

A Peek into Pandora's Box: The Medical Excuse Marijuana Controversy

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ABSTRACT. The smoking of marijuana for medicinal applications is a volatile and difficult issue for the medical and regulatory communities which has reached the forefront of discussions of public policy.

Any consideration of this issue must take into account the substantial toxicity, impurity, and morbidity associated with marijuana use. Several states have passed ballot initiatives or legislation that allow a medical excuse for possession of marijuana. These initiatives bypass the Food and Drug Administration process of proving safety and efficacy, and they have created serious regulatory dilemmas for state regulatory boards. Several examinations of the issue have consistently drawn question to the validity of smoking an impure substance while voicing concern for the well being of patients in need. The historical, social, medical, and legal issues are examined. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2003 by The Haworth Press, Inc. All rights reserved.]

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HISTORY

In 1972, the Department of Justice Drug Enforcement Administration (DEA) was petitioned to reschedule marijuana from a Schedule I drug (unable to be prescribed, high potential for abuse, not currently accepted for medicinal use, and lack of safety of the drug) to a Schedule II drug (high potential for abuse, currently accepted for medical use, but able to be prescribed).¹

This rescheduling petition was initiated by the National Organization for the Reform of Marijuana Laws (NORML), Alliance for Cannabis Therapeutics (ACT), and the Cannabis Corporation of America. It is significant that these organizations lobby for the legalization of marijuana and have neither a medical base, nor do they represent any accredited or respected medical entity.

Because of continued controversy surrounding the rescheduling of marijuana, Administrative Law Judge Francis Young was retained by the DEA in 1988 to rule on the merits of rescheduling marijuana to Schedule II. Judge Young ruled that marijuana should be rescheduled to Schedule II for nausea associated with cancer chemotherapy and spasticity.² He concluded, however, that insufficient evidence existed to warrant use of crude marijuana for glaucoma or other applications.

The administrator of the DEA ultimately denied the petition to reschedule. In the face of extensive expert testimony provided to the DEA which opposed the rescheduling of marijuana, the marijuana lobby only produced evidence consisting of anecdotes and testimony of a handful of physicians with limited or no clinical experience with the medical areas in question. During the rescheduling hearings it became clear that crude, especially smoked, marijuana had not been accepted as a medicine by any reputable medical entity.

The denial of the rescheduling petition by the DEA resulted in an appeal by marijuana advocates to the United States Court of Appeals for the District of Columbia. In a decision handed down in February 1994³ the Court set forth the guidelines that only rigorous scientific proof can satisfy the requirement of "currently accepted medical use" (Table 1). Crude marijuana does not meet these guidelines.

TABLE 1. Criteria for Designation for a Drug to Be Considered a Medicine⁹¹

1. The drug's chemistry must be known and reproducible.
2. There must be adequate safety studies.
3. There must be adequate and well-controlled studies proving efficacy.
4. The drug must be accepted by *qualified* experts.
5. The scientific evidence must be widely available.

Several voter initiatives have been undertaken by marijuana advocates to circumvent the FDA process and the DEA scheduling rules. While not actually legalizing marijuana for medical use, the initiatives create a "defense to possession" for those possessing a medical recommendation to use marijuana. The ballot initiatives were heavily financed by individuals and organizations who seek the legalization of marijuana and other drugs (Table 2, and Appendix 1). The funding bought media consultants, airtime, and legal expertise. While the initiatives were promoted as being "compassionate" for suffering patients, they also created legal protection to those claiming medical ailments as justification for possession and personal use.

The danger of such ballot initiatives is that they create an atmosphere of "medicine by popular vote" rather than the rigorous processes required by federal law that all medicines must undergo. There also exists great concern that the movement to accept marijuana for medicinal applications is having the secondary effect of softening public attitudes on marijuana use. In the 2002 election cycle, initiatives in Florida, Michigan, and Ohio ostensibly sought to

TABLE 2. Examples of Funding for State Marijuana Ballot Initiatives

Proposition 215 California (California Secretary of State)		Arizona-2000, HB 2518 (Arizona Secretary of State)	
George Soros	\$550,000	As of 11/4/99	
Peter Lewis	\$500,000	George Soros	\$105,000
John Sperling	\$200,000	Peter Lewis	\$105,000
George Zimmer	\$100,000	John Sperling	\$105,000
Life AIDS Lobby	\$344,750		
TEAMSTERS	\$195,000	Massachusetts-Initiative P H4976 (Mass. Secretary of State)	
(ILLEGAL CONTRIBUTION)		As of December 31, 1999	
TOTAL	\$1,889,750	Peter Lewis	\$122,500
		George Soros	\$122,500
Proposition 36 California		John Sperling	\$122,500
George Soros	\$983,080	Arizona 2002 Proposition 203	
Peter Lewis	\$1,026,337	Soros	\$406,467
John Sperling	\$1,066,337	Sperling	\$590,383
Proposition 200 Arizona (Arizona Secretary of State)		Ohio Drug Treatment Initiative 2002	
George Soros	\$430,000	Bogus treatment initiative	
Drug Policy Foundation	\$200,000	Soros	\$271,276
Peter Lewis	\$330,000	Sperling	\$271,276
John Sperling	\$430,000	Lewis	\$271,276
Social Policy Reform	\$100,000		
TOTAL	\$1,490,000	Nevada 2002	
		\$1.6 million raised, \$184,000 of this from small donors.	

require treatment for drug-related arrests. Underlying what would be perceived as a positive change, however, were no controls on what drugs nor what criminal acts would be eligible for treatment. Furthermore, the definitions of "treatment" were generally quite loose. Even literacy or vocational training could have qualified for hard core felons with long-standing drug problems. The Florida and Michigan propositions did not require drug abstinence even during treatment. All three created a situation where criminal addicts would have statutory preference for treatment over non-criminals and were deemed unconstitutional.

This year, proposals in San Francisco and San Diego would require the cities to provide marijuana to individuals with medical excuses. This type of action puts the cities in the difficult situation of assessing the validity of excuses, the purity of the marijuana, and the potency of the marijuana. It also raises the question as to what legal risks the cities would be exposed to if complications such as accidents, infections, or other problems which might arise from the marijuana provided.

Recently, the Justice department filed an injunction in United States District Court against the Oakland Cannabis Buyers Cooperative in an attempt to close down the apparent open dealing of marijuana. This injunction was overturned upon appeal. A subsequent appeal to the United States Supreme Court has set the legal tone for the medicinal marijuana issue. The Supreme Court⁴ ruled on May 14, 2001 that the Controlled Substances Act may not be violated by the sale of marijuana for medicinal purposes, and that there is no medical necessity exception to the Controlled Substances Act's prohibitions on manufacturing and distributing marijuana. The Supreme Court decision will likely have a chilling effect on future legislation and litigation regarding the use of marijuana for medicinal purposes.

Serious regulatory questions have also been raised regarding the standard of care that have not been adequately dealt with by ballot initiatives (Table 3). These questions may serve as a template for regulatory boards who are faced with the medical excuse marijuana issue. Unfortunately, regulatory agencies have also been handed a difficult situation to assess.

MEDICINAL APPLICATIONS OF THC OR MARIJUANA

Several medical surveys have examined physician attitudes regarding the use of marijuana for medicinal purposes. Kleiman and Doblin reported⁵ that 48% of the respondents would prescribe marijuana if rescheduled for legal prescription. Upon closer review, the survey had a low response rate of approximately 40%. Respondents only accounted for 9% of practicing oncologists. Sixteen percent of those surveyed felt that marijuana was effective in 50% or

TABLE 3. Standards to Consider Before Recommending Marijuana (adapted from reference 92)

- * Is there documentation that the patient has had failure of all other conventional medications to treat his or her ailment? Have you counseled the patient (documented by the patient's signed informed consent) regarding the medical risks of the use of marijuana—at a minimum to include infection, pulmonary complications, suppression of immunity, impairment of driving skills, and habituation?
- * Has the patient misused marijuana or other psychoactive and addictive drugs?
- * Do you periodically provide drug testing of the patient who has been prescribed marijuana, and have patients been excluded from being prescribed marijuana who are found to be using other illicit drugs? Who does the drug testing and by what means?
- * Is the use of smoked marijuana part of a study and/or will the monitoring of that use be under the supervision of an investigational review board?
- * Have you carefully reviewed exactly which patients should be allowed to use this drug medicinally and for how long?
- * Do you carefully examine and consistently follow up patients who use smoked marijuana as a medical treatment, including pulmonary function testing, evaluation of immune status, and the presence of any super infection?
- * Have you exercised due care in assuring the standardization of the tetrahydrocannabinol potency content of the marijuana to be considered for medicinal use and whether it is free of microbial contaminants?
- * Because marijuana is a federally controlled substance, has a system been established in the state to track all patients and their source of marijuana, as with other controlled substances? Are you complying with such requirements?
- * Will you be required to be licensed by the state or federal government?
- * Have you shown knowledge, training, or certification in addiction medicine? Do you have demonstrable knowledge of the physiologic effects of marijuana, its side effects, and its interaction with other drugs before prescribing it?

more of patients. Unfortunately, inaccurate interpretations of this survey were widely released, widely publicized by the media, and incorrectly gave the impression that *about half* of oncologists generally want smoked marijuana available as medicine.

The author of this survey, Rick Doblin, was a student at Harvard at that time. He is also the President of the Multidisciplinary Association for Psychedelic Studies (MAPS). MAPS specializes in trying to gain legal access and status for psychedelic substances and marijuana. Doblin has openly admitted that this study was initiated so that the results could be used in the marijuana re-scheduling suit against the DEA.

Concurrent with Doblin and Kleiman, Schwartz surveyed oncologists in the Washington D.C. area⁶ and determined that pure THC in pill form ranked ninth in preference for the treatment of mild nausea and sixth for the treatment of severe nausea. It is important to recognize that this form of THC is not smoked marijuana.

Only 12% had recommended THC (by prescription or illegally) for more than 50 patients. It was felt that nausea was relieved in only 50% of patients and that 25% had adverse side effects.

Because of the exclusion of newer antiemetics from the two earlier surveys, Schwartz and Voth⁷ surveyed 1500 clinical adult oncologists in 1994 with a 75% response rate. Over 88% of respondents had never recommended crude marijuana to patients. Twelve percent had ever recommended a marijuana cigarette, and 1% of the respondents estimated that they had recommended crude marijuana more often than 5 times per year. Only 9% said that they would prescribe crude marijuana more than ten times per year. In contrast, the median annual use of the antiemetics ondansetron (Zofran) and granisetron (Kytril) was 250 prescriptions. Furthermore, the support of making crude marijuana available to patients was strongest among physicians who also supported the concept of general legalization of marijuana for recreational use.

In 1993, Grinspoon published a compilation of anecdotes⁸ which now serves as the bible of the "medical excuse marijuana" movement. He suggests that marijuana should be used for nausea associated with cancer chemotherapy, glaucoma, wasting in AIDS, depression, menstrual cramps, pain, and miscellaneous ailments. His anecdotes contained no controls, no standardization of dose, no quality control, and no independent medical evaluation for efficacy or toxicity.

The discussion of historical uses of marijuana cited in Grinspoon's book include such cultures as India, Asia, the Middle East, South Africa, and South America and are considered by the medical excuse marijuana movement as evidence of appropriate medical uses of the drug. The Chinese allegedly used marijuana to "quicken the mind, induce sleep, cure dysentery, stimulate appetite, relieve headaches, and cure venereal disease." One of Grinspoon's references from 1860 states marijuana provided beneficial medical effects "without interfering with the actions of the internal organs." Such folk medicine applications of marijuana from the 1700s and 1800s are referenced by the authors as evidence justifying the modern medical applications.

The field of medicine in those earlier years was fraught with potions and herbal remedies. Many of those were absolutely useless, or conversely were harmful to unsuspecting subjects. This situation gave rise to the development and evolution of our current Food and Drug Administration and drug scheduling processes.

Advocates of marijuana contend that the smoking of marijuana has the advantage of providing a rapidly absorbed, titratable dose of THC. While rapid absorption could be an advantage in some arenas, neither anecdotal nor controlled studies have delineated whether anti-emetic qualities appear before, after, or concurrent to the intoxicating effects. Indeed, the therapeutic end point for successful administration of smoked marijuana has not been established.

Research on the utility of THC has demonstrated some effectiveness of the purified form of the drug in treating nausea associated with cancer chemotherapy or appetite stimulation, but even researchers are cautious about using smoked substances. Tramer⁹ evaluated the state of the research on cannabinoids and concluded that in selected patients they may be useful as mood enhancing agents, but serious adverse side effects will likely limit their usefulness. They also stated,

These results should make us think hard about the ethics of clinical trials of cannabinoids when safe and effective alternatives are known to exist and when efficacy of cannabinoids is known to be marginal. (p. 6)

An example of the therapeutic benefits of cannabinoids for nausea was work by Sallan et al.¹⁰ who dealt with pure THC in the treatment of chemotherapy-associated nausea, not smoked marijuana. Chang¹¹ tested THC and then followed treatment failures with marijuana, thus conclusions regarding effectiveness cannot be readily attributed to either THC or crude marijuana. Levitt et al.¹² actually determined that purified THC was more effective than smoked marijuana.

Vinciguerra et al.¹³ found that smoked marijuana had some beneficial effect for nausea in patients who had failed other conventional forms of antiemetic therapy. Responders tended to have had prior marijuana experience. This study was uncontrolled and patients' self-evaluated results. Smokers were required to inhale deeply, hold the smoke for ten seconds, and then smoke four cigarettes completely each day of chemotherapy. Twenty-five percent refused to smoke the marijuana. Over 20% of the subjects dropped out of the smoking group prior to the end of the study and 22% of the remaining subjects reported no benefit from smoking marijuana. Dosing was also variable because of the fact that the dose was rounded to the nearest one-fourth marijuana cigarette and no THC levels were checked for consistency of dose response.

Mattes et al.¹⁴ evaluated oral and rectal suppository preparations of THC in comparison to smoked marijuana for appetite stimulation. All of the study subjects were experienced marijuana users thus accounting for a relatively high drug acceptance. Smoked marijuana was no more effective than suppository THC in stimulating appetite as measured by caloric energy intake. Rectal suppositories and oral THC were dosed at 2.5 mg twice daily. Smoking marijuana

required the subjects to inhale over 3 seconds, hold the smoke deeply in their lungs for 12 seconds, and then continue the process until the cigarette was smoked to a stub. The plasma THC levels peaked more quickly with the inhaled THC, but also fell more quickly, whereas the suppository THC maintained a more sustained level.

Several comprehensive reviews have been undertaken to assess the potential medical uses of marijuana. Voth and Schwartz extensively reviewed available therapies for chemotherapy associated nausea, glaucoma, multiple sclerosis, and appetite stimulation¹⁵ and concluded that no compelling need exists to make crude marijuana available as a medicine for physicians to prescribe. They recommended that the most appropriate direction for cannabinoid research is to research specific cannabinoids or synthetic analogs rather than pursuing the smoking of marijuana as a way to deliver THC.

Former Assistant Secretary of Health Lee¹⁶ at the request of Congress solicited opinions from investigators at the National Institute on Allergy and Infectious Diseases, who commented on the AIDS wasting syndrome; the National Cancer Institute which commented on the use of marijuana as an antiemetic in cancer chemotherapy; the National Eye Institute which commented on marijuana's use in glaucoma; and the National Institute for Neurological Disorders and Stroke which commented on marijuana's role as an antispasticity drug in multiple sclerosis.

The summary opinion stated:

This evaluation indicates that sound scientific studies supporting these claims are lacking despite anecdotal claims that smoked marijuana is beneficial. Scientists at the National Institutes of Health indicate that after carefully examining the existing preclinical and human data, there is no evidence to suggest that smoked marijuana might be superior to currently available therapies for glaucoma, weight loss associated with AIDS, nausea and vomiting associated with cancer chemotherapy, muscle spasticity associated with multiple sclerosis, or intractable pain.

The National Institutes of Health reconsidered this issue in 1997¹⁷ and has called for further research into alternate delivery systems for pure THC as well as research into the comparative efficacy of marijuana with newer available medicines which have added heightened efficacy to medication regimes. The summary also expressed concern over pulmonary, neuro, and immunotoxicity of cannabis.

In 1997 the White House Office of National Drug Control Policy commissioned the National Academy of Science, Institute of Medicine (IOM) to evaluate the utility of marijuana for medicinal applications.¹⁸ The study concluded (Table 4) that the challenge for future research will be to find cannabinoids

TABLE 4. Institute of Medicine (IOM) Recommendations⁹³

Recommendation 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone. Scientific data indicate the potential therapeutic value of cannabinoid drugs for pain relief, control of nausea and vomiting, and appetite stimulation. This value would be enhanced by a rapid onset of drug effect.

Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems. The psychological effects of cannabinoids are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy.

Recommendation 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence perceived medical benefits, should be evaluated in clinical trials. Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory diseases, but the data that could conclusively establish or refute this suspected link have not been collected.

Recommendation 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent. Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues.

Recommendation 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months); be conducted in patients with conditions for which there is reasonable expectation of efficacy; be approved by institutional review boards; and collect data about efficacy.

If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, non-smoked cannabinoid delivery systems.

Recommendation 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- failure of all approved medications to provide relief has been documented;
- the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;
- such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness;
- and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

which enhance therapeutic benefits while minimizing side effects such as intoxication and dysphoria. Useful delivery systems for isolated or synthetic cannabinoids could include nasal sprays, metered dose inhalers, transdermal patches, and suppositories. The future for medicinal applications of cannabinoids and whether cannabinoids are equal or superior to existing medicines remains to be determined, but the IOM evaluation is particularly clear on the smoking of marijuana:

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The advocates for marijuana would have the public and policy makers incorrectly believe that crude marijuana is the only treatment alternative for large populations of patients who are inadequately treated for the nausea associated with chemotherapy, glaucoma, multiple sclerosis, and other ailments. Numerous effective medications are however currently available for conditions such as nausea. To date, no compelling data substantiates the existence of significant numbers of marginally treated or untreated patients for the maladies which marijuana is advanced.

MEDICAL COMPLICATIONS OF MARIJUANA USE

Marijuana continues to be widely used in our society. While its use declined in the late 1980s and early 1990s, a trend toward increasing use has recently been seen in high school students¹⁹ (Table 5). Marijuana remains the most frequently used illegal drug. The chronic use of marijuana has now been demonstrated to be associated with higher utilization of the health care system and associated cost,²⁰ a long suspected phenomenon.

The negative side effect profile of marijuana far exceeds most of the other effective agents available. In the studies performed to examine THC for chemotherapy-associated nausea, elderly patients could not tolerate the drug well. Chronic, daily doses of the drug would be necessary to treat many of the proposed medical conditions. This would unnecessarily expose the patients to the toxic effects.

Mental, affective, and behavioral effects are the most easily recognized consequences of acute and chronic marijuana use. Concentration, motor coordination, and memory²¹⁻²⁵ are all adversely impacted.

TABLE 5. Drug Use Rates—Marijuana⁹⁴

	PERCENT OF HIGH SCHOOL SENIORS USE OF MARIJUANA									
	1978	1986	1987	1988	1991	1992	1993	1994	1995	2000
LAST 12 Mo.	50.2	39	36	33.1	23.9	21.9	26	30.7	35	36.5
LAST 30 DAYS	37.1	23.4	21	18	13.8	11.9	15.5	19	21.2	21.6
DAILY	10.7	4.0	3.3	2.7	2.0	1.9	2.4	3.6	4.6	6.0

The ability to perform complex tasks, such as flying²⁶⁻²⁷ is impaired even 24 hours after the acute intoxication phase. The association of marijuana use with trauma and intoxicated motor vehicle operation is also well established.²⁸⁻³³ Evaluations³⁴ of the effect of marijuana on driving have determined that the combination of blood alcohol concentrations (BAC) of 0.07 and marijuana at 100 µg/kg gave effects similar to BAC alone of 0.09. Blood alcohol concentrations of 0.07 and marijuana levels of 200 µg/kg demonstrated effects similar to a BAC alone of 0.14 when measuring reaction time, on-road performance, and vehicle following. The study concluded, "Under marijuana's influence, drivers have reduced capacity to avoid collisions if confronted with the sudden need for evasive action." A second related study found that BAC of .05 combined with moderate marijuana had significant drop in the visual search frequency. This is of central importance in an ambulatory environment where patients may smoke marijuana and then drive automobiles.

Several biochemical models have demonstrated abnormal changes in brain cells, brain blood flow, and evidence of brain wave changes.³⁵⁻³⁶ Pathologic behavior such as psychosis is also associated with marijuana use.³⁷⁻³⁹ Solowij et al. reported that the ability to focus attention and filter out irrelevant information was progressively impaired with the number of years of use, but was not related to the frequency of use.⁴⁰ Solowij also determined in a separate report that even among ex-cannabis smokers, the inability to reject complex irrelevant information persisted despite a mean abstinence of two years from marijuana use.⁴¹

In an examination of college students,⁴² daily use of marijuana was associated with impairment of "executive functions" such as learning of lists, perseverations, and attention. In that study, heavy use was defined as use only 29 out of the last 30 days which could have actually been as little as one time daily.

Positron scanning⁴³ of subjects whose mean use of marijuana was 17 times per week for last 2 years found lower blood flow in a large region of the posterior cerebellum. Not only does this have implications on motor coordination

and function, but also cognition, timing, processing sensory information, and attention.

Despite arguments from marijuana advocates to the contrary, marijuana is a dependence-producing drug. Strangely, in the course of the DEA rescheduling hearings, the marijuana petitioners admitted that "marijuana has a high potential for abuse and that abuse of the marijuana plant may lead to severe psychological or physical dependence" (2). This dependence and associated "addictive" behaviors have been well described in the marijuana literature.⁴⁴⁻⁴⁹ Marijuana dependence consists of both a physical dependence (tolerance and subsequent withdrawal) and a psychological dependence. Withdrawal from marijuana has been demonstrated in both animals⁵⁰ and humans.⁵¹

The gateway effect of marijuana along with tobacco and alcohol is also well established in research.^{52,53} The use of cocaine and heroin is virtually always preceded by marijuana. Kandel and co-workers have pioneered research in this area and continue to find clear evidence of a gateway phenomenon.^{54,55} Golub and Johnson contends that the importance of marijuana as a gateway drug has actually increased in recent years.⁵⁶

While the dependence producing properties of marijuana are probably a minimal issue for chemotherapy associated nausea when treatment is required short term or sporadically, it is a major issue for the chronic daily use necessary for glaucoma, AIDS wasting syndrome, and other alleged chronic applications.

The respiratory difficulties associated with marijuana use preclude the inhaled route of administration as a medicine. Smoking marijuana is associated with higher concentrations of tar, carbon monoxide, and carcinogens than are found in cigarette smoking.⁵⁷ Marijuana adversely impairs some aspects of lung function and causes abnormalities in the respiratory cell lines from large airways to the alveoli.⁵⁸⁻⁶⁶ Marijuana smoke causes inflammatory changes in the airways of young people that are similar to the effects of tobacco.⁶⁷ In addition to these cellular abnormalities and consequences, contaminants of marijuana smoke are known to include various pathogenic bacteria and fungi.⁶⁸⁻⁷⁰ Those with impaired immunity are at particular risk for the development of disease and infection when these substances are inhaled.

The effects of marijuana on the unborn were long suspected after original studies in Rhesus monkeys demonstrating spontaneous abortion. While these are insignificant issues for terminal cancer patients, they are serious issues for young women potentially using marijuana for migraines or dysmenorrhea.

Exposure to marijuana during pregnancy,⁷¹⁻⁷⁶ is associated with changes in size, weight, and neurologic abnormalities in the newborn. A very alarming association also exists between maternal marijuana use and the development of non-lymphocytic leukemia in offspring.⁷⁷⁻⁷⁸ Additionally, hormonal function in both males and females is disrupted.⁷⁹⁻⁸³ The potential for hormonal abnor-

malities in the unborn is undetermined, but real. Day et al. identified a negative effect on intelligence parameters among three year olds when mothers used marijuana during the first and second trimesters of pregnancy.⁸⁴ Dahl et al. have discovered sleep disruption among three year olds when exposed during pregnancy.⁸⁵ Consistent with the reports of delayed performance, Fried⁸⁶ reported that children exposed in utero demonstrate increased behavioral problems, language comprehension, sustained attention, and memory at age 4.

One of the earliest findings in marijuana research was the effect on various immune functions, which is now evidenced by an inability to fight herpes infections and the discovery of a blunted response to therapy for genital warts during cannabis consumption.^{87,88} Abnormal immune function is, of course, the cornerstone of problems associated with HIV. The use of chronic THC in smoked form for AIDS wasting not only exposes the patient to unnecessary pathogens, but also risks further immunosuppression. Evaluation of the effect of THC on NK-kB has suggested a possible effect on the HIV genome.⁸⁹ In chronic use or use in populations at high risk for infection and immune suppression, the risks are unacceptable.

LOOKING TOWARD THE FUTURE

Bypassing the usual safety and efficacy process of the FDA is a dangerous and unnecessary precedent which widely enhances the availability and acceptance of marijuana. Smoking an impure and toxic substance is of questionable value in the modern medical armamentarium. It is no more reasonable to consider crude marijuana a medical treatment than it is to consider tobacco as medicine.

If marijuana is to be examined for medicinal applications, rigorous research protocols should be focused on pure THC or other cannabinoids rather than crude forms of marijuana. Examples could include the formulation of rectal suppository or aerosol forms, nasal inhalers, or transdermal delivery systems of dronabinol. An exciting new arena of THC analogs and synthetic cannabinoids may yet produce cannabinoid-like substances which enhance efficacy while having minimal or no toxicity.⁹⁰ Naturally occurring substances with medicinal value are well known to medicine. Substances such as Digitalis are found in foxglove plant, but modern medicine either purifies or synthesizes such substances to create pure and reliable medicine. The same can be done for the therapeutically beneficial cannabinoids found in marijuana.

While recognizing that there may exist a small group of inadequately treated patients for whom isolated or synthetic cannabinoids may be beneficial, the general use of crude or leaf marijuana for medicinal purposes cannot be supported except in highly circumscribed, controlled, research settings.

Regulatory agencies have a critically important role in the examination of the use of marijuana. They have, unfortunately, been handed a difficult problem to monitor, which has emerged from an atmosphere of "medicine by popular vote." The use of marijuana in states who allow it needs to be tempered by careful patient selection and monitoring. Unless marijuana were approved as a safe and effective treatment by the FDA, allowing it to be used as a medicine is a step backward to the times of potions and herbal remedies.

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APPENDIX 1. States Adopting Medical Excuse Marijuana

Arizona*	Nevada***
Alaska	Oregon
California**	Washington
Colorado	Hawaii****
Maine	Maryland*****

* Arizona Proposition 203 (a follow up to prop 200) in 2002 was voted down. It decriminalized up to 2 ounces of marijuana possession. If an individual could produce a recommendation from any type of health-related provider, the department of public safety (i.e., state police) would have been required to produce marijuana out of seized stores.

** Proposition 215 allows marijuana to be used with a recommendation from a physician. The subsequent initiative, Proposition 36, prohibits incarceration of first and second offenders. The California initiative will only allow 30 days in jail maximum for offenders beyond the first and second offense. Prop. 36 specifically prohibits any funding for drug testing, choosing instead to trust drug addicts to hold themselves accountable; prohibits payment for any treatment over 12 months; does not provide funding for treatment programs to help addicts in California prisons. Since the initiation of Prop 36, courts have been flooded with addicts electing "treatment." Forty percent of the defendants who opted for rehabilitation failed to appear or dropped out of treatment programs in the first 6 months of the initiative.

***Nevada 2002 voters rejected an initiative to legalize marijuana possession.

****Hawaii legislature passed defense to possession legislation.