1986*a*, 1988*a*; 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 1986*a*, 1988*a*; 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 1988*a*). 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 1986*a*). 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. 1984*a*). 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 1988*b*). 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.

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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-tetrahydrocannibinol (^{9}-THC) is equipotent to morphine in rats (tailflick test), and more potent than morphine in mice (hotplate test), other studies showed that ^{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/^{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 ^{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 ^{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/^{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 ^{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 ^{9}-THC over a 6-hour observation period (Noyes et al. 1975*a*). 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 ^{9}-THC and 60 and 120 mg of codeine over a 7-hour observation period (Noyes et al. 1975*b*). Codeine 120 mg

and ^{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 ^{9}-THC, 10 mg, peaked at the third hour. As in the first study, the 20 mg dose of ^{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. 1975*b*). Mental clouding, thinking impairment, disconnected thought, disorientation, slurred speech, and impaired memory were much more prominent after both doses of ^{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 ^{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 ^{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.

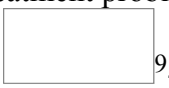
2. What are the major unanswered scientific questions?

Since oral ^{9}-THC has some analgesic activity, it is highly likely that smoked marijuana has some analgesic activity in some kinds of clinical pain. Because ^{9}-THC from smoked marijuana is absorbed directly into the pulmonary circulation, this route of administration results in a ^{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 ^{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 ^{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  ^{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/  ^{9}-THC might be as an adjuvant when added to a regimen of standard analgesics.

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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.

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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.

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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.

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.

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Appetite Stimulation/Cachexia

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 (^{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:

Does smoking marijuana increase total energy intake in patients with catabolic illness?

Does marijuana use alter energy expenditure?

Does marijuana use alter body weight, and to what extent?

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.

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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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UNITED STATES DEPARTMENT OF JUSTICE
Drug Enforcement Administration
In The Matter Of
MARIJUANA RESCHEDULING PETITION
Docket No. 86-22
OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF ADMINISTRATIVE LAW JUDGE
FRANCIS L. YOUNG, Administrative Law Judge
DATED: SEPTEMBER 6, 1988

UNITED STATES DEPARTMENT OF JUSTICE
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FRANCIS L. YOUNG, Administrative Law Judge

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DATED: SEP 6 1988

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UNITED STATES DEPARTMENT OF JUSTICE
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OPINION AND RECOMMENDED RULING, FINDINGS OF FACT, CONCLUSIONS OF LAW AND DECISION OF ADMINISTRATIVE LAW JUDGE.

1.

INTRODUCTION

This is a rulemaking pursuant to the Administrative Procedure Act, 5 U.S.C. § 551, et seq., to determine whether the marijuana plant (Cannabis sativa L) considered as a whole may lawfully be transferred from Schedule I to Schedule II of the schedules established by the Controlled Substances Act (the Act), 21 U.S.C. § 801, et seq. None of the parties is seeking to "legalize" marijuana generally or for recreational purposes. Placement in Schedule II would mean, essentially, that physicians in the United States would not violate Federal law by prescribing marijuana for their patients for legitimate therapeutic purposes. It is contrary to Federal law for physicians to do this as long as marijuana remains in Schedule I. This proceeding had its origins

on May 18, 1972 when the National Organization for the Reform of Marijuana Laws (NORML) and two other groups submitted a petition to the Bureau of Narcotics and Dangerous Drugs (BNDD) [footnote 1], predecessor

1 The powers and authority granted by the Act to the Attorney General were delegated to the Director of BNDD and subsequently to the Administrator of DEA. 28 C.F.R. § 0.100, et seq.

agency to the Drug Enforcement Administration (DEA or the Agency), asking that marijuana be removed from Schedule I and freed of all controls entirely, or be transferred from Schedule I to Schedule V where it would be subject to only minimal controls. The Act by its terms had placed marijuana in Schedule I thereby declaring, as a matter of law that it had no legitimate use in therapy in the United States and subjecting the substance to the strictest level of controls. The Act had been in effect for just over one year when NORML submitted its 1972 petition.

On September 1, 1972 the Director of BNDD announced his refusal to accept the petition for filing, stating that he was not authorized to institute proceedings for the action requested because of the provisions of the Single Convention on Narcotic Drugs, 1961. NORML appealed this action to the United States Court of Appeals for the District of Columbia Circuit. The court held that the Director had erred in rejecting the petition without "a reflective consideration and analysis," observing that the Director's refusal "was not the kind of agency action that promoted the kind of interchange and refinement of views that is the lifeblood of a sound administrative process." NORML v. Ingersoll, 162 U.S. App. D.C. 67, 497 F.2d 654, 659 (1974). The court remanded the matter in January 1974 for further proceedings not inconsistent with its opinion, "to be denominated a consideration on the merits." Id.

A three-day hearing was held at DEA [footnote 2] by Administrative Law Judge Lewis Parker in January 1975. The judge found in NORML's favor on several issues but the Acting Administrator of DEA entered a final order denying NORML's petition "in all respects." NORML again petitioned the court for review. Finding fault

2 DEA became the successor agency to BNDD in a reorganization carried out pursuant to Reorganization Plan No. 2 of 1973, eff. July 1, 1973. 38 Fed Reg. 15932 (1973).

with DEA's final order the court again remanded for further proceedings not inconsistent with its opinion. NORML v. DEA, 182 U.S. App. D.C. 114, 559 F.2d 735 (1977). The Court directed the then-Acting Administrator of DEA to refer NORML's petition to the Secretary of the Department of Health, Education and Welfare (HEW) for findings and, thereafter, to comply with the rulemaking procedures outlined in the Act at 21 U.S.C. § 811 (a) and (b).

On remand the Administrator of DEA referred NORML's petition to HEW for scientific and medical evaluation. On June 4, 1979 the Secretary of HEW advised the Administrator of the results of the HEW evaluation and recommended that marijuana remain in Schedule I. Without holding any further hearing the Administrator of DEA proceeded to issue a final order ten days later denying NORML's petition and declining to initiate proceedings to transfer marijuana from Schedule I. 44 Fed. Reg. 36123 (1979). NORML went back to the Court of Appeals.

When the case was called for oral argument there was discussion of the then-present status of the matter. DEA had moved for a partial remand. The court found that "reconsideration of all the issues in this case would be appropriate" and again remanded it to DEA, observing: "We regrettably find it necessary to remind respondents [DEA and HEW] of an agency's obligation on remand not to 'do anything which is contrary to either the letter or spirit of the mandate construed in the light of the opinion of [the] court deciding the case.'" (Citations omitted.) NORML v. DEA, et al., No. 79.1660, United States Court of Appeals for the District of Columbia Circuit, unpublished order filed October 16, 1980. DEA was directed to refer all the substances at issue to the Department of Health and Human Services (HHS), successor agency to HEW, for scien-

tific and medical findings and recommendations on scheduling. DEA did so and HHS has responded. In a letter dated April 1, 1986 the then-Acting Deputy Administrator of DEA requested this administrative law judge to commence hearing procedures as to the proposed rescheduling of marijuana and its components.

After the Judge conferred with counsel for NORML and DEA, a notice was published in the Federal Register on June 24, 1986 announcing that hearings would be held on NORML's petition for the rescheduling of marijuana and its components commencing on August 21, 1986 and giving any interested person who desired to participate the opportunity to do so. 51 Fed. Reg. 22946 (1986).

Of the three original petitioning organizations in 1972 only NORML is a party to the present proceeding. In addition the following entities responded to the Federal Register notice and have become parties, participating to varying degrees: the Alliance for Cannabis Therapeutics (ACT), Cannabis Corporation of America (CCA) and Carl Eric Olsen, all seeking transfer of marijuana to Schedule II; the Agency, National Federation of Parents for Drug free Youth (NFP) and the International Association of Chiefs of Police (IACP), all contending that marijuana should remain in Schedule I.

Preliminary prehearing sessions were held on August 21 and December 5, 1986 and on February 20, 1987. [footnote 3] During the preliminary stages, on January 20, 1987, NORML filed an amended petition for rescheduling. This new petition abandoned NORML's previous requests for the complete descheduling of marijuana or rescheduling to Schedule V. It asks only that marijuana be placed in Schedule II.

At a prehearing conference on February 20, 1987 this amended petition was

3 Transcripts of these three preliminary prehearing sessions are included in the record.

discuss. [footnote 4] All Parties present stipulated, for the purpose of this proceeding, that marijuana has a high potential for abuse and that abuse of the marijuana plant may lead to severe psychological or physical dependence. They then agreed that the principal issue in this proceeding would be stated thus:

Whether the marijuana plant, considered as a whole, [footnote 5] may

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4 The transcript of this prehearing conference and of the subsequent hearing session comprise 15 volumes numbered as follows:

Vol. I	-	Prehearing Conference, October 16, 1987
Vol. II	-	Cross Examination, November 19, 1987
Vol. III	-	Cross Examination, December 8, 1987
Vol. IV	-	Cross Examination, December 9, 1987
Vol. V	-	Cross Examination, January 5, 1988
Vol. VI	-	Cross Examination, January 6, 1988
Vol. VII	-	Cross Examination, January 7, 1988
Vol. VIII	-	Cross Examination, January 26, 1988
Vol. IX	-	Cross Examination, January 27, 1988
Vol. X	-	Cross Examination, January 28, 1988
Vol. XI	-	Cross Examination, January 29, 1988
Vol. XII	-	Cross Examination, February 2, 1988
Vol. XIII	-	Cross Examination, February 4, 1988
Vol. XIV	-	Cross Examination, February 5, 1988
Vol. XV	-	Oral Argument, June 10, 1988

Pages of the transcript are cited herein by volume and page, e.g. "Tr. V-96"; "G-" identifies an Agency exhibit.

5 Throughout this opinion the term marijuana" refers to "the marijuana plant, consider as a whole".

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lawfully be transferred from Schedule I to Schedule II of the schedules established by the Controlled Substances Act.

Two subsidiary issues were agreed on, as follows:

1. Whether the marijuana plant has a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions.

2. Whether there is a lack of accepted safety for use of the marijuana plant under medical supervision.

As stated above, the parties favoring transfer from Schedule I to Schedule II are NORML, ACT, CCA and Carl Eric Olsen. Those favoring retaining marijuana in Schedule I are the Agency, NFP and IACP.

During the Spring and Summer of 1987 the parties identified their witnesses and put the direct examination testimony of each witness in writing in affidavit form. Copies of these affidavits were exchanged. Similarly, the parties assembled their proposed exhibits and exchanged copies. Opportunity was provided for each party to submit objections to the direct examination testimony and exhibits proffered by the others. The objections submitted were considered by the administrative law judge and ruled on. The testimony and exhibits not excluded were admitted into the record. Thereafter hearing sessions were held at which witnesses were subjected to cross-examination. These sessions were held in New Orleans, Louisiana on November 18 and 19, 1987; in San Francisco, California on December 8 and 9, 1987; and in Washington, D.C. on January 5 through 8 and 26 through 29, and on February 2, 4 and 5, 1988. The parties have submitted proposed findings and conclusions and briefs. Oral arguments were heard by the judge on June 10, 1988 in Washington.

II.

RECOMMENDED RULING

It is recommended that the proposed findings and conclusions submitted by the parties to the administrative law judge be rejected by the Administrator except to the extent they are included in those hereinafter set forth; for the reason that they are irrelevant or unduly repetitious or not supported by a preponderance of the evidence. 21 C.F.R. § 1316.65(a)(1).

III.

ISSUES

As noted above, the agreed issues are as follows:

Principle issue:

Whether the marijuana plant, considered as a whole, may lawfully be transferred from Schedule I to Schedule II of the schedules established by the Controlled Substances Act.

Subsidiary issues:

1. Whether the marijuana plant has a currently accepted medical use in treatment in the United States, or a currently accepted medical use with severe restrictions.

2. Whether there is a lack of accepted safety for use of the marijuana plant under medical supervision.

IV.

STATUTORY REQUIREMENTS FOR SCHEDULING

The Act provides (21 U.S.C. § 812(b)) that a drug or other substance may not be placed in any schedule unless certain specified findings are made with respect to it. The findings required for Schedule I and Schedule II are as follows:

> Schedule I. -
>
> (A) The drug or other substance has a high potential for abuse.
>
> (B) The drug or other substance has no currently accepted medical use in treatment in the United States.
>
> (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.
>
> Schedule II. -
>
> (A) The drug or other substance has a high potential for abuse.
>
> (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
>
> (C) Abuse of the drug or other substances [sic] may lead to severe psychological or physical dependence.

As noted above the parties have stipulated, for the purpose of this proceeding, that marijuana has a high potential for abuse and that abuse of it may lead to severe psychological or physical dependence. Thus the dispute between the two sides in this proceeding is narrowed to whether or not marijuana has a currently accepted medical use in treatment in the United States, and whether or not there is a lack of accepted safety for use of marijuana under medical supervision.

The issues as framed here contemplate marijuana's being placed only in

Schedule I or Schedule II. The criteria for placement in any of the other three schedules established by the Act are irrelevant to this proceeding.

V.

ACCEPTED MEDICAL USE IN TREATMENT

- CHEMOTHERAPY

With respect to whether or not marijuana has a "currently accepted medical use in treatment in the United States" for chemotherapy patients, the record shows the following facts to be uncontroverted.

Findings Of Fact

1. One of the most serious problems experienced by cancer patients undergoing chemotherapy for their cancer is severe nausea and vomiting caused by their reaction to the toxic (poisonous) chemicals administered to them in the course of this treatment. This nausea and vomiting at times becomes life threatening. The therapy itself creates a tremendous strain on the body. Some patients cannot tolerate the severe nausea and vomiting and discontinue treatment. Beginning in the 1970's there was considerable doctor-to-doctor communication in the United States concerning patients known by their doctors to be surreptitiously using marijuana with notable success to overcome or lessen their nausea and vomiting.

2. Young patients generally achieve better control over nausea and vomiting from smoking marijuana than do older patients, particularly when the older patient has not been provided with detailed information on how to smoke marijuana.

3. Marijuana cigarettes in many cases are superior to synthetic THC capsules in reducing chemotherapy-induced nausea and vomiting. Marijuana

cigarettes have an important, clear advantage over synthetic THC capsules in that the natural marijuana is inhaled and generally takes effect more quickly than the synthetic capsule which is ingested and must be processed through the digestive system before it takes effect.

4. Attempting to orally administer the synthetic THC capsule to a vomiting patient presents obvious problems - it is vomited right back up before it can have any effect.

5. Many physicians, some engaged in medical practice and some teaching in medical schools, have accepted smoking marijuana as effective in controlling or reducing the severe nausea and vomiting (emesis) experienced by some cancer patients undergoing chemotherapy for cancer.

6. Such physicians include board-certified internists, oncologists and psychiatrists. (Oncology is the treatment of cancer through the use of highly toxic chemicals, or chemotherapy.)

7. Doctors who have come to accept the usefulness of marijuana in controlling or reducing emesis resulting from chemotherapy have dose so as the result of reading reports of studies and anecdotal reports in their professional literature, and as the result of observing patients and listening to reports directly from patients.

8. Some cancer patients who have acknowledged to doctors that they smoke marijuana for emesis control have indicated in their discussions that, although they may have first smoked marijuana recreationally, they accidentally found that doing so helped reduce the emesis resulting from their chemotherapy. They consistently indicated that they felt better and got symptomatic relief from the intense nausea and vomiting caused by the chemotherapy. These patients

were no longer simply getting high, but were engaged in medically

treating their illness, albeit with an illegal substance. Other chemotherapy patients began smoking marijuana to control their emesis only after hearing reports that the practice had proven helpful to others. Such patients had not smoked marijuana recreationally.

9. This successful use of marijuana has given many cancer chemotherapy patients a much more positive outlook on their overall treatment, once they were relieved of the debilitating, exhausting and extremely unpleasant nausea and vomiting previously resulting from their chemotherapy treatment.

10. In about December 1977 the previously underground patient practice of using marijuana to control emesis burst into the public media in New Mexico when a young cancer patient, Lynn Pearson, began publicly to discuss his use of marijuana. Mr. Pearson besought the New Mexico legislature to pass legislation making marijuana available legally to seriously ill patients whom it might help. As a result, professionals in the public health sector in New Mexico more closely examined how marijuana might be made legally available to assist in meeting what now openly appeared to be a widely recognized patient need.

11. In many cases doctors have found that, in addition to suppressing nausea and vomiting, smoking marijuana is a highly successful appetite stimulant. The importance of appetite stimulation in cancer therapy cannot be overstated. Patients receiving chemotherapy often lose tremendous amounts of weight. They endanger their lives because they lose interest in food and in eating. The resulting sharp reduction in weight may well affect their prognosis. Marijuana smoking induces some patients to eat. The benefits are obvious, doctors have found. There is no significant loss of weight. Some patients will gain weight.

This allows them to retain strength and makes them better able to fight the cancer. Psychologically, patients who can continue to eat even while receiving chemotherapy maintain a balanced outlook and are better able to cope with their disease and its treatment, doctors have found.

12. Synthetic anti-emetic agents have been in existence and utilized for a number of years. Since about 1980 some new synthetic agents have been developed which appear to be more effective in controlling and reducing chemotherapy-induced nausea and vomiting than were some of those available in the 1970's. But marijuana still is found more effective for this purpose in some people than any of the synthetic agents, even the newer ones.

13. By the late 1970's in the Washington, D.C. area there was a growing recognition among health care professionals and the public that marijuana had therapeutic value in reducing the adverse effects of some chemotherapy treatments. With this increasing public awareness came increasing pressure from patients on doctors for information about marijuana and its therapeutic uses. Many patients moved into forms of unsupervised self-treatment. While such self-treatment often proved very effective, it has certain hazards, ranging from arrest for purchase or use of an illegal drug to possibly serious medical complications from contaminated sources or adulterated materials. Yet, some patients are willing to run these risks to obtain relief from the debilitating nausea and vomiting caused by their chemotherapy treatments.

14. Every oncologist known to one Washington, D.C. practicing internist and board-certified oncologist has had patients who used

marijuana with great success to prevent or diminish chemotherapy-induced nausea and vomiting. Chemotherapy patients reporting directly to that Washington doctor that they

have smoked marijuana medicinally vomit less and eat better than patients who do not smoke it. By gaining control over their severe nausea and vomiting these patients undergo a change of mood and have a better mental outlook than patients who, using the standard anti-emetic drugs, are unable to gain such control.

15. The vomiting induced by chemotherapeutic drugs may last up to four days following the chemotherapy treatment. The vomiting can be intense, protracted and, in some instances, is unendurable. The nausea which follows such vomiting is also deep and prolonged. Nausea may prevent a patient from taking regular food or even much water for periods of weeks at a time.

16. Nausea and vomiting of this severity degrades the quality of life for these patients, weakening them physically, and destroying the will to fight the cancer. A desire to end the chemotherapy treatment in order to escape the emesis can supersede the will to live. Thus the emesis, itself, can truly be considered a life-threatening consequence of many cancer treatments. Doctors have known such cases to occur. Doctors have known other cases where marijuana smoking has enabled the patient to endure, and thus continue, chemotherapy treatments with the result that the cancer has gone into remission and the patient has returned to a full, active satisfying life.

17. In San Francisco chemotherapy patients were surreptitiously using marijuana to control emesis by the early 1970's. By 1976 virtually every young cancer patient receiving chemotherapy at the University of California in San Francisco was using marijuana to control emesis with great success. The use of marijuana for this purpose had become generally accepted by the patients and increasingly by their physicians as a valid and effective form of treatment. This was particularly true for younger cancer patients, somewhat less common for

older ones. By 1979 about 25% to 30% of the patients seen by one San Francisco oncologist were using marijuana to control emesis, about 45 to 50 patients per year. Such percentages and numbers vary from city to city. A doctor in Kansas City who sees about 150 to 200 new cancer patients per year found that over the 15 years 1972 to 1987 about 5% of the patients he saw, or a total of about 75, used marijuana medicinally.

18. By 1987 marijuana no longer generated the intense interest in the world of oncology that it had previously, but it remains a viable tool, commonly employed, in the medical treatment of chemotherapy patients. There has evolved an unwritten but accepted standard of treatment within the community of oncologists in the San Francisco, California area which readily accepts the use of marijuana.

19. As of the Spring of 1987 in the San Francisco area, patients receiving chemotherapy commonly smoked marijuana in hospitals during their treatments. This in-hospital use, which takes place in rooms behind closed doors, does not bother staff, is expected by

physicians and welcomed by nurses who, instead of having to run back and forth with containers of vomit, can treat patients whose emesis is better controlled than it would be without marijuana. Medical institutions in the Bay area where use of marijuana obtained on the streets is quite common, although discrete, include the University of California at San Francisco Hospital, the Mount Zion Hospital and the Franklin Hospital. In effect, marijuana is readily accepted throughout the oncologic community in the bay area for its benefits in connection with chemotherapy. The same situation exists in other large metropolitan areas of the United States.

20. About 50% of the patients seen by one San Francisco oncologist

during the year 1987 were smoking marijuana medicinally. This is about 90 to 95 individuals. This number is higher than during the previous ten years due to the nature of this physician's practice which includes patients from the "tenderloin" area of San Francisco, many of whom are suffering from AIDS-related lymphosarcoma. These patients smoke marijuana to control their nausea and vomiting, not to "get high." They self-titrate, i.e., smoke the marijuana only as long as needed to overcome the nausea, to prevent vomiting.

21. The State of New Mexico set up a program in 1978 to make marijuana available to cancer patients pursuant to an act of the State legislature. The legislature had accepted marijuana as having medical use in treatment. It overwhelmingly passed this legislation so as to make marijuana available for use in therapy, not just for research. Marijuana and synthetic THC were given to patients, administered under medical supervision, to control or reduce emesis. The marijuana was in the form of cigarettes obtained from the Federal government. The program operated from 1979 until 1986, when funding for it was terminated by the State. During those seven years about 250 cancer patients in New Mexico received either marijuana cigarettes or THC. Twenty or 25 physicians in New Mexico sought and obtained marijuana cigarettes or THC for their cancer patients during that period. All of the oncologists in New Mexico accepted marijuana as effective for some of their patients. At least ten hospitals involved in this program in New Mexico, in which cancer patients smoked their marijuana cigarettes. The hospitals accepted this medicinal marijuana smoking by patients. Voluminous reports filed by the participating physicians make it clear that marijuana is a highly effective anti-emetic substance. It was found in the New Mexico program to be far superior to the best available conventional

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anti-emetic drug, compazine, and clearly superior to synthetic THC pills. More than 90% of the patients who received marijuana within the New Mexico program reported significant or total relief from nausea and vomiting. Before the program began cancer patients were surreptitiously smoking marijuana in New Mexico to lessen or control their emesis resulting from chemotherapy treatments. They reported to physicians that it was successful for this purpose. Physicians were aware that this was going on.

22. In 1978 the Louisiana legislature became one of the first-State legislatures in the nation to recognize the efficacy of marijuana in controlling emesis by enacting legislation intended to make marijuana available by prescription for therapeutic use by chemotherapy patients.

This enactment shows that there was widespread acceptance in Louisiana of the therapeutic value of marijuana. After a State Marijuana Prescription Review Board was established, pursuant to that legislation, it became apparent that, because of Federal restrictions, marijuana could be obtained legally only for use in cumbersome, formal research programs. Eventually a research program was entered into by the State, utilizing synthetic THC, but without much enthusiasm, since most professionals who had wanted to use marijuana clinically, to treat patients, had neither the time, resources nor inclination to get involved in this limited, formal study. The original purpose of the Louisiana legislation was frustrated by the Federal authorities. Some patients, who had hoped to obtain marijuana for medical use legally after enactment of the State legislation, went outside the law and obtained it illicitly. Some physicians in Louisiana accept marijuana as having a distinct medical value in the treatment of the nausea and vomiting associated with certain types of chemotherapy treatments.

23. In 1980 the State of Georgia enacted legislation authorizing a therapeutic research program for the evaluation of marijuana as a medically recognized therapeutic substance. Its enactment was supported by letters from a number of Georgia oncologist and other Georgia physician, including the Chief of oncology at Grady Hospital and staff oncologist at Emory University Medical Clinic. Sponsors of the legislation originally intended the enactment of a law making marijuana available for clinical, therapeutic use by patients. The bill was referred to as the "Marijuana-as-Medicine" bill. The final legislation was crafted, however, of necessity, merely to set up a research program in order to obtain marijuana from the one legitimate source available - the Federal Government, which would not make the substance available for any other purpose other than conducting a research program. The act was passed by an overwhelming majority in the lower house of the legislature and unanimously in the Senate. In January 1983 an evaluation of the program, which by then had 44 evaluable marijuana smoking patient-participants, accepted marijuana smoking as being an effective anti-emetic agent.

24. In Boston, Massachusetts in 1977 a nurse in a hospital suggested to a chemotherapy patient, suffering greatly from the therapy and at the point of refusing further treatment, that smoking marijuana might help relieve his nausea and vomiting. The patient's doctor, when asked about it later, stated that many of his younger patients were smoking marijuana. Those who did so seemed to have less trouble with nausea and vomiting. The patient in question obtained some marijuana and smoked it, in the hospital, immediately before his next chemotherapy treatment. Doctors, nurses, and orderlies coming into the room as he finished smoking realized what the patient had been doing. None of them

made any comment. The marijuana was completely successful with this patient, who accepted it as effective in controlling his nausea and vomiting. Instead of being sick for weeks following chemotherapy, and having trouble going to work, as had been the case, the patient was ready to return to work 48 hours after that chemotherapy treatment. The patient thereafter always smoked marijuana, in the hospital, before chemotherapy. The doctors were aware of it, openly approved of it and encouraged him to continue. The patient resumed eating regular meals and

regained lost eight, his mood improved markedly, he became more active and outgoing and began doing things together with his wife that he had not done since beginning chemotherapy.

25. During the remaining two years of this patient's life, before his cancer ended it, he came to know other cancer patients who were smoking marijuana to relieve the adverse effects of their chemotherapy. Most of these patients had learned about using marijuana medically from their doctors who, having accepted its effectiveness, subtly encouraged them to use it.

26. A Boston psychiatrist and professor, who travels about the country, has found a minor conspiracy to break the law among oncologists and nurses in every oncology center he has visited to let patients smoke marijuana before and during cancer chemotherapy. He has talked with dozens of these health care oncologists who encourage their patients to do this and who regard this as an accepted medical usage of marijuana. He has known nurses who have obtained marijuana for patients unable to obtain it for themselves.

27. A cancer patient residing in Beaverton, Michigan smoked marijuana medicinally in the nearby hospital where he was undergoing chemotherapy from early 1979 until he died of his cancer in October of that year. He smoked it in

his hospital room after his parents made arrangements with the hospital for him to do so. Smoking marijuana controlled his post-chemotherapy nausea and vomiting, enabled him to eat regular-meals again with his family, and he became outgoing and talkative. His parents accepted his marijuana smoking as effective and helpful. Two clergymen, among others, brought marijuana to this patient's home. Many people at the hospital supported the patient's marijuana therapy, none doubted its helpfulness or discouraged it. This patient was asked for help by other patients. He taught some who lived nearby how to form the marijuana cigarettes and properly inhale the smoke to obtain relief from nausea and vomiting. When an article about this patient's smoking marijuana appeared in a local newspaper, he and his family heard from many other cancer patients who were doing the same. Most of them made an effort to inform their doctors. Most Physicians who knew their patients smoked marijuana medicinally approved, accepting marijuana's therapeutic helpfulness in reducing nausea and vomiting.

28. In October 1979 the Michigan legislature enacted legislation whose underlying purpose was to make marijuana available therapeutically for cancer patients and others. The State Senate passed the bill 29-5, the House of Representatives 100-0. In March 1982 the Michigan legislature passed a resolution asking the Federal Congress to try to alter Federal policies which prevent physicians from prescribing marijuana for legitimate medical applications and prohibit its use in medical treatments.

29. In Denver, Colorado a teenage cancer patient has been smoking marijuana to control nausea and vomiting since 1986. He has done this in his hospital room both before and after chemotherapy. His doctor and hospital staff know he does this. The doctor has stated that he would prescribe marijuana for

this patient if it were legal to do so. Other patients in the Denver area smoke marijuana for the same purpose. This patient's doctor, and nurses with whom he comes in contact, understand that cancer patients smoke marijuana to reduce or control emesis. They accept it.

30. In late 1980 a three year old boy was brought by his parents to a hospital in Spokane, Washington. The child was diagnosed as having cancer. Surgery was performed. Chemotherapy was begun. The child became extremely nauseated and vomited for days after each chemotherapy treatment. He could not eat regularly. He lost strength. He lost weight. His body's ability to ward off common infections, other life-threatening infections, significantly decreased. Chemotherapy's after-effects caused the child great suffering. They caused his watching parents great suffering. Several standard, available anti-emetic agents were tried by the child's doctors. None of them succeeded in controlling his nausea or vomiting. Learning of the existence of research studies with THC or marijuana the parents asked the child's doctor to arrange for their son to be the subject of such a study so that he might have access to marijuana. The doctor refused, citing the volume of paperwork and record-keeping detail required in such programs and his lack of administrative personnel to handle it.

31. The child's mother read an article about marijuana smoking helping chemotherapy patients. She obtained some marijuana from friends. She baked cookies for her child with marijuana in them. She made tea for him with marijuana in it. When the child ate these cookies or drank this tea in connection with his chemotherapy, he did not vomit. His strength returned. He regained lost weight. His spirits revived. The parents told the doctors and nurses at the hospital of their giving marijuana to their child. None objected.

They all accepted smoking marijuana as effective in controlling chemotherapy induced nausea and vomiting. They were interested to see the results of the cookies.

32. Soon this child was riding a tricycle in the hallways of the Spokane hospital shortly after his chemotherapy treatments while other children there were still vomiting into pans, tied to intravenous bottles in an attempt to re-hydrate them, to replace the liquids they were vomiting up. Parents of some of the other patients asked the parents of this "lively" child how he seemed to tolerate his chemotherapy so well. They told of the marijuana use. Of those parents who began giving marijuana to their children, none ever reported back encountering any adverse side effects. In the vast majority of these cases, the other parents reported significant reduction in their children's vomiting and appetite stimulation as the result of marijuana. The staff, doctors and nurses at the hospital knew of this passing on of information about marijuana to other parents. They approved. They never told the first parents to hide their son's medicinal use of marijuana. They accepted the effectiveness of the cookies and the tea containing marijuana.

33. The first child's cancer went into remission. Then it returned and spread. Emotionally drained, the parents moved the family back to San Diego, California to be near their own parents. Their son was admitted to a hospital in San Diego. The parents informed the doctors, nurses and social workers there of their son's therapeutic use of marijuana. No one objected. The child's doctor in San Diego strongly supported the parent's giving marijuana to him. Here in California, as in Spokane, other parents noticed the striking difference between their

children after chemotherapy and the first child.

Other parents asked the parents of the first child about it, were told of the use of marijuana, tried it with their children, and saw dramatic improvement. They accepted its effectiveness. In the words of the mother of the first child: ". . . When your kid is riding a tricycle while his other hospital buddies are hooked up to IV needles, their heads hung over vomiting buckets, you don't need a federal agency to tell you marijuana is effective. The evidence is in front of you, so stark it cannot be ignored." [footnote 6]

34. There is at least one hospital in Tucson, Arizona where medicinal use of marijuana by chemotherapy patients is encouraged by the nursing staff and some physicians.

35. In addition to the physicians mentioned in the Findings above, mostly oncologists and other practitioners, the following doctors and health care professionals, representing several different areas of expertise, accept marijuana as medically useful in controlling or reducing emesis and testified to that effect in these proceedings:

a. George Goldstein, Ph.D., psychologist, Secretary of Health for the State of New Mexico from 1978 to 1983 and chief administrator in the implementation of the New Mexico program utilizing marijuana;

b. Dr. Daniel Danzak, psychiatrist and former head of the New Mexico program utilizing marijuana;

c. Dr. Tod Mikuriya, psychiatrist and editor of Marijuana: Medical Papers, a book presenting an historical perspective of marijuana's medical use;

d. Dr. Norman Zinberg, general psychiatrist and Professor of Psychiatry at Harvard Medical School since 1951;

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6 Affidavit of Janet Andrews, ACT rebuttal witness, par. 98.

e. Dr. John Morgan, psychopharmacologist, Board-certified in Internal Medicine, full Professor and Director of Pharmacology at the City University of New York;

f. Dr. Phillip Jobe, neuropsychopharmacologist with a practice in Illinois and former Professor of Pharmacology and Psychiatry at the Louisiana State University School of Medicine in Shreveport, Louisiana, from 1974 to 1984;

g. Dr. Arthur Kaufman, formerly a general practitioner in Maryland, currently Vice-President of a private medical consulting group involved in the evaluation of the quality of care of all the U.S. military hospitals throughout the world, who has had extensive experience in drug abuse treatment and rehabilitation programs;

h. Dr. J. Thomas Ungerleider, a full Professor of Psychiatry at the University of California in Los Angeles with extensive

experience in research on the medical use of drugs;

i. Dr. Andrew Weil, ethnopharmacologist, Associate Director of Social Perspectives in Medicine at the College of Medicine at the University of Arizona, with extensive research on medicinal plants; and

j. Dr. Lester Grinspoon, a practicing psychiatrist and Associate Professor at Harvard Medical School.

36. Certain law enforcement authorities have been outspoken in their acceptance of marijuana as an antiemetic agent. Robert T. Stephan, Attorney General of the State of Kansas, and himself a former cancer patient, said of chemotherapy in his affidavit in this record: "The treatment becomes a terror." His cancer is now in remission. He came to know a number of health care professionals whose medical judgment he respected. They had accepted marijuana

as having medical use in treatment. He was elected Vice President of the National Association of Attorneys General (NAAG) in 1983. He was instrumental in the adoption by that body in June 1983 of a resolution acknowledging the efficacy of marijuana for cancer and glaucoma patients. The resolution expressed the support of NAAG for legislation then pending in the Congress to make marijuana available on prescription to cancer and glaucoma patients. The resolution was adopted by an overwhelming margin. NAAG's President, the Attorney General of Montana, issued a statement that marijuana does have accepted medical uses and is improperly classified at present. The Chairman of NAAG's Criminal Law and Law Enforcement Committee, the Attorney General of Pennsylvania, issued a statement emphasizing that the proposed rescheduling of marijuana would in no way affect or impede existing efforts by law enforcement authorities to crack down on illegal drug trafficking.

37. At least one court has accepted marijuana as having medical use in treatment for chemotherapy patients. On January 23, 1978 the Superior Court of Imperial County, California issued orders authorizing a cancer patient to possess and use marijuana for therapeutic purposes under the direction of a physician. Another order authorized and directed the Sheriff of the county to release marijuana from supplies on hand and deliver it to that patient in such form as to be usable in the form of cigarettes.

38. During the period 1978-1980 polls were taken to ascertain the degree of public acceptance of marijuana as effective in treating cancer and glaucoma patients. A poll in Nebraska brought slightly over 1,000 responses - 83% favored making marijuana available by prescription, 12% were opposed, 5% were undecided. A poll in Pennsylvania elicited 1,008 responses - 83.1% favored availability by prescription, 12.2% were opposed, 4.7% were undecided. These

two surveys were conducted by professional polling companies. The Detroit Free Press conducted a telephone poll in which 85.4% of those responding favored access to marijuana by prescription. In the State of Washington the State Medical Association conducted a poll in which 80% of the doctors belonging to the Association favored controlled availability

of marijuana for medical purposes.

Discussion

From the foregoing uncontroverted facts it is clear beyond any question that many people find marijuana to have, in the words of the Act, an "accepted medical use in treatment in the United States" in effecting relief for cancer patients. Oncologists, physicians treating cancer patients, accept this. Other medical practitioners and researchers accept this. Medical faculty professors accept it. Nurses performing hands-on patient care accept it.

Patients accept it. As counsel for CCA perceptively pointed out at oral argument, acceptance by the patient is of vital importance. Doctors accept a therapeutic agent or process only if it "works" for the patient. If the patient does not accept, the doctor cannot administer the treatment. The patient's informed consent is vital. The doctor ascertains the patient's acceptance by observing and listening to the patient. Acceptance by the doctor depends on what he sees in the patient and hears from the patient. Unquestionably, patients in large numbers have accepted marijuana as useful in treating their emesis. They have found that it "works". Doctors, evaluating their patients, can have no basis more sound than that for their own acceptance.

Of relevance, also, is the acceptance of marijuana by state attorneys-

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general, officials whose primary concern is law enforcement. A large number of them have no fear that placing marijuana in Schedule II, thus making it available for legitimate therapy, will in any way impede existing efforts of law enforcement authorities to crack down on illegal drug trafficking.

The Act does not specify by whom a drug or substance must be "accepted [for] medical use in treatment" in order to meet the Act's "accepted" requirement for placement in Schedule II. Department of Justice witnesses told the Congress during hearings in 1970 preceding passage of the Act that "the medical Profession" would make this determination, that the matter would be "determined by the medical community." The Deputy Chief Counsel of BNDD, whose office had written the bill with this language in it, told the House subcommittee that "this basic determination . . . is not made by any part of the federal government. It is made by the medical community as to whether or not the drug has medical use or doesn't". [footnote 7]

No one would seriously contend that these Justice Department witnesses meant that the entire medical community would have to be in agreement on the usefulness of a drug or substance. Seldom, if ever, do all lawyers agree on a point of law. Seldom, if ever, do all doctors agree on a medical question. How many are required here? A majority of 51%? It would be unrealistic to attempt a plebiscite of all doctors in the country on such a question every time it arises, to obtain a majority vote.

In determining whether a medical procedure utilized by a doctor is actionable as malpractice the courts have adopted the rule what it is acceptable

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7 Drug Abuse Control Amendments - 1970: Hearings on H.R. 11701 and H.R. 13743 Before the Subcommittee on Public Health and Welfare of the House Committee on Interstate and Foreign Commerce, 91st Congress, 2d Sess. 678, 696, 718 (1970) (Statement of John E. Ingersoll, Director, BNDD).

for a doctor to employ a method of treatment supported by a respectable minority of physicians.

In Hood v. Phillips, 537 S.W. 2d 291 (1976) the Texas Court of Civil Appeals was dealing with a claim of medical malpractice resulting from a surgical procedure claimed to have been unnecessary. The court quoted from an Arizona court decision holding that

> a method of treatment, as espoused and used by . . . a respectable minority of physicians in the United States, cannot be said to be an inappropriate method of treatment or to be malpractice as a matter of law even though it has not been accepted as a proper method of treatment by the medical profession generally.

Ibid. at 294. Noting that the Federal District court in the Arizona case found a "respectable minority" composed of sixty-five physicians throughout the United States, the Texas court adopted as "the better rule" to apply in its case, that

> a physician is not guilty of malpractice where the method of treatment used is supported by a respectable minority of physicians.

Ibid.

In Chumbler v. McClure, 505 F.2d 489 (6th Cir. 1974) the Federal courts were dealing with a medical malpractice case under their diversity jurisdiction, applying Tennessee law, The Court of Appeals said:

> . . . The most favorable interpretation that may be placed on the testimony adduced at trial below is that there is a division of opinion in the medical profession regarding the use of Premarin in the Treatment of cerebral vascular insufficiency, and that Dr. McClure was alone among neurosurgeons in Nashville in using such therapy. The test for malpractice and for community standards is not to be determined solely by a plebiscite. Where two or more schools of thought exist among competent members of the medical profession concerning proper medical treatment for a given ailment, each of which is supported by responsible

> medical authority, it is not malpractice to be among the minority in a given city who follow: one of the accepted schools.

505 F.2d at 492 (Emphasis added). See, also, Leech v. Bralliar, 275 F.Supp. 897 (D.Ariz., 1967).

How do we ascertain whether there exists a school of thought supported by responsible medical authority, and thus "accepted"? We listen to the physicians.

> The court and jury must have a standard measure which they are to use in measuring the acts of a doctor to determine whether he exercised a reasonable degree of care and skill; they are not permitted to set up and use any arbitrary or artificial standard of measurement that the jury may wish to apply. The proper standard of measurement is to be established by testimony of physicians, for it is a medical question.

Hayes v. Brown, 133 S.E. 2d. 102 (Ga., 1963) at 105.

As noted above, there is no question but that this record shows a great many physicians, and others, to have "accepted" marijuana as having a medical use in the treatment of cancer patients' emesis. True, all physicians have not "accepted" it. But to require universal, 100% acceptance would be unreasonable. Acceptance by "a respectable minority" of physicians is all that can reasonably be required. The record here establishes conclusively that at least "a respectable minority" of physicians has "accepted" marijuana as having a "medical use in treatment in the United states." That others may not makes no difference.

The administrative law judge recommended this same approach for determining whether a drug has an "accepted medical use in treatment" in The Matter Of MDMA Scheduling, Docket No. 84-48. The Administrator, in his first final rule in that proceeding, issued on October 8, 1986 [footnote 8], declined to adopt this approach. He

8 51 Fed. Reg. 36552 (1986).

ruled, instead, that DEA's decision on whether or not a drug or other substance had an accepted medical use in treatment in the United States would be determined simply by ascertaining whether or not "the drug or other substance is lawfully marketed in the United States pursuant to the Federal Food, Drug and Cosmetic Act of 1938 . . . ." [footnote 9]

The United States Court of Appeals for the First Circuit held that the Administrator erred in so ruling. [footnote 10] That court vacated the final order of October 8, 1986 and remanded the matter of MDMA's scheduling for further consideration. The court directed that, on remand, the Administrator would not be permitted to treat the absence of interstate marketing approval by FDA as conclusive evidence on the question of accepted medical use under the Act.

In his third final rule [footnote 11] of the matter of the scheduling of MDMA the Administrator made a series of findings of fact as to MDMA, the drug there under consideration, with respect to the evidence in that record. On those findings he based his last final rule in the case. [footnote 12]

9 Ibid., at 36558.

10 Grinspoon v. Drug Enforcement Administration, 828 F.2d 881 (1st. Cir., 1987).

11 53 Fed. Reg. 5156 (1988). A second final rule had been issued on January 20, 1988. It merely removed MDMA from Schedule I pursuant to the mandate of the Court of Appeals which had voided the first final rule placing it there. Subsequently the third final rule was issued, without any further hearings, again placing MDMA in Schedule I. There was no further appeal.

12 In neither the first nor the third final rule in the MDMA case does the Administrator take any cognizance of the statements to the Congressional committee by predecessor Agency officials that the determination as to "accepted medical use in treatment" is to be made by the medical community and not by any part of the federal government. See page 27, above. It is curious that the administrator makes no effort whatever to show how the BNDD representatives were mistaken or to explain why he now has abandoned their interpretation. They wrote that language into the original bill.

That third final rule dealing with MDMA is dealing with a synthetic, "simple", "single-action" drug. What might be appropriate criteria for a "simple" drug like MDMA may not be appropriate for a "complex" substance with a number of active components. The criteria applied to MDMA, a synthetic drug, are not appropriate for application to marijuana, which is a natural plant substance.

The First Circuit Court of Appeals in the MDMA case told the Administrator that he should not treat the absence of FDA interstate marketing approval as conclusive evidence of lack of currently accepted medical use. The court did not forbid the Administrator from considering the absence of FDA approval as a factor when determining the existence of accepted medical use. Yet on remand, in his third final order, the Administrator adopted by reference 18 of the numbered findings he had made in the first final order. Each of these findings had to do with requirements imposed by FDA for approval of a new drug application (NDA) or of an investigational new drug exemption (IND). These requirements deal with data resulting from controlled studies and scientifically conducted investigations and test.

Among those findings incorporated into the third final MDMA order from the first, and relied on by the Administrator, was the determination and recommendation of the FDA that the drug there in question was not "accepted". In relying on the FDA's action the Administrator apparently overlooked the fact that the FDA clearly stated that it was interpreting "accepted medical use" in the Act as being equivalent to receiving FDA approval for lawful marketing under the FDCA. Thus the Administrator accepted as a basis for his MDMA third final rule the FDA recommendation which was based upon a statutory interpretation which the Court

of Appeals had condemned.

The Administrator in that third final rule made a series of further findings. Again, the central concern in these findings was the content of test results and the sufficiency or adequacy of studies and scientific reports. A careful reading of the criteria considered in the MDMA third

final order reveals that the Administrator was really considering the question: Should the drug be accepted for medical use?; rather than the question: Has the drug been accepted for medical use? By considering little else but scientific test results and reports the Administrator was making a determination as to whether or not, in his opinion, MDMA ought to be accepted for medical use in treatment.

The Agency's arguments in the present case are to the same effect. In a word, they address the wrong question. It is not for this Agency to tell doctors whether they should or should not accept a drug or substance for medical use. The statute directs the Administrator merely to ascertain whether, in fact, doctors have done so.

The MDMA third final order mistakenly looks to FDA criteria for guidance in choosing criteria for DEA to apply. Under the Food, Drug and Cosmetic Act the FDA is deciding - properly, under that statute - whether a new drug should be introduced into interstate commerce. Thus it is appropriate for the FDA to rely heavily on test results and scientific inquiry to ascertain whether a drug is effective and whether it is safe. The FDA must look at a drug and pass judgment on its intrinsic qualities. The DEA, on the other hand, is charged by 21 U.S.C. § 812(b)(1)(B) and (2)(B) with ascertaining what it is that other people have done with respect to a drug or substance: "Have they accepted it?;" not "Should they accept it?"

In the MDMA third final order DEA is actually making the decision that doctors have to make, rather than trying to ascertain the decision which doctors have made. Consciously or not, the Agency is undertaking to tell doctors what they should or should not accept. In so doing the Agency is acting beyond the authority granted in the Act.

It is entirely proper for the Administrator to consider the pharmacology of a drug and scientific test results in connection with determining abuse potential. But abuse potential is not in issue in this marijuana proceeding.

There is another reason why DEA should not be guided by FDA criteria in ascertaining whether or not marijuana has an accepted medical use in treatment. These criteria are applied by FDA pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act (FDCA), as amended. [footnote 13] When the FDA is making an inquiry pursuant to that legislation it is looking at a synthetically formed new drug. The marijuana plant is anything but a new drug. Uncontroverted evidence in this record indicates that marijuana was being used therapeutically by mankind 2000 years before the Birth of Christ. [footnote 14]

Uncontroverted evidence further establishes that in this country today "new drugs" are developed by pharmaceutical companies possessing resources sufficient to bear the enormous expense of testing a new drug, obtaining FDA approval of its efficacy and safety, and marketing it successfully. No company undertakes the investment required unless it has a patent on the drug, so it can recoup its development costs and make a profit. At oral argument Government counsel conceded that "the FDA system is constructed for pharmaceutical companies. I won't

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13 21 U.S.C. § 355.

14 Alice M. O'Leary, direct, par. 9.

deny that." [footnote 15]

Since the substance being considered in this case is a natural plant rather than a synthetic drug, it is unreasonable to make FDA-type criteria determinative of the issue in this case, particularly so when such criteria are irrelevant to the question posed by the act: does the substance have an accepted medical use in treatment?

Finally, the Agency in this proceeding relies in part on the FDA's recommendation that the Administrator retain marijuana in Schedule I. But, as in the MDMA case, that recommendation is based upon FDA's equating "accepted medical use" under the Act with being approved for marketing by FDA under the Food, Drug and Cosmetic Act, the interpretation condemned by the First Circuit in the MDMA case. See Attachment A, p.24, to exhibit G-1 and exhibit G-2.

The overwhelming preponderance of the evidence in this record establishes that marijuana has a currently accepted medical use in treatment in the United States for nausea and vomiting resulting from chemotherapy treatments in some cancer patients. To conclude otherwise, on this record, would be unreasonable, arbitrary and capricious.

15 Tr. XV-37.

VI.

ACCEPTED MEDICAL USE IN TREATMENT
- GLAUCOMA

Findings of Fact

The preponderance of the evidence establishes the following facts with respect to the accepted medical use of marijuana in the treatment of glaucoma.

1. Glaucoma is a disease of the eye characterized by the excessive accumulation of fluid causing increased intraocular pressure, distorted vision and, ultimately, blindness. In its early stages this pressure can sometimes be relieved by the administration of drugs. When such medical treatment fails adequately to reduce the intraocular pressure (IOP), surgery is generally resorted to. Although useful in many cases, there is a high incidence of failure with some types of surgery. Further, serious complications can occur as a result of invasive surgery. Newer, non-invasive procedures such as laser trabeculoplasty are thought by some to offer much greater efficacy with fewer complications. Unless the IOP is relieved and brought to a satisfactory level by one means or another, the patient will go blind.

2. Two highly qualified and experienced ophthalmologists in the United States have accepted marijuana as having a medical use in treatment for glaucoma. They are John C. Merritt, M.D. and Richard D. North, M.D. Each of them is both a clinician, treating patients, and a researcher. Dr. Merritt is also a professor of ophthalmology. Dr. North has served as a medical officer in ophthalmology for the Department of Health, Education and Welfare and has worked with the Public Health Service and FDA.

3. Dr. Merritt's experience with glaucoma patients using marijuana medicinally includes one Robert Randall and, insofar as the evidence here establishes per petitioners' briefs, an unspecified number of other patients, something in excess of 40.

4. Dr. North has treated only one glaucoma patient using marijuana medicinally - the same Robert Randall mentioned immediately above. Dr. North had monitored Mr. Randall's medicinal use of marijuana for nine years as of May 1987

5. Dr. Merritt has accepted marijuana as having an important place in the treatment of "End Stage" glaucoma. "End Stage" glaucoma, essentially, defines a patient who has already lost substantial amounts of vision; available glaucoma control drugs are no longer able adequately to reduce the intraocular pressure (IOP) to prevent further, progressive sight loss; the patient, lacking additional IOP reductions, will go blind.

6. Robert S. Hepler, M.D., is a highly qualified and experienced ophthalmologist. He has done research with respect to the effect of smoking marijuana on glaucoma. In December 1975 he prescribed marijuana for the same Robert Randall mentioned above as a research subject. Dr. Hepler found that large dosages of smoked marijuana effectively reduced Robert Randall's IOP into the safe range over an entire test day. He concluded that the only known alternative to preserve Randall's sight which would avoid the significant risks of surgery is to include marijuana as part of Randall's prescribed medical regimen. He further concluded in 1977 that, if marijuana could have been legally prescribed, he would have prescribed it for Randall as part of Randall's regular glaucoma maintenance program had he been Randall's personal physician.

Nonetheless, in 1987 Dr. Hepler was of the opinion that marijuana did not have a currently accepted medical use in the United States for the treatment of glaucoma.

7. Four glaucoma patients testified in these proceedings. Each has found marijuana to be of help in controlling IOP.

8. In 1984 the treatment of glaucoma with Cannabis was the subject of an Ophthalmology Grand Rounds at the University of California, San Francisco. A questionnaire was distributed which queried the ophthalmologists on cannabis therapy for glaucoma patients refractory to standard treatment. Many of them have glaucoma patients who have asked about marijuana. Most of the responding ophthalmologists believed that THC capsules or smoked marijuana need to be available for patients who have not benefited significantly from standard treatment.

9. In about 1978 an unspecified number of persons in the public health service sector in New Mexico, including some physicians, accepted marijuana as having medical use in treating glaucoma.

10. A majority of an unspecified number of ophthalmologists known to Arthur Kaufman, M.D., who was formerly in general practice but now is employed as a medical program administrator, accept marijuana as having medical use in treatment of glaucoma.

11. In addition to the physicians identified and referred to in the findings above, the testimony of patients in this record establishes that no more than three or four other physicians consider marijuana to be medically useful in the treatment of glaucoma in the United States. One of those Physicians actually wrote a prescription for marijuana for a patient, which, of course, she was unable to have filled.

12. There are test results showing that smoking marijuana has reduced the IOP in some glaucoma patients. There is continuing research underway in the United States as to the therapeutic effect of marijuana on glaucoma.

Discussion

Petitioners' briefs fail to show that the preponderance of the evidence in the record with respect to marijuana and glaucoma establishes that a respectable minority of physicians accepts marijuana as being useful in the treatment of glaucoma in the United States.

This conclusion is not to be taken in any way as criticism of the opinions of the ophthalmologists who testified that they accept marijuana for this purpose. The failure lies with petitioners. In their briefs they do not point out hard, specific evidence in this record sufficient to establish that a respectable minority of physicians has accepted their position.

There is a great volume of evidence here, and much discussion in the briefs, about the protracted case of Robert Randall. But when all is said and done, his experience presents but one case. The record contains sworn testimony of three ophthalmologists who have treated Mr. Randall. One of them tells us of a relatively small number of other glaucoma patients whom he has treated with marijuana and whom he knows to have responded favorably. Another of these three doctors has successfully treated only Randall with marijuana. The third testifies, despite his successful experience in treating Randall, that marijuana does not have an accepted use in such treatment.

In addition to Robert Randall, Petitioners point to the testimony of three other glaucoma patients. Their case histories are impressive, but they contribute

little to the carrying of Petitioner's burden of showing that marijuana is accepted for medical treatment of glaucoma by a respectable minority of physicians. See pages 26-29, above.

Petitioners have in evidence copies of a number of newspaper clippings reporting statements by persons claiming that marijuana has helped their glaucoma. The administrative law judge is unable to give significant weight to this evidence. Had these persons testified so as to have been subject to cross-examination, a different situation would be presented. But these newspaper reports of extra-judicial statements, neither tested by informed inquiry nor supported by a doctor's opinion, are not entitled to much weight. They are of little, if any,

materiality.

Beyond the evidence referred to above there is a little other "hard" evidence, pointed out by petitioners, of Physicians accepting marijuana for treatment of glaucoma. Such evidence as that concerning a survey of a group of San Francisco ophthalmologists is ambiguous, at best. The relevant document establishes merely that most of the doctors on the grand round, who responded to an inquiry, believed that the THC capsules or marijuana ought to be available.

In sum, the evidence here tending to show that marijuana is accepted for treatment of glaucoma falls far, far short of quantum of evidence tending to show that marijuana is accepted for treatment of emesis in cancer patients. The preponderance of the evidence here, identified by petitioners in their briefs, does not establish that a respectable minority of physicians has accepted marijuana for glaucoma treatment.

VII.

ACCEPTED MEDICAL USE IN TREATMENT - MULTIPLE SCLEROSIS, SPASTICITY AND HYPERPARATHYROIDISM

Findings Of Fact

The preponderance of the evidence clearly establishes the following facts with respect to marijuana's use in connection with multiple sclerosis, spasticity and hyperparathyroidism.

1. Multiple sclerosis is the major cause of neurological disability among young and middle-aged adults in the United States today. It is a life-long disease. It can be extremely debilitating to some of its victims but it does not shorten the life span of most of them. Its cause is yet to be determined. It attacks the myelin sheath, the coating or insulation surrounding the message-carrying nerve fibers in the brain and spinal cord. Once the myelin sheath is destroyed, it is replaced by plaques of hardened tissue known as sclerosis. During the initial stages of the disease nerve impulses are transmitted with only minor interruptions. As the disease progresses, the plaques may completely obstruct the impulses along certain nerve systems. These obstructions produce malfunctions. The effects are sporadic in most individuals and the effects often occur episodically, triggered either by malfunction of the nerve impulses or by external factors.

2. Over time many patients develop spasticity, the involuntary and abnormal contraction of muscle or muscle fibers. (Spasticity can also result from serious injuries to the spinal cord, not related to multiple sclerosis.)

3. The symptoms of multiple sclerosis vary according to the area of

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the nervous system which is affected and according to the severity of the disease. The symptoms can include one or more of the following:

weakness, tingling, numbness, impaired sensation, lack of coordination, disturbances in equilibrium, double vision, loss of vision, involuntary rapid movement of the eyes (nystagmus), slurred speech, tremors, stiffness, spasticity, weakness of limbs, sexual dysfunction, paralysis, and impaired bladder and bowel functions.

4. Each person afflicted by multiple sclerosis is affected differently. In some persons, the symptoms of the disease are barely detectable, even over long periods of time. In these cases, the persons can live their lives as if they did not suffer from the disease. In others, more of the symptoms are present and acute, thereby limiting their physical capabilities. Moreover, others may experience sporadic, but acute, symptoms.

5. At this time, there is no known prevention or cure for multiple sclerosis. Instead, there are only treatments for the symptoms of the disease. There are very few drugs specifically designed to treat spasticity. These drugs often cause very serious side effects. At the present time two drugs are approved by FDA as "safe" and "effective" for the specific indication of spasticity. These drugs are Dantrium and Lioresal baclofen.

6. Unfortunately, neither Dantrium nor Lioresal is a very effective spasm control drug. Their marginal medical utility, high toxicity and potential for serious adverse effects make these drugs difficult to use in spasticity therapy.

7. As a result, many physicians routinely prescribe tranquilizers, muscle relaxants, mood elevators and sedatives such as Valium to patients experiencing spasticity. While these drugs do not directly reduce spasticity

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they may weaken the patient's muscle tone, thus making the spasms less noticeable. Alternatively, they may induce sleep or so tranquilize the patient that normal mental and physical functions are impossible.

8. A healthy, athletic young woman named Valerie Cover was stricken with multiple sclerosis while in her early twenties. She consulted several medical specialists and followed all the customary regimens and prescribed methods for coping with this debilitating disease over a period of several years. None of these proved availing. Two years after first experiencing the symptoms of multiple sclerosis her active, productive life - as an athlete, Navy officer's wife and mother - was effectively over. The Social Security Administration declared her totally disabled. To move about her home she had to sit on a skateboard and push herself around. She spent most of her time in bed or sitting in a wheelchair.

9. An occasional marijuana smoker in her teens, before her marriage, she had not smoked it for five years as of February 1986. Then a neighbor suggested that marijuana just might help Mrs. Cover's multiple sclerosis, having read that it had helped cancer patient's control their emesis. Mrs. Cover acceded to the suggestion.

10. Just before smoking the marijuana cigarette produced by her neighbor, Mrs. Cover had been throwing up and suffering from spasms. Within five minutes of smoking part of the marijuana cigarette she stopped vomiting, no longer felt nauseous and noticed that the intensity of her spasms was significantly reduced. She stood up unaided.

11. Mrs. Cover began smoking marijuana whenever she felt nauseated. When she did so it controlled her vomiting, stopped the nausea and increased her

appetite. It helped ease and control her spasticity. Her limbs were much easier to control. After three months of smoking marijuana she could walk unassisted, had regained all of her lost weight, her seizures became almost nonexistent. She could again care for her children. She could drive an automobile again. She regained the ability to lead a normal life.

12. Concerned that her use of this illegal substance might jeopardize the career of her Navy officer husband, Mrs. Cover stopped smoking marijuana several times. Each time she did so, after about a month, she had retrogressed to the point that her multiple sclerosis again had her confined to bed and wheelchair or skateboard. As of the Spring of 1987 Mrs. Cover had resumed smoking marijuana regularly on an "as needed" basis. Her multiple sclerosis symptoms are under excellent control. She has obtained a full-time job. She still needs a wheelchair on rare occasions, but generally has full use of her limbs and can walk around with relative ease.

13. Mrs. Cover's doctor has accepted the effectiveness of marijuana in her case. He questioned her closely about her use of it, telling her that it is the most effective drug known in reducing vomiting. Mrs. Cover and her doctor are now in the process of filing an Investigational New Drug (IND) application with FDA so that she can legally obtain the marijuana she needs to lead a reasonably normal life.

14. Martha Hirsch is a young woman in her mid-thirties. She first exhibited symptoms of multiple sclerosis at age 19 and it was diagnosed at that time. Her condition has grown progressively worse. She has been under the care of physicians and hospitalized for treatment. Many drugs have been prescribed for her by her doctors. At one point in 1983 she listed the drugs that had been

prescribed for her. There were 17 on the list. None of them has given her the relief from her multiple sclerosis symptoms that marijuana has.

15. During the early stages in the development of her illness Ms. Hirsch found that smoking marijuana improved the quality of her life, keeping her spasms under control. Her balance improved. She seldom needed to use her cane for support. Her condition lately has deteriorated. As of May 1987 she was experiencing severe, painful spasms. She had an indwelling catheter in her bladder. She had lost her locomotive abilities and was wheelchair bound. She could seldom find marijuana on the illegal market and, when she did, she often could not afford to purchase it. When she did obtain some, however, and smoked it, her entire body seemed to relax, her spasms decreased or disappeared, she slept better and her dizzy spells vanished. The relaxation of her leg muscles after smoking marijuana has been confirmed by her personal care attendant's examination of them.

16. The personal care attendant has told Ms. Hirsch that she,

the attendant, treats a number of patients who smoke marijuana for relief of multiple sclerosis symptoms. In about 1980 another patient told Ms. Hirsch that he knew many patients who smoke marijuana to relieve their spasms. Through him she met other patients and found that marijuana was commonly used by many multiple sclerosis patients. Most of these persons had told their doctors about their doing so. None of those doctors advised against the practice and some encouraged it.

17. Among the drugs prescribed by doctors for Ms. Hirsch was ACTH. This failed to give her any therapeutic benefit or to control her spasticity. It did produce a number of adverse effects, including severe nausea and vomiting which, in turn, were partly controlled by rectally administered anti-emetic

drugs.

18. Another drug prescribed for her was Lioresal, intended to reduce her spasms. It was not very effective in doing. But it did cause Ms. Hirsch to have hallucinations. On two occasions, while using this drug, Ms. Hirsch "saw" a large fire in her bedroom and called for help. There was no fire. She stopped using that drug. Ms. Hirsch has experienced no adverse reactions with marijuana.

19. Ms. Hirsch's doctor has accepted marijuana as beneficial for her. He agreed to write her a prescription for it, if that would help her obtain it. She has asked him if he would file an IND application with the FDA for her. He replied that the paperwork was "overwhelming". He indicated willingness to put the paper work together.

20. When Greg Paufler was in his early twenties, employed by Prudential Insurance Company, he began to experience the first symptoms of multiple sclerosis. His condition worsened as the disease intensified. He had to be hospitalized. He lost the ability to walk, to stand. Diagnosed as having multiple sclerosis, a doctor prescribed ACTH for him, an intensive form of steroid therapy. He lost all control over his limbs and experienced severe, painful spasms. His arms and legs became numb.

21. ACTH had no beneficial effects. The doctor continued to prescribe it many months. ACTH made Paufler ravenously hungry and he began gaining a great deal of weight. ACTH caused fluid retention and Paufler became bloated, rapidly gaining weight. His doctor thought Paufler should continue this steroid therapy, even though it caused the adverse effects mentioned plus the possibility of sudden heart attack or death due to respiratory failure. Increased dosages

of this FDA-approved drug caused fluid to press against Paufler's lungs making it difficult for him to breathe and causing his legs and feet to become swollen. The steroid therapy caused severe, intense depression marked by abrupt mood shifts. Throughout, the spasms continued and Paufler's limbs remained out of control. The doctor insisted that ACTH was the only therapy likely to be of any help with the multiple sclerosis, despite its adverse effects. Another, oral, steroid was eventually substituted.

22. One day Paufler became semi-catatonic while sitting in his living room at home. He was rushed to the hospital emergency room. He nearly died. Lab reports indicated, among other things, a nearly total lack of potassium in his body. He was given massive injections of potassium in the emergency room and placed on an oral supplement. Paufler resolved to take no more steroids.

23. From time to time, prior to this point, Paufler had smoked marijuana socially with visiting friends, seek some relief from his misery in a temporary "high". He now began smoking marijuana more often. After some weeks he found that he could stand and then walk a bit. His doctor dismissed the idea that marijuana could be helpful with multiple sclerosis, and Paufler, himself, was skeptical at first. He began discontinuing it for a while, then resuming.

24. Paufler found that when he did not smoke marijuana his condition worsened, he suffered more intense spasms more frequently. When he smoked marijuana, his condition would stabilize and then improve; spasms were more controlled and less severe; he felt better; he regained control over his limbs and could walk totally unaided. His vision, often blurred and unfocused, improved. Eventually he began smoking marijuana on a daily basis. He ventured outdoors. He was soon walking half a block. His eyesight returned to normal.

His central field blindness cleared up. He could focus well enough to read again. One evening he went out with his children and found he could kick a soccer ball again.

25. Paufler has smoked marijuana regularly since 1980. Since that time his multiple sclerosis has been well controlled. His doctor has been astonished at Paufler's recovery. Paufler can now run. He can stand on one foot with his eyes closed. The contrast with his condition, several years ago, seems miraculous. Smoking marijuana when Paufler feels an attack coming on shortens the attack. Paufler's doctor has looked Paufler in the eye and told him to keep doing whatever it is he's doing because it works. Paufler and his doctor are exploring the possibility of obtaining a compassionate IND to provide legal access to marijuana for Paufler.

26. Paufler learned in about 1980 of the success of one Sam Diana, a multiple sclerosis patient, in asserting the defense of "medical necessity" in court when charged with using or possessing marijuana. He learned that doctors, researchers and other multiple sclerosis patients had supported Diana's position in the court proceeding.

27. Irwin Rosenfeld has been diagnosed as having Pseudo Pseudo Hypoparathyroidism. This uncommon disease causes bone spurs to appear and grow all over the body. Over the patient's lifetime hundreds of these spurs can grow, any one of which can become malignant at any time. The resulting cancer would spread quickly and the patient would die.

28. Even without development of a malignancy, the disease causes enormous pain. The spurs press upon adjacent body tissue, nerves and organs. In Rosenfeld's case, he could neither sit still nor lie down, nor could he walk,

without experiencing pain. Working in his furniture store in Portsmouth, Virginia, Mr. Rosenfeld was on his feet moving furniture all day long. The lifting and walking caused serious problems as muscles and tissues rubbed over the spurs of bone. He tore muscles and hemorrhaged almost daily.

29. Rosenfeld's symptoms first appeared about the age of ten. Various drugs were prescribed for him for pain relief. He was taking extremely powerful narcotics. By the age of 19 his therapy included 300 mg. of Sopor (a powerful sleeping agent) and very high doses of Dilaudid. He was found to be allergic to barbiturates. Taking massive doses of pain control drugs, as prescribed, made it very difficult for Rosenfeld to function normally. If he took enough of them to control the pain, he could barely concentrate on his schoolwork. By the time he reached his early twenties Rosenfeld's monthly drug intake was between 120 to 140 Dilaudid tablets, 30 or more Sopor sleeping pills and dozens of muscle relaxants.

30. At college in Florida Rosenfeld was introduced to marijuana by classmates. He experimented with it recreationally. He never experienced a "high" or "buzz" or "floating sensation" from it. One day he smoked marijuana while playing chess with a friend. It had been very difficult for him to sit for more than five or ten minutes at a time because of tumors in the backs of his legs. Suddenly he realized that, absorbed in his chess game, and smoking marijuana, he had remained sitting for over an hour - with no pain. He experimented further and found that his pain was reduced whenever he smoked marijuana.

31. Rosenfeld told his doctor of his discovery. The doctor opined that it was possible that the marijuana was relieving the pain. Something

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certainly was - there was a drastic decrease in Rosenfeld's need for such drugs as Dilaudid and Demerol and for sleeping pills. The quality of pain relief which followed his smoking of marijuana was superior to any he had experienced before. As his dosages of powerful conventional drugs decreased, Rosenfeld became less withdrawn from the world, more able to interact and function. So he has continued to the present time.

32. After some time Rosenfeld's doctor accepted the fact that the marijuana was therapeutically helpful to Rosenfeld and submitted an IND application to FDA to obtain supplies of it legally for Rosenfeld. The doctor has insisted, however, that he not be publicly identified. After some effort the IND application was granted. Rosenfeld is receiving supplies of marijuana from NIDA. Rosenfeld testified before a committee of the Virginia legislature in about 1979 in support of legislation to make marijuana available for therapeutic purposes in that State.

33. In 1969, at age 19, David Branstetter dove into the shallow end of a swimming pool and broke his neck. He became a quadriplegic, losing control over the movement of his arms and legs. After being hospitalized for 18 months he returned home. Valium was prescribed for him to reduce the severe spasms associated with his condition. He became mildly addicted to Valium. Although it helped mask his spasms, it made Branstetter more withdrawn and less able to take care of himself. He stopped taking Valium for fear of the consequences of long-term addiction. His spasms then became uncontrollable, often becoming so bad they would throw him from his wheelchair.

34. In about 1973 Branstetter began smoking marijuana recreationally. He discovered that his severe spasms stopped whenever he smoked marijuana.

Unlike Valium, which only masked his symptoms and caused him to feel drunk and out of control, marijuana brought his spasmodic condition under control without impairing his faculties. When he was smoking marijuana regularly he was more active, alert and outgoing.

35. Marijuana controlled his spasms so well that Branstetter could go out with friends and he began to play billiards again. The longer he smoked marijuana the more he was able to use his arms and hands. Marijuana also improved his bladder control and bowel movements.

36. At times the illegal marijuana Branstetter was smoking became very expensive and sometimes was unavailable. During periods when he did not have marijuana his spasms would return, preventing Branstetter from living a "normal" life. He would begin to shake uncontrollably, his body would feel tense, and his muscles would spasm.

37. In 1979 Branstetter was arrested and convicted of possession of marijuana. He was placed on probation for two years. During that period he continued smoking marijuana and truthfully reported this, and the reason for it, to his probation officer whenever asked about it. No action was taken against Branstetter by the court or probation authorities because of his continuing use of marijuana, except once in the wake of his publicly testifying about it before the Missouri legislature. Then, although adverse action was threatened by the judge, nothing was actually done.

38. In 1981 Branstetter and a friend, a paraplegic, participated in a research study testing the therapeutic effects of synthetic THC on spasticity. Placed on the THC Branstetter found that it did help control his spasms but appeared to became less effective with repeated use. Also, unlike marijuana,

synthetic THC had a powerful mind-altering effect he found annoying. When the study ended the researcher strongly suggested that Branstetter continue smoking marijuana to control his spasms.

39. None of Branstetter's doctors have told him to stop smoking marijuana while several, directly and indirectly, have encouraged him to continue. Branstetter knows of almost 20 other patients, paraplegics, quadriplegics and multiple sclerosis sufferers, who smoke marijuana to control their spasticity.

40. In 1981 a State of Washington Superior Court judge, sitting without a jury, found Samuel D. Diana not guilty of the charge of unlawful possession of marijuana. In so doing the judge upheld Diana's defense of medical necessity. Diana had been a multiple sclerosis patient since at least 1973. He testified that smoking marijuana relieved his symptoms of double vision, tremors, unsteady walk, impaired hearing, tendency to vomit in the mornings and stiffness in the joints of his hands and legs.

41. Among the witnesses was a physician who had examined defendant Diana before and after he had used marijuana. This doctor testified that marijuana had been effective therapeutically for Diana, that other medication had proven ineffective for Diana and that, while marijuana may have some detrimental effects, Diana would receive more benefit than harm from smoking it. The doctor was not aware of any other drug that would be as effective as marijuana for Mr. Diana. Other witnesses included three persons afflicted with multiple sclerosis who testified in detail as to marijuana's beneficial effect on their illness.

42. In acquitting defendant Diana of unlawful possession of marijuana the trial judge found that the three requirements for the defense of medical necessity had been established, namely: defendant's reasonable belief that his

use of marijuana was necessary to minimize the effects of multiple sclerosis; the benefits derived from its use are greater than the harm sought to be prevented by the controlled substances law; and no drug is as effective as marijuana in minimizing the effects of the disease in the defendant.

43. Denis Petro, M.D., is a neurologist of broad experience, ranging from active practice in neurology to teaching the subject in medical school and employment by FDA as a medical officer reviewing IND's and NDA's. He has also been employed by pharmaceutical companies and has served as a consultant to the State of New York. He is well acquainted with the case histories of three patients who have successfully utilized marijuana to control severe spasticity when other, FDA-approved drugs failed to do so. Dr. Petro knows of other cases of patients who, he has determined, have effectively used marijuana to control their spasticity. He has heard reports of additional patients with multiple sclerosis, paraplegia and quadriplegia doing the same. There are reports published in the literature known to Dr. Petro, over the period at least 1970 - 1986, of clinical tests demonstrating that marijuana and THC are effective in controlling or reducing spasticity in patients.

44. Large numbers of paraplegic and quadriplegic patients, particularly in Veterans Hospitals, routinely smoke marijuana to reduce spasticity. While this mode of treatment is illegal, it is generally tolerated, if not openly encouraged, by physicians in charge of such wards who accept this practice as being of benefit to their patients. There are many spinal cord injury patients in Veterans Hospitals.

45. Dr. Petro sought FDA approval to conduct research with spasticity patients using marijuana. FDA refused but, for reasons unknown to him, allowed

him to make a study using synthetic THC. He and colleagues made such a study. They concluded that synthetic THC effected a significant reduction in spasticity among multiple sclerosis patients, but study participants who had also smoked marijuana reported consistently that marijuana was more effective.

46. Dr. Petro accepts marijuana as having a medical use in the treatment of spasticity in the United States. If it were legally available and he was engaged in an active medical practice again, he

would not hesitate to prescribe marijuana, when appropriate, to patients afflicted with uncontrollable spasticity.

47. Dr. Petro presented a paper to a meeting of the American Academy of Neurology. The paper was accepted for presentation. After he presented it Dr. Petro found that many of the neurologists present at this most prestigious meeting were in agreement with his acceptance of marijuana as having a medical use in the treatment of spasticity.

48. Dr. Andrew Weil, a general medicine practitioner in Tucson, Arizona, who also teaches at the University of Arizona College of Medicine, accepts marijuana as having a medical use in the treatment of spasticity. In multiple sclerosis patients the muscles become tense and rigid because their nerve supply is interrupted. Marijuana relieves this spasticity in many patients, he has found. He would prescribe it to selected patients if it were legally available,

49. Dr. Lester B. Collins, III, a neurologist, then treating about 20 multiple sclerosis patients a year, seeing two or three new ones each year, stated in 1983 that he had no doubt that marijuana worked symptomatically for some multiple sclerosis patients. He said that it does not alter the course of

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the disease but it does relieve the symptoms of spasticity.

50. Dr. John P. Morgan, board certified in internal medicine, Professor of Medicine and Director of Pharmacology at CCNY Medical School in New York and Associate Professor of Medicine and Pharmacology at Mt. Sinai School of Medicine, accepts marijuana as having medical use in treatment in the United States. If he were practicing medicine and marijuana were legally available he would prescribe it when indicated to patients with legitimate medical needs.

Discussion

Based upon the rationale set out in pages 26 to 34, above, the administrative law judge concludes that, within the meaning of the Act, 21 U.S.C. § 812(b)(2)(B), marijuana "has a currently accepted medical use in treatment in the United States" for spasticity resulting from multiple sclerosis and other causes. It would be unreasonable, arbitrary and capricious to find otherwise. The facts set out above, uncontroverted by the Agency, establish beyond question that some doctors in the United States accept marijuana as helpful in such treatment for some patients. The record here shows that they constitute a significant minority of physicians. Nothing more can reasonably be required. That some doctors would have more studies and test results in hand before accepting marijuana's usefulness here is irrelevant.

The same is true with respect to the hyperparathyroidism from which Irvin Rosenfeld suffers. His disease is so rare, and so few physicians appear to be familiar with it, that acceptance by one doctor of marijuana as being useful in treating it ought to satisfy the requirement for a significant minority. The Agency points to no evidence of record tending to establish that marijuana is

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not accepted by doctors in connection with this most unusual ailment. Refusal to acknowledge acceptance by a significant minority, in light of the case history detailed in this record, would be unreasonable, arbitrary and capricious.

VIII.

ACCEPTED SAFETY FOR USE UNDER MEDICAL SUPERVISION

With respect to whether or not there is "a lack of accepted safety for use of [marijuana] under medical supervision", the record shows the following facts to be uncontroverted.

Findings of Fact

1. Richard J. Gralla, M.D., an oncologist and Professor of Medicine who was an Agency witness, accepts that in treating cancer patients oncologists can use the cannabinoids with safety despite their side effects.

2. Andrew T. Weil, M.D., who now practices medicine in Tucson, Arizona and is on the faculty of the College of Medicine, University of Arizona, was a member of the first team of researchers to perform a Federal Government authorized study into the effects of marijuana on human subjects. This team made its study in 1968. These researchers determined that marijuana could be safely used under medical supervision. In the 20 years since then Dr. Weil has seen no information that would cause him to reconsider that conclusion. There is no question in his mind but that marijuana is safe for use under appropriate medical supervision.

3. The most obvious concern when dealing with drug safety is the possibility of lethal effects. Can the drug cause death?

4. Nearly all medicines have toxic, potentially lethal effects. But marijuana is not such a substance. There is no record in the extensive medical literature describing a proven, documented cannabis-induced fatality.

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5. This is a remarkable statement. First, the record on marijuana encompasses 5,000 years of human experience. Second, marijuana is now used daily by enormous numbers of people throughout the world. Estimates suggest that from twenty million to fifty million Americans routinely, albeit illegally, smoke marijuana without the benefit of direct medical supervision. Yet, despite this long history of use and the extraordinarily high numbers of social smokers, there are simply no credible medical reports to suggest that consuming marijuana has caused a single death.

6. By contrast aspirin, a commonly used, over-the-counter medicine, causes hundreds of deaths each year.

7. Drugs used in medicine are routinely given what is called an LD-50. The LD-50 rating indicates at what dosage fifty percent of

test animals receiving a drug will die as a result of drug induced toxicity. A number of researchers have attempted to determine marijuana's LD-50 rating in test animals, without success. Simply stated, researchers have been unable to give animals enough marijuana to induce death.

8. At present it is estimated that marijuana's LD-50 is around 1:20,000 or 1:40,000. In layman terms this means that in order to induce death a marijuana smoker would have to consume 20,000 to 40,000 times as much marijuana as is contained in one marijuana cigarette. NIDA-supplied marijuana cigarettes weigh approximately .9 grams. A smoker would theoretically have to consume nearly 1,500 pounds of marijuana within about fifteen minutes to induce a lethal response.

9. In practical terms, marijuana cannot induce a lethal response as a result of drug-related toxicity.

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10. Another common medical way to determine drug safety is called the therapeutic ratio. This ratio defines the difference between a therapeutically effective dose and a dose which is capable of inducing adverse effects.

11. A commonly used over-the-counter product like aspirin has a therapeutic ratio of around 1:20. Two aspirins are the recommended dose for adult patients. Twenty times this dose, forty aspirins, may cause a lethal reaction in some patients, and will almost certainly cause gross injury to the digestive system, including extensive internal bleeding.

12. The therapeutic ratio for prescribed drugs is commonly around 1:10 or lower. Valium, a commonly used prescriptive drug, may cause very serious biological damage if patients use ten times the recommended (therapeutic) dose.

13. There are, of course, prescriptive drugs which have much lower therapeutic ratios. Many of the drugs used to treat patients with cancer, glaucoma and multiple sclerosis are highly toxic. The therapeutic ratio of some of the drugs used in antineoplastic therapies, for example, are regarded as extremely toxic poisons with therapeutic ratios that may fall below 1:1.5. These drugs also have very low LD-50 ratios and can result in toxic, even lethal reactions, while being properly employed.

14. By contrast, marijuana's therapeutic ratio, like its LD-50, is impossible to quantify because it is so high.

15. In strict medical terms marijuana is far safer than many foods we commonly consume. For example, eating ten raw potatoes can result in a toxic response. By comparison, it is physically impossible to eat enough marijuana to induce death.

16. Marijuana, in its natural form, is one of the safest therapeutically

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active substances known to man. By any measure of rational analysis marijuana can be safely used within a supervised routine of medical care.

17. Some of the drugs most widely used in chemotherapy treatment of cancer have adverse effects as follows:

> Cisplatin, one of the most powerful chemo-therapeutic agents used on humans - may cause deafness; may lead to life-threatening kidney difficulties and kidney failure; adversely affects the body's immune system, suppressing the patient's ability to fight a host of common infections.
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> Nitrogen Mustard, a drug used in therapy for Hodgkins disease - nauseates; so toxic to the skin that, if dropped on the skin, this chemical literally eats it away along with other tissues it contacts; if patient's intravenous lead slips during treatment and this drug gets on or under the skin the patient may suffer serious injury including temporary, and in extreme cases, permanent, loss of use of the arm.
>
> Procarbizine, also used for Hodgkins disease - has known psychogenic, i.e., emotional, effects.
>
> Cyoxin, also known as Cyclophosphanide - suppresses patient's immune system response; results in serious bone marrow depletion; studies indicate this drug may also cause other cancers, including cancers of the bladder.
>
> Adriamycan, has numerous adverse effects; is difficult to employ in long term therapies because it destroys the heart muscle.

While each of these agents has its particular adverse effects, as indicated above, they also cause a number of similar, disturbing adverse effects. Most of these drugs cause hair loss. Studies increasingly indicate all of these drugs may cause other forms of cancer. Death due to kidney, heart or respiratory failure is a very real possibility with all of these agents and the margin for error is minimal. Similarly, there is a danger of overdosing a patient weakened by his cancer. Put simply, there is very great risk associated with the medical

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use of these chemicals agents. Despite these high risks, all of these drugs are considered "safe" for use under medical supervision and are regularly administered to patients on doctor's orders in the United States today.

18. There have been occasional instances of panic reaction in patients who have smoked marijuana. These have occurred in marijuana-naive persons, usually older persons, who are extremely anxious over the forthcoming chemotherapy and troubled over the illegality of their having obtained the marijuana. Such persons have responded to simple person-to-person communication with a doctor and have sustained no long term mental or physical damage. If marijuana could be legally obtained, and administered in an open, medically-supervised session rather than surreptitiously, the few instances of such adverse reaction doubtless would be reduced in number and severity.

19. Other reported side effects of marijuana have been minimal.

Sedation often results. Sometimes mild euphoria is experienced. Short periods of increased pulse rate and of dizziness are occasionally experienced. Marijuana should not be used by persons anxious or depressed or psychotic or with certain other health problems. Physicians could readily screen out such patients if marijuana were being employed as an agent under medical supervision.

20. All drugs have "side effects" and all drugs used in medicine for their therapeutic benefits have unwanted, unintended, sometimes adverse effects.

21. In medical treatment "safety" is a relative term. A drug deemed "safe" for use in treating a life-threatening disease might be "unsafe" if prescribed for a patient with a minor ailment. The concept of drug "safety" is relative. Safety is measured against the consequences a patient would confront in the absence of therapy. The determination of "safety" is made in terms of

whether a drug's benefits outweigh its potential risks and the risks of permitting the disease to progress.

22. In the context of glaucoma therapy, it must be kept in mind that glaucoma, untreated, progressively destroys the optic nerve and results in eventual blindness. The danger, then, to patients with glaucoma is an irretrievable loss of their sight.

23. Glaucoma is not a mortal disease, but a highly specific, selectively incapacitating condition. Glaucoma assaults and destroys the patient's most evolved and critical sensory ability, his or her vision. The vast majority of patients afflicted with glaucoma are adults over the age of thirty. The onset of blindness in middle age or later throws patients into a wholly alien world. They can no longer do the work they once did. They are unable to read a newspaper, drive a car, shop, walk freely and do all the myriad things sighted people take for granted. Without lengthy periods of retraining, adaptation and great effort these individuals often lose their sense of identity and ability to function. Those who are young enough or strong-willed enough will regain a sense of place, hold meaningful jobs, but many aspects of the life they once took for granted cannot be recaptured. Other patients may never fully adjust to their new, uncertain circumstances.

24. Blindness is a very grave consequence. Protecting patients from blindness is considered so important that, for ophthalmologists generally, it justifies the use of toxic medicines and uncertain surgical procedures which in other contexts might be considered "unsafe." In practice, physicians often provide glaucoma patients with drugs which have many serious adverse effects.

25. There are only a limited number of drugs available for the

treatment of glaucoma. All of these drugs produce adverse effects. While several government witnesses lightly touched on the side effects of these drugs, none provided a full or detailed description of their known adverse consequences.

26. The adverse physical consequences resulting from the chronic use of commonly employed glaucoma control drugs include a vast range of unintended complications from mild problems like drug induced fevers, skin rashes, headaches, anorexia, asthma, pulmonary difficulties, hypertension, hypotension and muscle cramps to truly serious, even life-threatening complications including the formation of cataracts, stomach and intestinal ulcers, acute respiratory distress, increases and decreases in heart rate and pulse, disruption of heart function, chronic and acute renal disease, and bone marrow depletion.

27. Finally, each FDA-approved drug family used in glaucoma therapy is capable of producing a lethal response, even when properly prescribed and used. Epinephrine can lead to elevated blood pressure which may result in stroke or heart attack. Miotic drugs suppress respiration and can cause respiratory Paralysis. Diuretic drugs so alter basic body chemistry they cause renal stones and may destroy the patient's kidneys or result in death due to heart failure. Timolol and related beta-blocking agents, the most recently approved family of glaucoma control drugs, can trigger severe asthma attacks or cause death due to sudden cardiac arrhythmias often producing cardiac arrest.

28. Both of the FDA-approved drugs used in treating the symptoms of multiple sclerosis, Dantrium and Lioresal, while accepted as "safe" can, in fact, be very dangerous substances. Dantrium or dantrolene sodium carries a boxed warning in the Physician's Desk Reference (PDR) because of its very high toxicity. Patients using this drug run a very real risk of developing sympto-

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matic hepatitis (fatal and nonfatal). The list of sublethal toxic reactions also underscores just how dangerous Dantrium can be. The PDR, in part, notes Dantrium commonly causes weakness, general malaise and fatigue and goes on to note the drug can also cause constipation, GI bleeding, anorexia, gastric irritation, abdominal cramps, speech disturbances, seizure, visual disturbances, diplopia, tachycardia, erratic blood pressure, mental confusion, clinical depression, renal disturbances, myalgia, feelings of suffocation and death due to liver failure.

29. The adverse effects associated with Lioresal baclofen are somewhat less severe, but include possibly lethal consequences, even when the drug is properly prescribed and taken as directed. The range on sublethal toxic reactions is similar to those found with Dantrium.

30. Norman E, Zinberg, M.D., one of Dr. Weil's colleagues in the 1968 study mentioned in finding 2, above, accepts marijuana as being safe for use under medical supervision. If it were available by prescription he would use it for appropriate patients.

31. Lester Grinspoon, M.D., practicing psychiatrist researcher and Associate Professor of Medicine at Harvard Medical School, accepts marijuana as safe for use under medical supervision. He believes its safety is its greatest advantage as a medicine in appropriate cases.

32. Tod H. Mikuriya, M.D., a psychiatrist practicing in Berkley, California who treats substance abusers as inpatients and outpatients, accepts marijuana as safe for use under medical supervision.

33. Richard D. North, M.D., who has treated Robert Randall for glaucoma with marijuana for nine years, accepts marijuana as safe for use

by his patient

under medical supervision. Mr. Randall has smoked ten marijuana cigarettes a day during that period without any evidence of adverse mental or physical effects from it.

34. John C. Merritt, M.D., an expert in ophthalmology, who has treated Robert Randall and others with marijuana for glaucoma, accepts marijuana as being safe for use in such treatment.

35. Deborah B. Goldberg, M.D., formerly a researcher in oncology and now a practicing physician, having worked with many cancer patients, observed them, and heard many tell of smoking marijuana successfully to control emesis, accepts marijuana is proven to be an extremely safe anti-emetic agent. When compared with the other, highly toxic chemical substances routinely prescribed to cancer patients, Dr. Goldberg accepts marijuana as clearly safe for use under medical supervision. (See finding 17, above.)

36. Ivan Silverberg, M.D., board certified in oncology and practicing that specialty in the San Francisco area, has accepted marijuana as a safe anti-emetic when used under medical supervision. Although illegal, it is commonly used by patients in the San Francisco area with the knowledge and acquiescence of their doctors who readily accept it as being safe for such use.

37. It can be inferred that all of the doctors and other health care professionals referred to in the findings in Sections V, VI and VII, above, who tolerate or permit patients to self-administer illegal marijuana for therapeutic benefit, accept the substance as safe for use under medical supervision.

Discussion

The Act, at 21 U.S.C. § 812(b)(1)(C), requires that marijuana be retained in Schedule I if "[t]here is a lack of accepted safety for use of [it] under medical supervision." If there is no lack of such safety, if it is accepted that this substance can be used with safety under medical supervision, then it is unreasonable to keep it in Schedule I.

Again we must ask - "accepted" by whom? In the MDMA proceeding the Agency's first Final Rule decided that "accepted" here meant, as in the phrase "accepted medical use in treatment", that the FDA had accepted the substance pursuant to the provisions of the Food, Drug and Cosmetic Act. 51 Fed. Reg. 36555 (1986). The Court of Appeals held that this was error. On remand, in its third Final Rule on MDMA, the Agency made the same ruling as before, relying essentially on the same findings, and on others of similar nature, just as it did with respect to "accepted medical use." 53 Fed. Reg. 5156 (1988).

The administrative law judge finds himself constrained not to follow the rationale in that MDMA third Final Order for the same reasons as set out above in Section V with respect to "accepted medical use" in oncology. See pages 30 to 33. Briefly, the Agency was looking primarily at the results of scientific tests and studies rather than at what

physicians had, in fact, accepted. The Agency was wrongly basing its decision on a judgment as to whether or not doctors ought to have accepted the substance in question as safe for use under medical supervision. The criteria the Agency applied in the MDMA third Final Rule are inappropriate. The only proper question for the Agency here is: Have a significant minority of physicians accepted marijuana as safe for use under medical supervision?

The gist of the Agency's case against recognizing marijuana's acceptance as safe is to assert that more studies, more tests are needed. The Agency has presented highly qualified and respected experts, researchers and others, who hold that view. But, as demonstrated in the discussion in Section V above, it is unrealistic and unreasonable to require unanimity of opinion on the question confronting us. For the reasons there indicated, acceptance by a significant minority of doctors is all that can reasonably be required. This record makes it abundantly clear that such acceptance exists in the United States.

Findings are made above with respect to the safety of medically supervised use of marijuana by glaucoma patients. Those findings are relevant to the safety issue even though the administrative law judge does not find accepted use in treatment of glaucoma to have been shown.

Based upon the facts established in this record and set out above one must reasonably conclude that there is accepted safety for use of marijuana under medical supervision. To conclude otherwise, on this record, would be unreasonable, arbitrary and capricious.

IX.

CONCLUSION AND RECOMMENDED DECISION

Based upon the foregoing facts and reasoning, the administrative law judge concludes that the provisions of the Act permit and require the transfer of marijuana from Schedule I to Schedule II. The Judge realizes that strong emotions are aroused on both sides of any discussion concerning the use of marijuana. Nonetheless it is essential for this Agency, and its Administrator, calmly and dispassionately to review the evidence of record, correctly apply the law, and act accordingly.

Marijuana can be harmful. Marijuana is abused. But the same is true of dozens of drugs or substances which are listed in Schedule II so that they can be employed in treatment by physicians in proper cases, despite their abuse potential.

Transferring marijuana from Schedule I to Schedule II will not, of course, make it immediately available in pharmacies throughout the country for legitimate use in treatment. Other government authorities, Federal and State, will doubtless have to act before that might occur. But this Agency is not charged with responsibility, or given authority, over the myriad other regulatory decisions that may be required before marijuana can actually be legally available. This Agency is charged merely with determining the placement of marijuana pursuant to the

provisions of the Act. Under our system of laws the responsibilities of other regulatory bodies are the concerns of those bodies, not of this Agency,

There are those who, in all sincerity, argue that the transfer of marijuana

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to Schedule II will "send a signal" that marijuana is "OK" generally for recreational use. This argument is specious. It presents no valid reason for refraining from taking an action required by law in light of the evidence. If marijuana should be placed in Schedule II, in obedience to the law, then that is where marijuana should be placed, regardless of misinterpretation of the placement by some. The reasons for the placement can, and should, be clearly explained at the time the action is taken. The fear of sending such a signal cannot be permitted to override the legitimate need, amply demonstrated in this record, of countless suffers for the relief marijuana can provide when prescribed by a physician in a legitimate case.

The evidence in this record clearly shows that marijuana has been accepted as capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision. It would be unreasonable, arbitrary and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record.

The administrative law judge recommends that the Administrator conclude that the marijuana plant considered as a whole has a currently accepted medical use in treatment in the United States, that there is no lack of accepted safety for use of it under medical supervision and that it may lawfully be transferred from Schedule I to Schedule II. The judge recommends that the Administrator transfer marijuana from Schedule I to Schedule II.

Dated: SEP 6 1988

Francis L. Young
Administrative Law Judge

CERTIFICATE OF SERVICE

This is to certify that the undersigned on SEP 6 1988, caused a copy of the foregoing to be delivered to

Madeleine R. Shirley, Esq.
Office of Chief Counsel
Drug Enforcement Administration
1405 I Street, N.W.
Washington, D.C. 20537

and caused a copy to be mailed, postage paid, to each of the following:

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Reform of Marijuana Laws
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Dianne L. Martin
Hearing Clerk

New England Journal of Medicine's Endorsement of Medical Marijuana

Daily Headlines

FEDERAL FOOLISHNESS AND MARIJUANA

by Jerome P. Kassirer, M.D., (Source:New England Journal of Medicine)

30 Jan 1997
United States

The advanced stages of many illnesses and their treatments are often accompanied by intractable nausea, vomiting, or pain. Thousands of patients with cancer, AIDS, and other diseases report they have obtained striking relief from these devastating symptoms by smoking marijuana. (1) The alleviation of distress can be so striking that some patients and their families have been willing to risk a jail term to obtain or grow the marijuana.

Despite the desperation of these patients, within weeks after voters in Arizona and California approved propositions allowing physicians in their states to prescribe marijuana for medical indications, federal officials, including the President, the secretary of Health and Human Services, and the attorney general sprang into action. At a news conference, Secretary Donna E. Shalala gave an organ recital of the parts of the body that she asserted could be harmed by marijuana and warned of the evils of its spreading use. Attorney General Janet Reno announced that physicians in any state who prescribed the drug could lose the privilege of writing prescriptions, be excluded from Medicare and Medicaid reimbursement, and even be prosecuted for a federal crime. General Barry R. McCaffrey, director of the Office of National Drug Control Policy, reiterated his agency's position that marijuana is a dangerous drug and implied that voters in Arizona and California had been duped into voting for these propositions. He indicated that it is always possible to study the effects of any drug, including marijuana, but that the use of marijuana by seriously ill patients would require, at the least, scientifically valid research.

I believe that a federal policy that prohibits physicians from alleviating suffering by prescribing marijuana for seriously ill patients is misguided, heavy-handed, and inhumane. Marijuana may have long-term adverse effects and its use may presage serious addictions, but neither long-term side effects nor addiction is a relevant issue in such patients. It is also hypocritical to forbid physicians to prescribe marijuana while permitting them to use morphine and meperidine to relieve extreme dyspnea and pain. With both these drugs the difference between the dose that relieves symptoms and the dose that hastens death is very narrow; by contrast, there is no risk of death from smoking marijuana. To demand evidence of therapeutic efficacy is equally hypocritical. The noxious sensations that patients experience are extremely difficult to quantify in controlled experiments. What really counts for a therapy with this kind of safety margin is whether a seriously ill patient feels relief as a result of the intervention, not whether a controlled trial "proves" its efficacy.

Paradoxically, dronabinol, a drug that contains one of the active ingredients in marijuana (tetrahydrocannabinol), has been available by prescription for more than a decade. But it is difficult to titrate the therapeutic dose of this drug, and it is not widely prescribed. By contrast, smoking marijuana produces a rapid increase in the blood level of the active ingredients and is thus more likely to be therapeutic. Needless to say, new drugs such as those that inhibit the nausea associated with chemotherapy may well be more beneficial than smoking marijuana, but their comparative efficacy has never been studied.

Whatever their reasons, federal officials are out of step with the public. Dozens of states have passed laws that ease restrictions on the prescribing of marijuana by physicians, and polls consistently show that the public favors the use of marijuana for such purposes. (1) Federal authorities should rescind their prohibition of the medicinal use of marijuana for seriously ill patients and allow physicians to decide which patients to treat. The government should change marijuana's status from that of a Schedule 1 drug (considered to be potentially addictive and with no current medical use) to that of a Schedule 2 drug (potentially addictive but with some accepted medical use) and regulate it accordingly. To ensure its proper distribution and use, the government could declare itself the only agency sanctioned to provide the marijuana. I believe that such a change in policy would have no adverse effects. The argument that it would be a signal to the young that "marijuana is OK" is, I believe, specious.

This proposal is not new. In 1986, after years of legal wrangling, the Drug Enforcement Administration (DEA) held extensive hearings on the transfer of marijuana to Schedule 2. In 1988, the DEA's own administrative-law judge concluded, "It would be unreasonable, arbitrary, and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record." (1) Nonetheless, the DEA overruled the judge's order to transfer marijuana to Schedule 2, and in 1992 it issued a final rejection of all requests for reclassification. (2)

Some physicians will have the courage to challenge the continued proscription of marijuana for the sick. Eventually, their actions will force the courts to adjudicate between the rights of those at death's door and the absolute power of bureaucrats whose decisions are based more on reflexive ideology and political correctness than on compassion.

Jerome P. Kassirer, M.D.

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Bookmark: http://www.mapinc.org/mmj.htm (Marijuana - Medicinal)

NORML's Review of Human Studies and Medical Marijuana (1996)

Review of Human Studies on Medical Use of Marijuana

by Dale H. Gieringer, Ph.D.
August 1996

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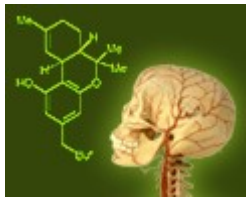

Summary: Human Studies on Medical Uses of Marijuana

There have been hundreds of studies on the medical uses of cannabis since its introduction to western medicine in the early nineteenth century. A review of the literature reveals over 65 human studies, most of them in the 1970s and early '80s.

- The best established medical use of smoked marijuana is as an anti-nauseant for cancer chemotherapy. Marijuana's efficacy was demonstrated in studies by half a dozen states, involving hundreds of subjects. Most research has found smoked marijuana superior to oral THC (Marinol). Many oncologists are currently recommending marijuana to their patients.
- Marijuana is widely used to treat nausea and appetite loss associated with AIDS, but the government has blocked research in this area. Studies have shown that marijuana helps improve appetite, and Marinol has been FDA approved for treatment of AIDS wasting syndrome. Nearly 10,000 PWAs were reported to be using marijuana through the San Francisco Cannabis Buyers' Club. However, the government has blocked efforts by Dr. Donald Abrams of the University of California at San Francisco to proceed with an FDA-approved study of marijuana and AIDS wasting syndrome, by refusing to grant him access to research marijuana. Research is badly needed on the relative merits of smoked and oral marijuana versus Marinol.
- There is much evidence, largely anecdotal, that marijuana is useful as an anti-convulsant for spinal injuries, multiple sclerosis, epilepsy, and other diseases. Similar evidence suggests marijuana may be useful as an analgesic for chronic pain from cancer and migraine as well as for rheumatism and a variety of auto-immune diseases. There is a conspicuous lack of controlled studies in this area; further research is needed.
- Cannabidiol, a constituent of natural marijuana not found in Marinol, appears to have distinctive therapeutic value as an anti-convulsant and hypnotic, and to counteract acute anxiety reactions caused by THC.
- It has been established that marijuana reduces intra-ocular pressure, the primary object of glaucoma therapy. Due to its psychoactivity, however, marijuana has not gained widespread acceptance in this application.
- Many patients report using marijuana as a substitute for more addictive and harmful psychoactive drugs, including prescription painkillers, opiates, and alcohol. Marijuana and Marinol have also been found useful as a treatment for depression and mood disorders in Alzheimer's and other patients. More research is needed.

The Complete Report:

Review of Human Studies on Medical Use of Marijuana

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Overview of Medical Marijuana Research

In its position paper, "Use of Marijuana as a 'Medicine,'" the California Narcotics Officers Association refers to "10,000 studies... documenting the harmful physical and psychological effects of smoking marijuana." This myth has been effectively debunked in a letter to Dr. Lester Grinspoon from NIDA's marijuana research librarian at the University of Mississippi, Beverly Urbanek, who writes, "We are totally in the dark as to where the statement that there are 10,000 studies showing the negative impact of marijuana could have originated." She explains that while her library has some 12,000 citations on cannabis, they cover a broad spectrum of economic, legal, horticultural, enforcement, and other nonhealth
issues, and are not categorized by negative or positive effects. Pursuing the issue further, it is possible to enumerate an impressive number of studies on marijuana's therapeutic uses. There is no space here to list or summarize all of them. The book, "Cannabinoids as Therapeutic Agents," edited by Dr. Raphael Mechoulam (CRC, 1986), includes copious references to research articles on cannabis' pharmacological effects, as follows:

- Pharmacohistory of Cannabis Sativa - 90 references;
- Therapeutic Potential of Cannabinoids in Neurological Disorders -155 references
- Ocular Effects - 70 references
- Cannabinoids as Antiemetics in Cancer - 91 references
- Cannabinoids and Analgesia - 136 references
- Bronchodilator Action of Cannabinoids - 67 references

Of course, there are some duplicates, and by no means all of these 609 references actually detail medicinal benefits of marijuana, but it certainly seems reasonable to estimate that there have been 100s of studies on medical use of marijuana.

Human Studies

Following is a summary of the human clinical and epidemiological studies on marijuana's therapeutic applications. We have not attempted to detail the great bulk of research, which consists of animal and in

vitro studies that are of more dubious relevance to human health. However, we have tried to include all human studies reported in the recent medical literature.

1. Anti-Nauseant for Cancer Chemotherapy

This is by far the best substantiated use of medical marijuana. There have been at least 31 human studies of marijuana and/or oral THC for cancer chemotherapy,[1] beginning with the pathbreaking work of Sallan and Zinberg, the first modern study of medical marijuana[2]. This doesn't count the studies in which the sponsors of Marinol got it FDA approved as "safe and effective" for cancer chemotherapy. Smoked marijuana was shown to be an effective anti-nauseant in 6 different state-sponsored clinical studies: [3] New Mexico (250 patients),[4] New York (199 patients),[5] California (98),[6] Tennessee (27),[7] Georgia (119),[8] and Michigan (165).[9]

Smoked marijuana was found to be superior to oral THC in the New Mexico and Tennessee studies, with efficacy rates of 90%. In New York and Tennessee, it was effective in patients who had not been helped by Marinol. In Michigan, patients found smoked marijuana preferable to a conventional prescription antinauseant
(Torecan). Other researchers have also reported smoked marijuana to be superior to THC.[10]

The California study was the least satisfactory, being highly biased towards oral THC (2000 patients were given oral THC, versus only 98 for marijuana): still, it found that marijuana was effective in 59% of patients, versus 57% for oral THC; however, 30% rated oral THC "highly effective," versus only 17% for marijuana. This is the only state study showing smoked marijuana inferior to Marinol.[11]

A survey of oncologists by Doblin and Kleiman reported that 44% of 1035 respondents had recommended marijuana to their patients (54% favored making it a prescription drug).[12]

2. Glaucoma

It is generally accepted - by the National Academy of Sciences and others -- that marijuana/THC reduces intraocular pressure (IOP), the basic aim of anti-glaucoma therapy.[13] This was shown in a series of experiments by Robert S. Hepler of UCLA, stemming from research aimed at finding out whether marijuana dilated pupils.[14] Hepler found a "statistically significant" drop in IOP in 429 subjects treated with marijuana or THC; a subset of 29 patients showed continued benefits during 94 days of treatment with no signs of tolerance.[15] The effects of THC/marijuana in reducing IOP were explored in a half-dozen other studies.[16]

Nonetheless, ophthalmologists have been reluctant to accept marijuana/THC because of its high psychoactivity. Efforts to develop topical cannabinoid eye drops as a non-psychoactive alternative have so far proven unfruitful.

The California Research Advisory Panel established a glaucoma research protocol under its cannabis research program of 1979-89, after finding interest in marijuana in its survey of ophthalmologists. The program flopped: only nine patients were treated; all chose to take Marinol instead of marijuana; and all eventually abandoned treatment.

3. AIDS & Appetite Stimulation

There have been no clinical studies on the use of marijuana for AIDS. Of course, one reason for this is that the government has blocked the study of Dr. Donald Abrams at the University of California at San Francisco by denying him access to research marijuana.

Nonetheless, Marinol has been FDA-approved as an appetite stimulant for treating AIDS wasting syndrome.[17]

There is also an extensive literature on smoked marijuana and appetite stimulation, including 4 clinical studies in which marijuana enhanced food intake and weight gain.[18]

Medical marijuana is widely used by AIDS patients. 80% of the SF Cannabis Buyers' Club's 11,000 customers are said to be PWAs.[19] A recent survey of HIV-positive gays in Australia found that onequarter were using marijuana therapeutically.[20]

Many AIDS patients prefer smoked marijuana to oral THC, due to its quickness of action, ease of controlling the dose, and absence of side-effects. In addition to appetite stimulation, many AIDS patients use marijuana for pain associated with neuropathy, shingles, etc.

An important concern about smoked marijuana that critics emphasize is the danger of respiratory infection in AIDS patients due to smoking. In particular, critics have cited a worrisome study by Caiaffa et al.,[21] showing a twofold increase in the rate of pneumonocystis carinii pneumonia (PCP) among HIV positive injection drug users who smoke illegal drugs (88% marijuana, 26% cocaine, 9% crack). There are a few problems with the study, notably that almost all of the subjects also smoked cigarettes; therefore, it's difficult to say whether the PCP was really due to marijuana.

In any case, these problems can be avoided by ingesting marijuana orally, which many AIDS patients in fact do. It's not clear whether oral marijuana has any medical benefits over Marinol, though it could certainly be more economical.

Another problem that critics like to emphasize is the supposed threat to PWAs posed by the immunosuppressive
properties of marijuana. Of course, these objections apply equally well to oral THC, which
has been approved for treatment of AIDS. Studies of THC’s effects on immunity have been contradictory, and do not lend themselves to easy interpretation.[22] There are hints that THC might actually help stimulate the immune system in some ways.[23]

Epidemiological studies have found no relation between marijuana use and development of AIDS.[24] One

recent study of 354 HIV-positive males actually found marijuana to be associated with a decreased rate of progression to AIDS, though the difference was not significant when adjusted for parameters reflecting the initial health of the study subjects.[25]

4. Muscle Spasticity, MS, Epilepsy & Spinal Injuries

The treatment of convulsions was the first major application of cannabis in Western medicine, attested by 19th-century authorities such as Dr. William O'Shaughnessy, the Ohio State Medical Committee, and Dr. John Russell Reynolds (who prescribed it to Queen Victoria for menstrual cramps).[26] Although well authenticated in traditional practice, modern research into this u sage has been scant, except for animal studies.

Altogether, there appear to be:

- 5 human case studies, involving a total of 8 patients, in which marijuana was reported to be useful for: epilepsy, multiple sclerosis, injury, and Tourette's syndrome;[27]
- 1 study in which 5 out of 8 spinal cord injury patients reported benefits from marijuana;[28]
- 3 more studies of THC for multiple sclerosis (total: 30 patients), in which benefits tended to be more subjective than objectively measurable;[29]
- 1 case study of THC for spinal cord injury[30]
- 2 clinical studies in which cannabidiol (CBD), a component of natural marijuana not found in Marinol, was found beneficial for grand mal epilepsy (15 subjects, double blind controls)31 and dystonia (5 patients, no controls).[32]
- 1 study in which a THC-related cannabinoid benefitted 2 out of 5 severely epileptic children;[33]
- 1 survey of 308 epileptic patients found that marijuana use appeared to delay the first onset of complex partial seizures.[34]
- 1 survey of 43 spinal cord injury patients at VA hospitals found that 56% smoked marijuana, and 88% reported that it reduced their muscle spasms.[35]

There have also been a couple of negative studies, finding no benefits of marijuana for Parkinsonism[36] or CBD for Huntington's corea.[37] Paradoxically, marijuana/THC has been reported to exacerbate spasticity or epilepsy on occasion, perhaps because of a rebound effect.

In a purported recent negative study on marijuana and multiple sclerosis, Dr. Harry Greenberg et al. at University of Michigan reported that marijuana impaired posture and balance in patients with spastic MS.[38] This should come as no surprise, since marijuana/THC also impairs balance in normal patients. In any event, MS patients don't use marijuana for posture/balance, but to reduce tremors and pain.

Cannabidiol:

There is considerable evidence from animal studies that CBD has distinctive anti-convulsant properties not found in THC.[39]

In addition, there is evidence that CBD can reduce the risk of panic reactions associated with THC. A study by Zuardi found that CBD reduces the anxiety-stimulating effects of THC, a leading cause of adverse reactions to Marinol.[40] This may be a reason why many patients prefer natural cannabis.

A controlled study of 15 insomniacs found that CBD helped subjects sleep better.[41]

5. Analgesia & Pain

Many patients report using marijuana for some form of pain relief. Cannabis was used as an analgesic from ancient times through the nineteenth century. This usage declined with the introduction of more potent opiates such as injected morphine. Cannabis continued to be regarded as a drug of choice for migraine into the 20th century.

Modern research is scant. Animal studies have tended to show analgesic effects, while human studies have been more conflicting:

- In a preliminary study by R. J. Noyes, patients reported that marijuana relieved migraine, menstrual cramps, postsurgical pain. [42]
- In a follow-up, Noyes found oral THC relieved chronic pain in 10 cancer patients.[43]
- In a second follow-up with 36 cancer patients, THC was as effective as codeine, but had more sideeffects.
[44]
- 2 other studies found marijuana and THC effective in reducing experimentally induced pain.[45]
- 1 study reported that 3 patients began to experience migraines only after giving up marijuana.[46]

Negative results have also been reported:

- 1 study failed to find THC beneficial for cancer pain, though it did help with depression and appetite.[47]
- 1 study found THC useless for artificially induced pain.[48]
- 1 study found marijuana increased sensitivity to electrically induced pain.[49]
- 1 study found CBD useless for neuropathic pain (10 patients).[50]

Inflammatory Diseases:

Marijuana is used by many patients for a wide variety of diseases characterized by inflammation. These include arthritis, rheumatism, lupus, multiple sclerosis, colitis, Crohn's disease, inflammatory gastritis, scleroderma, endometriosis, psoriasis, and pruritis. These diseases are thought to be auto-immune in nature. It is possible that the supposed immune suppressive properties of cannabis are beneficial for such conditions.

Unfortunately, there have been no clinical studies of this phenomenon. However, a variety of animal and

laboratory studies have shown that cannabinoids have anti-inflammatory properties.[51] One mouse study even suggested that a non-cannabinoid ingredient of marijuana may be involved.[52]

Asthma:

Although this isn't (and shouldn't be) an indication of choice for medical marijuana, three human studies have shown that smoking marijuana produces bronchodilation, thereby relieving asthma attacks.[53] Two other studies confirmed the same effects with THC.[54] Efforts to develop a smokeless THC inhaler proved unsuccessful.

Depression & Mental Illness:

Opponents of medical marijuana such as the CNOA have charged that marijuana causes depression. In fact, marijuana is more often used to treat depression; hence its notorious reputation as a euphoriant. Human studies have been inconsistent. One study found that marijuana helped relieve depression in cancer patients;[55] another found no benefit for clinical depression.[56]

A survey of 79 mental patients found that those who used marijuana reported relief from depression, anxiety, insomnia, and physical discomfort, as well as fewer hospitalizations;[57] a second survey also found fewer hospitalizations in schizophrenics who used marijuana.[58] Some psychiatrists are currently prescribing Marinol for depression.

A recent pilot study by the Unimed Corporation found that Marinol helped relieve mood disturbances and anorexia in 12 Alzheimer's patients.[59]

Violence:

Many opponents absurdly charge that marijuana aggravates violence. To this, the best answer is that of the National Academy of Science in Marihuana and Health (1982, p. 128):

"Both retrospective and experimental studies in human beings have failed to yield evidence that marijuana use leads to increased aggression. Most of these studies suggest quite the contrary effect. Marijuana appears to have a sedative effect, and it may reduce somewhat the intensity of angry feelings and the probability of interpersonal aggressive behavior."

Alcoholism & Drug Dependence:

Cannabis is often used as a substitute for other, more dangerous drugs, including prescription narcotics, opiates and alcohol. Cannabis has been proposed as a treatment for alcoholism as well as opiate addiction.[60] However, a single controlled study of cannabis to treat alcoholics proved unsuccessful.[61] There is some epidemiological evidence that substitution of marijuana for alcohol and o ther drugs tends to reduce drug abuse and accident costs.[62] Many cannabis buyers club members say they use marijuana as a substitute for prescription narcotics.[63]

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Footnotes

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3 For a summary, see Robert Randall, ed., *Marijuana, Medicine and the Law*, Vol . 2 (Galen Press, Wash. DC) 1989, pp. 36ff.

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5 New York: 199 patients evaluated; all had failed previous anti-nauseants (some also failed THC); marijuana 89.7%-100% effective at 3 hospitals. ACT Official State Reports, Vol II, Exhibit 15, "Evaluation of the Antiemetic Properties of Inhalation Marijuana in Cancer Patients Receiving Chemotherapy Treatment," NY Dept of Health, Office of Public Health, Chapter 810, Laws of 1980 Article 33-A, Public Health Law, September 1981; ACT Exhibit 16-C, "Impressions from the National Conference

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6 California: 98 patients received marijuana; 59% found effective against strong emetics; 57% of 257 patients found THC-only effective; 17% rated marijuana "very effective" vs 30% for THC. "Cannabis Therapeutic Research Program," Report to the Cal. Legislature by California Research Advisory Panel, Jan. 1989. See also Randall, Vol 2, pp. 55-63.
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Marinol vs. Natural Cannabis - Pros, Cons and Options for Patients

Marinol vs. Natural Cannabis

Pros, Cons and Options for Patients

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Introduction

Marinol[1] (dronabinol) is the only US FDA-approved synthetic cannabinoid. It is often marketed as a legal pharmaceutical alternative to natural cannabis.

Marinol is manufactured as a gelatin capsule containing synthetic delta-9-tetrahydrocannabinol (THC) in sesame oil. It is taken orally and is available in 2.5mg, 5mg and/or 10mg dosages. Marinol may be prescribed for the treatment of cachexia (weight loss) in patients with AIDS and for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Despite FDA approval[2], Marinol typically provides only limited relief to select patients, particularly when compared to natural cannabis and its cannabinoids. Marinol should remain a legal option for patients and physicians; however, federal and state laws should be amended to allow for those patients who are unresponsive to synthetic THC the ability to use natural cannabis and its cannabinoids as a medical therapy without fear of arrest and/or criminal prosecution. By prohibiting the possession and use of natural cannabis and its cannabinoids, patients are unnecessarily restricted to use a synthetic substitute that lacks much of the therapeutic efficacy of natural cannabis.

I. Marinol Lacks Several of the Therapeutic Compounds Available in Natural Cannabis

Chemical compounds in cannabis, known as cannabinoids, are responsible for its numerous therapeutic benefits. Scientists have identified 66 naturally occurring cannabinoids.[3]

The active ingredient in Marinol, synthetic delta-9-tetrahyrdocannabinol (THC), is an analogue of one such compound, THC. However, several other cannabinoids available in cannabis -- in addition to naturally occurring terpenoids (oils) and flavonoids (phenols) -- have also been clinically demonstrated to possess therapeutic utility. Many patients favor natural cannabis to Marinol because it includes these other therapeutically active cannabinoids.

For example, cannabidol (CBD) is a non-psychoactive cannabinoid that has been clinically demonstrated to have analgesic, antispasmodic, anxiolytic, antipsychotic, antinausea, and anti-rheumatoid arthritic properties.[4]

Animal and human studies have shown CBD to possess anti-convulsant properties, particularly in the treatment of epilepsy.5 Natural extracts of CBD, when administered in combination with THC, significantly reduce pain, spasticity and other symptoms in multiple sclerosis (MS) patients unresponsive to standard treatment medications.6

Clinical studies also demonstrate CBD to be neuroprotective against glutamate neurotoxicity7 (i.e. stroke), cerebral infarction8 (localized cell death in the brain), and ethanol-induced neurotoxicity,9 with CBD being more protective against glutamate neurotoxicity than either ascorbate (vitamin C) or alpha-tocopherol (vitamin E).10 Clinical trials have also shown CBD to possess anti-tumoral properties,11 inhibiting the growth of glioma (brain tumor) cells in a dose dependent manner and selectively inducing apoptosis (programmed cell death) in malignant cells.12

Additional cannabinoids possessing clinically demonstrated therapeutic properties include: cannabinol (anticonvulsant13 and anti-inflammatory14 activity); cannabichromine (anti-inflammatory15 and antidepressant16 activity); and cannabigerol (anti-tumoral17 and analgesic18 activity). Natural cannabis' essential oil components (terpenoids) exhibit anti-inflammatory properties19 and its flavonoids possess antioxidant activity.20 Emerging clinical evidence indicates that cannabinoids may slow disease progression21 in certain autoimmune and neurologic diseases, including multiple sclerosis22 (MS), Amyotrophic Lateral Sclerosis23 (Lou Gehrig's disease) and Huntington's Disease.24

Clinical data indicate that the synergism of these compounds is likely more efficacious25 than the administration of synthetic THC alone.26 For example, McPartland and Russo write: "Good evidence shows that secondary compounds in cannabis may enhance beneficial effects of THC. Other cannabinoid and non-cannabinoid compounds in herbal cannabis ... may reduce THC-induced anxiety, cholinergic deficits, and immunosuppression. Cannabis terpenoids and flavonoids may also increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide anti-inflammatory activity."27 In an *in vitro* model of epilepsy, natural cannabis extracts performed better than THC alone.28 In human trials, patients suffering from multiple sclerosis experienced greater symptomatic relief from sublingual natural cannabis extracts than from the administration of oral THC.29 In 2005, Health Canada approved the oral spray Sativex30 -- which contains precise ratios of the natural cannabinoid extracts THC and CBD, among other compounds -- for prescription use for MS-related symptoms.31

II. Marinol is More Psychoactive Than Natural Cannabis

Patients prescribed Marinol frequently report that its psychoactive effects are far greater than those of natural cannabis. Marinol's adverse effects include: feeling "high," drowsiness, dizziness, confusion, anxiety, changes in mood, muddled thinking, perceptual difficulties, coordination impairment, irritability, and depression.32 These psychoactive effects may last four to six hours.33 About one-third of patients prescribed Marinol report experiencing one or some of these adverse effects.34

Marinol’s oral route of administration is responsible, in part, for its heightened psychoactivity compared to inhaled cannabis. Once swallowed, Marinol passes from the stomach to the small intestine before being absorbed into the bloodstream. Following absorption, Marinol passes through the liver where a significant proportion of the drug is metabolized into other chemicals.35 One of these chemicals, 11-hydroxy-THC, may be four to five times more potent than natural THC,36 and is produced in greater quantities.37 Thus, patients administered Marinol experience the psychoactive effects of both THC and 11-hydroxy-THC, greatly increasing the likelihood that they will suffer from an adverse psychological reaction. By comparison, only minute quantities of 11-hydroxy-THC are produced when cannabis is inhaled.38 Moreover, Marinol lacks the compound cannabidiol, which possesses anxiolytic activity and likely modifies and/or diminishes much of THC's psychoactivity in natural cannabis.39

III. Cannabis Vaporization Offers Advantages Over Orally Administered THC

Vaporization is an alternative method of cannabis administration that holds distinct advantages over both smoking and oral administration. Cannabis vaporization suppresses respiratory toxins by heating cannabis to a temperature where cannabinoid vapors form (typically around 180-190 degrees Celsius), but below the point of combustion where noxious smoke and

associated toxins (i.e., carcinogenic hydrocarbons) are produced (near 230 degrees Celsius).40 Although a comprehensive review of cannabis and health conducted by the National Academy of Sciences Institute of Medicine found "no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use,"41 studies have found that heavy cannabis smokers face a higher risk of contracting bronchitis and respiratory illnesses.42 This risk is likely not due to the inhalation of cannabinoids, but rather to the exposure of noxious smoke. Because vaporization can deliver therapeutic doses of cannabinoids while reducing the users intake of pyrolytic smoke compounds, it is considered to be a preferred and likely safer method of cannabis administration than smoking.43

In practice, cannabis vaporization offers considerable advantages over oral THC consumption. While the oral ingestion of Marinol avoids the potential risks of smoking, it has significant drawbacks. Because of synthetic THC's poor bioavailability, only 5-20 percent of an oral dose ever reaches the bloodstream44 and the drug may not achieve peak effect until four hours after dosing.45 Moreover, because Marinol is metabolized slowly, its therapeutic and psychoactive effects may be unpredictable and vary considerably, both from one person to another, and in the same person from one episode of use to another.46 By contrast, cannabis vaporization delivers cannabinoids to the bloodstream almost instantaneously.47 Vaporization's rapid onset also allows patients to self regulate their dosage of cannabinoids by immediately ceasing inhalation when/if their psychoactive effects become unpleasant.48 After oral administration of Marinol, patients have no choice but to experience the full psychoactive effects of the dose consumed. These dysphoric effects may last several hours.

Because of its rapid onset, vaporized cannabis is more desirable than Marinol for patients requiring a fast-acting therapeutic agent, such as those combating oncoming attacks of nausea, seizures or muscle spasms. Cannabis vaporization also offers a unique advantage to patients suffering from nausea and vomiting because it allows them an alternative delivery route to swallowing. Cancer and HIV/AIDS patients often report that their stomachs cannot hold down Marinol capsules during bouts of severe nausea49 and many rely on natural cannabis and cannabinoids for symptom control.50 In a 1994 survey of oncologists, respondents ranked synthetic THC ninth on a list of available antiemetic medications.51 In another survey of oncologists, 44 percent of respondents said that they believed natural cannabis to be more efficacious than oral synthetic THC; only 13 percent of respondents rated Marinol more effective.52 A 1997 survey of physicians found that a majority preferred megestrol acetate over Marinol as an appetite stimulant in patients with HIV/AIDS.53

As a result of Marinol's slow onset and poor bioavailablity, scientists are now in the process of developing a new formulation of pulmonary dronabinol, delivered with a pressurized metered dose inhaler.54 In a Phase I study, pulmonary Marinol delivered via an inhaler provided rapid systemic absorption. Unlike oral synthetic THC, it's possible that pulmonary Marinol "could offer an alternative for patients when a fast onset of action is desirable."55 However, FDA approval of pulmonary Marinol and/or its inhaler remains years away. Sativex, an oral cannabis spray consisting of natural cannabinoid extracts, has greater bioavailability and is faster acting than oral synthetic THC. Clinical trials comparing its bioavailability and time of peak onset compared to vaporized cannabis have not been performed, though anecdotal reports indicate that vaporized cannabis and its cannabinoids likely possess greater bioavailability and are faster acting than the Sativex spray.

IV. Marinol is More Expensive Than Natural Cannabis

Synthetic THC is a costly and difficult compound to manufacture.56 Much of this cost is passed on to the patient consumer, particularly if the full cost of Marinol (approximately $200 to $800 per month,57 depending on the dosage) is borne out of pocket. Patients, particularly those with chronic conditions, often report that Marinol's market cost limits their use of the drug.58 Doctors also report that Marinol's high cost dissuades them from prescribing it to patients. In one survey of HIV/AIDS specialists, among respondents who had never prescribed Marinol to their patients, 33 percent cited the high cost of the drug as the reason.59 Natural cannabis, even at its inflated black market value, often remains far less costly for patients than oral synthetic THC.60

V. Patients Ultimately Prefer Natural Cannabis to Marinol

In the 1970s and 1980s, several states conducted patient trials61 of natural cannabis'

effectiveness as an anti-emetic in cancer patients unresponsive to conventional therapies. Some state protocols allowed patients to choose between inhaled cannabis[62] and synthetic THC. In those studies which compared natural cannabis to dronabinol, inhaled cannabis was equal to or better than the oral administration of synthetic THC.[63]

For example, researchers at the Tennessee Board of Pharmacy found a "23 percent higher success rate among those patients smoking than among those patients administered THC capsules" in the treatment of nausea and/or vomiting associated with cancer chemotherapy.[64]

Researchers in New Mexico observed similar findings. "When the routes of [drug] administration were analyzed separately, it was found that inhalation was far superior to ingestion: 90.39 percent of the patients in the group that inhaled the marijuana showed improvement while only 59.65 percent of the patients in the group that orally ingested the delta-9-THC showed improvement," they concluded.[65]

Researchers at the California Board of Pharmacy found that inhaled cannabis and oral THC produced similar results in patients. However, physicians still rated natural cannabis as slightly more effective than oral THC as an anti-emetic.[66]

A 1988 New York State pilot study comparing inhaled cannabis to oral THC in cancer chemotherapy patients who were unresponsive to standard antiemetic agents found: "Twenty-nine percent of patients who failed oral THC responded to the cigarette form. ... Our results demonstrate that inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy."[67]

Today, several patient populations continue to use natural cannabis and its cannabinoids in large numbers despite its illegality and the availability of Marinol. A 2005 British survey of more than 500 HIV/AIDS patients found that one-third of respondents use natural cannabis for symptomatic relief, with more than 90 percent of them reporting that it improves their appetite, muscle pain and other symptoms.[68] A previous US survey found that approximately one out of four patients with HIV had used natural cannabis medicinally in the past month.[69]

Cannabis use is also prevalent among patients with neurologic disorders. Nearly four out of ten Dutch patients with prescriptions for "medical grade cannabis" (cannabis provided by Dutch pharmacies with a standardized THC content of 10.2 percent) use it to treat MS or spinal cord injuries, according to survey data published in 2005 in the journal *Neurology*.[70] Perceived efficacy is greater among respondents who inhale cannabis versus those who ingest it orally, the study found.[71]

A 2002 British survey of MS patients found that 43 percent of respondents used natural cannabis therapeutically, with about half admitting they used it regularly.[72] Seventy-six percent said they would do so if cannabis were legal.[73] A Canadian survey of MS patients found that 96 percent of respondents were "aware cannabis was potentially therapeutically useful for MS and most (72 percent) supported [its] legalization for medicinal purposes."[74] Sixteen percent of respondents answered that they use natural cannabis for medical purposes to treat symptoms of anxiety/depression, spasticity and chronic pain.[75]

A more recent Canadian survey published in *Neurology* reported that 14 percent of MS[76] patients and 21 percent of respondents with epilepsy had used medical cannabis in the past year.[77] Among epileptics, twenty-four percent of respondents said that they believed that cannabis was an effective therapy for the disease.[78] A 2002 survey of patients with Parkinson's Disease (PD) found that 25 percent of respondents had tried cannabis, with nearly half of those saying that it provided them symptomatic relief.[79]

Conclusion

Oral synthetic THC, legally available by prescription as Marinol, often provides only limited relief to a select group of patients, particularly when compared to natural cannabis and its cannabinoids. Patients often experience minimal relief from Marinol and many experience unwanted side effects. In addition, many physicians are hesitant to prescribe the drug, and some patients are unable to afford it. Despite Marinol's legality, many patient populations continue to risk arrest and criminal prosecution to use natural cannabis medically, and most report experiencing greater therapeutic relief from it.

The active ingredient in Marinol is a synthetic analogue of only one of the compounds in

cannabis that is therapeutically beneficial to patients. By prohibiting the possession and use of natural cannabis and its cannabinoids, patients are unnecessarily burdened to use a synthetic substitute that lacks much of the therapeutic efficacy of natural cannabis and its cannabinoids.

Marinol should remain a legal option for patients and physicians and the development of additional cannabis-based pharmaceuticals should be encouraged. However, federal and state laws should be amended to allow for those patients who are unresponsive to synthetic THC, or simply desire an alternative to oral dronabinol, the ability to use natural cannabis and its cannabinoids as a legal medical therapy without fear of arrest and/or criminal prosecution.

Endnotes

1 Marinol is produced and marketed by Unimed Pharmaceuticals, a subsidiary of Solvay Pharmaceuticals.

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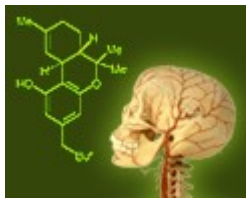
NORML's Statement on the Medical Use of Marijuana - Science Supports Amending Federal Law

NORML's Statement on the Medical Use of Marijuana - Science Supports Amending Federal Law

Introduction

PDF



"Federal authorities should rescind their prohibition of the medical use of marijuana for seriously ill patients and allow physicians to decide which patients to treat. The government should change marijuana's status from that of a Schedule I drug ... to that of a Schedule II drug ... and regulate it accordingly."
- *The New England Journal of Medicine*, January 30, 1997

Introduction

Marijuana prohibition applies to everyone, including the sick and dying. Of all the negative consequences of prohibition, none is as tragic as the denial of medicinal cannabis to the tens of thousands of patients who could benefit from its therapeutic use.

Evidence Supporting Marijuana's Medical Value

Top

Written references to the use marijuana as a medicine date back nearly 5,000 years.[1] Western medicine embraced marijuana's medical properties in the mid-1800s, and by the beginning of the 20th century, physicians had published more than 100 papers in the Western medical literature recommending its use for a variety of disorders.[2] Cannabis remained in the United States pharmacopoeia until 1941, removed only after Congress passed the Marihuana Tax Act which severely hampered physicians from prescribing it. The American Medical Association (AMA) was one of the most vocal organizations to testify against the ban, arguing that it would deprive patients of a past, present and future medicine.[3]

Modern research suggests that cannabis is a valuable aid in the treatment of a wide range of clinical applications.[4] These include pain relief -- particularly of neuropathic pain (pain from nerve damage) -- nausea, spasticity, glaucoma, and movement disorders.[5] Marijuana is also a powerful appetite stimulant, specifically for patients suffering from HIV, the AIDS wasting syndrome, or dementia.[6] Emerging research suggests that marijuana's medicinal properties may protect the body against some types of malignant tumors[7] and are neuroprotective.[8]

Currently, more than 60 U.S. and international health organizations -- including the American Public Health Association [9] , Health Canada[10] and the Federation of American Scientists[11] -- support granting patients immediate legal access to medicinal marijuana under a physician's supervision. (Click here for a complete listing of organizations.) Several others, including the American Cancer Society[12] and the American Medical Association[13] support the facilitation of wide-scale, clinical research trials so that physicians may better assess cannabis' medical potential. In addition, a 1991 Harvard study found that 44 percent of oncologists had previously advised marijuana therapy to their patients.[14] Fifty percent responded they would do so if marijuana was legal. A more recent national survey performed by researchers at Providence Rhode Island Hospital found that nearly half of physicians with opinions supported legalizing medical marijuana.[15]

Government Commissions Back Legalization

Top

Virtually every government-appointed commission to investigate marijuana's medical potential has issued favorable findings. These include the U.S. Institute of Medicine in 1982[16] the Australian National Task Force on Cannabis in 1994[17] and the U.S. National Institutes of

Health Workshop on Medical Marijuana in 1997.[18]

More recently, Britain's House of Lord's Science and Technology Committee found in 1998 that the available evidence supported the legal use of medical cannabis.[19] MPs determined: "The government should allow doctors to prescribe cannabis for medical use. ... Cannabis can be effective in some patients to relieve symptoms of multiple sclerosis, and against certain forms of pain. ... This evidence is enough to justify a change in the law."[20] The Committee reaffirmed their support in a March 2001 follow-up report criticizing Parliament for failing to legalize the drug.[21]

U.S. investigators reached a similar conclusion in 1999. After conducting a nearly two-year review of the medical literature, investigators at the National Academy of Sciences, Institute of Medicine affirmed: "Scientific data indicate the potential therapeutic value of cannabinoid drugs ... for pain relief, control of nausea and vomiting, and appetite stimulation. ... Except for the harms associated with smoking, the adverse effects of marijuana use are within the range tolerated for other medications."[22] Nevertheless, the authors noted cannabis inhalation "would be advantageous" in the treatment of some diseases, and that marijuana's short- term medical benefits outweigh any smoking-related harms for some patients. Predictably, federal authorities failed to act upon the IOM's recommendations, and instead have elected to continue their long-standing policy of denying marijuana's medical value.

Administrative Ruling Supports Medical Use Top

NORML first raised this issue in 1972 in an administrative petition filed with the Drug Enforcement Administration. NORML's petition called on the federal government to reclassify marijuana under the Controlled Substances Act as a Schedule II drug so that physicians could legally prescribe it. Federal authorities initially refused to accept the petition until mandated to do so by the US Court of Appeals in 1974, and then refused to properly process it until again ordered by the Court in 1982.

Fourteen years after NORML's initial petition in 1986, the DEA finally held public hearings on the issue before an administrative law judge. Two years later, Judge Francis Young ruled that the therapeutic use of marijuana was recognized by a respected minority of the medical community, and that it met the standards of other legal medications. Young found: "Marijuana has been accepted as capable of relieving distress of great numbers of very ill people, and doing so with safety under medical supervision. It would be unreasonable, arbitrary and capricious for DEA to continue to stand between those sufferers and the benefits of this substance in light of the evidence in this record."[23] Young recommended, "The Administrator transfer marijuana from Schedule I to Schedule II, to make it available as a legal medicine."

DEA Administrator John Lawn rejected Young's determination, choosing instead to invoke a differing set of criteria than those used by Judge Young. The Court of Appeals allowed Lawn's reversal to stand, effectively continuing the federal ban on the medical use of marijuana by seriously ill patients. It is urgent that state legislatures and the federal government act to correct this injustice.

Public Support for Medical Marijuana Top

Since 1996, voters in fourteen states -- Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont and Washington -- have adopted initiatives exempting patients who use marijuana under a physician's supervision from state criminal penalties. (Click here for a summary of state medical marijuana laws.) These laws do not legalize marijuana or alter criminal penalties regarding the possession or cultivation of marijuana for recreational use. They merely provide a narrow exemption from state prosecution for defined patients who possess and use marijuana with their doctor's recommendation. Available evidence indicates that these laws are functioning as voters intended, and that reported abuses are minimal.

As the votes in these states suggest, the American public clearly distinguishes between the medical use and the recreational use of marijuana, and a majority support legalizing medical use for seriously ill patients. A March 2001 Pew Research Center poll[24] reported that 73 percent of Americans support making marijuana legally available for doctors to prescribe, as did a 1999 Gallup poll.[25] Similar support has been indicated in every other state and nationwide poll that has been conducted on the issue since 1995. (Click here for a complete

listing of polls.) Arguably, few other public policy issues share the unequivocal support of the American public as this one.

Medical Marijuana and the Supreme Court Top

The Supreme Court ruled on May 14, 2001 that federal law makes no exceptions for growing or distributing marijuana by third party organizations (so-called "cannabis buyers' cooperatives"), even if the goal is to help seriously ill patients using marijuana as a medicine. Nevertheless, the Court's decision fails to infringe upon the rights of individual patients to use medical cannabis under state law, or the ability of legislators to pass laws exempting such patients from criminal penalties. This fact was affirmed by Justices Stevens, Ginsburg and Souter, who wrote in a concurring opinion: "By passing Proposition 215, California voters have decided that seriously ill patients and their primary caregivers should be exempt from prosecution under state laws for cultivating and possessing marijuana. ... This case does not call on the Court to deprive all such patients of the benefit of the necessity defense to federal prosecution when the case does not involve any such patients."

NORML filed an amicus curiae (friend of the court) brief in this case, and hoped the Court would protect California's patient-support efforts from federal prosecution. The sad result of this decision is that tens of thousands of seriously ill patients who use marijuana to relieve their pain and suffering no longer have a safe and secure source for their medical marijuana. NORML calls on our elected officials to correct this injustice and is currently lobbying Congress to legalize marijuana as a medicine.

Endnotes

1. L. Grinspoon and J. Bakalar. 1997. *Marihuana the Forbidden Medicine* (second edition). New Haven, CT: Yale University Press; B. Zimmerman et al. 1998. Is Marijuana the Right Medicine for You? A Factual Guide to Medical Uses of Marijuana. New Canaan, CT: Keats Publishing.

2. T. Mikuriya. (Ed.) 1973. *Marijuana: Medical Papers 1839-1972*. Oakland: Medi-Comp Press.

3. AMA (American Medical Association) Legislative Counsel William C. Woodword told Congress on July 12, 1937: **"The obvious purpose of and effect of this bill is to impose so many restrictions on the medicinal use [of cannabis] as to prevent such use altogether. ... It may serve to deprive the public of the benefits of a drug that on further research may prove to be of substantial benefit."**

4. Several books explore this issue in further detail. These include: A. Mack and J. Joy. 2001. *Marijuana as Medicine: The Science Beyond the Controversy*. Washington, DC: National Academy Press; L. Iverson. 2000. The Science of Marijuana. New York: Oxford University Press; B. Zimmerman et al. 1998. *Is Marijuana the Right Medicine for You?*; C. Conrad. 1997. *Hemp for Health: The Medicinal and Nutritional Uses of Cannabis Sativa*. Rochester VT: Healing Arts Press; L. Grinspoon and J. Bakalar J. 1997. *Marihuana the Forbidden Medicine*; E. Rosenthal et al. 1997. Marijuana Medical Handbook. Oakland: Quick American Archives; and R. Mechoulam. (Ed.) 1986. *Cannabinoids as Therapeutic Agents*. Boca Raton: CRC Press.

5. NSW (New South Wales) Working Party on the Use of Cannabis for Medicinal Purposes. 2000. *Report of the Working Party on the Use of Cannabis for Medical Purposes*. Sydney: Parliament House; J. Joy et al. 1999. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; House of Lords Select Committee on Science and Technology. 1998. Ninth Report. *Cannabis: The Scientific and Medical Evidence*. London: The Stationary Office; J. Morgan and L. Zimmer. 1997. *Marijuana Myths, Marijuana Facts: A Review of the Scientific Evidence*. New York: Lindesmith Center; Grinspoon and Bakalar. 1997. *Marihuana the Forbidden Medicine*.

6. Joy et al. 1999. *Marijuana and Medicine: Assessing the Science Base*.

7. I. Galve-Roperph et al. 2000. Antitumoral action of cannabinoids: involvement of sustained ceramide accumulation of ERK activation. *Nature Medicine* 6: 313-319.

8. M. Van der Stelt et al. 2001. Neuroprotection by delta-9 tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. *The Journal of Neuroscience* 21: 6475-6479; J. Joy et al. 1999. *Marijuana and Medicine: Assessing the Science Base*.

9. APHA (American Public Health Association) Resolution 9513: "Access to Therapeutic

Marijuana/Cannabis," adopted November 1995 states in part, **"[The APHA] encourages research of the therapeutic properties of various cannabinoids and combinations of cannabinoids, and ... urges the Administration and Congress to move expeditiously to make cannabis available as a legal medicine."**

10. Health Canada legalized the possession and cultivation of medical marijuana on July 31, 2001.

11. The FAS' (Federation of American Scientists) position on medical marijuana, adopted November 1994, states in part: **"Based on much evidence, from patients and doctors alike, on the superior effectiveness and safety of whole cannabis compared to other medications, ... the President should instruct the NIH and the Food and Drug Administration to make efforts to enroll seriously ill patients whose physicians believe that whole cannabis would be helpful to their conditions in clinical trials, both to allow data-gathering and to provide an alternative to the black market while the scientific questions about the possible utility of cannabis are resolved."**

12. In a July 24, 1997 letter to California Senator John Vasconcellos, American Cancer Society Legislative Advocate Theresa Renken wrote: **"[California Senate Bill] 535 focuses on medical marijuana research. [The] American Cancer Society ... Supports S.B. 535 because it is consistent with our long-held position of supporting research of any agent or technique for which there may be evidence of a therapeutic advantage."**

13. AMA (American Medical Association) Council on Scientific Affairs 1997 Report #10: Medical Marijuana contains the following statements supporting a physician's right to freely discuss marijuana therapy with a patient, and favoring further research into medical marijuana's therapeutic potential: **"The AMA recommend that adequate and well-controlled studies of smoked marijuana be conducted in patients who have serious conditions for which preclinical, anecdotal or controlled evidence suggests possible efficacy, including AIDS wasting syndrome, severe acute or delayed emesis induced by chemotherapy, multiple sclerosis, spinal cord injury, dystonia and neuropathic pain."**

14. R. Doblin and M. Kleiman. 1991. Marijuana as anti-emetic medicine: a survey of oncologists attitudes and experiences. *Journal of Clinical Oncology* 9: 1275-1280.

15. Reuters News Wire. April 23, 2001. "Physicians divided on medical marijuana."

16. **"Cannabis and its derivatives have shown promise in a varieties of disorders. The evidence is most impressive in glaucoma, ... asthma, ... and in [combating] the nausea and vomiting of cancer chemotherapy. ... Smaller trials have suggested cannabis might also be useful in seizures, spasticity, and other nervous system disorders."** Conclusion of the National Academy of Sciences Institute of Medicine. 1982. *Marijuana and Health*. Washington, DC: National Academy Press.

17. **"First, there is good evidence that THC is an effective anti-emetic agent for patients undergoing cancer chemotherapy. ... Second, there is reasonable evidence for the potential efficacy of THC and marijuana in the treatment of glaucoma, especially in cases which have proved resistant to existing anti-glaucoma agents. Further research is ... required, but this should not prevent its use under medical supervision. ... Third, there is sufficient suggestive evidence of the potential usefulness of various cannabinoids as analgesic, anti- asthmatic, anti-spasmodic, and anti-convulsant agents."** W. Hall et al. 1994. *The health and psychological consequences of cannabis use: Monograph prepared for the National Task for on Cannabis*. Canberra: Australian Government Publishing Service.

18. **"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, nausea and vomiting following anti-cancer therapy, neurological and movement disorders, analgesia [and] glaucoma."** Conclusions of the National Institutes of Health. 1997. *Workshop on the Medical Utility of Marijuana: Report to the Director*. Bethesda: National Institutes of Health.

19. House of Lords Select Committee on Science and Technology. 1998. Ninth Report: *Cannabis: the Scientific and Medical Evidence*. London: The Stationary Office.

20. "Lords Say, Legalise Cannabis for Medical Use." 1998. Press Release. House of Lords Select Committee on Science and Technology Press Office.

21.**"We are concerned that the MCA [Medicines Control Agency] approach to the licensing of cannabis-based medicines ... place the requirements of safety and the needs of patients in an unacceptable balance. ... Patients with severe conditions such as multiple sclerosis are being denied the right to make informed choices about their medication. There is always some risk in taking any medication, ... but these concerns should not prevent them from having access to what promises to be the only effective medication available to them."** Conclusion of the British House of Lords Select Committee on Science and Technology. 2001. Second Report: Therapeutic Uses of Cannabis. London: The Stationary Office.

22. J. Joy et al. 1999. *Marijuana and Medicine: Assessing the Science Base*.

23. In the Matter of Marihuana Rescheduling Petition, Docket 86-22, Opinion, Recommended Ruling, Findings of Fact, Conclusions of Law, and Decision of Administrative Law Judge, September 6, 1988. Washington, DC: Drug Enforcement Administration.

24. Seventy-three percent of respondents supported allowing doctors "to prescribe marijuana." Sample size: 1,513.

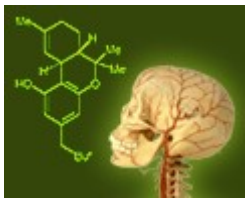
25. Seventy-three percent of respondents said they "would vote for making marijuana legally available for doctors to prescribe." Sample size: 1,018. Released March 1999.

updated: **Jan 30, 2010**

Guest Editorial in the Journal of American Medical Association, by L. Grinspoon, M.D. "Marijuana as Medicine -- A Plea for Reconsideration" (June 21, 1995)

Marijuana as Medicine - A Plea for Reconsideration

Guest Editorial in the Journal of
American Medical Association
by L. Grinspoon MD



JAMA, June 21, 1995
Vol 273, No. 23
Lester Grinspoon, MD
James B. Bakalar, JD

Between 1840 and 1900, European and American medical journals published more than 100 articles on the therapeutic use of the drug known then as Cannabis indica (or Indian hemp) and now as marihuana. It was recommended as an appetite stimulant, muscle relaxant, analgesic, hypnotic, and anticonvulsant. As late as 1913 Sir William Osler recommended it as the most satisfactory remedy for migraine.

Today the 5000 year medical history of cannabis has been almost forgotten. Its use declined in the early 20th century because the potency of preparations was variable, responses to oral ingestion were erratic, and alternatives became available -- injectable opiates and, later, synthetic drugs such as aspirin and barbiturates. In the United States, the final blow was struck by the Marihuana Tax Act of 1937. Designed to prevent nonmedical use, this law made cannabis so difficult to obtain for medical purposes that it was removed from the pharmacopeia. It is now confined to Schedule I under the Controlled Substances Act as a drug that has a high potential for abuse, lacks an accepted medical use, and is unsafe for use under medical supervision.

In 1972 the National Organization for the Reform of Marijuana Laws petitioned the Bureau of Narcotics and Dangerous Drugs, later renamed the Drug Enforcement Administration (DEA), to transfer marihuana to Schedule II so that it could be legally prescribed. As the proceedings continued, other parties joined, including the Physicians Association for AIDS (Acquired Immunodeficiency Syndrome) Care. It was only in 1986, after many years of legal maneuvering, that the DEA acceded to the demand for the public hearings required by law. During the hearings, which lasted 2 years, many patients and physicians testified and thousands of pages of documentation were introduced. In 1988 the DEA's own administrative law judge, Francis L. Young, declared that marihuana in its natural form fulfilled the legal requirement of currently accepted medical use in treatment in the United States. He added that it was "one of the safest therapeutically active substances known to man."[1] His order that the marihuana plant be transferred to Schedule II was overruled, not by any medical authority, but by the DEA itself, which issued a final rejection of all pleas for reclassification in March 1992.

Meanwhile, a few patients have been able to obtain marihuana legally for therapeutic purposes. Since 1978, legislation permitting patients with certain disorders to use marihuana with a physician's approval has been enacted in 36 states.

Although federal regulations and procedures made the laws difficult to implement, 10 states eventually established formal marihuana research programs to seek Food and Drug Administration (FDA) approval for Investigational New Drug (IND) applications. These programs were later abandoned, mainly because the bureaucratic burden on physicians and patients became intolerable.

Growing demand also forced the FDA to institute an Individual Treatment IND (commonly referred to as a Compassionate IND) for the use of physicians whose patients needed marihuana because no other drug would produce the same therapeutic effect. The application process was made enormously complicated, and most physicians did not want to become involved, especially since many believed there was some stigma attached to prescribing

cannabis. Between 1976 and 1988 the government reluctantly awarded about a half dozen Compassionate INDs for the use of marihuana. In 1989 the FDA was deluged with new applications from people with AIDS, and the number granted rose to 34 within a year. In June 1991, the Public Health Service announced that the program would be suspended because it undercut the administration's opposition to the use of illegal drugs.
After that no new Compassionate INDs were granted, and the program was discontinued in March 1992. Eight patients are still receiving marihuana under the original program; for everyone else it is officially a forbidden medicine.

And yet physicians and patients in increasing numbers continue to relearn through personal experience the lessons of the 19th century. Many people know that marihuana is now being used illegally for the nausea and vomiting induced by chemotherapy. Some know that it lowers intraocular pressure in glaucoma. Patients have found it useful as an anticonvulsant, as a muscle relaxant in spastic disorders, and as an appetite stimulant in the wasting syndrome of human immunodeficiency virus infection. It is also being used to relieve phantom limb pain, menstrual cramps, and other types of chronic pain, including (as Osler might have predicted) migraine.2 Polls and voter referenda have repeatedly indicated that the vast majority of Americans think marihuana should be medically available.

One of marihuana's greatest advantages as a medicine is its remarkable safety. It has little effect on major physiological functions. There is no known case of a lethal overdose; on the basis of animal models, the ratio of lethal to effective dose is estimated as 40,000 to l. By comparison, the ratio is between 3 and 50 to 1 for secobarbital and between 4 and 10 to l for ethanol. Marihuana is also far less addictive and far less subject to abuse than many drugs now used as muscle relaxants, hypnotics, and analgesics. The chief legitimate concern is the effect of smoking on the lungs. Cannabis smoke carries even more tars and other particulate matter than tobacco smoke. But the amount smoked is much less, especially in medical use, and once marihuana is an openly recognized medicine, solutions may be found. Water pipes are a partial answer; ultimately a technology for the inhalation of cannabinoid vapors could be developed. Even if smoking continued, legal availability would make it easier to take precautions against aspergilli and other pathogens. At present, the greatest danger in medical use of marihuana is its illegality, which imposes much anxiety and expense on suffering people, forces them to bargain with illicit drug dealers, and exposes them to the threat of criminal prosecution.

The main active substance in cannabis, 9-tetrahydrocannabinol (9-THC), has been available for limited purposes as a Schedule II synthetic drug since 1985. This medicine, dronabinol (Marinol), taken orally in capsule form, is sometimes said to obviate the need for medical marihuana. Patients and physicians who have tried both disagree. The dosage and duration of action of marihuana are easier to control, and other cannabinoids in the marihuana plant may modify the action of 9-THC. The development of cannabinoids in pure form should certainly be encouraged, but the time and resources required are great and at present unavailable. In these circumstances, further isolation, testing, and development of individual cannabinoids should not be considered a substitute for meeting the immediate needs of suffering people.

Although it is often objected that the medical usefulness of marihuana has not been demonstrated by controlled studies, several informal experiments involving large numbers of subjects suggest an advantage for marihuana over oral 9-THC and other medicines. For example, from 1978 through 1986 the state research program in New Mexico provided marihuana or synthetic 9-THC to about 260 cancer patients receiving chemotherapy after conventional medications failed to control their nausea and vomiting. A physician who worked with the program testified at a DEA hearing that for these patients marihuana was clearly superior to both chlorpromazine and synthetic 9-THC.[3] It is true that we do not have studies controlled according to the standards required by the FDA -- chiefly because legal, bureaucratic, and financial obstacles are constantly put in the way. The situation is ironic, since so much research has been done on marihuana, often in unsuccessful attempts to prove its dangerous and addictive character, that we know more about it than about most prescription drugs.

Physicians should offer more encouragement to controlled research, but it too has limitations. Individual therapeutic responses can be obscured by the statistical results of group experiments in which there is little effort to identify the specific features of a patient that affect

the drug response.

Furthermore, much of our knowledge of synthetic medicines as well as plant derivatives comes from anecdotal evidence. For example, as early as 1976 several small, methodologically imperfect, and relatively obscure studies had shown that taking an aspirin a day could prevent a second heart attack. In 1988 a large-scale experiment demonstrated dramatic effects. This story is suggestive, because marihuana, like aspirin, is a substance known to be unusually safe and to have enormous potential health benefits.

Cannabis can also bring about immediate relief of suffering measurable in a study with only one subject. In the experimental method known as the single-patient randomized trial, active and placebo treatments are administered randomly in alternation or succession to a patient. The method is often useful when large-scale controlled studies are impossible or inappropriate because the disorder is rare, the patient is atypical, or the response to the treatment is idiosyncratic. Many patients, either deliberately or because of unreliable supplies, have informally carried out somewhat similar experiments by alternating periods of cannabis use with periods of no use in the treatment of various disorders.[2]

The American Medical Association was one of the few organizations that raised a voice in opposition to the Marihuana Tax Act of 1937, yet today most physicians seem to take little active interest in the subject, and their silence is often cited by those who are determined that marihuana shall remain a forbidden medicine. Meanwhile, many physicians pretend to ignore the fact that their patients with cancer, AIDS, or multiple sclerosis are smoking marihuana for relief; some quietly encourage them. In a 1990 survey, 44% of oncologists said they had suggested that a patient smoke marihuana for relief of the nausea induced by chemotherapy.[4] If marihuana were actually unsafe for use even under medical supervision, as its Schedule I status explicitly affirms, this recommendation would be unthinkable. It is time for physicians to acknowledge more openly that the present classification is scientifically, legally, and morally wrong.

Physicians have both a right and a duty to be skeptical about therapeutic claims for any substance, but only after putting aside fears and doubts connected with the stigma of illicit nonmedical drug use. Advocates of medical use of marihuana are sometimes charged with using medicine as a wedge to open a way for "recreational" use. The accusation is false as applied to its target, but expresses in a distorted form a truth about some opponents of medical marihuana: they will not admit that it can be a safe and effective medicine largely because they are stubbornly committed to exaggerating its dangers when used for nonmedical purposes.

We are not asking readers for immediate agreement with our affirmation that marihuana is medically useful, but we hope they will do more to encourage open and legal exploration of its potential. The ostensible indifference of physicians should no longer be used as a justification for keeping this medicine in the shadows.

Endnotes:

1. In the Matter of Marihuana Rescheduling Petition, Docket 86-22 opinion, Recommended Ruling, Findings of Fact, Conclusions of Law, and Decision of Administrative Law Judge, September 6, 1988. Washington, DC: Drug Enforcement Agency; 1988.

2. Grinspoon L, Bakalar J. Marihuana, the Forbidden Medicine. New Haven, Conn Yale University Press, 1993. (pp133-136)

3. In the Matter of Marihuana Rescheduling Petition Docket 86-22, Affidavit of Daniel Dansac, M.D. Washington, DC: Drug Enforcement Agency; 1987.

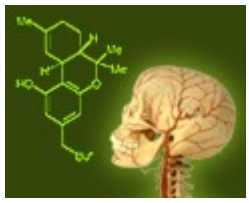
4. Doblin R, Kleiman MAR. Marihuana as anti-emetic medicine; a survey of oncologists' attitudes and experiences. J Clin Oncol. 1991;9:1276-1290.

News magazine article, "The more things change, the more they stay the same..."

The more things change, the more they stay the same...

Out Of Joint

The case for medicinal marijuana.
By Brian Hecht



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Last week the Public Health Service announced that it will phase out its program of allowing seriously ill patients to smoke marijuana. The reason seems to have little to do with the effectiveness of pot in relieving various medical symptoms and a lot to do with the politics of the "drug war." With the recent attention pot has received as an appetite enhancer in AIDS cases, the government correctly anticipated a flood of applications from AIDS patients for "compassionate" approval of the drug. AIDS activists, who have had much success in liberalizing the prescription drug approval process, may have met their match.

The debate over the medical use of marijuana started two decades ago and has hinged on its effectiveness in treating glaucoma, spasticity, and chemotherapy-induced nausea. Pot, like heroin, is classified by the Drug Enforcement Administration as a Schedule I drug, which means it has a high potential for abuse, induces harmful side effects, and has "no currently accepted medical use in treatment in the United States. "Pot advocates argue that marijuana should be moved to the category of Schedule II drugs, which also have a high potential for abuse and can have bad side effects, but are considered to be useful medically and thus can be prescribed by physicians. Interestingly, cocaine -- the drug war's No. 1 bogey -- is a Schedule II drug.

In 1985 the government did recognize that the principal active ingredient in marijuana -delta-9-tetrahydrocannabinol, or THC-has medical use. A synthetic drug containing THC is now available by prescription under the name Marinol, manufactured by Unimed Pharmaceuticals.

Why does the government allow THC pills but not marijuana joints? THC has been put through a level of testing acceptable to the Food and Drug Administration. Because of the expense, this typically requires a pharmaceutical-industry corporate sponsor, which pot -- a plant that grows like a weed and requires no processing -- is unlikely to attract.

Nevertheless, in response to a 1972 petition for rescheduling filed by NORML and other pot advocacy groups, in 1988 DEA administrative law judge Francis L. Young ruled that the ban on prescription pot is "unreasonable, arbitrary, and capricious."

The DEA chose to ignore his recommendation for rescheduling, calling the medical use of marijuana a "cruel and dangerous hoax." Then this April the U.S. Court of Appeals in D.C. ordered the DEA to change three of its eight criteria for reclassification. Under those three criteria, a drug can be removed from Schedule I only if it is generally (i.e., legally available and used in the medical community; by definition, the court noted, these are conditions that an illegal drug can never meet. The decision might appear to be a big victory for the medical rise of marijuana. But the court did approve five of the DEA criteria, and pot advocates, who think the DEA will have no trouble reshaping the other three to satisfy the court, see this judicial path to rescheduling as effectively closed.

The only other path (short of congressional action) is through the FDA, which has the authority to tell the DEA that a drug has "currently accepted medical use" and that it should be rescheduled. The hope among pot and AIDS activists had been that the onslaught of "compassionate" approval applications by AIDS patients and their doctors -- which began last year when two AIDS patients, Barbara and Kenny Jenks, were arrested for growing marijuana to treat themselves -- would force the FDA to recognize marijuana's medical use. Instead, the Public Health Service, which oversees the FDA, has supported its decision with the same

argument the DEA has been using for years: evidence of the medical value of marijuana is purely anecdotal and the drug has not been rendered safe.

Pot advocates acknowledge that although there is copious research on marijuana, they are short on the kinds of institutionally sponsored studies that would typically satisfy the FDA. And since marijuana treatment of appetite loss in AIDS patients is very new, there are no formal studies. Nevertheless, there is plenty of evidence to suggest that the medical benefits of using marijuana outweigh the risks. The debate can be boiled down to three questions

1. Is the drug safe?
2. Does it work? and
3. How does it compare with other available drugs?

The DEA argues that marijuana contains more than 400 chemicals, which appear in widely varying proportions and whose chemical properties are not completely known, Marijuana's side effects, it claims, are intensive, though not fully understood. Pot causes acute changes in heart and circulation rates, has "produced genetic and non-genetic birth defects in many animal species," can reduce sperm count, and "may also have a toxic effect on the human brain." Lately the government, especially Herbert Kleber of the Office of National Drug Control Policy, has been pointing out the irony of using marijuana -- which itself suppresses the immune system -- in treating Acquired Immune Deficiency Syndrome.

Although pot advocates dispute the extent of marijuana's side effects, they point out that all drugs have side effects, and that in the case of pot, as with other drugs, such reactions (even immune suppression) need to be weighed against the benefits. They note that government-approved THC also suppresses the immune system (it gets you high too.) They add that common anti-emetic (anti- vomiting) drugs such as Compazine and Decadron can have side effects far worse than those of marijuana, such as liver damage and death. Dr. Ivan Silverberg, an oncologist who has spoken with hundreds of cancer patients who use marijuana, testified in 1988 that "the only side effect I've seen would bill be sedation," which he characterized as "mild." A study conducted by the state of 'New Mexico found adverse effects in only three of 250 patients tested.

And if we may venture into the realm of "anecdotal" evidence, it is worth noting that tens of million of Americans -- including U.S. senators, prospective Supreme Court judges, and maybe even First Ladies -- have smoked pot without suffering noticeable damage. No one has ever died of a marijuana overdose; the lethal dosage is so high that no human could ever smoke enough pot to kill himself.

So is pot effective? The DEA, argues that its use in treating nausea, glaucoma, and spasticity has not been sufficiently proved by double-blind studies.

And the evidence for AIDS treatment, it claims, is nonexistent. Yet in 1973, Dr. Leo E. Hollister of the Veterans Administration Hospital in Palo Alto proved scientifically what anyone who has ever smoked pot will tell you: marijuana gives you the munchies. Dr. Ernest Abel of Berkeley confirmed Hollister's results later that year. In a now famous 1975 study, Drs. Steven Sallan and Norman Zinberg at Boston's Sidney Farber Cancer Research Center also confirmed that pot is effective as an anti-emetic. And a 1979 double-blind and placebo-controlled study by Dr. Alfred Chang of the National Cancer Institute confirmed the 1975 results. Several states, including New Mexico, Michigan, and New York, in independent studies over the last twenty years, have also proved pot's effectiveness as an anti-emetic. And besides, notes Dr. John Morgan of CUNY Medical School, there is no rule that saves a drug must be the best at what it does to warrant approval. If it is effective in even a small number of cases, it deserves serious attention as a therapeutic product.

The new Health and Human Services policy directive says that patients applying for medicinal marijuana must first try Marinol. But pot advocates point out that marijuana is more effective than Marinol. In a 1988 study by Dr. Vincent Vinciguerra published in the New York State Journal of Medicine, 29 percent of those who did not respond to oral THC did respond to smoked marijuana. The NCI/Chang study found that smoke from marijuana, absorbed through the lungs, acts on the brain almost immediately, while orally ingested pills can leave a nauseous cancer patient to suffer for several hours. Besides, notes CUNY's Morgan, "It is absurd that we only have an oral tablet" to treat vomiting. It's like treating diarrhea with a suppository.

But if the government is truly looking to satisfy its "currently accepted medical use" criteria, officials should turn to a just-published study in the Journal of Clinical Oncology, conducted by Richard Doblin and Mark A. R. Kleiman of Harvard's Kennedy School. Forty-eight percent of oncologists responding said they would prescribe marijuana to some of their patients if it were legal. Fifty-four percent said they thought smoked marijuana should be available by prescription, and 44 percent said they had recommended pot to a patient, even though it is illegal.

In justifying the new decision. PHS chief James 0. Mason told me: "It puts the government in sort of a tenuous situation to be passing out marijuana cigarettes that can be used by a person that can cloud their judgment if they choose to use an automobile or get out in the street or in the context of sexual behavior. I think it sends a signal that's not the best signal." Mason's rationale was uncannily prophesied by Judge Young in his 1988 decision: "There are those who, in all sincerity, argue that the transfer of marijuana to Schedule II will 'send a signal' that marijuana is , 'ok' generally for recreational use. This argument is specious. . . . If marijuana should be placed in Schedule II, in obedience to the law, then that is where marijuana should be placed, regardless of misinterpretation of the placement by some." The fact that AIDS has been added to the list of conditions treatable by pot should have helped, not hindered, efforts at reclassification.

Marijuana, it seems, does indeed cloud the mind. But in this instance, the clouded minds are in government buildings, not in doctors' offices or patients' sick rooms.

Newt Gingrich's Letter Supporting Medical Marijuana, published in the Journal of American Medicine (JAMA, 1982)

Newt Gingrich's Letter Supporting Medical Marijuana

The following letter by Rep. Newt Gingrich, former Speaker of the House, in support of medical access to marijuana originally appeared in the **March 19, 1982** issue of the Journal of the American Medical Association (JAMA).

To the Editor,

The American Medical Association's Council on Scientific Affairs should be commended for its report, "Marijuana: Its Health Hazards and Therapeutic Potential" (1981;246:1823). Not only does the report outline evidence of marijuana's potential harms, but it distinguishes this concern from the legitimate issue of marijuana's important medical benefits. All too often the hysteria that attends public debate over marijuana's social abuse compromises a clear appreciation for this critical distinction.

Since 1978, 32 states have abandoned the federal prohibition to recognize legislatively marijuana's important medical properties. Federal law, however, continues to define marijuana as a drug "with no accepted medical use," and federal agencies continue to prohibit physician-patient access to marijuana. This outdated federal prohibition is corrupting the intent of the state laws and depriving thousands of glaucoma and cancer patients of the medical care promised them by their state legislatures.

On September 16, 1981, Representatives Stewart McKinney and I introduced legislation designed to end bureaucratic interference in the use of marijuana as a medicant.

We believe licensed physicians are competent to employ marijuana, and patients have a right to obtain marijuana legally, under medical supervision, from a regulated source. The medical prohibition does not prevent seriously ill patients from employing marijuana; it simply deprives them of medical supervision and denies them access to a regulated medical substance. Physicians are often forced to choose between their ethical responsibilities to the patient and their legal liabilities to federal bureaucrats.

Representative McKinney and I hope the Council will take a close and careful look at this issue. Federal policies do not reflect a factual or balanced assessment of marijuana's use as a medicant. The Council, by thoroughly investigating the available materials, might well discover that its own assessment of marijuana's therapeutic value has, in the past, been more than slightly shaded by federal policies that are less than neutral.

Newt Gingrich
House of Representatives
Washington, DC

Institute of Medicine Report Endorsing Medical Marijuana (1982)

Institute of Medicine Report Endorsing Medical Marijuana

Marijuana and Health

Report of a Study by a Committee of the Institute of Medicine
Division of Health Sciences Policy
(1982)

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institutes of Medicine. The members of the committee chosen for this report were chosen for their special competences and with regard for appropriate balance. This report has been reviewed by a group other than the authors.

Chapter 7 - Therapeutic Potential and Medical Uses of Marijuana

Summary

(p. 150)

Cannabis and its derivatives have shown promise in the treatment of a variety of disorders. The evidence is most impressive in glaucoma, where their mechanism of action appears to be different from the standard drugs; in asthma, where they approach isoproterenol in effectiveness; and in the nausea and vomiting of cancer chemotherapy, where they compare favorably with phenothiazines. Smaller trials have suggested cannabis might also be useful in seizures, spasticity, and other nervous system disorders. Effective doses usually produce psychotropic and cardiovascular effects and can be troublesome, particularly in older patients.

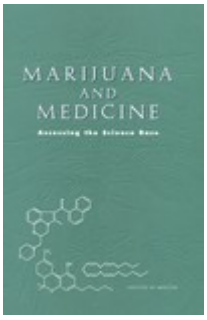
Although marijuana has not been shown unequivocally superior to any existing therapy for any of these conditions, several important aspects of its therapeutic potential should be appreciated. First, its mechanisms of action and its toxicity in several diseases are different from those of drugs now being used to treat those conditions; thus, combined use with other drugs might allow greater therapeutic efficacy without cumulative toxicity. Second, the differences in action suggest new approaches to understanding both the diseases and the drugs used to treat them. Last, there may be an opportunity to synthesize derivatives of marijuana that offer better therapeutic ratios than marijuana itself.

Recommendations for Research

The committee believes that the therapeutic potential of cannabis and its derivatives and synthetic analogues warrants further research along the lines described in this chapter. There also may be significant heuristic benefits to be derived from the study of the biological mechanisms by which these compounds act.

Some therapeutic promise seems to be offered by synthetic cannabinoid analogues. The committee recommends that particular attention be paid to the treatment of chemotherapy-induced nausea and vomiting in cancer patients because current management of this important and widespread problem is inadequate and studies suggest that cannabinoids may have some special advantage. Cannabinoids or their analogues may also find a place in the management of resistant glaucoma, of severe intractable asthma, and of certain forms of seizures that are resistant to standard therapy. Continued carefully contracted clinical trials in these areas seem worthwhile at this time, as do studies of the usefulness of cannabinoids in the usefulness of muscle spasticity.

Institute of Medicine's "Marijuana and Medicine: Assessing the Science Base" (1999) (book no. 0309071550)



MARIJUANA AND MEDICINE

Assessing the Science Base

Janet E. Joy, Stanley J. Watson, Jr., and
John A. Benson, Jr., *Editors*
Division of Neuroscience and Behavioral Health
INSTITUTE OF MEDICINE

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.