Marihuana as Medicine: A Plea for Reconsideration

by Lester Grinspoon, MD James B. Bakalar, JD

Journal of the American medical Association, June, 1995

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." 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 Mach 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 1. By comparison, the ratio is between 3 and 50 to 1 for secobarbital and between 4 and 10 to 1 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, [delta-9]- tetrahydrocannabinol ([delta-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 [delta-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 [delta-9]-THC and other medicines. For example, from 1978 through 1986 the state research program in New Mexico provided marihuana or synthetic [delta-9]-THC to about 250 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 [delta-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 ironical, 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(pp.133-135)

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.

1. In the Matter of Marijuana 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.
3. In the Matter of Marijuana Rescheduling Petition, Docket 86- 22, Affidavit of Daniel Daneac, M.D. Washington, DC: Drug Enforcement Agency; 1987.
4. Doblin R., Kleiman M.A.R. Marihuana as anti-emetic medicine: a survey of oncologists' attitudes and experiences. J Clin Oncol, 1991;9:1275-1290. From the Department of Psychiatry, Harvard Medical School, and the Massachusetts Mental Health Center, Boston. Reprint requests to Harvard Medical School, 74 Fenwood Rd, Boston, MA 02115 (Dr Grinspoon). JAMA, June 21, 1995 -- Vol. 273, No. 23, pp. 1875-1876