ROBERT A. RAICH (State Bar No. 147515)
1970 Broadway, Suite 1200
Oakland, California 94612
Telephone: (510) 338-0700

GERALD F. UELMEN (State Bar No. 39909)
Santa Clara University, School of Law
Santa Clara, California 95053
Telephone: (408) 554-5729

JAMES J. BROSNAHAN (State Bar No. 34555)
ANNETTE P. CARNEGIE (State Bar No. 118624)
ANDREW A. STECKLER (State Bar No. 163390)
CHRISTINA KIRK-KAZHE(State Bar No. 192158)
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
Telephone: (415) 268-7000

Attorneys for Defendants
OAKLAND CANNABIS BUYERS' COOPERATIVE AND JEFFREY JONES

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA,

Plaintiff,

v.

CANNABIS CULTIVATOR'S CLUB, et al.,

Defendants.

AND RELATED ACTIONS.

No. C 98-00085 CRB
C 98-00086 CRB
C 98-00087 CRB
C 98-00088 CRB
C 98 00089 CRB
C 98 00245 CRB

**DECLARATION OF LESTER GRINSPOON, M.D., IN SUPPORT OF DEFENDANTS' RESPONSE TO SHOW CAUSE ORDER**

Date: September 28, 1998
Time: 10:00 a.m.
Courtroom: 8

Hon. Charles R. Breyer

I, LESTER GRINSPOON, M.D., declare:

1. I am an Associate Professor of Psychiatry, at Harvard Medical School in Boston, Massachusetts, where I have taught for more than 35 years. I am also Editor of The Harvard Mental Health Letter. My area of research is psychoactive drugs. I am particularly interested in the medicinal properties of cannabis. If called as a witness, I could and would testify competently to the facts set forth below. I have attached a copy of my *Curriculum Vitae* as Exhibit A. For the Court's convenience, where appropriate I have provided footnotes referencing the sources upon which I have relied.

2. I received a bachelor's degree in 1951 from Tufts College. I received a doctorate in 1955 from Harvard Medical School. I subsequently completed an internship in Medicine at Beth Israel Hospital in Boston, Massachusetts (1955-1956), and a residency in psychiatry at Massachusetts Mental Health Center (1958-1961). I received further training as a field instructor for the National Cancer Institute in Los Angeles, California (1956-1958).

3. Since joining the Harvard Medical School faculty in 1973, I have held numerous positions, including Associate Clinical Professor, Assistant Clinical Professor, and Senior Psychiatrist for the Massachusetts Mental Health Center. My other research and teaching appointments include, Assistant in Medicine for University of Southern California School of Medicine (1956-1958), Director of the Clinical Research Center for Massachusetts Mental Health Center (1961-1968), Consultant in Psychiatry and Research for Boston State Hospital (1963-1970) and an Examiner for the American Board of Psychiatry and Neurology (1969-present). I have also held several positions for the American Psychiatric Association such as Vice-Chairperson (1975-1977) and Chairperson for the Council on Research (1977-1979), Vice-Chairperson (1979-1980) and Chairperson for Scientific Program Committee (1980-1984).

4. I serve on several professional and community boards. These include many years as a member of the Beneficial Plant Research Association (1980-1984), the Drug Policy Foundation (1987-present), Physicians for Human Rights (1986-present), the Drug Research Group (1995-present), and Scientific and Policy Advisors of the American Council on Science and Health (1997 -

present). I recently served as Chairperson for the Board of Directors for the National Organization for the Reform of Marihuana Laws (1993-1995). I was also a faculty member for the Zinberg Center for Addiction Studies in Cambridge, Massachusetts (1993-1996). I am currently on several Editorial Boards, including editor for the Harvard Mental Health Letter (1984-present), the Journal of Social Pharmacology (1985-present), and Addiction Research (1991-present).

5. I have testified before the National Marijuana Commission Subcommittee of the Senate Small Business Committee in 1972, the House Select Committee on Narcotics in 1977, 1979 and 1989, the Controlled Substances Advisory Committee, the Drug Abuse Research Advisory Committee in 1978, the Senate Judiciary Committee in 1980, and the House Judiciary Committee, Sub-Committee on Crime in 1997. I am also a frequent presenter at national and international conferences.

6. I have authored and co-authored some 154 articles in scholarly and professional journals, most of which deal with clinical comparisons of drug therapies. I have contributed chapters of medical textbooks, research publications, clinical protocols and conference reports. My work has been published in the *Journal of Clinical Endocrinology and Metabolism*, *New England Journal of Medicine*, *Journal of the National Cancer Institute*, *Mental Patients in Transition*, *Science Digest*, *Archives of General Psychiatry*, *Comprehensive Psychiatry*, *Clinical Medicine*, *Journal of Psychiatric Research*, *Psychosomatic Medicine*, *Diseases of the Nervous System*, *American Journal of Psychiatry*, *Scientific America*, *Psychopharmacologia*, *International Journal of Psychiatry*, *Encyclopedia of Science and Technology*, *International Narcotic Report*, *New York Law Journal*, *Journal of Consulting and Clinical Psychology*, *Drug Therapy*, *World Journal of Psychosynthesis*, *Medical Tribune*, *Contemporary Drug Problems*, *Social Science and Medicine*, *Villanova Law Review*, *Congressional Digest*, *Biological Psychiatry*, *The Sciences*, *Journal of Ethnopharmacology*, *Handbook on Drug Abuse*, *The Hastings Center Report*, *Harvard Mental Health Letter*, *Harper's*, *Nova Law Review*, *New Harvard Guide to Psychiatry*, *Journal of State Government*, *Cancer Treatment & Marijuana Therapy*, *Journal of Drug Issues*, *North Carolina Journal of International Law & Commercial Regulation*, *Encyclopedia of Human Biology*, *Drugs, Society and Behavior*,

*Journal of American Medical Association*, *University of West Los Angeles Law Review*, and *Journal of Psychoactive Drugs*.

7. I have authored and co-authored some 13 books, several of which deal with the history and medical use of cannabis. These books include *Marihuana Reconsidered* (Harvard University Press, 2d ed. 1977), *Psychedelic Drugs Reconsidered* (Basic Books, 2d ed. 1981), *Psychedelic Reflections* (Human Sciences Press, 1982), *The Long Darkness: Psychological and Moral Perspectives on Nuclear Winter* (Yale University Press, 1986), and *Marihuana, The Forbidden Medicine* (Yale University Press, Revised Edition 1997).

8. Based on my research, I have found that cannabis is remarkably safe. Although not harmless, it is surely less toxic than most of the conventional medicines it could replace if it were legally available. Despite its use by millions of people over thousands of years, cannabis has never caused an overdose death. The most serious concern is respiratory system damage from smoking, but that can easily be addressed by increasing the potency of cannabis and by developing the technology to separate the particulate matter in marijuana smoke from its active ingredients, the cannabinoids (prohibition, incidentally, has prevented this technology from flourishing). Once cannabis regains the place in the U.S. Pharmacopoeia that it lost in 1941 after the passage of the Marihuana Tax Act (1937), it will be among the least toxic substances in that compendium. Right now the greatest danger in using cannabis medically is the illegality that imposes a great deal of anxiety and expense on people who are already suffering.

9. I have done extensive research on the history of the use of cannabis for medical purposes, as well as its legal regulation in the United States. The marijuana, cannabis, or hemp plant is one of the oldest psychoactive plants known to humanity. A native plant of central Asia, cannabis may have been cultivated as much as ten thousand years ago. It was certainly cultivated in China by 4000 B.C. and in Turkestan by 3000 B.C. It has long been used as a medicine in India, China, the Middle East, Southeast Asia, South Africa, and South America. The first evidence of the medicinal use of cannabis was published during the reign of the Chinese Emperor Chen Nun five thousand years ago. Cannabis was recommended for, among other things, malaria and rheumatic pains.

Another Chinese herbalist recommended a mixture of hemp, resin, and wine as an analgesic during surgery. Hemp was also noted as a remedy by Galen and other physicians of the classical and Hellenistic eras, and it was highly valued in medieval Europe.

10. Between 1840 and 1900, more than one hundred papers on the therapeutic uses of cannabis were published in American and European medical journals. It was recommended as an appetite stimulant, muscle relaxant, analgesic, sedative, anticonvulsant, and as a treatment for opium addiction. A professor at the Medical College of Calcutta, W.B. O'Shaughnessy, was the first Western physician to observe the use of cannabis as a medicine. He gave cannabis to animals, satisfied himself that it was safe, and began to use it with patients suffering from rabies, rheumatism, epilepsy, and tetanus. In a report published in 1839, he wrote that he had found tincture of hemp (a solution of cannabis in alcohol, taken orally) to be an effective analgesic. He was also impressed with its muscle relaxant properties and called it "an anticonvulsive remedy of the greatest value." In 1890, J.R. Reynolds, a British physician, summarized thirty years of experience with *Cannabis indica*, finding it valuable in the treatment of various forms of neuralgia, including tic douloureux (a painful facial neurological disorder), and added that it was useful in preventing migraine attacks. He also found it useful for certain kinds of epilepsy, for depression, and sometimes for asthma and dysmenorrhea.

11. The medical use of cannabis was in decline by 1890. It was believed that the potency of cannabis preparations was too variable, and that individual responses to orally ingested cannabis seemed erratic and unpredictable. Another reason for the neglect of research on the analgesic properties of cannabis was that the greatly increased use of opiates after the invention of the hypodermic syringe in the 1850s allowed soluble drugs to be injected for faster pain relief; hemp products are insoluble in water and so cannot easily be administered by injection. Toward the end of the nineteenth century, the development of such synthetic drugs as aspirin, chloral hydrate, and barbiturates, also contributed to the decline of cannabis as a medicine. But these new drugs had, and still have today, striking disadvantages. More than a thousand people die from aspirin-induced bleeding each year in the United States, and barbiturates are, or course, far more dangerous.

12. Cannabis use in the United States was particularly a matter of state or federal regulation until 1915, when the first state, California, prohibited marijuana possession or sale. In 1930, the year in which the Federal Bureau of Narcotics was founded, only sixteen states had laws prohibiting the use of cannabis. In contrast, by 1937, nearly every state had adopted legislation outlawing cannabis. Sociologists have speculated that pressure from the liquor lobby figured among the more subtle factors in this sudden legal onslaught. More important, lack of scientific understanding concerning the effects of cannabis enabled the unsubstantiated statements of the Federal Bureau of Narcotics to go substantially unchallenged. The Marihuana Tax Act of 1937 was the culmination of a series of efforts on the part of the Federal Bureau of Narcotics to generate anti-marijuana legislation.

13. One might have expected physicians looking for better analgesics and hypnotics to turn to cannabinoid substances, but the Marihuana Tax Act of 1937 undermined any such experimentation. The Marihuana Tax Act of 1937 imposed a transfer tax upon certain dealings in marijuana. The Marihuana Tax Act of 1937 provided that anyone who imports, manufactures, produces, compounds, sells, deals in, dispenses, prescribes, administers, or gives away marijuana was required to register, record transactions and pay special taxes depending on the defined purposes. Those who failed to comply were subject to large fines or prison for tax evasion. Although, it was ostensibly designed to prevent nonmedical use of cannabis, the Marihuana Tax Act of 1937 made cannabis so difficult to obtain, that cannabis was removed from the United States Pharmacopoeia and National Formulary in 1941. The Boggs Act of 1951 established mandatory prison terms and large fines for violation of any federal drug law, and the Narcotic Control Act of 1956 strengthened those penalties.

14. In the 1960s, however, the public began to rediscover the medical value of cannabis, as letters appeared in lay publications from people who had learned that it could relieve their asthma, nausea, muscle spasms, or pain and wanted to share that knowledge with readers who were familiar with the drug. Meanwhile, legislative concern about recreational use of cannabis increased, and in 1970 Congress passed the Comprehensive Drug Abuse Prevention and Control Act (also called the

Controlled Substances Act), which assigned psychoactive drugs to five schedules and placed cannabis in Schedule I, the most restrictive.

15. A few patients have been able to obtain medical cannabis legally in the last twenty years. Beginning in the 1970s, thirty-five states passed legislation that would have permitted medical use of cannabis but for the federal law. Several of those states actually established special research programs, with the permission of the federal government, under which patients who were receiving cancer chemotherapy would be allowed to use cannabis. These projects demonstrated the value of both smoked marijuana and oral THC (tetrahydrocannabinol). The FDA approved oral THC (Marinol) as a prescription medicine in 1986. In 1976, the federal government introduced the Individual Treatment Investigational New Drug program (commonly referred to as the Compassionate IND), which provided cannabis to a few patients whose doctors were willing to undergo the paperwork-burdened and time-consuming application process. About three dozen patients eventually received cannabis before the program was discontinued in 1992, and eight survivors are still receiving it — the only persons in the country for whom it is not a forbidden medicine.

16. The most effective spur to the movement for medical marijuana came from the discovery that it could prevent the AIDS wasting syndrome. It is not surprising that the Physicians Association for AIDS Care was one of the medical organizations that endorsed the California initiative prohibiting criminal prosecution of medical marijuana users.

17. I have conducted an extensive review of the literature concerning medical uses of cannabis and I am familiar with studies on the topic. Review of medical literature is a commonly used research tool. I have also studied clinically many patients who have used cannabis for the relief of a variety of symptoms; this clinical experience forms the basis of my book, *Marihuana, The Forbidden Medicine*. In my book I provide first-person accounts of the ways that cannabis alleviates symptoms of cancer chemotherapy, multiple sclerosis, osteoarthritis, glaucoma, AIDS and depressions, as well as symptoms of such less common disorders as Crohn's disease, diabetic gastroparesis, and post-traumatic stress disorder. The patient narratives illustrate not only cannabis's

therapeutic properties but also the unnecessary further pain and anxiety imposed on sick people who must obtain cannabis illegally.

18. Cannabis has several uses in the treatment of cancer. As an appetite stimulant, it can help to slow weight loss in cancer patients. It may also act as a mood elevator. But the most common use is the prevention of nausea and vomiting associated with cancer chemotherapy. About half of patients treated with anticancer drugs suffer from severe nausea and vomiting, which are not only unpleasant and painful but a threat to the effectiveness of the therapy. Retching can cause tears of the esophagus and rib fractures, prevent adequate nutrition, and lead to fluid loss. Some patients find the nausea so intolerable they say they would rather die than go on. The antiemetics most commonly used in chemotherapy are metoclopramide (Reglan), the relatively new ondansetron (Zofran), and the newer granisetron (Kytril). Unfortunately, for many cancer patients these conventional antiemetics do not work at all or provide little relief.

19. The suggestion that cannabis might be used in the treatment of cancer arose in the early 1970s when some young patients receiving cancer chemotherapy found that marijuana smoking reduced their nausea and vomiting. In one study of 56 patients who got no relief from standard antiemetic agents, 78% became symptom-free when they smoked marijuana.[1] Oral tetrahydrocannabinol (THC) has proved effective where the standard drugs were not,[2] but smoking generates faster and more predictable results because it raises THC concentration in the blood more easily to the needed level. Also, it may be hard for a nauseated patient to take oral medicine. In fact, there is strong evidence that most patients suffering from nausea and vomiting prefer smoked marijuana to oral THC.

---

[1] Vinciguerra, V., et al. Inhalation Marihuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* 1988; 88:525-527. (Attached as Exhibit B).

[2] Sallan, S.E., et al. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *New England Journal of Medicine* 1975; 293:795-797. (Attached as Exhibit C).

20. Oncologists may be ahead of other physicians in recognizing the therapeutic potential of cannabis. In the spring of 1990, two investigators randomly selected more than 2,000 members of the American Society of Clinical Oncology (one-third of the membership and mailed them an anonymous questionnaire to learn their views on the use of cannabis in cancer chemotherapy. Almost half of the recipients responded. Although the investigators acknowledged that this group was self-selected and that there might be a response bias, their results provide a rough estimate of the views of specialists on the use of Marinol (dronabinol, oral synthetic THC) and smoked marijuana. Only 43% said the available legal antiemetic drugs (including Marinol) provided adequate relief to all or most of their patients, and only 46% said the side effects of these drugs were rarely a serious problem. Forty-four percent had recommended the illegal use of cannabis to at least one patient, and half would prescribe it to some patients if it were legal. On average, they considered smoked marijuana more effective than Marinol and roughly as safe.[3]

21. Cannabis is also useful in the treatment of glaucoma, the second leading cause of blindness in the United States. In this disease, fluid pressure within the eyeball increases until it damages the optic nerve. About a million Americans suffer from the form of glaucoma (open angle) treatable with cannabis. Glaucoma is treated chiefly with eyedrops containing betablockers such as timolol (Timoptic), which inhibit the activity of epinephrine (adrenaline). They are effective but may have serious side effects such as inducing depression, aggravating asthma, slowing the heart rate, and increasing the risk of heart failure. Cannabis causes a dose-related, clinically significant drop in intraocular pressure that lasts several hours in both normal subjects and those with the abnormally high ocular tension produced by glaucoma. Oral or intravenous THC has the same effect, which seems to be specific to cannabis derivatives rather than simply a result of sedation. Cannabis does

---

[3] Doblin R. Kleiman M. Marihuana as anti-emetic medicine: a survey of oncologists' attitudes and experiences. *Journal of Clinical Oncology* 1991; 9:1275-80. (Attached as Exhibit D).

not cure the disease, but it can retard the progressive loss of sight when conventional medication fails and surgery is too dangerous.[4]

22. About 20% of epileptic patients do not get much relief from conventional anticonvulsant medications. Cannabis has been explored as an alternative at least since 1975 when a case was reported in which marijuana smoking, together with the standard anticonvulsants Phenobarbital and diphenylhydantoin, was apparently necessary to control seizures in a young epileptic man.[5] The cannabis derivative that is most promising as an anticonvulsant is cannabidiol. In one controlled study, cannabidiol in addition to prescribed anticonvulsants produced improvement in seven patients with grand mal convulsions; three showed great improvement. Of eight patients who received a placebo instead, only one improved.[6] There are patients suffering from both grand mal and partial seizure disorders who find that smoked marijuana allows them to lower the doses of conventional anticonvulsant medications or dispense with them altogether. Furthermore, anticonvulsants have many potentially serious side effects, including bone softening, anemia, swelling of the gums, double vision, hair loss, headaches, nausea, decreased libido, impotence, depression, and psychosis. Overdoses or idiosyncratic reactions may lead to loss of motor coordination, coma or even death.

23. There are many case reports of cannabis smokers using the drug to reduce pain: post-surgery pain, headache, migraine, menstrual cramps, and so on. Ironically, the best alternative analgesics are the potentially addictive and lethal opioids. In particular, cannabis is becoming increasingly recognized as the most effective treatment for the pain that accompanies muscle spasm, which is often chronic and debilitating, especially in paraplegics, quadriplegics, other victims of

---

[4] Hepler, R.S., et al. Ocular Effects of Marihuana Smoking. M.C. Braude, S. Szara (eds.). *The Pharmacology of Marihuana*. New York: Raven Press, 1976.

[5] Consroe, Paul F., et al. Anticonvulsant nature of Marihuana smoking. *Journal of the American Medical Association* 1975; 234-306-307. (Attached as Exhibit E).

[6] Cunha, J.M., et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980; 21:175-185. (Attached as Exhibit F).

traumatic nerve injury, and people suffering from multiple sclerosis or cerebral palsy. Many of them have discovered that cannabis not only allows them to avoid the risks of other drugs, but also reduces muscle spasms and tremors; sometimes they are even able to leave their wheelchairs.[7]

24. One of the most common causes of chronic pain is osteoarthritis, which is usually treated with synthetic analgesics. The most widely used of these drugs — aspirin, acetaminophen (Tylenol), and nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen — are not addictive, but they are often insufficiently powerful. Furthermore, they have serious side effects. Stomach bleeding and ulcer induced by aspirin and NSAIDs are the most common serious adverse drug reactions reported in the United States, causing an estimated 7,000 deaths each year. Acetaminophen can cause liver damage or kidney failure when used regularly for long periods of time; a recent study suggests it may account for 10% of all cases of end-stage renal disease, a condition that requires dialysis or a kidney transplant.[8] Cannabis, as I pointed out earlier, has never been shown to cause death or serious illness. The University of Iowa conducted a study of cannabis for the relief of pain. Researchers gave oral THC or placebo at random to hospitalized cancer patients who were in severe pain. The THC relieved pain for several hours in doses as low as 5-10 mg, and for even longer at 20 mg. At this dose and in this setting, THC proved to be a sedative as well. It had few physical side effects than other commonly used analgesics.[9]

25. Oncologists are legally permitted to administer the synthetic THC (Marinol) orally in capsule form. But inhaled cannabis may be necessary for several reasons. For one thing, oral THC is

---

[7] Petro, D. J., Ellenberger, C., Treatment of human spasticity with delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 1981; 21:413-416. (Attached as Exhibit G).

[8] Perneger, T.V., Whelton, P., Klag, M.J. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs. *New England Journal of Medicine* 1994; 331:25:1675-1679. (Attached as Exhibit H).

[9] R. Noyes, S. F. Brunk, D. A. Baram, and A. Canter, "Analgesic Effect of Delta-9-tetrahydrocannabinol," *Journal of Clinical Pharmacology* 15 (February-March 1975): 139-143. (Attached as Exhibit I).

subject to the variances of bioavailability. This means that two patients who take the same amount may absorb different proportions of the dose, and a given patient may respond differently on different days, depending on the condition of the intestinal tract and other factors. Furthermore, the effects of smoked cannabis are perceived almost immediately, so patients can smoke slowly and take only what they need for a therapeutic effect. Patients who swallow Marinol may discover after an hour or so that they have taken too much for comfort or not enough to relieve their symptoms. In any case, a patient who is severely nauseated and constantly vomiting may find it almost impossible to the capsule down. Furthermore, Marinol makes some patients anxious and uncomfortable. Smoked cannabis, unlike Marinol, contains other substances which reduces anxiety caused by the THC.

26. In theory, all the therapeutic properties of cannabis could be used if individual cannabinoids in addition to THC were isolated and made available separately as medicines. But this would be an enormously complicated procedure. Research sponsors would have to determine the therapeutic potential and evaluate the safety of sixty or more substances, synthesize each one found to be useful, and package it as a pill or aerosol. As some of these substances probably act synergistically, it would also be necessary to look at various combination of them. However no drug company would provide the resources needed for such a project because cannabis can not be patented, it is a plant material containing many chemicals rather than a single one and no drug in the present pharmacopoeia is delivered by smoking.

27. More than 300,000 Americans have died of AIDS. Nearly a million are infected with HIV, and at least a quarter of a million have AIDS. Although the spread of AIDS has slowed among homosexual men, the reservoir is so huge that the number of cases is sure to grow. Women and children as well as both heterosexual and homosexual men are now being affected; the disease is spreading most rapidly among intravenous drug abusers and their sexual partners. The disease can be attacked with anti-viral drugs, of which the best known are zidovudine (AZT) and protease inhibitors. Unfortunately, these drugs sometimes cause severe nausea that heightens the danger of semi-starvation for patients who are already suffering from nausea and losing weight because of the illness — a condition sometimes called the AIDS wasting syndrome.

28. Cannabis is particularly useful for patients who suffer from AIDS because it not only relieves the nausea but retards weight loss by enhancing appetite. In one study the body weight and caloric intake of twenty-seven marijuana users and ten control subjects were compared for twenty-one days on a hospital research ward. The marijuana smokers ate more than the controls and gained weight; the controls did not. When they stopped smoking marijuana, they immediately started to eat less.[10] When it helps patients regain lost weight, it can prolong life. Although Marinol has been shown to relieve nausea and retard or reverse weight loss in patients with HIV infection, most patients prefer smoked cannabis for the same reasons that cancer chemotherapy patients prefer smoked cannabis. Cannabis is more effective and has fewer unpleasant side effects, and the dosage is easier to adjust. Many patients report that cannabis provides an appetite and pain relief without the semi-comatose effect of narcotics.

29. Opponents of medical cannabis often object that the evidence of its usefulness, although strong, comes only from case reports and clinical experience. It is true that there are no double-blind controlled studies meeting the standards of the Food and Drug Administration, chiefly because legal, bureaucratic, and financial obstacles have been constantly put in the way. However, we know more about cannabis than about most prescription drugs. Furthermore, individual therapeutic responses are often obscured in group experiments, and case reports and clinical experience are the source of much of our knowledge of drugs. As Dr. Louis Lasagna has pointed out, controlled experiments were not needed to recognize the therapeutic potential of chloral hydrate, barbiturates, aspirin, insulin, or penicillin.[11] Nor was that the way we learned about the use of

---

[10] I. Greenberg, J. Kuehnle, J. H. Mendelson, and J. G. Bernstein, "Effects of Marijuana Use of Body Weight and Caloric Intake in Humans," *Journal of Psychopharmacology* (Berlin) 49 (1976): 79-84. (Attached as Exhibit J).

[11] Lasagne, L. Clinical trials in the natural environment. C. Stiechele, W. Abshagan, J. Kich-Weser (eds.). *In Drugs Between Research and Regulations*. New York: Springer-Verlag, 1985: 45-49. (Attached as Exhibit K).

propranolol for hypertension, diazepam for status epilepticus, and imipramine for enuresis. All these drugs had originally been approved for other purposes.

30. In the experimental method known as the single patient randomized trial, active and placebo treatments are administered randomly in alternation or succession. The method is often used when large-scale controlled studies are inappropriate because the disorder is rare, the patient is atypical, or the response to treatment is idiosyncratic.[12] Several patients have told me that they assured themselves of cannabis's effectiveness by carrying out such experiments on themselves, alternating periods of cannabis use with periods of abstention. I am convinced that the medical reputation of cannabis is derived partly from similar experiments conducted by many other patients.

31. Some physicians may regard it as irresponsible to advocate use of a medicine on the basis of case reports, which are sometimes disparaged as merely "anecdotal" evidence which counts apparent successes and ignores apparent failures. That would be a serious problem only if cannabis were a dangerous drug. The years of effort devoted to showing that cannabis is exceedingly dangerous have proved the opposite. It is safer, with fewer serious side effects, than most prescription medicines, and far less addictive or subject to abuse than many drugs now used as muscle relaxants, hypnotics, and analgesics.

32. Based on the best available medical information, it is evident that cannabis should be made available even if only a few patients could get relief from it, because the risks are so small. For example, as I mentioned, many patients with multiple sclerosis find that cannabis reduces their muscle spasma and pain. A physician may not be sure that such a patient will get more relief from cannabis than from the standard drugs baclofen, dantrolene, and diazepam — all of which are potentially dangerous or addictive — but it is almost certain that a serious toxic reaction to cannabis will not occur. Therefore the potential benefit is much greater than any potential risk.

---

[12] Larson, E.B. N-of-1 clinical trials: A technique for improving medical therapeutics. *Western Journal of Medicine* 1990; 152:52-56; Guyatt, G.H., Keller, J.L., Jaeschke, R., et al. The N-of-1 randomized controlled trial: Clinical usefulness. *Annals of Internal Medicine* 1990; 112:293-299. (Attached as Exhibit L).

33. During the past few years, the medical uses of cannabis have become increasingly clear to many physicians and patients, and the number of people with direct experience of these uses has been growing. Therefore, the discussion is now turning from whether cannabis is an effective medicine to how it should be made available.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed this 11 th day of September, 1998, at Boston, Massachusetts.

LESTER GRINSPOON, M.D.

**EXHIBIT A**

# LESTER GRINSPOON, M.D.

Date of birth: June 24, 1928, Newton, Massachusetts

Marital status: married, three children

## EDUCATION:

| | |
|---|---|
| 1951 | B.S., Tufts College, Medford, Massachusetts, magna cum laude. |
| 1955 | M.D., Harvard Medical School, Boston, cum laude. |

## POSTGRADUATE TRAINING AND EXPERIENCE:

| | |
|---|---|
| 1955-1956 | Intern in Medicine, Beth Israel Hospital, Boston, Massachusetts. |
| 1956-1958 | Field Investigator for the National Cancer Institute, Los Angeles, California. |
| 1958-1961 | Resident in Psychiatry, Massachusetts Mental Health Center, (Chief of Drug Unit 1959-1960; Chief of Service 1960-1961). |

## RESEARCH AND TEACHING APPOINTMENTS:

| | |
|---|---|
| 1950-1951 | Olmstead Fellow in Biology, Tufts College, Medford, Massachusetts |
| 1956-1958 | Assistant in Medicine, University of Southern California School of Medicine, Los Angeles, California |
| 1958-1959 | Teaching Fellow in Psychiatry, Harvard Medical School, Boston, Massachusetts |
| 1961-1962 | Assistant in Psychiatry, Harvard Medical School, Boston, Massachusetts |
| 1961-1963 | Lecturer on Social Relations, Harvard University, Cambridge, Massachusetts |
| 1962-1964<br>1962-1965 | Instructor in Psychiatry, Harvard Medical School, Boston, Massachusetts |
| 1961-1991 | Senior Psychiatrist, Massachusetts Mental Health Center, Boston, Massachusetts |
| 1964-1965 | Clinical Associate in Psychiatry, Harvard Medical School, Boston, Massachusetts |

1965-1968 Assistant Clinical Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts

1968-1973 Associate Clinical Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts

1973- Associate Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts.

OTHER APPOINTMENTS:

1961-1968 Director, Clinical Research Center, Massachusetts Mental Health Center

1962 Director, Summer Institute on Alternative Ways of Handling Conflict: Behavioral Science Research Toward Peace, Sponsored by the American Academy of Arts and Sciences

1963-1970 Consultant in Psychiatry and Research, Boston State Hospital

1969- Examiner, American Board of Psychiatry and Neurology

1972-1988 Advisory Board, National Organization for the Reform of Marijuana Laws

1973-1974 Budget Committee, American Psychiatric Association

1973- Executive Director, Massachusetts Mental Health Research Corporation

1974-1979 Consultant, Task Force on Interface between Psychiatry and Industry, American Psychiatric Association

1974-1979 Council on Research, American Psychiatric Association

1975-1977 Vice-Chairperson, Council on Research, American Psychiatric Association

1976-1981 Advisory Board, The Center for the Study of Non-Medical Drug Use

1977-1979 American Psychiatric Association Representative to the American Association for the Advancement of Science

1977-1979 Chairperson, Council on Research, American Psychiatric Association

| | |
|---|---|
| 1979-1980 | Vice-Chairperson, Scientific Program Committee, American Psychiatric Association |
| 1979-1980 | Chairperson, Subcommittee on Awards for Scientific Exhibits, American Psychiatric Association |
| 1979- | Council on Marihuana and Health, National Organization for the Reform of Marijuana Laws |
| 1980-1984 | Chairperson, Scientific Program Committee, American Psychiatric Association |
| 1980-1984 | Scientific Advisory Board, Beneficial Plant Research Association |
| 1984-1985 | Chairperson, Task Force on Soviet/American Relations, American Psychiatric Association |
| 1986-1990 | Founding Board of Directors, Physicians for Human Rights |
| 1987- | Advisory Board, The Drug Policy Foundation |
| 1987- | Board of Advisors, The Albert Hofmann Foundation |
| 1989- | Vice President, International Antiprohibitionist League |
| 1989-1991 | Advisory Board, Civil Liberties Union of Massachusetts/ACLU |
| 1989-1991 | Board of Directors, Center for Psychological Studies in the Nuclear Age |
| 1990- | Advisory Board, Physicians for Human Rights |
| 1990-1992 | Board of Directors, Drug Policy Foundation |
| 1991-1993 | Board of Directors, Civil Liberties Union of Massachusetts |
| 1993-1996 | Faculty Member, Zinberg Center for Addiction Studies, Cambridge, Massachusetts |
| 1994-1995 | Chairperson, Board of Directors, National Organization for the Reform of Marihuana Laws |
| 1995- | Advisory Board, The Drug Research Group |
| 1997- | Board of Scientific and Policy Advisors of the American Council on Science and Health |

1997- Honorary Member, Arbeitsgemeinschaft Cannabis als Medizin (Alliance for Cannabis as Medicine), Germany

1997- International Advisory Committee, Physicians for Human Rights

EDITORIAL BOARDS:

1982-1984 Editor, Psychiatry Update: The American Psychiatric Association Annual Review; Volumes I-III

1982-1993 Journal of Psychiatric Research

1984- Editor, The Harvard Mental Health Letter

1985- Journal of Social Pharmacology

1985- The Harvard Health Letter

1991- Addiction Research

OTHER PROFESSIONAL ACTIVITIES:

Testified before legislative committees in the states of Massachusetts, Colorado, New Jersey, Washington, Vermont, and New York. Also testified before the National Marijuana Commission (1972), the House Armed Services Committee (1962), the Monopoly Subcommittee of the Senate Small Business Committee (1976), the House Select Committee on Narcotics (1977, 1979, 1989), the Controlled Substances Advisory Committee, the Drug Abuse Research Advisory Committee (1978), and the Senate Judiciary Committee (1980), etc.

HONORARY SOCIETIES:

Phi Beta Kappa
Alpha Omega Alpha
Boylston Society, Harvard Medical School
Columbia University Seminar Associate

PROFESSIONAL ORGANIZATIONS:

Massachusetts Medical Society
American Psychiatric Association (Fellow)
American Association for the Advancement of Science (Fellow)
Group for the Advancement of Psychiatry
Society of Biological Psychiatry
World Federation of Mental Health

**MEDICAL LICENSING AND CERTIFICATION:**

Diplomate, National Board of Medical Examiners
Licensed, State of Massachusetts
Diplomate, American Board of Psychiatry

**PSYCHOANALYTIC TRAINING:**

Graduate, Boston Psychoanalytic Institute, Boston, Massachusetts, April 1967

Member, Boston Psychoanalytic Society, Boston, Massachusetts, 1967-1985

**AWARDS:**

Mencken Award: Honorable Mention Winner for contribution to Dealing with Drugs, 1988

Alfred R. Lindesmith Award for Achievement in the Field of Scholarship, a $10,000 award of the Drug Policy Foundation, Washington, D.C., 1990*

Norman E. Zinberg Award for Marihuana Research, an award of The National Organization for the Reform of Marijuana Laws, Washington, D.C., 1990

---

*see citation, page 23

**PUBLICATIONS:**

1. Grinspoon, L., Sagild, U., Blum, H.P., and Marble, A.: Changes in circulating eosinophils in juvenile diabetics in response to epinephrine, ACTH, and hypoglycemia. Journal of Clinical Endocrinology and Metabolism, 13:753-768, 1953.

2. Alexander, B., Meyers, L., Kenny, J., Goldstein, R., Gurewich, V., and Grinspoon, L.: Blood coagulation in pregnancy: Proconvertin and prothrombin, and the hypercoagulable state. New England Journal of Medicine, 254:358-363, 1956.

3. Grinspoon, L. and Dunn, J.E.: A study of the frequency of achlorhydria among Japanese in Los Angeles. Journal of the National Cancer Institute, 22:617-631, 1959.

4. Ewalt, J.R., Alexander, G.L., and Grinspoon, L.: Changing practices: A plea and some predictions. Mental Hospitals, 11(6):9-13, June 1960.

5. Grinspoon, L., Courtney, P.H., and Bergen, H.M.: The usefulness of a structured parents' group in rehabilitation. In Mental Patients in Transition, Greenblatt, M., Levinson, D.J., and Klerman, G.L. (eds.). Springfield, Illinois: Charles C. Thomas, Publishers, 1961, pp. 229-260.

6. Grinspoon, L. and Lieberman, E.J.: Escape from the bomb: Anxiety, anger, and the "enemy." The New Republic, September 4, 1961, pp. 10-15.

7. Grinspoon, L. and Lieberman, E.J.: Our psychological retreat from the bomb. Science Digest, 50:1-6, 1961.

8. Grinspoon, L. and Cohen, R.E.: The introduction of a part-time hospitalization program into an acute psychiatric treatment service. New England Journal of Medicine, 267:752-756, 1962.

9. Grinspoon, L.: The psychological problems of life in a fall-out shelter. In No Place to Hide, Melman, S. (ed.). New York: Grove Press, 1962.

10. Cohen, R.E. and Grinspoon, L.: Limit setting as a corrective ego experience. Archives of General Psychiatry, 8:74-79, 1963.

11. Grinspoon, L., Heath, L.M., Barron, M.W., Jones, M.R., and Furtado, L.P.: A day care program on an inpatient service. Mental Hospitals, 1(5):259-264, May 1963.

12. Grinspoon, L.: Fallout shelters and mental health. Resident Physician, 9:76-81, May 1963. Also in Medical Times, 91(6):517-520, June 1963.

13. Grinspoon, L. and Greenblatt, M.: Pharmacotherapy combined with other treatment methods. Presented at the Third World Congress of Psychiatry, Montreal, June 4-10, 1961. Published in Comprehensive Psychiatry, 4:256-262, 1963.

14. Grinspoon, L. and Cohen, R.E.: A new approach to the hospitalization of the mentally ill. Clinical Medicine, 70:1983-1995, 1963.

15. Grinspoon, L.: Decision-maker's dilemma. Harvard Medical Alumni Bulletin, 38(5):37-41, Summer 1964.

16. Grinspoon, L.: Fallout shelters and the unacceptability of disquieting facts. In The Threat of Impending Disaster: Contribution to the Psychology of Stress, Grosser, G., Wechsler, H. and Greenblatt, M. (eds.). Cambridge, Massachusetts: MIT Press, 1964, pp. 117-130.

17. Grinspoon, L.: Interpersonal constraints and the decision-maker. In International Conflict and Behavioral Science: The Craigville Papers, Fisher, R. (ed.). New York: Basic Books, 1964, pp. 238-247.

18. Grinspoon, L.: The truth is not enough. In International Conflict and Behavioral Science: The Craigville Papers, Fisher, R. (ed.). New York: Basic Books, 1964, pp. 272-281.

19. Grinspoon, L., Shader, R.I., Chatterjee, S., and Cohler, J.: Side effects and double-blind studies -- I: a clinical comparison between thioridazine hydrochloride and a combination of phenobarbital and atropine sulfate. Journal of Psychiatric Research, 2:247-256, 1964.

20. Post, J.M., Swanson, J.F., and Grinspoon, L.: Cyclic staff responses to chronic schizophrenic patients. Perspectives in Psychiatric Care, 2(3):13-23, 1964.

21. Shader, R.I., Cohler, J., Elashoff, R., and Grinspoon, L.: Phenobarbital and atropine in combination: An active control substance for phenothiazine research. Journal of Psychiatric Research, 2:169-183, 1964.

22. Crider, A., Grinspoon, L., and Mahler, B.: Autonomic and psychomotor correlates of premorbid adjustment in schizophrenia. Psychosomatic Medicine, 27:201-206, 1965.

23. Cohler, J., Grinspoon, L., and Fleiss, J.: An extreme situation on a chronic schizophrenic treatment ward. Journal for the Study of Interpersonal Processes, 28:359-367, 1965.

24. Crider, A., Maher, B., and Grinspoon, L.: The effect of sensory input on the reaction time of schizophrenic patients of good and poor premorbid history. Psychosomatic Science, 2:47-48, 1965.

25. Cohler, J., Grinspoon, L., Shader, R.I., and Chatterjee, S.: Behavioral correlates of the guessing game. Archives of General Psychiatry, 15:279-287, 1966.

26. Grinspoon, L. and Menninger, R.W.: Introduction to the range of human conflict: A symposium. Bulletin of the Menninger Clinic, 30:265-266, 1966.

27. Levine, F., Shader, R.I., Whitney, N., and Grinspoon, L.: The observers and the observed: The effect of doing ratings on staff-patient contact patterns. Journal of Consulting Psychology, 30:456-457, 1966.

28. Alexander, S., Shader, R., and Grinspoon, L.: Electrocardiographic effects of thioridazine hydrochloride (Mellaril R). Lahey Clinic Foundation Bulletin, 6(2):207-215, 1967.

29. Grinspoon, L., Ewalt, J., and Shader, R.I.: Long-term treatment of chronic schizophrenia: A preliminary report. International Journal of Psychiatry, 4(2):116-141, August 1967. Reprinted in Anthology of Selected References from the Balanced Service System, State of New York Department of Mental Hygiene, Division of Mental Health, July 1974, pp. 80-95.

30. Shader, R.I. and Grinspoon, L.: Schizophrenia, oligospermia, and the phenothiazines. Diseases of the Nervous System, 28:240-244, 1967.

31. Bergen, H., Grinspoon, L., and Eliashof, B.: Conflicting staff and family demands on schizophrenic patients. Hospital and Community Psychiatry, 19(3):84-87, March 1968.

32. Bergen, J.R., Frohman, C.E., Mittag, T.W., Arthur, R.E., Warner, K.A., Grinspoon, L., and Freeman, H.: Plasma factors in schizophrenia: A cooperative study. Archives of General Psychiatry, 18:471-476, 1968.

33. Grinspoon, L., Ewalt, J., and Shader, R.I.: Psychotherapy and pharmacotherapy in chronic schizophrenia. American Journal of Psychiatry, 124:1645-1652, 1968. Reprinted in Anthology of Selected References from the Balanced Service System, State of New York Department of Mental Hygiene, Division of Mental Health, July 1974, pp. 96-110.

34. Bergen, H., and Grinspoon, L.: On the relationship of staff-family interactions and deterioration of the patient. Psychiatric Opinion, 5(5):38-43, October 1968.

35. Grinspoon, L.: Psychosocial constraints on the important decision-maker. American Journal of Psychiatry, 1074-1082, 1969.

36. Messier, M., Finnerty, R., Botvin, C., and Grinspoon, L.: A follow-up study of intensively treated chronic schizophrenic patients. American Journal of Psychiatry, 125:1123-1127, 1969. Also published in The Schizophrenic Syndrome, R. Cancro (ed.). New York: Brunner/Mazel, 1971.

37. Stern, M., Fram, D., Wyatt, R., Grinspoon, L., and Tursky, B.: All-night sleep studies of acute schizophrenics. Archives of General Psychiatry, 20:470-477, 1969.

38. Wyatt, R., and Grinspoon, L.: Behavioral and skin potential response correlations in chronic schizophrenia. Comprehensive Psychiatry, 10:196-200, 1969.

39. Pavy, D., Grinspoon, L., and Shader, R.I.: Word frequency measures of verbal disorders in schizophrenia. Diseases of the Nervous System, 30:553-556, 1969.

40. Grinspoon, L.: Marihuana. Scientific American, 221(6):17-25, December 1969. Reprinted In Contemporary Psychology: Readings from Scientific American, San Francisco: W.H. Freeman and Company, 1972, pp. 89-97.

41. Meltzer, H., Shader, R.I., and Grinspoon, L.: The behavioral effects of nicotinamide adenine dinucleotide in chronic schizophrenia. Psychopharmacologia (Berl). 15:144-152, 1969.

42. Shader, R.I., Grinspoon, L., Ewalt, J.R., and Zahn, D.A.: Drug responses in schizophrenia. Presented at the Conference, "Schizophrenia: An Appraisal," November 14-16, 1968, New York. Published in Schizophrenia: Current Concepts and Research, D.V. Siva Sankar (ed.). New York: PJD Publications, 1969, pp. 161-173.

43. Grinspoon, L.: The utility of psychotherapy with schizophrenia. International Journal of Psychiatry, 8(4):727-729, 1969.

44. Shader, R.I. and Grinspoon, L.: The effect of social feedback on chronic schizophrenic patients. Comprehensive Psychiatry, 11:196-199, 1970.

45. Wyatt, R.J., Stern, M., Fram, D.H., Tursky, B., and Grinspoon, L.: Abnormalities in skin potential fluctuation during the sleep of acute schizophrenic patients. Psychosomatic Medicine, 32:301-308, 1970.

46. Meltzer, H.Y., Grinspoon, L., and Shader, R.I.: Serum creatine phosphokinase and aldase activity in acute schizophrenic patients and their relatives. Comprehensive Psychiatry, 11:552-558, 1970.

47. Fowles, D.C., Watt, N.F., Maher, B.A., and Grinspoon, L.: Autonomic arousal in good and premorbid schizophrenics. British Journal of Social and Clinical Psychology, 9:136-147, 1970.

48. Grinspoon, L.: Marihuana. In International Journal of Psychiatry: Current Issues in Psychiatry, Volume 9, J. Aronson (ed.). New York: Science House, 1970, pp. 488-516.

49. Grinspoon, L.: Marihuana. In Encyclopedia of Science and Technology, New York: McGraw-Hill Book Company, 1971, pp. 260-263.

50. Shader, R.I., Grinspoon, L., Harmatz, J.S., and Ewalt, J.R.: The therapist variable. American Journal of Psychiatry, 127:1009-1012, 1971.

51. Grinspoon, L.: Marijuana: Who smokes it and why? Mademoiselle, May 1981, pp. 180-181, 217-219.

52. Grinspoon, L.: Review of Artificial Paradise, Charles Baudelaire, trans. by Ellen Fox. The New York Times Review, October 24, 1971, p.58.

53. Grinspoon, L.: Marihuana and society. In Tracks: Directions in the Field of Drug Abuse. From the office of Massachusetts Attorney General Robert H. Quinn, October 1971 (No.6), pp. 1-3. Reprinted in International Narcotic Report, International Narcotic Enforcement Officers Association, April 1972.

54. Grinspoon, L.: Marihuana: An argument in support of legalization. New York Law Journal, December 6, 1971, pp. 27, 29.

55. Levine, F.M. and Grinspoon, L.: Telemetered heart rate and skin potential of a chronic schizophrenic patient especially during periods of hallucinations and periods of talking. Journal of Consulting and Clinical Psychology, 37:345-350, 1971.

56. Grinspoon, L.: The question of legalization. In Drugs, Adelstein, M.E. and Pival, J.G. (eds.). New York: St. Martin's Press, 1972, pp. 75-87.

57. Grinspoon, L. and Hedblom, P.: Amphetamine abuse. Drug Therapy, 2(1):83-99, January 1972.

58. Grinspoon, L.: Half a loaf: A reaction to the marihuana report. Saturday Review: Science, Guest Editorial, April 15, 1972, pp. 21-22.

59. Grinspoon, L.: A critique of "Marihuana -- A Signal of Misunderstanding." In Tracks: Directions in the Field of Drug Abuse. From the office of Massachusetts Attorney General Robert H. Quinn, June 1972 (No. 9), pp. 2-3. Reprinted in World Journal of Psychosynthesis, October 1974.

60. Grinspoon, L. and Hedblom, P.: Amphetamines reconsidered. Saturday Review: Science, July 8, 1972, pp. 33-41, 45-46.

61. Grinspoon, L.: Review of Ups and Downs: Drugging and Duping, Julius Rice. New England Journal of Medicine, 287(13):673-674, 1972.

62. Grinspoon, L.: Stoned thinking. Review of The Natural Mind, by Andrew Weil. New York Times Book Review, October 15, 1972, pp. 27-29.

63. Grinspoon, L.: The therapeutic potential of cannabis. Drug Therapy, 2(10):53-63, October 1972.

64. Grinspoon, L.: Marihuana and student health (Viva Schatia Kanzer Memorial Lecture published as a monograph). Mental Health Association of Westchester, White Plains, N.Y., October 1972.

65. Grinspoon, L.: Review of Tulsa, Larry Clark. Medical Tribune, 13(42):1,8, November 1, 1972.

66. Grinspoon, L. and Persky, A.: Psychiatry and U.F.O. reports. In UFOs: A Scientific Debate, C. Sagan and T. Page (eds.). Ithaca: Cornell University Press, 1972, pp. 233-246.

67. Grinspoon, L.: Marihuana and brain damage: A criticism of the study by A.M.G. Campbell, et al. Contemporary Drug Problems, Fall 1972, pp. 811-814.

68. Semrad, E.V., Grinspoon, L., and Fienberg, S.E.: Development of an ego profile scale. Archives of General Psychiatry, 28:70-77, January 1973.

69. Grinspoon, L.: Review of Uses of Marihuana, Solomon Snyder. Social Science and Medicine, 7:90-91, 1973.

70. Grinspoon, L.: Review of Marihuana: Deceptive Weed, Gabriel Nahas. New England Journal of Medicine, 288(13):692-693, 1973.

71. Grinspoon, L.: Marihuana reconsidered. In The Solution of Social Problems: Five Perspectives, M.S. Weinberg and E. Rubington (eds.). New York: Oxford University Press, 1973, pp. 251-269.

72. Grinspoon, L.: Legislative process and social reform: Marihuana reconsidered. In Contemporary Problems of Drug Abuse: A National Symposium for Law and Medical Students. Villanova Law Review, 18:897-910, 1973.

73. Grinspoon, L. and Hedblom, P.: Marihuana and amphetamine: a mirror image relationship. Contemporary Drug Problems, 2:665-682, 1973.

74. Grinspoon, L. and Singer, S.: Amphetamines in treatment of hyperkinetic children. Harvard Educational Review, 443(4):515-555, 1973. Reprinted in The Rights of Children, J.A. Butler and Donald Fost-Gross (eds.). Cambridge, Mass., 1974, and in Progress in Child Psychiatry and Child Development, S. Chess and A. Thomas (eds.). New York: Brunner/Mazel, 1975.

75. Grinspoon, L.: Review of The Marihuana Problem in the City of New York, Mayor La Guardia's Committee on Marihuana. New England Journal of Medicine, 289(24):1319-1320, December 13, 1973.

76. Grinspoon, L., Ewalt, J.R., and Shader, R.I.: L'experience du Massachusetts Mental Health Center: Un essai therapeutique poursuivi avec des schizophrenes chroniques (The experience of the Massachusetts Mental Health Center: A therapeutic trial with chronic schizophrenics). In Traitments au Long Cours des Etats Psychotiques (Long-term Treatments of Psychotic States), G. Chiland and P. Bequart (eds.). Toulouse: Edouard Privat, 1974, pp. 245-258.

77. Grinspoon, L. and Singer, S.: Amphetamines in the treatment of hyperkinetic children. In Tracks: Directions in the Field of Drug Abuse (No. 16), June 1974, pp. 1, 4.

78. Grinspoon, L.: Review of The Marihuana Problem in the City of New York, Mayor La Guardia's Committee on Marihuana. Contemporary Drug Problems, 3:175-178, Spring 1974.

79. Grinspoon, L. and Singer, S.: Drugs for overactive school children: Therapy or abuse? Parents' Magazine, November 1974, pp. 52-53, 103-106.

80. Grinspoon, L.: Review of The Marihuana Conviction: A History of Marihuana Prohibition in the United States, Richard J. Bonnie and Charles H. Whitebread II. New England Journal of Medicine, 292(7):374-375, February 13, 1975.

81. Grinspoon, L.: Drug dependence: Non-narcotic agents. Comprehensive Textbook of Psychiatry - II, A.M. Freedman, H.I. Kaplan, and B.J. Sadock (eds.). Baltimore: Williams & Wilkins Company, 1975, pp. 1317-1331.

82. Grinspoon, L. and Shader, R.I.: Psychotherapy and drugs in schizophrenia. In Drugs in Combination with Other Therapies, M. Greenblatt (ed.). New York: Grune & Stratton, 1975, pp. 49-66.

83. Grinspoon, L. and Singer, S.: Amphetamines in the treatment of hyperkinetic children: A note of caution. Psychopharmacology of Childhood, D.V. Siva Sankar (ed.). Westbury, New York: PJD Publications Limited, 1976.

84. Grinspoon, L.: Review of Sensual Drugs: Deprivation and Rehabilitation of the Mind, Hardin B. Jones and Helen C. Jones. The New York Times Book Review, March 27, 1977, pp. 22-26.

85. Grinspoon, L. and Bakalar, J.B.: The amphetamines: medical uses and health hazards. Psychiatric Annals, 7(8):6-24, August 1977.

86. Grinspoon, L., Ewalt, J.R. and Shader, R.I.: The therapeutic trial carried out at the Massachusetts Mental Health Center with chronic schizophrenic patients. In Long-term Treatments of Psychotic States, C. Chiland (ed.). New York: Human Sciences Press, 1977, pp. 375-396.

87. Statement on marihuana before the Select Committee on Narcotics Abuse and Control of the U.S. House of Representatives. March 15, 1977. In Congressional Digest, February 1979.

88. Grinspoon, L. and Bakalar, J.B.: Marihuana: health hazards and medical benefits. In Controversy in Psychiatry, J.P. Brady and H.K.H. Brodie (eds.). Philadelphia: W.B. Saunders Co., 1978, pp. 881-904.

89. Grinspoon, L. and Bakalar, J.B.: Drug abuse, crime, and antisocial personality: Some conceptual issues. In The Psychopath: A Comprehensive Study of Sociopathic Disorders and Behaviors, W.H. Reid (ed.). New York: Brunner/Mazel, 1978, pp. 234-243.

90. McLerran, A.E., Grinspoon, L., and Gudeman, J.E.: A surfeit of surveys: Escalating data demands of community mental health centers. Hospital and Community Psychiatry, April 1979, pp. 243-247.

91. Grinspoon, L. and Bakalar, J.B.: Cocaine. In Handbook on Drug Abuse, R.I. DuPont, A. Goldstein, and J. O'Donnell, (eds.). Washington, D.C.: U.S. Government Printing Office, 1979, pp. 241-247.

92. Grinspoon, L. and Bakalar, J.B.: The amphetamines: Medical uses and health hazards. In Amphetamine Use, Misuse, and Abuse, D.E. Smith, D.R. Wesson, M.E. Buxton, et al (eds.). Boston: G.K. Hall and Co., 1979, pp. 18-34.

93. Grinspoon, L.: A note of caution regarding the use of medication for school problems. In Minimal Brain Dysfunction: A Developmental Approach, L. Stern and E. Denhoff (eds.). New York: Masson Publishing Co., 1979, pp. 177-183.

94. Bergen, J.R., Grinspoon, L., Pyle, H.M., Martinez, J.L., and Pennell, R.B.: Immunologic studies in schizophrenic and control subjects. Biological Psychiatry, 15(3):369-379, June 1980.

95. Grinspoon, L. and Bakalar, J.B.: Drug dependence: non-narcotic agents. In Comprehensive Textbook of Psychiatry-III, H.I. Kaplan, A.M. Freedman, and B.J. Sadock (eds.). Baltimore: Williams and Wilkins Co., 1980, pp. 1614-1629.

96. Grinspoon, L. and Bakalar, J.B.: Is marihuana hazardous to your health? In Psychiatry at the Crossroads, J.P. Brady and H.K.H. Brodie (eds.). Philadelphia: W.B. Saunders Co., 1980, pp. 71-94.

97. Grinspoon, L.: LSD reconsidered: Should clinical research be resumed? The Sciences, 21(1):20-23, January 1981.

98. Grinspoon, L. and Bakalar, J.B.: Marihuana. In Substance Abuse: Clinical Problems and Perspectives, J.H. Lowinson and P. Ruiz (eds.). Baltimore: Williams & Wilkins Co., 1981, pp. 140-147.

99. Grinspoon, L. and Bakalar, J.B.: Coca and cocaine as medicines: An historical review. Journal of Ethnopharmacology, 3:149-159, 1981.

100. Grinspoon, L. and Bakalar, J.B.: Adverse effects of cocaine: Selected issues. In Research Developments in Drug and Alcohol Use, R.B. Millman, P. Cushman, and J.H. Lowinson (eds.). New York: New York Academy of Sciences, 1981, pp. 125-131.

101. Dickey, B., Gudeman, J.E., Hellman, S., Donatelle, A., and Grinspoon, L.: A follow-up of deinstitutionalized chronic patients four years after discharge. Hospital and Community Psychiatry, 32(5):326-330, May 1981.

102. Gudeman, J.E., Dickey, B., Rood, L., Hellman, S., and Grinspoon, L.: Alternative to the back ward: The quarterway house. Hospital and Community Psychiatry, 32(5):330-334, May 1981.

103. Grinspoon, L. and Bakalar, J.B.: Psychedelic drug therapies: Should their use be reconsidered? Interdisciplinary Science Reviews, 6(3):191-194, September 1981.

104. Grinspoon, L. and Bakalar, J.B.: The psychedelic drug therapies. In Current Psychiatric Therapies, Vol. 20, J.H. Masserman (ed.). New York: Grune & Stratton, 1981, pp. 275-283.

105. Grinspoon, L.: Cocaine. In Handbook on Drug Abuse, B. Wilford (ed.). Chicago: American Medical Association, 1981.

106. Grinspoon, L.: The threat of nuclear war. American Journal of Psychiatry, Editorial, 139(10):1313-1314, October 1982.

107. Grinspoon, L.: Review of Marijuana as Medicine, Roger A. Roffman. New England Journal of Medicine, 307(20):1280, November 11, 1982.

108. Menninger, R.W., Grinspoon, L., Ottenberg, Perry, et al: The Child and Television Drama: The Psychosocial Impact of Cumulative Viewing, GAP Committee on Social Issues. New York: Mental Health Materials Center, 1982.

109. Mills, M.J., Gutheil, T.G., Igneri, M.A. and Grinspoon, L.: Mental patients' knowledge of in-hospital rights. American Journal of Psychiatry, 140(2):225-228, February 1983.

110. Bakalar, J.B. and Grinspoon, L.: Why drug policy is so harsh. The Hastings Center Report, 13(4):34-39, August 1983.

111. Grinspoon, L.: Crisis behavior. Bulletin of the Atomic Scientists, 40(4):25-28, April 1984.

112. Grinspoon, L. and Bakalar, J.B.: Freebasing cocaine. Forum, The Harvard Mental Health Letter, 1(1):8, July 1984.

113. Bakalar, J.B. and Grinspoon, L.: Drug control: Three analogies. Journal of Psychoactive Drugs, 16(2):107-118, April-June 1984.

114. Bakalar, J.B. and Grinspoon, L.: Drug abuse policies and social attitudes to risk taking. In Feeling Good and Doing Better: Ethics and Nontherapeutic Drug Use, T.H. Murray, W. Gaylin, and R. Macklin (eds.). Clifton, N.J.: The Humana Press, 1984, pp. 13-26.

115. Grinspoon, L. and Bakalar, J.B.: What is MDMA? Forum, The Harvard Mental Health Letter. 2(2):8, August 1985.

116. Grinspoon, L.: Review of The New Psychiatry: How Modern Psychiatrists Think About Their Patients, Theories, Diagnoses, Drugs, Psychotherapies, Power, Training, Families, and Private Lives, Jerrold S. Maxmen. New England Journal of Medicine, 313(8):523, August 22, 1985.

117. Grinspoon, L.: What is our drug problem and what should be done about it? Forum participant, Harper's, 271(1627):39-51, December 1985.

118. Grinspoon, L. and Bakalar, J.B.: MDMA -- a potential psychotherapeutic drug? The Psychiatric Times, 3(1):4,5,18, January 1986.

119. Grinspoon, L. and Bakalar, J.B.: Can drugs be used to enhance the psychotherapeutic process? American Journal of Psychotherapy, 40(3):393-404, July 1986.

120. Grinspoon, L. and Bakalar, J.B.: Medical uses of illicit drugs. In Dealing With Drugs: Consequences of Government Control, Ronald Hamowy (ed.). San Francisco, CA: Pacific Research Institute for Public Policy, 1987, pp. 183-210.

121. Grinspoon, L.: A proposal for regulation and taxation of drugs. Nova Law Review, 11(3):927-930, Spring 1987.

122. Grinspoon, L. and Bakalar, J.B.: Substance use disorders. In The New Harvard Guide to Psychiatry, Armand M. Nicholi, Jr. (ed.). Boston, MA: Harvard University Press, 1988, Chapter 19.

123. Grinspoon, L. and Bakalar, J.B.: The further social evolution of cocaine. In Drugs and Society: A Critical Reader, Maureen E. Kelleher, Bruce K. MacMurray, and Thomas M. Shapiro (eds.). Dubuque, Iowa: Kendall/Hunt Publishing Co., 1988.

124. Grinspoon, L.: The harmfulness tax: a proposal for regulation on taxation of drugs. In The Cost of Prohibition on Drugs: Papers of the International Anti-prohibitionism Forum, Brussels, September 28--October 1, 1988.

125. Bakalar, J.B. and Grinspoon, L: Testing psychotherapies and drug therapies: The case of psychedelic drugs. In Ecstasy: The Clinical Pharmacological and Neurotoxicological Effects of the Drug MDMA. Stephen J. Peroutka (ed.). Boston, MA: Klower Academic Publishers, 1989.

126. Grinspoon, L. and Bakalar, J.B.: What is phencyclidine? Forum, The Harvard Medical School Mental Health Letter, 6(7):8, January 1990.

127. Grinspoon, L. and Bakalar, J.B.: The harmfulness tax: a New approach to drug control. Hospital and Community Psychiatry, Editorial, 41(5):483, May 1990.

128. Grinspoon, L.: The harmfulness tax: Legalize and tax drugs. Journal of State Government, 63(2):46-49, April-June 1990.

129. Grinspoon, L.: Testimony of Lester Grinspoon, M.D. In Cancer Treatment & Marijuana Therapy, R.C. Randall (ed.). Washington, D.C.: Galen Press, 1990.

130. Grinspoon, L. and Bakalar, J.B.: Arguments for a harmfulness tax. Journal of Drug Issues, 20(4): 599-604, Fall 1990.

131. Grinspoon, L.: Marijuana enhances the lives of some people. In Drug Prohibition and the Conscience of Nations, Arnold S. Trebach and Kevin B. Zeese (eds.). Washington, D.C.: The Drug Policy Foundation, 1990.

132. Goldman, M.J., Grinspoon, L., and Hunter-Jones, S.: Ritualistic use of fluoxetine by a former substance abuser. American Journal of Psychiatry, 147(10):1377, October 1990.

133. Grinspoon, L.: The harmfulness tax: A proposal for regulation and taxation of drugs. North Carolina Journal of International Law & Commercial Regulation, 15(3):505-510, Fall 1990.

134. Grinspoon, L. and Bakalar, J.B.: Non-narcotic drug use and abuse. Encyclopedia of Human Biology, Volume 5, Academic Press, 1991.

135. Grinspoon, L.: Drug war fatality: the medical potential of illicit drugs. Harvard Medical Alumni Bulletin, 65(1):24-28, Summer 1991.

136. Grinspoon, L.: Marijuana in a time of psychopharmacological McCarthyism. In Searching for Alternatives: Drug-Control Policy in the United States, Melvyn B. Krauss and Edward P. Lazear (eds.). Stanford, CA: Hoover Institution Press, 1991.

137. Grinspoon, L. and Bakalar, J.B.: Marihuana. In Substance Abuse: A Comprehensive Textbook, Second Edition, Joyce H. Lowinson, Pedro Ruiz, and Robert B. Millman (eds.). Baltimore, MD: Williams & Wilkins, 1992.

138. Grinspoon, L. and Bakalar, J.B.: The war on drugs: A peace proposal. New England Journal of Medicine 360:5:357-360, Feb. 3, 1994.

139. Grinspoon, L. e Bakalar, J.B.: L'errore piu grave? Liberare la societa dalla droga on l'uso della forza. Medicina delle Tossicodipendenze, Italian Journal of the Addictions (September 1994), pp. 4-9.

140. Grinspoon, L.: Should marijuana be legalized as a medicine? Yes, it's a beneficial drug. The World & I: A Chronicle of our Changing Era Current Issues, Commentary (June 1994), pp. 92, 94-97. Reprinted in: Drugs, Society, and Behavior, Annual Editions, Article 47, 1995/1996, pp. 231-23.

141. Grinspoon, L. and Bakalar, J.B.: Marihuana as medicine: A plea for reconsideration. Journal of the American Medical Association, Commentary, 273:23:1875-1876, June 21, 1995.

142. Grinspoon, L., Bakalar, J.B., and Doblin, R.: Marijuana, the AIDS wasting syndrome, and the U.S. government. New England Journal of Medicine, Letter to the Editor 333:10:670-671, September 7, 1995.

143. Grinspoon, L. and Bakalar, J.B.: Marihuana, the forbidden medicine. University of West Los Angeles Law Review 27:29-72, 1996.

144. Grinspoon, L.: Marihuana as medicine. Hempworld (Fall 1996), pp. 32-36.

145. Grinspoon, L: Marihuana: An old medicine for a new millennium. In The Pioneers of Reform: Reflections and Visions. Policy Papers prepared for the 10th International Conference on Drug Policy Reform, Arnold S. Trebach, Whitney A. Taylor, Rob Stewart, and Scott Ehlers (eds). Washington, D.C.: The Drug Policy Foundation Press, 1996, pp. 139-143.

146. Grinspoon, L.: Cannabis: Wonder drug of the '90s. In Cannabis Science: From Prohibition to Human Right. Lorenz Böllinger (ed.). Frankfurt am Main: Die Deutsche Bibliothek - CIP - Einheitsaufnahme, 1997, pp. 139-146.

147. Grinspoon, L. and Bakalar, J.B.: Smoke screen. Playboy Forum, June 1997, pp. 49-53.

148. Grinspoon, L. and Bakalar, J.B.: Marihuana. In Substance Abuse: A Comprehensive Textbook, Third Edition. Joyce H. Lowinson, Pedro Ruiz, Robert B. Millman, and John G. Langrod (eds.). Baltimore: Williams & Wilkins, 1997.

149. Grinspoon, L. and Bakalar, J.B.: Marijuana addiction. Letter to Science, 177: August 8, 1997, p. 749.

150. Grinspoon, L. and Bakalar, J.B.: Nonnarcotic drug use and abuse. Encyclopedia of Human Biology, Second Edition, Volume 6. Renato Dulbecco (ed.). Academic Press: 1997.

151. Grinspoon, L. and Bakalar, J.B.: Missed Opportunities? Beneficial Uses of Illicit Drugs. In: The Control of Drugs and Drug Users. Ross Coomber (ed.). United Kingdom: Harwood Academic Publishers, 1997.

152. Grinspoon, L. and Bakalar, J.B.: The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research. Journal of Psychoactive Drugs, 30(2): 171-177, April-June 1998.

153. Grinspoon, L.: Prescribing the Forbidden Medicine. Playboy Forum, August 1998, pp. 41-43.

154. Grinspoon, L.: Marihuana: An Old Medicine for a New Millennium. In: How to Legalize Drugs. Jefferson M. Fish (ed.). Northvale, New Jersey: Jason Aronson, Inc., 1998, pp.421-429.

**ON-LINE PUBLICATIONS:**

1. Grinspoon, L.: Marihuana, Medicine, and Politics. Family Medical Practice On-Line 1996; www.priory.com/journals/fam/grinspn.htm.

**ABSTRACTS:**

A1. Shader, R.I., Taymor, M., and Grinspoon, L.: Schizophrenia, oligospermia, and the phenothiazines -- II: studies on follicle stimulating hormone. In Proceedings of the Fourth World Congress of Psychiatry, Madrid, Spain, September 4-11, 1966.

A2. Grinspoon, L., Ewalt, J.R., and Shader, R.I.: A study of long-term treatment of chronic schizophrenia. In Proceedings of the Fourth World Congress of Psychiatry, Madrid, Spain, September 4-11, 1966.

**MONOGRAPHS:**

M1. Grinspoon, L. and Bakalar, J.B.: The Harvard Medical School Mental Health Review, Drug Abuse and Dependence. Boston, 1990.

M2. Grinspoon, L. and Bakalar, J.B.: The Harvard Medical School Mental Health Review, Alcohol Abuse and Dependence. Boston, 1990.

M3. Grinspoon, L. and Bakalar, J.B.: The Harvard Medical School Mental Health Review, Schizophrenia. Boston, 1990.

M4. Grinspoon, L. and Bakalar, J.B.: The Harvard Medical School Mental Health Review, Depression and Other Mood Disorders. Boston, 1991.

M5. Grinspoon, L. and Bakalar, J.B.: The Harvard Medical School Mental Health Review, Drug Abuse and Addiction, Boston, 1993.

**BOOKS:**

B1. Grinspoon, L.: Marihuana Reconsidered. Cambridge, Mass.: Harvard University Press, 1971. Behavioral Science Book Service Edition, 1971. Bantam Book Edition, 1971.

Grinspoon, L.: Marihuana Reconsidered, Second Edition. Cambridge, Mass.: Harvard University Press, 1977.

Grinspoon, L.: Marihuana Reconsidered, Classic Reprint Edition. San Francisco: Quick American Archive Press, April 1994.

Grinspoon, L.: Marijuana. Edizione Italiana. Milano, Italy: Irra-Apogeo srl, 1996.

B2. Grinspoon, L., Ewalt, J.R., and Shader, R.I.:

Schizophrenia: Pharmacotherapy and Psychotherapy. Baltimore: Williams and Wilkins Co., 1972.

Grinspoon, L., Ewalt, J.R., and Shader, R.I.: Esquizofrenia: Farmacoterapia y Psicoterapia. Buenos Aires: Ediciones Troquel, 1977.

B3. Grinspoon, L. and Hedblom, P.: The Speed Culture: Amphetamine Use and Abuse in America. Cambridge, Mass.: Harvard University Press, 1975.

B4. Grinspoon, L. and Bakalar, J.B.: Cocaine: A Drug and Its Social Evolution. New York: Basic Books, 1976.

Grinspoon, L. and Bakalar, J.B.: Cocaine: Une drogue et son évolution sociale. Montréal: Éditions l'ÉTINCELLE, 1978.

Grinspoon, L. and Bakalar, J.B.: Cocaine: A Drug and Its Social Evolution, Revised Edition. New York: Basic Books, 1985.

B5. Grinspoon, L. and Bakalar, J.B.: Psychedelic Drugs Reconsidered. New York: Basic Books, 1979.

Grinspoon, L. and Bakalar, J.B.: Psychedelic Drugs Reconsidered, Second Edition with Annotated Bibliography. New York: Basic Books, 1981.

Grinspoon, L. and Bakalar, J.B.: Psychedelic Drugs Reconsidered, A Drug Policy Classic Reprint. New York: The Lindesmith Center, 1997.

B6. Grinspoon, L. and Bakalar, J.B. (eds.): Psychedelic Reflections. New York: Human Sciences Press, 1983.

B7. Grinspoon, L. (ed.): Psychiatry 1982: The American Psychiatric Association Annual Review, Vol. I. Washington, D.C.: American Psychiatric Press, 1982.

B8. Grinspoon, L. (ed.): Psychiatry Update: The American Psychiatric Association Annual Review, Vol. II. Washington, D.C.: American Psychiatric Press, 1983.

B9. Grinspoon, L. (ed.): Psychiatry Update: The American Psychiatric Association Annual Review, Vol. III. Washington, D.C.: American Psychiatric Press, 1984.

B10. Bakalar, J.B. and Grinspoon, L.: Drug Control In a Free Society. New York: Cambridge University Press, 1985.

B11. Grinspoon, L. (ed.): The Long Darkness: Psychological and Moral Perspectives on Nuclear Winter. New Haven: Yale University Press, 1986.

B12. Grinspoon, L. and Bakalar, J.B.: Marihuana, The Forbidden Medicine. New Haven: Yale University Press, 1993.

Grinspoon, L. and Bakalar, J.B.: Marihuana, die Verbotene Medizin. Frankfurt, Germany: Zweitausendeins, 1994.

Grinspoon, L. and Bakalar, J.B.: Cannabis: la médecine interdite. Paris, France: Éditions du Lézard, 1995.

Grinspoon, L. and Bakalar, J.B.: Marijuana, la medicina proibita. Padova, Italy: Franco Muzzio Editore, 1995.

Grinspoon, L. and Bakalar, J.B.: Marihuana, de verboden medicijn. Utrecht, The Netherlands: Uitgeverij Het Spectrum B.V., 1996.

Grinspoon, L. and Bakalar, J.B.: Marihuana, the Forbidden Medicine. Japanese translation. Tokyo, Japan: Motovun Co., 1996.

Grinspoon, L. and Bakalar, J.B.: Marihuana, the Forbidden Medicine. Czech translation. Bratislava, Slovakia: CAD Press, 1996.

Grinspoon, L. and Bakalar, J.B.: Marihuana, la medicina prohibida. Barcelona, Spain: Ediciones Paidós Ibérica, S.A., 1997.

Grinspoon, L. And Bakalar, J.B.: Marihuana, the Forbidden Medicine. Zagreb, Croatia, 1997.

B13. Grinspoon, L. and Bakalar, J.B.: Marihuana, The Forbidden Medicine, Revised and Expanded Edition. New Haven: Yale University Press, 1997.

Citation for
The Alfred R. Lindesmith Award for Achievement
in the Field of Scholarship

Presented to Dr. Lester Grinspoon
1990

Dr. Lester Grinspoon of Harvard Medical School is the complete medical scholar. His research and writing have covered a broad spectrum but perhaps his most important work has been his pursuit of truth about the nature of certain illegal drugs. In the course of that work, like Alfred R. Lindesmith, he upset many powerful people, including some in the medical establishment, who viewed impartial research on feared drugs as tantamount to heresy. Yet, in the face of that criticism, Dr. Grinspoon has persisted in his heretical pursuit of truth.

Although his earlier medical education had convinced him that the drug was dangerous, upon reviewing all of the available scientific and clinical evidence, he found marijuana to be relatively benign and to have several helpful applications for human beings.

Dr. Grinspoon was one of the most important witnesses in the suit which won a ruling from the chief administrative law judge of the DEA that marijuana was one of the safest therapeutically active drugs known to the human race.

Lester Grinspoon represents all those scholars who report the results of their research truthfully, despite the political consequences of this unwelcomed honesty.

EXHIBIT B

Vincent Vinciguerra, MD; Terry Moore, MSW; Eileen Brennan, RN

October 1988/ New York State Journal of Medicine pp. 525-527

ABSTRACT: A prospective pilot study of the use of inhalation marijuana as an antiemetic for cancer chemotherapy was conducted. Fifty-six patients who had no improvement with standart antiemetic agents were treated and 78% demonstrated a positive response to marijuana. Younger age and prior marijuana exposure were factors that predicted response to treatment. Toxicity was mild and consisted primarily of sedation and xerostomia. This preliminary trial suggests the usefulness of inhalation marijuana as an antiemetic agent. Because of the lack of a randomized placebo control group, the precise role of this agent is unclear. Further studies should include derivatives of this substance in combination with standard effective drugs to control chemotherapy-induced nausea and vomiting.

(NY State J Med
1988; 88: 525-527)

>From the Don Monti Division of Oncology, Department of Medicine, North Shore University Hospital, Manhasset, NY, and the Department of Medicine, Cornell University Medical College, New York, NY.
Address correspondence to Dr. Vinciguerra, Chief, Division of Oncology/Hematology, North Shore University Hospital, 300 Community Dr, Manhasset, NY 11030.
Supported in part by the Don Monti Memorial Research Foundation, Community Clinical Oncology Program (CCOP) grant #CA-53579, and the New York State Department of Health.

A great deal of clinical information has recently been generated concerning the efficacy of various antiemetic agents for patients treated with cancer chemotherapy. (1-3). Without effective control of nausea and vomiting, patient compliance with potentially curative chemotherapy programs diminishes, compromising not only quality but quantity of life. Effective new chemotherapeutic agents could never be successfully tested in clinical trials if they possessed potent emetic side-effects.
Although a number of agents have recently been found to be active, including metoclopramide, (4,5) haloperidol, (6) dexamethasone, (7) and lorazepam, (8) the need to introduce newer agensts and combination antiemetic therapy may be necessary for continued control of symptoms. Also, complete control of nausea and vomiting during anticancer treatment must take into account not only the physical effects but also the psychological ones. Control of anxiety through behavior modification and relaxation is an effective antiemetic treatment of anticipatory nausea and vomiting. (9)

Natural and synthetic cannabinoids are known to be effective antiemetic agents. (10-12) Delta-9-tetrahydrocannabinol (THC) has been found to be superior to prochlorperazine. (13) Also, patients who are refractory to standart antiemetic agents have significant reduction in nausea and vomiting with oral THC. (14) There is little information on the efficacy of inhalation marijuana aside from anecdotal reports from patients who obtained the drug privately.
As a part of a New York State Department of Health program, North Shore University Hospital conducted a preliminary study of the use of inhalation marijuana as an antiemetic agent for cancer chemotherapy. The purpose of this study was to evaluate the efficacy of inhalation marijuana for patients refractory to standard agents, to identify patient characteristics to predict response, and to evaluate toxicity and patient acceptance of this form of treatment.

## METHODS

Patients with histologically confirmed malignancies who were actively receiving chemotherapy were entered into the protocol. Eligibility criteria included: 18 years of age or older, refractoriness to conventional antiemetic agents, and absence of severe cardiac or psychiatric disease. Patients had to agree not to drive or operate heavy machinery or a motor vehicle for at least 12 hours after the last dose of marijuana. Central nervous system depressants including alcohol were prohibited during the administration of marijuana.

Marijuana cigarettes were supplied by the National Institute on Drug Abuse (NIDA) to the New York State Department of Health. All patients were instructed on standard smoking procedures. The patient inhales deeply, holds the inhalation for ten seconds, and then exhales. After waiting 10 to 15 seconds, the cycle is repeated. The total dose is completed within five minutes. A flame-proof holder was available to permit delivery of nearly all of the cigarette appropriate to the patient's dosage. The dose schedule, which was calculated to the nearest one-fourth cigarette; was 5 mg THC/m2, starting 6-8 hours prior to chemotherapy and every 4-6 hours thereafter, for a total dose of four doses per day on each day of chemotherapy (one cigarette= 10.8 mg THC). In order to prevent cigarettes from drying out and causing harsh smoke, patients were instructed to keep the cigarettes in the refrigerator or humidified.
This was a nonrandomized study where patients served as their own controls. Patients were asked to self-rate their status by completing a patient evaluation form after each therapeutic episode. Nausea was graded on a scale from 1 (none) to 4 (severe), vomiting was graded from 1 (none) to 5 (10+ times), appetite was graded from 1(none) to 5 (above normal), and physical state was graded from 1 (very weak) to 4 (above normal), and mood was graded from 1 (very depressed to 5 (very happy). Based on the degree of nausea, vomiting, food intake, physical state, and over-all mood, patients rated the overall effectiveness of marijuana as none, moderately effective, and very effective.
Physician investigators were approved by the Hospital's Patient Qualification Review Board. Physicians utilized the official New York State triplicate prescription form as their research order for medication. Informed consent was obtained from all patients and the procedures followed were approved by an institutional research committee.

RESULTS

Seventy-four patients entered the study and 56 were evaluable. Eighteen patients who had initially agreed to be treated with marijuana later decided not to participate. Eighteen patients rated the marijuana very effective (34%) and 26 patients rated it moderately effective (44%) for an overall response rate of 78% (44/56). Twelve patients (22%) noted no benefit.

TABLE I. Patient Characteristics (Percent)

Responders Nonresponders P
Value
(N=44) (N=12)

Female 64 75
NS*
Mean age (yr) 41 51
(median) (40) (54)
Breast cancer 36 33
NS
Lymphoma 34 25
NS
Prior radiation therapy 30 8
NS
Prior THC 29 20
NS
Prior Marijuana 52 17
0.06
Euphoria 60 36
NS
(high)
Smoker 53 38
NS

*NS= not significant
Standard deviation= 11.9
Standard deviation= 15.6

Characteristics of responding and nonresponding patients are listed in Table I. While no statistically significant differences were noted between responders and nonresponders with regard to sex, type of diagnosis, prior radiation therapy, prior oral THC treatment, incidence of euphoria, or

smoking history, it is important to remember that the sample sizes were small, making interpretation of differences difficult. Patients who responded to marijuana cigarettes were more likely to be younger, median age 40 vs 54 for nonresponders, and had prior marijuana exposure, 52% vs 17% (p= 0.06).
The most common diagnoses for this group of patients were breast cancer, lymphoma, lung cancer, colon cancer, ovarian cancer, testicular cancer, sarcoma, acute leukemia, and myeloma. The most common emetic chemotherapeutic agents were cyclophosphamide, doxorubicin, cis-platinum, procarbazine, methotrexate, dacartazine, and streptozocin, given either singly or in combination. Four of seven patients treated with cis-platinum responded favorably to marijuana cigarettes.
Toxic side effects included sedation in 88%, dry mouth in 77%, dizziness in 39%, and confusion in 13%. Anxiety, headache, and fantasizing were also seen but were less common. There was no toxicity in 13% of patients (Table II).

TABLE II. Percent Toxicity

| | |
|---|---|
| Sedation | 88 |
| Dry Mouth | 77 |
| Dizziness | 39 |
| Confusion | 13 |
| Anxiety | 11 |
| Headache | 11 |
| Fantasizing | 11 |
| None | 13 |

## DISCUSSION

The results of this prospective study suggest that inhalation marijuana is active in controlling nausea and vomiting resulting from chemotherapy. Marijuana benefited patients who were treated with a wide range of chemotherapeutic agents including drugs which have considerable emetogenic potential. A prior report by Chang et al (15) documented effectiveness of oral THC and inhaled marijuana against high-dose methotrexate, which normally has mild gastrointestinal toxicity. While most experience indicates that THC is generally ineffective against cis-platinum-induced emesis, benefit was seen in a small number of patients treated in our program with this agent.
Since this was a single arm, nonrandomized, outpatient program, this study lacks a controlled placebo group. Nevertheless, the patients acted as their own controls, having previously failed standard antinausea medications. They evaluated marijuana based on their subjective rating of the severity of nausea, vomiting, appetite and food intake, mood, and physical state after chemotherapy treatment. A placebo-controlled, randomized inpatient study which quantitates all emetic episodes would obviously provide objective and precise information. (16)
Failure to respond to oral THC does not preclude benefit from inhaled marijuana. Twenty-nine percent of patients who failed oral THC responded to the cigarette form. This is not unexpected, since only 5-10% of orally administered THC is absorbed, whereas inhaled marijuana has a five-to tenfold greater bioavailability. (17) Clearly, oral THC is an effective treatment for chemotherapy-induced emesis. Most studies have demonstrated THC to be better than placebo and comparable to prochlorperazine. (18)
The major obstacle related to the oral and inhaled cannabinoids is the route of administration. Patients with anticipatory vomiting do not retain the oral THC. Because of its poor water solubility, parenteral adminstration of cannabinoids has been difficult. The only cannabinoid available for parenteral use, levonantradol, is currently being investigated and has documented activity comparable to THC. (19) Perhaps intranasal or transdermal forms of THC will be developed and found to be clinically useful.
Patient characteristcs were evaluated to identify factors which would predict response to marijuana. There were no significant differences between responders and nonresponders with regard to sex, diagnosis, prior radiation therapy, prior THC ingestion, induced euphoria, and history of cigarette smoking. The only factors that approached significance were young age and prior marijuana intake. Unlike the experience with oral THC, experiencing a euphoric high was not a prerequisite to obtaining the antiemetic effect with marijuana. (20)
The mechanism of the antiemetic action of cannabinoids is unknown. Inhibition of prostaglandin and cyclic adenosine monophosphate has been

suggested. Its major action is more likely related to its effect on the brain, as marijuana causes central nervous system depression and impairment of brain function. At the cellular level, cannabinoids interfere with the synthesis of nucleic acids and chromosome proteins. (21)
Some of the problems encountered in this study which could influence interpretation of the results were the low patient accrual and the fact that nearly 25% of patients who initially consented refused to receive treatment. Reasons for patients' refusal to participate included physician and patient bias against smoking, harshness of smoke from the cigarettes, and preference for oral THC capsules. The major objection was related to the social stigma attached to the use of marijuana. Many patients rejected the idea of "smoking pot" at home and exposing their children to the implications of this type of medication. Should this therapy become available in a different vehicle of administration, patient acceptance would significantly improve.
Our results demonstrate that inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy. A randomized, controlled trial would, however, be necessary to accurately define the exact role of this drug. Toxic effects are well tolerated and the availability of a parenteral form would improve patient utilization of this agent. Future antiemetic protocols should include the active ingredient of marijuana in combination with current effective agents.

Acknowledgments. The authors thank Rosemarie Galderisi and Annie Middleton for their assistance.

REFERENCES

1. Seigel LJ, Longo DL: The control of chemotherapy-induced emesis. Ann Intern Med 1981; 95: 352-359.
2. Frytak S, Moertel CG: Management of nausea and vomiting in the cancer patient. JAMA 1981; 245: 393-396.
3. Bakowski MT: Advances in anti-emetic therapy. Cancer Treat Rev 1984; 11: 237-256.
4. Meyer BR, Lewin M, Drayer DE, et al: Optimizing metoclopramide control of cisplatin-induced emesis. Ann Intern Med 1984; 100: 393-395.
5. Kris MG, Gralla RJ, Tyson LB, et al: Improved control of cisplatin-induced emesis with high-dose metoclopramide, and with combinations of metoclopramide, dexamethasone, and diphenhydramine. Results of consecutive trials in 225 patients. Cancer 1985; 55: 527-534.
6. Neidhart JA, Gagen M, Young D, et al: Specific antiemetics for specific cancer chemotherapeutic agents: Haloperidol versus benzquinamide. Cancer 1981; 47: 1439-1443.
7. Cassileth PA, Lusk EJ, Torri S, et al: Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy. Arch Intern Med 1983; 143: 1347-1349.
8. Bishop J, Oliver I, Wolf M, et al: Lorazepam: A randomized, double blind, crossover study of a new antiemetic in patients receiving cytotoxic chemotherapy and prochlorperazine. J Clin Incol 1984; 2: 691-695.
9. Morrow GR: Clinical characteristics associated with the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment. J Clin Oncol 1984; 2: 1170-1176.
10. Laszlo J: Tetrahydrocannabinol: From pot to prescription [editorial]. Ann Intern Med 1979; 91: 916-918.
11. Stack P: The pharmacologic profile of nabilone: A new antiemetic agent Ca Treat Rev 1982; 9 (suppl B): 11-16.
12. Frytak S, Moertel CG, O'Fallon J, et al: Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. Ann Intern Med 1979; 91: 825-830.
13. Sallan SE, Cronin C, Zelen M, et al: Antiemetics in patients receiving chemotheraply for cancer. A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med 1980; 302: 135-138.
14. Lucas VS, Laszlo J: Delta-9-tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. JAMA 1980; 243: 1241-1243.
15. Chang AE, Shilling D, Stillma RC, et al: Delta-9-tetrahydrocannabinol as an ant;iemetic in cancer patients receiving high-dose methotrexate. Ann Intern med 1979; 91: 819-824.
16. Carey MP, Burish TG, Brenner DE: Delta-9-tetrahydrocannabinol in cancer chemotherapy: Research problems and issues. Ann Intern Med 1983; 99: 106-114
17. Nahas GG: Current status of marijuana research. Symposium on marijuana held July 1978 in Reims, France. JAMA 1979; 242: 2775-2778.

18. Poster DS, Penta JS, Bruno S, et al: Delta-9-tetrahydrocannabinol in clinical oncology. JAMA 1981; 245: 2047-2051.
19. Citron ML, Herman TS, Vreeland F, et al: Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. Ca Treat Rev 1985; 69: 109-112.
20. Ungerleider JT, Andrysiak T, Fairbanks L, et al: Cannabis and cancer chemotherapy. Cancer 1982; 50: 636-645.
21. Council on Scientific Affairs: Marijuana. Its health hazards and therapeutic potentials. JAMA 1981; 246: 1823-1827.

**EXHIBIT C**

# Antiemetic Effect of Delta-9-Tetrahydrocannabinol in Patients Receiving Cancer Chemotherapy

*Sallan, Stephen E., Norman E. Zinberg, and Emil Frei. "Antiemetic Effect of Delta-9-Tetrahydrocannabinol in Patients Receiving Cancer Chemotherapy." **The New England Journal of Medicine**. Vol. 293(16) (1975): 795-797.*



**Contents**



(Top)

## i. Abstract

Anecdotal accounts suggested that smoking marihuana decreases the nausea and vomiting associated with cancer chemotherapeutic agents. Oral delta-9-tetrahydrocannabinol was compared with placebo in a controlled, randomized, "double-blind" experiment. All patients were receiving chemotherapeutic drugs known to cause nausea and vomiting of central origin. Each patient was to serve as his own control to determine whether tetrahydrocannabinol had an antiemetic effect. Twenty- two patients entered the study, 20 of whom were evaluable. For all patients an antiemetic effect was observed in 14 of 20 tetrahydrocannabinol courses and in none of 22 placebo courses. For patients completing the study, response occurred in 12 of 15 courses of tetrahydrocannabinol and in none of 14 courses of placebo ($P < 0.001$). No patient vomited while experiencing a subjective "high." Oral tetrahydrocannabinol has antiemetic properties and is significantly better than a placebo in reducing vomiting caused by chemotherapeutic agents.

(Top)

## I. Introduction

Nausea and vomiting of central origin occur after the administration of a variety of cancer chemotherapeutic agents and frequently constitute the major morbidity associated with such treatment. Control with classic antiemetics is incomplete and variable.

Anecdotal accounts from patients suggested that smoking marihuana before receiving intravenous anti- tumor drugs resulted in diminution of nausea and vomiting, and, in contradistinction to the usual post- therapeutic anorexia, some were able to take food shortly after therapy. Effects of marijuana on nausea and vomiting in human beings deserve to be reported. It has been demonstrated that oral delta-9- tetrahydrocannabinol (THC) causes the same physiologic effects as smoking marijuana (1,2).

The purpose of this study was to determine the effects of orally administered THC on

nausea and vomiting in patients receiving cancer chemotherapy.

(Top)

**I. Patients, Materials and Methods**

Twenty-two patients known to have a variety of neoplasms were enrolled in the study. Ten males and 12 females ranging in age from 18 to 76 years (median of 29.5) participated. Twenty patients had previously received cancer chemotherapeutic agents known to cause nausea and vomiting (adriamycin, 5-azacytidine, nitrogen mustard, imidazole carboxamide, procarbazine, high-dose cyclophosphamide or high-dose methotrexate, or combinations thereof). Twenty of the 22 were known to be refractory to conventional antiemetics. The other two patients had never been treated with chemotherapy before entering the study. Pregnant women and patients with a past history of emotional instability or untoward reactions to psychoactive drugs were not eligible.

The study was thoroughly explained to the patients. They were told that they would receive a placebo or a "marihuana-like drug for the purpose of controlling nausea and vomiting." Subjects agreed not to smoke marihuana during the course of the study.

THC was supplied by the National Institute on Drug Abuse. The drug was suspended in 0.12 ml of sesame oil and supplied in gelatin capsules. Identical-appearing placebo capsules contained only sesame oil. Initially, THC dosage was 15 mg given every four hours for three doses. Because of some variability in responses, the dose was changed to 10 mg per square meter body-surface area per dose. Nineteen patients received 15-mg doses, and three 20-mg doses.

A randomized, "double-blind," crossover experiment was employed, each patient t being used as his own control. Optimally, patients received three one-day courses of drug (either THC or placebo). Each course consisted of three doses of drug, the first taken two hours before and the other two and six hours after chemotherapy. Patients were randomized to receive courses in one of four sequences: THC-placebo-THC; THC-placebo-placebo; placebo-THC-placebo; or placebo-THC-THC.

Nausea, vomiting, and food intake were assessed by the patient on the day after treatment through the use of self-administered questionnaires. In addition, the patient, nurses, and other personnel in contact with the patient were interviewed by one of us (S.E.S.), who also reviewed the questionnaires and nurses' notes.

(Top)

**II. Results**

Definitions of responses are based upon a comparison of THC and placebo courses.

Complete response to THC means that there was no vomiting in patients for whom the same antitumor drugs caused unequivocal moderate to severe vomiting after placebo. Conversely, a complete response to placebo theoretically is possible, but never occurred.

Partial response to THC means that there was at least a 50 per cent reduction in vomiting as compared to placebo after the same chemotherapy. Included in this group are the patients whose vomiting, which occurred shortly after chemotherapy during a placebo course, was delayed until escape from control of THC. These patients attained a "high" that wore off before the next dose, or after the last dose of THC, and during this time vomiting "broke

through." A partial response to placebo is also a theoretical possibility but never occurred.

No response to the THC means that there was either no decrease or less than a 50 per cent reduction in vomiting as compared with placebo after the same antitumor drugs. No response to placebo means that the patients vomited after chemotherapy as often or more often than after THC.

Absence of vomiting after both THC and placebo makes the response unevaluable because there was neither demonstrable emetic effect of chemotherapy nor antiemetic effect of THC or placebo. One patient who had no prior chemotherapy before entering the study, was excluded from analysis for this reason.

Eleven patients completed three courses of treatment, two completed two courses, and nine completed one course.

One of the 11 never vomited and was excluded from evaluation as noted above. The remaining 10 patients received 30 courses of drug, but a single course was excluded from analysis because the dose of cancer chemotherapeutic agent was reduced by 50 per cent. Therefore, 29 courses were evaluated: 14 placebo and 15 THC. All courses of placebo resulted in no response. Of the THC courses, there were five complete responses, seven partial responses, and three no responses. The therapeutic response derived from the THC was independent of the sequence of THC or placebo courses administered. Accepting complete and partial responses as positive responses, the difference between THC and placebo is highly significant (chi-square with Yates's correction $P<0.001$).

Of the two patients who completed two courses in the study, one died of disease, and the other decided to smoke marihuana, thus becoming ineligible to continue. Both these patients had no response after placebo; after THC, both had partial responses.

Nine patients received one course of treatment. Six had placebo only, and five of them vomited after chemotherapy. The patient who did not vomit after placebo had no prior chemotherapy. His response to placebo, therefore, is unevaluable because of the impossibility of differentiating an antiemetic effect of placebo from the emetic effect of chemotherapy. Of the six, two voluntarily withdrew from the study because they did not want to risk another placebo course, one had chemotherapy discontinued, one died of disease, and two are still in the study. Three had THC only. Of these, two vomited and left the study, and the third went off study because of THC toxicity.

In summary, 20 courses of THC were administered, resulting in five complete responses, nine partial responses, three no responses, and three unevaluable responses. Twenty-two courses of placebo resulted in no complete responses, no partial responses, 16 no responses, and six unevaluable responses.

(Top)

**III. Side Effects**

Of 16 patients receiving THC, 13 (81 per cent) experienced a "high." This effect was characterized by mood changes, which varied and consisted of one or more of the following: easy laughing; elation; heightened awareness; mild aberrations of fine motor co-ordination; and minimal distortion of their activities and interactions with others. There were no hangovers or delayed effects.

The next most common side effect was somnolence. For one third of the patients,

somnolence curtailed activities for two to six hours, but the patients were easily aroused. Another third had somnolence which did not curtail activities; the remainder experienced no somnolence.

Toxicity characterized by paranoid ideation, apprehension, fear, panic, and frightening visual hallucinations has been reported after single THC doses of 35 mg (2). Only two of our patients (9 per cent) experienced THC toxicity, both after three doses of 20 mg. One had visual distortions lasting for a few seconds, and the other reported visual hallucinations of 10 minutes' duration and depression of several hours.

(Top)

**IV. Discussion**

The results of this placebo-controlled "double-blind" study demonstrate that THC has antiemetic effects.

The study was designed to compare THC with placebo. It was not designed to evaluate placebo effect. No comparisons were made between placebo and absence of placebo, or between placebo and retrospective emesis control. If a placebo effect exists in this clinical and investigative setting, THC cannot be evaluated.

No patient vomited while experiencing a subjective "high." No "highs" were reported after placebo. In some patients, the "high" wore off before the next THC dose, and during this interval, nausea and vomiting frequently occurred. After this study, patients taking THC received their next dose as soon as the "high" began wearing off. Preliminary results indicate that this dose-scheduling adjustment sustains the antiemetic effect of THC.

Variability in gastrointestinal absorption of orally administered THC between, but not within, individual subjects has been reported (2). Three of our patients (19 per cent) reported the absence of a "high" after THC. The lack of THC effect ("high" and antiemesis) in at least some patients may be related to failure of absorption. Some patients who did not attain a "high" after the initial dose were able to do so with subsequent doses. This effect may be analogous to the experience of Weil et al (3) with smoked marihuana: failure to respond to an initial dose of marihuana, and then response to subsequent doses. This phenomenon may also be related to induction of hepatic microsomal enzymes necessary for drug metabolism as suggested by Lemberger er al (4).

Patients became "high" 20 to 60 minutes after ingestion of drug. The duration of the "high" varied from one to five hours, but was usually two to three hours, suggesting that the rigid four-hourly schedule between doses was probably too long for some patients, and possibly explaining some partial responses. When dosage was based on body-surface area, less variability in onset and duration of effects was noted.

Time of onset, duration of effect, and intensity of "high" were unrelated to previous marihuana use. Six patients admitted prior use of marihuana, but only one was considered more than an occasional user (defined here as smoking less than once a week).

It has been demonstrated that orally administered THC results in the same physiologic effects as inhaled marihuana (1,2). The previous studies showing inhaled marihuana to be more potent than oral THC (1) were probably in error because the THC was delivered in poorly absorbed vehicles (2). Inhalation appears to be more suitable for patients with suboptimal gastrointestinal absorption.

Hollister has shown that the effects of smoked THC clearly resemble those of marihuana (5). We have made preliminary observations comparing the antiemetic effect of smoked marihuana and oral THC. The marihuana belonged to individual patients and, therefore, was neither qualitatively nor quantitatively controlled. For most patients, both smoked and oral routes had identical effects. Theoretically, smoking might be the preferable route since it may result in less variability of absorption than the gastrointestinal route. Moreover, smoking provides greater opportunity for individual patient control by permitting the patient to regulate and maintain the "high."

THC has been reported to have a biphasic clinical effect, with initial stimulation and elation followed by sleepiness and tranquillity (6). With other antiemetics, such as the phenothiazine derivatives, sedative effect seems to parallel antiemetic effect (7). Although somnolence occurred in about two thirds of out patients, in the dosage used, THC prevented or reduced vomiting in most patients without appreciable curtailment of activities.

Appetite stimulation follows the smoking of marihuana (8). Four of our patients reported food intake "more than usual" after chemotherapy when taking THC. No patient reported this effect after placebo.

These data demonstrate that THC is an effective antiemetic for patients receiving cancer chemotherapy. Failure of response in 19 per cent of patients receiving THC perhaps is explicable on the basis of pharmacologic factors. THC can be used safely in the dosage of 10 mg per square meter per dose every four hours for at least three doses. Lack of effectiveness for some patients might be correctable by shortening the interval between doses to maintain a "high." The safety of such a dose-schedule adjustment is still to be determined.

(Top)

**V. References**

1. Isbell H, Gorodetzsky CW, Jasinski D, et al: Effects of (-) delta-9-tetrahydrocannabinol in man. Psychopharmacologia 11: 184-188, 1967
2. Perez-Reyes M, Lipton MA, Timmons MC, et al: Pharmacology of orally administered delta-9- tetrahydrocannabinol. Clin Pharmacol Ther 14:48-55,1973
3. Weil AT, Zinberg NE, Nelsen JM: Clinical and psychological effects of marihuana in man. Science 162:1234-1242, 1968
4. Lemberger L, Tamarkin NR, Axelrod J, et al: Delta-9-tetrahydrocannabinol: metabolism and disposition in long-term marihuana smokers. Science 173:72-74, 1971
5. Hollister LE: Tetrahydrocannabinol isomers and homologues: contrasted effects of smoking. Nature 227:968-969, 1970
6. Idem: Structure-activity relationships in man of cannabis constituents, and homologs and metabolites of delta-9-tetrahydrocannabinol. Pharmacology 11:3-11,1974
7. Moertel CG, Reitemeier RJ: Controlled clinical studies of orally administered antiemetic drugs. Gastroenterology 57:262-268, 1969
8. Hollister LE: Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine. Clin Pharmacol Ther 12:44-49, 1971

*We are indebted to Drs. Lester Grinspoon and Yvonne Bishop for assistance in this investigation.*

Back to Focal Point: Medicinal Marijuana

(Top)

home | in the news | online library | cites & sources | about tlc | articles

**EXHIBIT D**

# Marijuana as Antiemetic Medicine: A Survey of Oncologists' Experiences and Attitudes

*Doblin, Richard E. and Mark A. R. Kleiman. "Marijuana as Antiemetic Medicine: A Survey of Oncologists' Experiences and Attitudes." **Journal of Clinical Oncology**. Vol. 9(7) (1991): 1314-1319.*



**Contents**



(Top)

## i. Abstract

A random-sample, anonymous survey of the members of the American Society of Clinical Oncology (ASCO) was conducted in spring 1990 measuring the attitudes and experiences of American oncologists concerning the antiemetic use of marijuana in cancer chemotherapy patients. The survey was mailed to about one third (N = 2,430) of all United States-based ASCO members and yielded a response rate of 43% (1,035). More, than 44% of the respondents report recommending the (illegal) use of marijuana for the control of emesis to at least one cancer chemotherapy patient. Almost one half (48%) would prescribe marijuana to some of their patients if it were legal. As a group, respondents considered smoked marijuana to be somewhat more effective than the legally available oral synthetic dronabinol [THC] Marinol; Unimed, Somerville, NJ) and roughly as safe. Of the respondents who expressed an opinion, a majority (54%) thought marijuana should be available by prescription. These results bear on the question of whether marijuana has a "currently accepted medical use," at issue in an ongoing administrative ad legal dispute concerning whether marijuana in smoked form should be available by prescription along with synthetic THC in oral form. This survey demonstrates that oncologists' experience with the medical use of marijuana is more extensive, and their opinions of it are more favorable, than the regulatory authorities appear to have believed.

(Top)

## i. Introduction

Marijuana (smoked) has been reported to be effective in treating emesis associated with cancer chemotherapy (1-4), but its use is currently prohibited by law (5). The main psychoactive ingredient in marijuana, tetrahydrocannabinol (THC; dronabinol), was approved in 1985 by the Food and Drug Administration (FDA) for use in the treatment of emesis. As marketed under the trade name Marinol (Unimed, Somerville, NJ) and synthetically formulated in sesame oil in gelatin capsules to be taken orally, almost 100,000 doses were prescribed in 1989 (6).

Litigation concerning the rescheduling of marijuana to permit its medical use has been making its way through the courts since 1972 (7). The central issue in the longstanding administrative and legal dispute, argued before the United States Court of Appeals (DC Circuit) on March 4, 1991 (8), is whether or not marijuana has a "currently accepted medical use in treatment in the United States." This is the standard for rescheduling required by the Uniform Controlled Substances Act of 1970 (5), which created the current system of drug scheduling. The Act does not further specify the standard.

In September 1988, after 2 years of Drug Enforcement Administration (DEA) administrative hearings, DEA Administrative Law Judge Francis Young issued a recommendation in favor of rescheduling marijuana. He ruled that the appropriate standard for current acceptance is identical to the one established for a successful defense in medical malpractice cases, which requires only that the medical practice at issue be accepted by a "respectable minority" of physicians (9). Ironically, the 1955 medical malpractice case that established this standard involved a lawsuit against an oncologist for the unsuccessful use of chemotherapy, which was then new and did not have the approval of the American Medical Association. The court stated that as long as there was no infallible cure and the doctor "did not engage in quackery by representing that he had one," the support of a respectable minority of peers would be sufficient to avoid malpractice liability. The court remarked "We [the court] are not physicians and we have no light on the subject except such as is shed by the testimony of physicians..." (10).

On December 29, 1989, the Administrator of DEA rejected Judge Young's recommendation and refused to reschedule marijuana on the grounds that medical use of marijuana was not currently accepted. The Administrator used an eight-part standard for determining current acceptance similar to the "safety and efficacy" standard used by the FDA to approve the marketing of new drugs by pharmaceutical companies (11). The DEA first articulated this standard in another rescheduling case in 1987, after the United States Court of Appeals (1st Circuit 1987) rejected its contention that FDA new drug approval itself was the appropriate standard (12). On April 26, 1991, the United States Court of Appeals (DC Circuit) (13) ruled that DEA's standard was impossible to meet, and was therefore invalid. The court remanded to the DEA its ruling rejecting Judge Young's recommendation in favor of the rescheduling of marijuana.

The extent of oncologists' acceptance of medical use of marijuana remains a disputed issue. Dr Ivan Silverberg, an oncologist and witness in the DEA hearings, testified, "There has evolved an unwritten but accepted standard of treatment within the oncologic community which readily accepts marijuana's use" (14). On the other hand, the DEA characterized the medical use of marijuana as a "cruel and dangerous hoax" (15). In a newspaper interview, DEA Associate Chief Counsel Steven Stone suggested that only a fringe group of oncologists accepted marijuana as an antiemetic. Stone remarked, "The Judge seems to hang his hat on what he calls a 'respectable minority of physicians.' What percent are you talking about? One half of one percent? One quarter of one percent?" (16). This report of oncologists experiences with and attitudes about marijuana as an antiemetic is based on a survey of these specialists conducted in the spring of 1990.

(Top)

**I. Subjects and Methods**

A random sample of the United States-based members of the American Society of Clinical Oncology (ASCO) was surveyed. The membership of ASCO, the only formal association of clinical oncologists in the United States, comprises about 80% of the approximately 5,000 board-certified oncologists and almost 60% of the approximately 11,700 oncologists

in the United States, including academic and research-oriented oncologists as well as clinicians in private practice. The survey was conducted independently of ASCO sponsorship.

The survey, responses to which were anonymous, was sent to about 35% (N = 2,430) of the total United States-based ASCO 1989 membership (N = 6,830). The 1,035 surveys returned resulted in a response rate of 43%, representing 15% of United States-based ASCO members and 9% of all oncologists in the United States. Of the respondents, 57 (6%) returned the survey unanswered, indicating that they did not treat patients. Other respondents did not answer every question. The data analysis is based on the total number of respondents answering each particular question.

The survey initially elicited personal information about the oncologist's year of graduation from medical school and size of practice. Oncologists were then asked to estimate the proportion of their cancer chemotherapy patients for whom the currently available antiemetics provided adequate relief or caused significant problems with side effects.

Respondents were asked how frequently they prescribed Marinol, whether any of their patients had used marijuana as an antiemetic, whether they had directly observed or discussed marijuana's medical use with patients, and whether they had ever recommended that a patient try marijuana.

Oncologists were also asked to estimate the proportion of their patients who reported effective emetic control or negative side effects from using marijuana or Marinol, to directly compare the safety and efficacy of marijuana and Marinol, and to estimate what proportion of their patients experienced net benefits from their use of marijuana.

Oncologists were further asked to respond to the statements "Marijuana can be effective in the control of emesis," "Marijuana can be used safely in the control of emesis," 'Marijuana should be given an accepted place in the antiemetic armamentarium," and "I find the use of Marinol in the control of emesis to be a legitimate, currently acceptable medical practice" by indicating strong agreement, agreement, strong disagreement, disagreement, or no opinion. Oncologists were also asked, if marijuana were legal, whether they would prescribe it to "many," "few," or "none" of their patients or if they needed more information.

(Top)

**II. Results**

Ten percent of the respondents graduated from medical school in the 1980s; almost one half (48%) of the respondents graduated from medical school in the 1970s; almost one third (31%) in the 1960s; 9% in the 1950s; and 2% in the 1940s. In 1989, almost one half (49%) of the respondents had an annual patient population of more than 225; almost one quarter (24%) treated between 150 and 225 patients; 18% treated between 75 and 150 patients; and 9% treated 75 or fewer patients.

Two hundred nine (21%) of oncologists reported that the available medicines provided inadequate relief to half or more of their patients (Fig 1). More than half (520, 54%) of the respondents reported that the available antiemetics caused significant problems with side effects in more than a "few" of their patients ( Fig 1).

Slightly more than 70% (686) of respondents reported that at least one of their patients had used marijuana as an antiemetic and that they had directly observed or discussed marijuana's medical use with that patient(s). Marinol had been prescribed by 557

respondents (57%).

A surprising proportion of respondents (432, 44%) said they had recommended marijuana to at least one patient. Only six respondents noted that they did so as part of a legally authorized research protocol. Not surprisingly, respondents who treated more than 150 patients per year were more likely to have recommended marijuana than respondents treating fewer than 150 patients (46% v 34%, $P < .05$). Respondents who graduated from medical school in the 1950s, the 1960s, or the 1970s had statistically similar rates of recommending marijuana (1950s, 46%; 1960s, 44%; 1970s, 44%). However, those who graduated during the 1980s had a significantly lower rate (30%. $P < .05$).

*Efficacy of Marijuana and Marinol*

Three hundred eighty-five respondents (64%) stated that marijuana was effective in 50% or more of their patients, and 266 (56%) reported the same of Marinol (Fig 2). The difference is statistically significant ($P = .008$).

Of the 277 respondents (28%) who felt they had sufficient information to compare marijuana directly with Marinol in terms of efficacy, 44% believed marijuana to be more effective, 13% believed Marinol to be more effective, and 43% thought they were about equally effective. Of those who reported a preference ($N = 157$), 121 (77%) thought marijuana was more effective than Marinol. The difference between 77% and 50% (the null hypothesis) is statistically significant below the .0001 level.

Six hundred eight respondents (63%) agreed with the statement affirming the efficacy of marijuana in the treatment of emesis (9% "strongly agreed" and 54% "agreed"), and 77 respondents (8%) disagreed (2% "strongly disagreed" and 6% "disagreed"). Two hundred eighty-three (29%) had no opinion. Of the respondents with opinions ($N = 685$), 89% believed marijuana to be effective in the control of emesis. Of respondents to a question concerning net benefits ($N = 644$), 409 (64%) reported that 50% or more of their patients experienced net benefits from marijuana. Only 15 (2%) reported that none of their patients experienced net benefits from marijuana.

*Safety of Marijuana and Marinol*

Two hundred twenty-four respondents (47%) stated that the use of Marinol caused negative side effects in 50% or more of their patients, and 235 (40%) reported the same about marijuana (Fig 3). The difference is statistically significant ($P = .018$).

Of the 288 respondents (29%) who felt they had sufficient information to compare marijuana with Marinol in terms of side effects, 20% believed marijuana to cause fewer problems with side effects, 23% believed Marinol to cause fewer problems, and 57% thought they were equal. Slightly more than half, 52% (65), of those who reported a preference (124) reported Marinol to cause fewer problems with side effects. The difference between 52% and 50% is not statistically significant ($P = .596$).

Four hundred seventy-eight respondents (49%) agreed with the statement affirming that marijuana could be safely used in the treatment of emesis (6% "strongly agreed" and 43% "agreed"), and 131 (14%) disagreed (4% "strongly disagreed" and 10% "disagreed"). Three hundred sixty-one (37%) had no opinion. Of the respondents with opinions ($N = 609$), almost four fifths (79%) believed that marijuana could be safely used to control emesis.

Almost half (423, 44%) of the respondents reported that they believe marijuana to be both safe and efficacious. Of respondents with opinions on both safety and efficacy ($N = 577$), 73% believe marijuana to be both safe and efficacious. There were no significant

differences in positive opinions of marijuana's safety and efficacy between respondents who treated 150 patients or fewer annually and those who treated more than 150 patients annually, or among respondents who graduated in different decades.

Three hundred twenty respondents (33% of all respondents) stated that marijuana should be accepted (5O% "strongly agreed" and 28% "agreed") and 279 (29%) felt that it should not (7% "strongly disagreed" and 22% "disagreed"); 364 (38%) expressed no opinion. Of the 599 respondents with opinions, 53% favored making marijuana available by prescription. The surplus of positive over negative opinions is within the bounds of sampling error ($P = .092$). There were no significant differences in rate of acceptance by size of patient population. However, respondents who graduated in the 1950s were significantly less likely to accept the medical use of marijuana (22%) than respondents who graduated in the 1960s (35% ), the 1970s (34%), or the 1980s (39%) ($P < .05$).

When asked whether Marinol should be accepted, 705 respondents (73%) agreed (20% "strongly agreed" and 53% "agreed") and 83 (9%) disagreed (2% "strongly disagreed" and 7% "disagreed"); 177 (18%) had no opinion. Of the 788 respondents with opinions, 89% accept the medical use of synthetic THC.

Almost half of the respondents (440, 48%) would prescribe marijuana to at least a few patients (4% to "many," 44% to "few") if it were legal; 200 (22%) would not prescribe it; and 274 (30%) said they would need more information. The 48% who would prescribe marijuana if it were legal is only slightly less than the 54% who have prescribed Marinol, which is legally available. Of those oncologists who had previously recommended marijuana to at least one patient ($N = 432$), 279 (65%) would prescribe marijuana to at least a few patients if it were legally available. Of those oncologists who had not recommended marijuana to at least one patient ($N = 550$), 161 (29%) report that they would prescribe marijuana to at least a few patients if it were legally available.

(Top)

**III. Discussion**

Although substantial, the response rate of 43% makes it difficult to determine precisely the views of the entire ASCO membership. The views of the sample who returned the survey may differ significantly from the views of those who did not. Since ASCO itself does not compile membership statistics for age, year of graduation from medical school, or patient population size, respondents cannot be compared with the full membership in these respects. However, no obvious anomalies in their characteristics were observed. Furthermore, the distribution of postmarks by state on the returned surveys - the main information available with which to evaluate response bias - very closely matched the geographic distribution of the survey forms mailed. Although there is nothing specific to suggest the presence of response bias, it cannot be ruled out. Therefore, all reported statistics should be considered indications of the general range of support for various propositions, rather than precise determinations.

The central empirical question the survey was designed to answer was whether a significant minority of the members of the ASCO supported the rescheduling of marijuana to permit its use in the treatment of nausea associated with cancer chemotherapy. The response rate is sufficiently large to resolve that question conclusively.

Of all oncologists with opinions responding to our survey, 54% supported rescheduling. Possible response bias makes it impossible to determine precisely whether a majority of the population with opinions actually holds that view. Ascertaining whether a significant minority of the population supports rescheduling is much simpler. A sensitivity analysis

varying the degree of acceptance of the medical use of marijuana by nonrespondents to the survey suggests that support for rescheduling marijuana is indeed present in at least a significant minority of our population. In the hypothetical event that all nonrespondents and all respondents without opinions were actually opposed to rescheduling, 13% of oncologists would remain in favor of rescheduling. If all nonrespondents and respondents without opinions were actually for rescheduling, 85% would support prescription availability of marijuana.

The survey data suggest that adding marijuana to the existing armamentarium of antiemetic agents would result in substantial benefits to patients. Oncologists believe smoked marijuana to be roughly as safe as legally available, oral synthetic THC (Marinol) and somewhat more effective. Of the oncologists responding to our survey, 44% - 73% of those with opinions - consider marijuana both safe and efficacious.

Oncologists may prefer to prescribe smoked marijuana over oral THC for several reasons. The bioavailability of THC absorbed through the lungs has been shown to be more reliable than that of THC absorbed through the gastrointestinal tract (17-18), smoking offers patients the opportunity to self-titrate dosages to realize therapeutic levels with a minimum of side effects, and there are active agents in the crude marijuana that are absent from the pure synthetic THC.

Although the survey did not ask whether marijuana or Marinol might be safer or more effective when used with specific patient groups, in space set aside for comments, 42 oncologists mentioned either that older patients had more problems with side effects from both Marinol and marijuana or that patients who had side effects tended to be inexperienced with marijuana. The increased prevalence of side effects in older patients may be a cohort effect and not an age effect. Marijuana and Marinol may be most useful in younger or marijuana-experienced patients.

More than four in 10 respondents (44%) report that they have recommended the (illegal) use of marijuana to control emesis to at least one cancer chemotherapy patient. The fact that so many physicians have advised patients to commit an illegal act to obtain marijuana suggests a substantial discrepancy between clinical and regulatory opinions. Almost half (48%) would prescribe it to some of their patients if it were legal.

The survey reported here of the opinions and experiences of clinicians is not a controlled clinical study of the use of marijuana as an antiemetic. Nevertheless, this survey demonstrates that oncologists' experience with the medical use of marijuana is more extensive, and their opinions of it are more favorable, than the regulatory authorities appear to have believed. It appears that current regulations create the somewhat anomalous situation that a substantial fraction of all practicing oncologists at least occasionally commit an act - ie, counseling a patient to acquire and use a controlled substance - that constitutes a crime and that at least in principle could lead to the revocation of their license.

(Top)

**References**

1. Evidence in Drug Enforcement Administration (DEA) Administrative Hearings, Judge Francis Young, Jr. presiding: Alliance for Cannabis Therapeutics Exhibits: Official State Reports, vol 2, 1988 (GA-Tab 8, MI-Tab 9, NJ-Tab 10, NM-Tab 15, NY-Tab 16, TN-Tab 17)
2. Randall RC (ed): Cancer Treatment and Marijuana Therapy. Washington, DC, Galen Press. 1990.
3. Vinciguerra V, Moore-Terry MSW, Brennan E: Inhalation marijuana as an

antiemetic for cancer chemotherapy. NY State J Med 88:525-527. 1988
4. American Medical Association (AMA) Council on Scientific Affairs: Marijuana: Its health hazards and therapeutic potentials. JAMA 246:1823-1827, 1981
5. Uniform Controlled Substances Act of 1970, 21 USC§800
6. Unimed Pharmaceuticals: Annual Report, December 1989. Somerville, NJ, Unimed Pharmaceuticals, 1989
7. 37 Federal Register 18093, September 1, 1972
8. Alliance for Cannabis Therapeutics (ACT) v Drug Enforcement Administration (DEA), US Court of Appeals 90-1019 (DC 2nd Circuit, filed January 19, 1990)
9. Ruling of DEA Administrative Law Judge Francis Young, Jr, DEA Administrative Hearings, September 6, 1988
10. Baldor v Roberts, 81 So2d 658. (Florida Supreme Court, 1955)
11. 54 Federal Register 53767-53785, December 29, 1989
12. Grinspoon v DEA. 828 F2d 881 (1st Circuit 1987)
13. Alliance for Cannabis Therapeutics (ACT) v Drug Enforcement Administration (DEA), 90-1019 (DC Circuit, April 26, 1991)
14. Testimony of Dr. Ivan Silverberg, in Randall RC (ed): Marijuana. Medicine and the Law, vol 1. Washington, DC, Galen Press, 1988, p 149
15. 54 Federal Register 53767-53785, December 29, 1989, p 53784
16. Slater L: Marijuana: Medicine or menace? Spinal Network, Winter, p 44, 1990
17. Chang A, Shiling D, Stillman R. et al: Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. Ann Intern Med 91:819-824, 1979
18. Ohisson A, Lindgren J-E, Wahlen A, et al: Plasma delta-9-tetrahydrocannibinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 28:409-416, 1980

(Top)

**Acknowledgment**

Joseph P. Newhouse, of the Kennedy School, reviewed both the survey instrument and this report and suggested several important improvements. Dr Jerome Jaffe, Director of the Addiction Research Center of the National Institute on Drug Abuse, also offered constructive suggestions.

(Top)

home | in the news | online library | cites & sources | about tlc | articles

# EXHIBIT E

Consroe/Epilepsy/1975

# ANTICONVULSANT NATURE OF MARIHUANA SMOKING

Journal of the American Medical Association Oct 20, 1975---Vol 234, No 3: 306-307

Paul . Consroe, PhD: George C. Wood, PhD; Harvey Buchsbaum, MD

>From the departments of pharmacology (Dr. Consroe) and pharmaceutical sciences (Dr. Wood), College of Pharmacy, and the Neurology Department, Tucson Medical Center (Dr. Buchsbaum), University of Arizona, Tucson

Marihuana smoking, in conjunction with therapeutic doses of pheno-barbital and diphenylhydantoin, was apparently necessary for controlling seizures in one 24-year-old epileptic patient.

ANECDOTAL accounts of beneficial therapeutic effects of Cannabis sativa have been known throughout recorded history. (1) The classic description by O'Shaughnessy (2) in 1842 of the ameliorative effects of marihuana extract on "infantile convulsions," "hydrophobia," and "lockjaw" invite speculation as to the anticonvulsant effect of the drug. Other 19th century physicians reported that marihuana preparations were of benefit in controlling various spastic and seizure states, (3,4) although entirely useless in states of "true chronic epilepsy" such as petit mal. (4) Synthetic derivatives of delta-9-tetrahydrocannabinol, the main psychoactive ingredient of marihuana, have been reported to be of val;ue in the treatment of human epilepsy, although explicit details are absent in the abstract-report. (3) Finally, there is also a published report in which grand mal convulsions in a 20-year-old man were exacerbated by smoking marihuana. (4)

These references are essentially the only available literature on the relationship between marihuana and human convulsions, which obviously indicates a paucity as well as a contradiction of information. The following case report describes the possible beneficial effect of marihuana in human epilepsy.

## Report of a Case

A 24-year-old man has been seen in a neurology outpatient clinic for a period of eight years for control of his epileptic seizures. His history included febrile convulsions at 3 years of age and epileptic seizures since the age of 16. Since that age, the patient has been taking diphenylhydantoin sodium, 100 mg four times a day, and phenobarbital, 30 mg four times a day. Control seizures with this regimen was incomplete, and the patient complained of attacks about once every two months. From the age of 16 to 22, the incidence of seizures increased to one attack per month to one per week.

At 22 years of age, the patient began smoking marihuana (two to five joints per night) while continuing the prescribed anticonvulsant drug therapy. During this period, attack did not occur as long as the patient continued to take the combination of all three drugs. The patient's condition could not be maintained on marihuana alone, because on two occasions he experienced an attack three to four days after running out of his prescribed medication.

Neurological work-up has recently been done on the patient and he has been thoroughtly interviewed, because of the possible association between marihuana and epileptsy. The patient was found to have abnormal paroxysmal bursts of spike and slow-wave electroencephalographic discharges bilaterally, and his condition was diagnosed as grand mal epilepsy. The patient showed no other physical or emotional disability and did not admit to smoking cigarettes, drinking alcohol, or taking any other drugs. Plasma level of diphenylhydantoin was 7.4 mcg / ml; ohenobarbital level was 11 mcg /ml; and folic acid, 4.5mcg / ml.

The patient apparently complies with his dosage regimen, since he has a history of regular clinic visits and refilled drug prescriptions.

## Comment

This case suggests that marihuana may possess an anticonvulsant

effect in human epilepsy. Previous reports have alluded to this possibility. (1-3,5) Moreover, the antiseizure properties of delta-9-tetrahydrocannabinol have been demonstrated in a wide variety of experimental animal species. (7-9) It has been shown in laboratory-animal seizure models that the tetrahydrocannabinols show a differential activity against major seizures without altering the sequelaw of minor seizures. (7) Thus, the present case appears to bear out the prediction from the animal studies while at the same time possibly explaining marihuana's observed lack of effect in petit mal epilepsy. (4)

Theoretical calculations can be made to elucidate the probable blood level range for delta-9-tetrahydrocannabinol. A sample of the patient's marijuana was analyzed for tetrahydrocannabinol content by gas chromatography, and was found to contain 1.2% by weight total cannabinoids. One twelfth of the total cannabinoids, or 0.1% by weight, was accounted for by delta-9-tetrahydrocannabinol. Assuming 1 gm of marihuana per joint and correcting for pyrolysis (50%) and lung-absorption losses (20%), the inhalation dose of delta-9-tetrahydrocannabinol to the patient (weight, about 65 kg [143]) would be 6.15 mcg / kg. It is known that doses of 5 mcg to 7 mcg / kg of delta-9-tetrahydrocannabinol produce psychological and physiological effects in steady marihuana smokers. (10) Moreover, after an intravenous bolus of delta-9-tetrahydrocannabinol, marihuana smokers show lower blood levels and shorter half-lives (28 hours) for the drug than nonusers (half-life, 57 hours). (10) Since the half-life is 28 hours in steady smokers and this patient used two to five joints per evening, little of the drug would be eliminated and the blood levels would be expected to climb rapidly during the evening.

The subtherapeutic blood level of diphenylhydantoin in this patient, 7.4 mcg / ml (normal range, 10 to 25) was not unexpected, since phenobarbital is know to induce the formation of enzymes that metabolize diphenylhydantoin. Even when the blood levels of diphenylhydantoin are less than the normal range, the combination of the two drugs is known to be clinically effective. (11) The blood level of 11 mcg / ml of phenobarbital found in this patient is within the normal therapeutic range (10 to 20).

In summary, marihuana smoking in conjunction with routine doses of phenobarbital and diphenylhydantoin was apparently necessary for controlling seizures in one 24-year-old patient. However, the present case is in direct contrast to the single previously reported case of marihuana smoking exacerbating seizures in one patient with grand mal epilepsy. (6) The possibility that delta-9-tetrahydrocannabinol or other cannabinoids may be useful or detrimental in major seizures needs further investigation.

This investigation was supported in part by National Institute of Mental Health grant MH23414
The analysis of marihuana for tetrahydrocannabinol was performed by Pharm Chem Laboratories, Palo Alto, Calif.

References

1. Mikurya TH: Marijuana in medicine, past, present, and future. Calif Med 110: 34-40, 1969.

2. O'Shaughnessy WB: On the preparation of Indian hemp or gunjah. Trans Med Physiol Soc Bengal 421-461, 1842.

3. Shaw J: On the use of Cannabis indica in tetanus, hydrophobia, cholera with remarks on its effects. Madras Medical Journal 5: 74-80, 1843.

4. Reynolds Jr: Therapeutic uses and toxic effects of Cannabis indica. Lancet 1: 637-638, 1890.

5. Davis JP, Ramsey HH: Antiepileptic actions of marijuana-active substances. Fed Proc 8: 284, 1949.

6. Keeler MH, Reifler CF: Grand mal convulsions subsequent to marijuana use. Dis Nerv Syst 28: 474-475, 1967.

7. Consroe PF, Man D: Effects of delta-8- and delta-9-tetrahydrocannabinol on experimentally induced seizures. Life Sci 13: 429-439, 1973.

8. Sofia RD, Soloman TA, Barry H: The anti-convulsant activity of delta-1-tetrahydrocannabinol in mice. Fed Proc 13: 305, 1971.

9. Killam KF, Killam EF: The action of tetrahydrocannabinol on EEG and photomyoclonic seizures in the baboon, in: Fifth International Congress of Pharmacology, San Francisco, Abstracts of Volunteer Papers. Bethesda, Md, American Society of Pharmacology and Experimental Therapeutics, 1972, p. 124.

10. Lemberger L, Tamarkin N, Axelrod J, et al: Delta-9-tetrahydrocannabinol: Metabolism and disposition in long-term marijuana smokers. Science 173: 72-74, 1971.

11. Hansten PD; Drug Interactions. Philadelphia, Lea & Febiger Publishers, 1972, pp 53-54.

# EXHIBIT F

# CHRONIC ADMINISTRATION OF CANNABIDIOL TO HEALTHY VOLUNTEERS AND EPILEPTIC PATIENTS

Pharmacology 21: 175-185 (1980)

Jomar M. Cunha, E.A. Carlini, Aparecido E. Pereira, Oswaldo L. Ramos, Camilo Pimentel, Rubens Gagliardi, W.L. Sanvito, N. Lander and R. Mechoulam

Departments de Psicobiologia, Departamento de Medicina, Departamento de Neurologia, Escola Paulista de Medicina; Departamento de Neurologia, Faculdade de Medicina da Santa Case, Sao Paulo, [Brazil] and Department of Natural Products, Pharmacy School, Hebrew University, Jerusalem

This work was supported by grant No. ROI DA 00875 from the US National Institutes of Mental Health (principal investigator: E.A. Carlini).

Key words. Cannabidiol--Epilepsy--Healthy volunteers

Abstract. In phase 1 of the study, 3 mg / kg daily of cannabidiol (CBD) was given for 30 days to 8 healthy human volunteers. Another 8 volunteers received the same number of identical capsules containing glucose as placebo in a double-blind setting. Neurological and physical examinations, blood and urine analysis, ECG and EEG were performed at weekly intervals. In phase 2 of the study, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200-300 mg daily of CBD or placebo. The drugs were administered for as long as 4 1/2 months. Clinical and laboratory examinations, EEG and ECG were performed at 15- or 30-day intervals. Throughout the experiment the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. 4 of the 8 CBD subjects remained almost free of convulsive crises throughout the experiment and 3 other patients demonstrated partial improvement in their clinical condition. CBD was ineffective in 1 patient. The clinical condition of 7 placebo patients remained unchanged whereas the condition of 1 patient clearly improved. The potential use of CBD as an antiepileptic drug and its possible potentiating effect on other antiepileptic drugs are discussed.

Anecdotal reports on the antiepileptic properties of marihuana (Cannabis sativa) are known since ancient times (Li, 1974). Rosenthal (1971) mentioned medieval Arab manuscripts in which cannabis is described as a treatment for epilepsy. During the 19th century several medical reports were published on the ameliorative effects of cannabis extracts on several forms of convulsions (O'Shaughnessy, 1842; Shaw, 1843; Reynolds, 1890).

In spite of these promising results and its low toxicity, the use of cannabis preparations for medical purposes progressively decreased. This was due to the absence of standardized preparations, the unknown chemical composition, and the psychotropic secondary effects produced by cannabis.

Cannabidiol (CBD) is the major neutral nonpsychoactive cannabinoid in most cannabis preparations. It was first isolated by Adams et al, in 1940 but its structure was elucidated only 23 years later (Mechoulam and Shvo, 1963). The main active component of cannabis is delta-1-tetrahydrocannabinol (delta-1-THC) which was isolated in pure form and its structure was determined by Gaoni and Mechoulam in 1964. It is also named delta-9-THC. Numerous other natural cannabinoids are known today (Mechoulam, 1973; Mechoulam et al, 1976).

The unraveling of the chemistry of C. sativa brought a new interest in its pharmacology, and quite expectedly many laboratories studied the anticonvulsant properties of its components especially since early reports had shown that some natural and synthetic cannabinoids protected rats from convulsions (Loewe and Goodman, 1947) and were of therapeutic value in epileptic children (Davis and Ramsey, 1949). More recently many reports have appeared attributing anticonvulsant properties to delta-1-THC and other cannabinoids, in a variety of experimental procedures (Garriott et al, 1968; Sofia et al, 1971; Consroe and Man, 1973; Karler et al, 1973, 1974; Plotnikoff, 1976). As a rule, delta-1-THC was the most studied

compound. Most of the results obtained confirmed the rather potent anticonvulsant property of this drug. Its possible use as an antiepileptic drug in humans has, however, been hindered by its known psychotropic effects.

Since Brazilian workers (Carlini et al, 1973; Izquierdo et al, 1973) first demonstrated the anticonvulsant effects of CBD, there have been several additional reports on the effectiveness of CBD and its derivatives in protecting experimental animals from convulsions induced by various procedures (Karler et al, 1973; Turkanis et al, 1974; Carlini et al, 1975; Karler and Turkanis, 1976; Consroe and Wolkin, 1977). Consroe and Wolkin (1977) demonstrated that CBD has a high protective index comparable to that of phenobarbital and a spectrum of anticonvulsant activity in rodents similar to that of phenytoin. CBD also enhances the anti-convulsant potency of both phenytoin and phenobarbital (Consroe and Wolkin, 1977; Chesher and Jackson, 1974; Chesher et al., 1975).

In addition to its favorable anticonvulsant effects and absence of toxicity in animals, CBD seems to be devoid of psychotropic activity and other undesirable side effects in humans. The lack of toxicity of CBD in animals was demonstrated by intraperitoneal injection of 50 mg / kg daily for 90 days in mice, oral ingestion of 5-20 mg / kg daily for 90 days and 50 mg / kg for 27 days by rats and intravenous injection of 1,000 mg / kg in rabbits. No toxicity was observed (Cunha and Carlini, to be published). In man, oral intake of doses from 15 to 160 mg / day (Karniol et al, 1974; Hollister, 1973; Carlini et al, 1979), inhalation of 0.15 mg / kg (Dalton et al, 1976a), and intravenous injection of 30 mg (Perez-Reyes et al, 1973; Hollister, 1973) were not followed by ill effects. Chronic oral administration of 10 mg daily for 21 days did not induce any change in neurological (including EEG), clinical (including ECG), psychiatric, blood and urine examinations (Mincis et al, 1973).

Another recent investigation in our laboratory (Consroe et al., 1979) showed that CBD neither interferes with several psychomotor and psychological functions in humans nor potentiates alcohol effects on these functions.

The above data led us to undertake the present investigation which was performed in two phases. In phase 1, 3--6 mg / kg of CBD (roughly corresponding to 200--400 mg / subject) was administered daily to healthy human volunteers for 30 days. In phase 2, patients suffering from secondary generalized epilepsy with temporal irritative activity received 200--300 mg of the drug for periods of up to 4.5 months.

Experiment 1 (Phase 1 of Study)

Material and Methods

Subjects
16 adult volunteers (11 men and 5 women) aged 22-35, with an average weight of 65 kg were chosen from the staff of Escola Paulista de Medicina. They were in good health showing neither clinical nor laboratory evidence of cardiovascular, renal, hepatic or other impairments. The institutional review committee at Escola Paulista de Medicina previously approved the protocol of the experiments.

On the first day of the experiment the patients were submitted to a complete medical check-up, including clinical and neurological examinations, EEG, ECG, blood tests (hematocrit, hemoglobin, leukocyte and erythrocyte counts, bilirubin, oxaloacetic and puruvic transaminases and creatinine) and urine tests ; (osmolarity, pH, albumin, leukocyte and erythrocyte counts, cylinders and crystals) in the Department of Medicine of the Hospital Sao Paulo of Escola Paulista de Medicina. On the 7th day, they returned to the hospital, signed the informed consent and were randomly divided in two groups of 8. Each group started the ingestion of identical gelatine capsules containing either glucose as placebo (control group) or CBD (experimental group). The experiment was performed on a double-blind basis and the subjects were instructed to ingest the assigned capsules, one in the morning and the second in the afternoon for 30 days. Each capsule contained an amount of CBD (or glucose) equivalent to 1.5 mg / kg, i.e. a daily dosage of 3.0 mg / kg. 1 volunteer took 4 capsules of CBD daily (6 mg / kg) on the last 3 days of the experiment.

On the 3rd, 7th, 15th, 31st and 37th days after the beginning of drug ingestion, the subjects returned to the hospital to undergo the

examinations described above.

Drug

Cannabidiol, in crystalline from (m.p. 66--67) was isolated from hashish of undetermined age. It was of Lebanese origin and was supplied by the Israeli Police. The isolation procedure has been described (Gaoni and Mechoulam, 1971). Part of the CBD was a gift from Makor Chemicals, P.O.B. 6570, Jerusalem

Results

General Observations
During the entire period of the experiment, the subjects did not report any symptoms suggestive of psychotropic effect of CBD. Of the 8 volunteers receiving the placebo, 1 gave up on the 21st day of the experiment for personal reasons; a second placebo subject reported sudoresis and 'palpitations' from the 7th to the 10th day in the veins of the feet, legs and head, stating that he had to uncover his feet to feel the palpitations less in order to sleep. Clinical and laboratory examinations were normal and the symptoms subsided after the 11th day without any measures on the part of the investigators.

Of the 8 volunteers receiving CBD, 2 reported somnolence, 1 during the first week and the other throughout the entire period of the experiment. A 3rd subject, with a history of mild insomnia, reported being able to sleep better during the first week of medication.

Neurological and clinical examinations, EEG and ECG tracings, and blood and urine analyses (detailed above) were within normal limits in the 16 subjects before, during and after the experiment.

Comments

It has been suggested that delta-1-THC and other cannabinoids may possess therapeutic potential as antidepressive drugs in patients with cancer (Regelson et al., 1975) or in the treatment of glaucoma (Hepler and Frank, 1971), asthma (Tashkin et al., 1972), etc. For a recent review see Mechoulam and Carlini (1978). However, acute administration of 20--60 mg of delta-1-THC induces a marked psychic change and has peripheral effects such as an increase in heart rate (Isbell et al., 1967; Kiplinger et al., 1971; Karniol et al., 1975) which would limit its therapeutic use.

In contrast, the present experiment shows that 3 mg / kg / day of CBD administered for 30 days (1 volunteer received 6 mg / kg / day during the last 3 days of experiment) did not induce any psychic or other side effects and was well tolerated by the 8 subjects. Thus CBD does not appear to have any toxic effect in humans when administered at the above dosage over a long period. This confirms our previous data obtained in animal (Cunha and Carlini, to be published).

In our opinion these findings justified the trial of the drug in epileptic patients.
Experiment 2 (Phase 2 of Study)

Material and Methods

Subjects
15 Epileptic patients, 11 women and 4 men, aged 14-49 (average 24 years), with a documented history of frequent convulsions for at least 1 year, were selected. These patients were not reacting satisfactorily to the prescribed antiepileptic drugs they were receiving (table 1) in spite of special care to assure that the patients were taking them properly. The patients were diagnosed as cases of secondary generalized epilepsy; EEG tracings revealed irritative activity with temporal projection. They had at least one generalized convulsive crisis weekly. Clinical and laboratory examinations showed no signs of renal, cardiovascular or hepatic disease. The experiment was performed in the Neurology Out-Patient Clinics of the Hospital Sao Paulo (8 patients) and the Hospital da Santa Case (t patients). Each patient was followed by the same investigator, beginning 2 weeks before first drug administration and then throughout the whole period of drug administration. In the 2 weeks before CBD or placebo administration, the number of focal and generalized convulsive crises was

recorded and considered as the baseline to evaluate treatment. On the first day of the experiment, the patients were submitted to the examinations described in experiment 1. They were randomly divided into one group of 8 (control group) and another group of 7 (CBD group) and returned to the hospital for 2 more days. After 1 week each group received placebo or CBD capsules in a double-blind procedure in addition to the antiepileptic drugs they were already receiving (see table 1). 1 placebo patient (Z.S.M.) was transferred to the CBD group after 1 month. Half of each group of patients was treated in each hospital. The patients were instructed to take 2 or 3 capsules daily (containing 100 mg of CBD or glucose) and to return to the hospital every week for clinical and / or laboratory examinations.

Clinical evaluation of drug treatment was made weekly using a scale with score 0-3, which took into consideration absence of convulsive crises or absence of generalization and self-reported subjective improvement (see tableII). According to this criterion all patients were scored 3 during the predrug phase (baseline).

Results

General Observations
During the curse of the experiment none of the 8 patients receiving CBD showed evidence of behavioral alterations which could be suggestive of a psychotropic effect. The minimum and maximum times of drug administration were 8 and 18 weeks for most patients (control and CBD groups). 2 of the placebo patients did not return after the end of the 4th week and 1 CBD patient after the 6th week. 1 placebo patient (Z.S.M.) whose condition remained unaltered during 4 weeks, wanted to give up the experiment, but remained in it after crossing over to the CBD group.

4 patients under CBD and 1 receiving placebo complained of somnolence during the experiment. Another CBD patient (M.C.P.) complained of painful gastric sensations after drug ingestion at the 6th week. These symptoms disappeared after prescription of an antacid and did not return throughout the experiment.

Table II. Criteria used to evaluate clinical efficacy of cannabidiol in epileptic patients

Score 0.....complete improvement
Score 1.....partial improvement
Score 2.....small improvement
Score 3.....without improvement

0 = Total absence of convulsive crises and self-reported subjective improvement.
1 = Absence of generalization of crises and self-reported subjective improvement.
2 = Only self-reported subjective improvement.
3 = No reduction in crises and no self-reported improvement.

Neurological Examination and EEG
Before drug treatment 1 CBD patient (N.D.) showed paresthetic walking towards the right, with spastic hypomotility of the right arm and leg, mainly of the right hand. He also presented a decrease in psychomotor functions. 2 other patients in the CBD group (A.A.S. and Z.S.M.) showed in examinations prior to the experiment some mental underdevelopment. Neurological examinations of all other patients were within normal limits.

Table III shows the results of the EEG analysis in a condensed form. Of the patients receiving CBD, 3 showed improvement in EEG pattern with signs of decrease in frequency of crises throughout the experiment. 2 placebo patients also had improved EEG patterns (J.O.R., and J.S.V.) on one occasion, with a return to their previous condition on subsequent examination.

Clinical Evaluation of Treatment
Clinical evaluation was performed weekly, scoring 0 - 3 points to each patient compared to its own baseline (see table II and 'methods' for details). At the end of the treatment, the median of weekly score for each patient was calculated. The results are presented in table IV. During the first week of treatment there was general improvement in almost all patients (placebo and CBD groups), but from the second week, all placebo patients with one exception (M.D.M.S.) returned to their previous clinical

state. At the end of the placebo treatment, 7 patients had a median of 3 (i.e. no improvement) whereas patient M.D.M.S. showed complete improvement (median 0). 2 placebo patients (J.S. and M.G.S.) with no improvement received the capsules for the 4th week of treatment but did not return. 3 other placebo patients (J.O.R.; J.S.V.; M.L.M.) remained under treatment for the period stated in table IV, after which it was decided to withdraw them from the experiment and to change the antiepileptic drugs they were receiving (see table I) in an attempt to improve their condition. Patient R.C. remained in the placebo group for 18 weeks and received all known antiepileptic drugs without success. Patient Z.S.M. was on placebo for 4 weeks without improvement and was subsequently transferred to 200 mg of CBD daily for 6 weeks (without her knowledge) with a small improvement (median 2).

Of the 8 patients receiving CBD, 4 showed considerable improvement in their clinical condition (median 0). However, in 1 case (M.C.P.) this was achieved by increasing the dosage to 300 mg.daily. Patient A.A.S., who showed much improvement from the first week, unfortunately moved to another city after completing 6 weeks of treatment with CBD. The 5th patient (F.R.F.) improved only partially (median 1) although he attained score 0 in clinical evaluation (no convulsive crisis and subjective improvement) in 7 out of the 16 weeks of treatment. 2 of the 3 remaining patients showed improvement (score 2) whereas the last patient (N.D.) did not improve at all in spite of increasing CBD to 300 mg daily for the last 2 weeks of treatment.

Table IV

JOR placebo 3
JS placebo 3
MGS Placebo 3
JSV placebo 3
MLM placebo 3
RC placebo 3
MDMSplacebo 0
ZSM placebo 3

ZSM CBD200 2
FRF CBD200 1
OEBNCBD200 0
AAS CBD200 0
ASR CBD200 2
NP CBD200
300 3
MCP CBD200
300 0

0 = complete improvement
3 = no improvement

Discussion

Treatment of epilepsy is based mainly on anticonvulsant drugs. However, even when properly administered in well-diagnosed cases, these drugs succeed in helping only about 70-75% of the epileptic patients, whereas about 30% of the patients do not benefit at all (Robb, 1975). Furthermore, all clinically effective antiepileptic drugs induce undesirable side effects at normal dosage (osteomalacia, megaloblastic anemia; gingival hyperplasia) or due to overdose (nystagmus, motor incoordination, coma and death) or to idiosyncratic reactions (Kutt and Louis, 1972).

As already stated in the introduction, many ancient reports mention the antiepileptic properties of cannabis. More recently Consroe et al. (1975) described an epileptic patient receiving phenobarbital and phenytoin without good results, who benefited by smoking marihuana. These accounts indicate that marihuana contains chemical entities which may possess anti-epileptic properties.

According to the present data, CBD may turn out to be a useful drug for the treatment of some cases of epilepsy. There is hardly any toxicity as shown in our phase 1 study; there were no changes in EEG, ECG, blood and urine analyses and neurological and clinical examinations were normal in 8 healthy volunteers receiving 3 mg / kg of CBD daily for 30 days. A similar absence of toxicity was also noted in our phase 2 study in

which 8 epileptic patients received 200 or 300 mg for up to 4 1/2 months. Furthermore, none of the 16 subjects receiving CBD showed any psychic delta-1-THC-type effects. The present data obtained after long-term administration also confirm previous reports showing the absence of toxicity in acute studies (Hollister, 1973; Carlini et al, 1979).

Somnolence reported by 3 healthy volunteers and 4 epileptic patients (43% of the subjects receiving the drug) was the only CBD side effect noted. A certain hypnotic effect is frequently observed with drugs which possess antiepileptic properties. We have in fact recently demonstrated that CBD does induce better sleep in human volunteers (Carlini et al., 1979). On the other hand, CBD induced a remarkable improvement (median 0) in 4 of 8 epileptic patients who remained almost free of convulsive crises during the entire period of the experiment. In a 5th patient (median 1), the crises were absent in 7 of the 16 weeks of treatment. All of these patients (as well as their relatives) reported subjective improvement. A similar subjective effect was also reported by 2 more patients and only in 1 patient CBD failed to induce any form of clinical benefit. This is in striking contrast to the results obtained with the 8 patients receiving placebo of whom 7 showed no improvement in their clinical condition.

However, EEG results were not as consistent as the clinical evaluation. As seen in table III, clinical improvement was not always followed by positive changes in the tracings. As the International League against Epilepsy (Commission on Antiepileptic Drugs) does not consider EEG mandatory in this type of research (Penry, 1973), EEG data were not included in the overall clinical evaluation of CBD effects. It should also be emphasized that the abnormal EEGs were present from the beginning of the experiment even though all patients were receiving known antiepileptic drugs. Furthermore, phenytoin and barbiturates fail to control the EEG abnormalities of epileptics in spite of being able to abolish their behavioral convulsions; phenytoin may even increase the prominence of focal spikes (Morrel et al., 1959; Millichap, 1969).

Wall et al. (1976) have reported pharmacokinetic studies in man with 3H-CBD injected intravenously into 5 healthy volunteers. They observed that 8% of the total initial dose (20 mg of CBD) was present in plasma 30 min after injection, to fall to 3% after 60 minutes. 3 days later, 33% was excreted in the feces and 16% in the urine, with 50% remaining in tissues and organs. Therefore, CBD seems to have a relatively long half-life, which favors its use as a drug in epileptics.

However, in spite of the large number of reports showing beneficial effects of cannabis and its preparations in many forms of experimental convulsions and in human epilepsy, a few reports claim the contrary. Feeney et al. (1976) showed that delta-1-THC in cats induced EEG changes resembling those observed in convulsions, and Perez-Reyes and Wingfield (1974) described a similar effect of CBD in man. In neither case, however, were behavioral convulsions observed. It is interesting in this context that phenytoin may increase activity of focal spikes (Millichap, 1969). To the best of our knowledge there is only one report attributing a worsening of an epileptic convulsive crisis (grand mal) following use of marihuana smoking (Keeler and Reifler, 1967), and we do not know of any cases described for CBD. Furthermore, in none of our 8 epileptic patients did we observe deterioration of clinical symptomatology or of EEG, but rather the opposite effect was true.

The mechanism by which CBD benefited our epileptic patients is not known. All 8 patients were also receiving known antiepileptic drugs which were by themselves, however, ineffective. One possibility is that CBD potentiated their action since enhancement by CBD of anticonvulsant activity of phenobarbital and phenytoin in animals has been demonstrated (Consroe and Wolkin, 1977; Chesher and Jackson, 1974; Chesher et al., 1975). In man, however, 50--500 mcg / kg CBD given in cigarette form is not able to alter plasma concentrations of secobarbital (Dalton et al., 1976b). The possibility that CBD acts per se should also be taken into consideration, as shown by several reports describing its direct anticonvulsant effects in animals.

In conclusion, we have found that CBD had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal foci, who did not benefit from know anti-epileptic drugs. Further research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans.

References

Adams, R.,; Hunt, M., and Clark, J.H.: Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. J. Am. chem. Soc. 62: 196-200 (1940).

Carlini, E.A.; Leite, J.R.; Tannhauser,M., and Berardi, A.C.: Cannabidiol and Cannabis sativa extract protect mice and rats against convulsive agents. J. Pharm. Pharmac. 25: 664-665 (1973).

Carlini, E.A.; Masur, J., and Magalhaes, C.C.P.B.: Possible hypnotic effect of cannabidiol on human beings. Preliminary study. Cienci Cult., S Paulo 31: 315-322 (1979).

Carlini, E.A.; Mechoulam, R., and Lander, N.: Anticonvulsant activity of four oxygenated cannabidiol derivates. Res. Commun. chem. Pathol. Pharmacol. 12: 1-15 (1975).

Chesher, G.B. and Jackson, D.M.: Anticonvulsant effects of cannabinoids in mice. Drug interactions within cannabinoids and cannabinoid interactions with phenytoin. Psychopharmacology 37: 255-264 (1974).

Chesher, G.B.; Jackson, D.M., and Malor, R.M.: Interaction of delta-9-tetrahydrocannabinol and cannabidiol with phenobarbitone in protecting mice from electrically induced convulsions. J. Pharm. Pharmac. 27: 608-609 (1975).

Consroe, P.F.; Carlini, E.A.; Zwicker, A.P., and Lacerda, L.A.: Human interaction effects of cannabidiol and alcohol. Psychopharmacology 66: 45-50 (1979).

Consroe, P.F. and Man, D.P.: Effects of delta-8- and delta-9-tetrahydrocannabinol on experimentally induced seizures. Life Sci. 13: 429-439 (1973).

Consroe, P.F. and Wolkin, A.: Cannabidiol-antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. J. Pharmac. exp. Ther. 201: 26-32 (1977).

Consroe, P.F.; Wood, G.C., and Buchsbaum, H.: Anticonvulsive nature of marihuana smoking. J. Am. med. Ass. 234: 306-307 (1975).

Dalton, W.S.; Martz, R.; Lemberger, L.; Rodda, B.E., and Forney, R.B.: Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. Clin. Pharmacol. Ther. 19: 300-309 (1976a).

Dalton, W.S.; Martz, R.; Rodda, B.E.; Lemberger, L., and Forney, R.B.: Influence of cannabidiol on secobarbital effects and plasma kinetics. Clin. Pharmacol. Ther. 20: 695-700 (1976b).

Davis, J.P. and Ramsey, H.H.: Antiepileptic actions of marihuana active substances. Abstract. Fed. Proc. 8: 284 (1949).

Feeney, D.M.; Spiker, M.D., and Weiss, G.K.: Marihuana and epilepsy: Activation of symptoms by delta-9-THC; in Cohen and Stillman, The therapeutic potential of marijuana (Plenum Press, New York 1976).

Gaoni, Y. and Mechoulam, R.: Isolation, structure and partial synthesis of an active constituent of hashish. J. Am. chem. Soc. 86: 1646-1647 (1964).

Gaoni, Y. and Mechoulam, R.: The isolation and structure of delta-1-THC and other neutral cannabinoids from hashish. J. Am. chem. Soc. 93: 217-224 (1971).

Garriott, J.C.; Forney, R.B.; Hughes, F.W., and Richards, A.B.: Pharmacologic properties of some cannabis related compounds. Archs int. Pharmacodyn. Ther. 171: 425-434 (1968).

Hepler, R.S. and Frank, I.R.: Marihuana smoking and intraocular pressure. J. Am. med. Ass. 217: 1392 (1971).

Hollister, L.E.: Cannabidiol and cannabinol in man. Experientia 29: 825-826 (1973).

Isbell, H.; Gorodetzsky, C.W.; Jasinski, D.; Claussen, U.; Spulak, F.V.,

and Korte, F.: Effects of (-) delta-9-transtetrahydrocannabinol in man. Psychopharmacologia 11: 184-188 (1967).

Izquierdo, I.; Orsingher, O.A., and Berardi, A.C.: Effect of cannabidiol and of other Cannabis sativa compounds on hippocampal seizure discharges. Psychopharmacologia 28: 95-102 (1973).

Karler, R.; Cely, W., and Turkanis, S.A.: The anticonvulsant activity of cannabidiol and cannabinol. Life Sci. 13: 1527-1531 (1973).

Karler, R.; Cely, W., and Turkanis, S.A.: Anticonvulsant of delta-9-tetrahydrocannabinol and its 11-hydroxy and 8-a-11-dihydroxymetabolites in the frog. Res. Commun. chem Pathol. Pharmacol. 9: 441-452 (1974).

Karler, R. and Turkanis, S.A.:The antiepileptic potential of the cannabinoids; in Cohen and Stilman, The therapeutic potential of marijuana (Plenum Press, New York 1976).

Karniol, I.G.; Shirakawa, I; Kasinsky, N.; Pfeferman, A., and Carlini, E.A.: Cannabidiol interferes with the effects of delta-9-tetrahydrocannabinol in man. Eur. J. Pharmacol. 28: 172-177 (1974).

Karniol, I.G.; Shirakawa, I.; Takahashi, R.N.; Knoebel, E., and Musty, R.E.: Effects of delta-9-tetrahydrocannabinol and cannabinol in man. Pharmacology 13: 502-512 (1975).

Keeler, M.H. and Reifler, C.B.: Grand mal convulsion subsequent to marijuana use. Dis. nerv. Syst. 28: 474-475 (1967).

Kiplinger, G.F.; Manno, J.E.; Rodda, B.E., and Forney, R.B.: Dose-response analysis of the effects of tetrahydrocannabinol in man. Clin. Pharmacol. Ther. 12: 650-657 (1971).

Kutt, H. and Louis, S.: Untoward effects of anticonvulsants. New Engl. J. Med. 826: 1316-1317 (1972).

Li, H.L.: An archeological and historical account of cannabis in China. J. econ. Bot. 28: 437-448 (1974).

Loewe, S. and Goodman, L.S.: Anticonvulsant action of marihuana-active substances. Abstract. Fed. Proc. 6: 352 (1947).

Mechoulam, R.: Marijuana. Chemistry, metabolism, pharmacology and clinical effects (Academic Press, New York 1973).

Mechoulam, R. and Carlini, E.A.: Toward drugs derived from cannabis. Naturwissenschaften 65: 174-179 (1978).

Mechoulam, R.; McCallum, N.K., and Burstein, S.: Recent advances in the chemistry and biochemistry of cannabis. Chem. Rev. 76: 75-112 (1976).

Mechoulam, R. and Shvo, Y.: The structure of cannabidiol. Tetrahedron 19: 2073-2078 (1963).

Millichap, J.G.: Relation of laboratory evaluation to clinical effectiveness of antiepileptic drugs. Epilepsia 10: 315-328 (1969).

Mincis, M.; Pfeferman, A.; Guimaraes, R.X.; Ramos, O.L.; Zukerman, E.; Karnio, I.G. Carlini, E.A.: Administracao cronica de canabidiol em seres humanos. Revta Asoc. med. Brasil 19: 185-190 (1973).

Morrel, F.; Bradley, W., and Ptashne, M.: Effects of drugs on discharge characteristics of chronic epileptogenic lesions. Neurology 9: 492-498 (1959).

O'Shaughnessy, W.B.: On the preparations of the Indian hemp or gunjah. Trans. med. Phys. Soc. Bombay 8: 421-461 (1842).

Penry, J.K.: Principles for clinical testing of antiepileptic drugs. Epilepsia 14: 451-458 (1973).

Perez-Reyes, M.; Timmons, M.C.; Davis, K.H., and Wall, M.E.: A comparison of the pharmacological activity in man of intravenously administered delta-9-tetrahydrocannabinol, cannabinol and cannabidiol. Experientia 29:

1368-1369 (1973).

Perez-Reyes, M. and Wingfield, M.: Cannabidiol and electroencephalographic epileptic activity. J. Am. med. Ass. 230: 1635 (1974).

Plotnikoff, N.P.: New benzopyrans: anticonvulsant activities; in Cohen and Stillman, the therapeutic potential of marijuana (Plenum Press, New York 1976).

Regelson, W.; Butler, J.R.; Schultz, J.; Kirt, T.; Peek, L., and Green, M.L.: delta-9-THC as an effective antidepressant and appetite stimulating agent in advanced cancer patients; in Braude and Szara, International conference on the pharmacology of cannabis (Raven Press, New York 1975).

Reynolds, J.R.: Therapeutic uses and toxic effects of Cannabis indica. Lancet i: 637-638 (1890).

Robb, P.: Focal epilepsy: the problem, prevalence and contributing factors. Adv. Neurol. 8: 11-22 (1975).

Rosenthal, F.: The herb hashish versus medieval Muslim society (Brill, Leiden 1971).

Shaw, J.: On the use of Cannabis indica in tetanus hydrophobia, and in cholera with remarks on its effects. Madras med. J. 5: 74-80 (1843).

Sofia, R.D.; Solomon, T.A., and Barry, H., III: The anticonvulsant activity of delta-1-tetrahydrocannabinol in mice. Abstract. Pharmacologist 13: 246 (1971).

Tashkin, D.P.; Shapiro, B.J., and Frank, I.M.: Acute pulmonary physiological effects of smoked marijuana and oral delta-9-tetrahydrocannabinol in healthy young men. New Engl. J. Med. 289: 336-341 (1972).

Turkanis, S.A.; Cely, W.; Olsen, D.M., and Karler, R.: Anticonvulsant properties of cannabidiol. Res. Commun. chem. Pathol. Pharmacol. 8: 213-246 (1974)

Wall,, M.E.; Brine, D.R., and Perez-Reyes, M.: Metabolism of cannabinoids in man; in Braude and Szara, The pharmacology of marihuana (Raven Press, New York 1976).

Jomar M. Cunha, Departamento de psicobiologia, Escola Paulista de Medicina, Rua Botucatu 862, 04023 Sao Paulo (Brasil)

EXHIBIT G

APER

Petro/MS/1981

# TREATMENT OF HUMAN SPASTICITY WITH DELTA-9-TETRAHYDROCANNABINOL

Denis J. Petro, M.D., and Carl Ellenberger, Jr., M.D. Bronx, NY

J Clin Pharmacol. 1981; 21: 413S--416S

Abstract: Spasticity is a common neurologic condition in patients with multiple sclerosis, stroke, cerebral palsy or an injured spinal cord. Animal studies suggest that THC has an inhibitory effect on polysynaptic reflexes. Some spastic patients claim improvement after inhaling cannabis. We tested muscle tone, reflexes, strength and performed EMGs before and after double-blinded oral administration of either 10 or 5 mg THC or placebo. The blinded examiner correctly identified the trials in which the patients received THC in seven of none cases. For the group, 10 mg THC significantly reduced spasticity by clinical measurement ($P<0.01$). Quadriceps EMG interference pattern was reduced in those four patients with primarily extensor spasticity. THC was administered to eight other patients with spasticity and other CNS lesions. Responses varied, but benefit was seen in three of three patients with "tonic spasms." No benefit was noted in patients with cerebellar disease.

Several patients with multiple sclerosis reported to us that their spasticity improved after smoking marihuana. Preliminary uncontrolled observations of these patients before and after inhalation of the drug suggested to us that the improvement in spasticity was a specific effect of the marihuana and not merely a result of the well-recognized euphoria or altered perception experienced by social users of the drug.

## Methods

We entered nine patients with spasticity, presumably of spinal origin and related to multiple sclerosis, into a double-blinded pilot study. The blinded observer examined each patient on three separate days, before and at 1 1/2-hour intervals after oral administration of a capsule containing either 10 mg, 5 mg, or no synthetic delta-9-tetrahydrocannabinol (THC). Absorption of oral THC is variable, about 90 per cent, but generally slower than that of inhaled THC. Blood levels and psychologic effects peak at 3 hours after ingestion. Because blood level determination is costly and may be unreliable, we did not determine levels.
The examiner rated deep tendon reflexes, muscular resistance to stretch in the legs, and abnormal reflexes each on a scale of 0 (absent) to 4 (abnormally increased) and tabulated the total divided by the number of observations as the "spasticity score" at 1 1/2 -hour intervals. For example, if both knee jerks were 3+, both ankle jerks were 3+, and both adductor jerks were 3+, the total was 18 and the spasticity score was 18/6= 3.0. Babinski signs were rated as 4+, their absence as 3+.
The examiner viewed the EMG interference pattern of the quadriceps muscle as the knee joint was flexed from 0 to 90 degrees at varying velocities. The examiner also assessed walking ability, inquired about the patient's subjective response and side effects of the drug, and measured vital signs.

## Results

Three patients reported feeling "loose" and better able to walk after receiving either 5 or 10 mg THC. The changes in spasticity scores for the treated and placebo groups are illustrated in Fig. 1. Differences between the groups at 180 minutes are significant ($P<0.01$); summed scores for the two treated groups differed significantly from summed scores of the placebo group ($P<0.005$). The spasticity scores of four patients improved more than two standard deviations from the mean after either 5 or 10 mg THC; one patient improved after placebo. Only two of the three patients who felt improved actually did so by objective criteria. On the basis of the spasticity scores, the blinded examiner identified correctly the placebo trials in seven of the nine patients.
The EMG index of spasticity proved to be impractical in five patients---in three because resistance to stretch was too severe and in two because electrical activity was too little to record. Among the remaining four patients, the interference pattern, by visual inspection, was reduced after treatment from the pretreatment pattern at comparable velocity of stretch.
Side effects of the 5- or 10-mg oral dosage were minimal. One

patient reported feeling "high" after 10 mg, and another reported a "high" after placebo. No other patients reported side effects at the relatively low doses we used.

Discussion

Our preliminary results suggest that THC or one of its synthetic derivatives warrants further study as a potential treatment for spasticity. Although many previous investigators have studied the effects of marihuana on complex motor tasks, we were not able to find previous studies of the effects of marihuana on spasticity in the medical literature. Experimental studies in animals suggest that THC has an inhibitory effect on polysynaptic reflexes mediated through the spinal cord. The results of differential sectioning of the neuraxis in cats by Dagirmangian and Boyd (1) suggest that the ability of several tetrahydrocannabinols to decrease polysynaptic flexion reflexes relates to its action in the region between the mesencephalon and first cervical segment. Kayaalp et al. (2) postulate that THC has an effect on both nerve conduction and skeletal muscle contraction. Sullivan (3) and colleagues found a dose-dependent loss of reflexes and muscular weakness in dogs.
Although THC has proved to be clinically useful in the treatment of nausea induced by cancer chemotherapy and in reducing intraocular pressure in glaucoma, the results of these trials have demonstrated several disadvantages of the drug. The first is its potential for psychologic effects that limits usage in higher doses than those we employed. The second drawback to regular clinical use of the drug and of its many derivatives is the observation that many of its therapeutic effects may diminish after a relatively short period of regular usage.

References

1. Dagirmangian R, Boyd ES. Some pharmacological effects of two tetrahydrocannabinols. J Pharmacol Exp Therap. 1962; 135: 25-33.

2. Kayaalp SA, Kaymakcalan S, Verimer T, Ilhan M, Onur R. In vitro neuro-muscular effects of delta-9-trans-tetrahydrocannabinol (THC). Arch Int Pharmacodyn. 1974; 212: 67-75.

3. Sullivan MF, Willard DH. The beagle dog as an animal model for marihuana smoking studies. Toxicol Appl Pharmacol. 1978; 45: 445-462.

Discussion of the Paper

Dr. Nahas: Were the subjects that you studied naive toward marijuana, and did you observe tolerance?

Dr. Petro: All of our patients were naive to marijuana. Anecdotally, other patients claim that they have been using marijuana for periods up to 15 years for control of spasticity, but research needs to cover a larger and better controlled sample before any definitive statement would be possible. No chronic studies have been done to evaluate drug tolerance in spasticity.

Dr. Ungerleider: Did you, as blinded examiner, interview the patients and perform the tests?

Dr. Petro: I did all of the evaluations of neurologic function.

Dr. Ungerleider: Did you know that they felt better before you evaluated them objectively?

Dr. Petro: No; I used only objective measures, the EMG criteria and the spasticity scores.

Dr. Lindblom: Have you considered the use of patients other than those with multiple sclerosis (MS)? We studied the effect of baclofen on spasticity, and found much spontaneous variability in MS patients. In addition, some are euphoric from the disease and cannabis might add to the euphoria and confuse the results with unspecific effects. Furthermore, there are several types of spasticity, and in the case of baclofen, we found that gamma-spasticity was reduced but alpha-spasticity was unaffected.

Dr. Petro: We had a population of MS patients that was rather large and

readily accessible. Certainly, in subjects with significant cerebellar disease, marijuana (or its derivatives) would appear to be contra-indicated because of relaxant effects. We examined the patient population readily available for study, which was MS patients, but as you suggest this is not the ideal group to study.
Dr. Gilbert: Poly-synaptic reflexes in the dog are very sensitive to THC. In the morphine-dependent animal during abstinence there is an increased activity in the hind limbs. That activity can be blocked with very low doses of THC, nantradol and nabilone, before we see any other effects of the drugs (see Gilbert et al., this monograph).

Dr. Dow: Could you elaborate on your conclusion that THC is not the ideal drug for spasticity?

Dr. Petro: Patients that report effects from marijuana don't like taking THC; after smoking a marijuana cigarette, they clearly have an improvement that is different from that seen from THC. As other related substances with more specific CNS effects become available, these should be studied ;in the treatment of spasticity.

EXHIBIT H

3RD ARTICLE of Level 1 printed in FULL format.


The New England Journal of Medicine (R)

N Engl J Med 1994; 331: 1675-1679

December 22, 1994

SECTION: ORIGINAL ARTICLES

LENGTH: 3337 words

TITLE: **Risk Of Kidney Failure Associated With The Use** Of Acetaminophen, Aspirin, And Nonsteroidal Antiinflammatory Drugs.

SOURCE: From the Welch Center for Prevention, Epidemiology, and Clinical Research (T.V.P., P.K.W., M.J.K.) and the Departments of Epidemiology (T.V.P., P.K.W., M.J.K.), Health Policy and Management (M.J.K.), and Medicine (P.K.W., M.J.K.), Johns Hopkins University School of Hygiene and Public Health and School of Medicine, Baltimore; and the Institute of Social and Preventive Medicine, University of Geneva, Geneva, Switzerland (T.V.P.). Address reprint requests to Dr. Perneger at the Institute of Social and Preventive Medicine, University of Geneva, Centre Medical Universitaire Case Postale, 1211 Geneva 4, Switzerland.

Supported by grants from the Swiss National Science Foundation (823B-025121 and 32-32609), the Schmidheiny Foundation, the American Heart Association, the National Kidney Foundation, and the Agency for Health Care Policy and Research (R03 HS 06978-01); by General Clinical Research Center grants (5MOIRR00722 and RR00035) from the National Center for Research Resources; and by a Health of the Public Award from the Pew Charitable Trusts and the Robert Wood Johnson Foundation. Dr. Klag is an Established Investigator of the American Heart Association.

AUTHOR: Perneger, Thomas V.; Whelton, Paul K.; Klag, Michael J.

ABSTRACT: Background. People who take analgesic drugs frequently may be at increased risk of end-stage renal disease (ESRD), but the extent of this risk remains unclear.

Methods. We studied 716 patients treated for ESRD and 361 control subjects of similar age from Maryland, Virginia, West Virginia, and Washington, D.C. The study participants were interviewed by telephone about their past use of medications containing acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs). For each analgesic drug, the average use (in pills per year) and the cumulative intake (in pills) were examined for any association with ESRD.

Results. Heavier acetaminophen use was associated with an increased risk of ESRD in a dose-dependent fashion. When persons who took an average of 0 to 104 pills per year were used for reference, the odds ratio of ESRD was 1.4 (95 percent confidence interval, 0.8 to 2.4) for those who took 105 to 365 pills per year and 2.1 (95 percent confidence interval, 1.1 to 3.7) for those who took 366 or more pills per year, after adjustment for race, sex, age, and intake of other

analgesic drugs. When persons who had taken fewer than 1000 pills containing acetaminophen in their lifetime were used for reference, the odds ratio was 2.0 (95 percent confidence interval, 1.3 to 3.2) for those who had taken 1000 to 4999 pills and 2.4 (95 percent confidence interval, 1.2 to 4.8) for those who had taken 5000 or more pills. Approximately 8 to 10 percent of the overall incidence of ESRD was attributable to acetaminophen use. A cumulative dose of 5000 or more pills containing NSAIDs was also associated with an increased odds of ESRD (odds ratio, 8.8), but the use of aspirin was not.

Conclusions. People who often take acetaminophen or NSAIDs have an increased risk of ESRD, but not those who often take aspirin. (N Engl J Med 1994;331:1675-9.)

TEXT:

Analgesic nephropathy was first described in the 1950s n1. Phenacetin was subsequently identified as the chief culprit and was withdrawn from the market. Evidence of the nephrotoxicity of other analgesic drugs -- acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs) -- is scanty and inconsistent n2. In a prospective study of Swiss factory workers, subjects who took salicylates had no excess of kidney disease n3. Of four case-control studies, one n4 reported no association between the ingestion of analgesic drugs and end-stage renal disease (ESRD), but the others found associations between ESRD and salicylates, n5 pyrazolones, n5 aspirin, n6 acetaminophen, n6 n7 and NSAIDs n8.

None of these case-control studies were entirely population-based. In three, patients with ESRD were drawn from the general population but were compared with hospitalized control subjects, n4 n5 n6 and in the fourth study subjects from the general population were compared with hospitalized patients with chronic kidney failure n7 n8. Because hospitalized patients may differ from members of the general population in their analgesic-drug use regardless of the presence of kidney disease, the associations found in these studies between renal failure and the use of analgesic drugs may be spurious. We report here a case-control study of over-the-counter analgesic drugs as risk factors for ESRD in which both the case patients and the control subjects were drawn from the general population.

## Methods

The study protocol was approved by the institutional review boards at Johns Hopkins University and the Health Care Financing Administration.

### Study Participants

We studied residents of Maryland, Virginia, West Virginia, and Washington, D.C., who were 20 to 64 years old and had telephones in their homes. People who lived in institutions, were absent from their homes for more than two weeks, or were unable to complete the interview (because of deafness or a language

barrier) were excluded from the study.

The case patients had to have ESRD and had to have started long-term dialysis between January and July 1991. They were drawn from the Mid-Atlantic Renal Coalition, a population-based registry of patients with ESRD. Of 978 persons in the registry, 752 were eligible to participate. The others were excluded for the following reasons: 93 did not have a private telephone, 65 had died, 19 were institutionalized, 14 had moved out of the study area, 8 had recovered their renal function, 8 were too sick to be interviewed, 7 had hearing problems, 5 did not speak English, 5 were hospitalized for more than two weeks, and 2 were more than 64 years old. Of the 752 eligible persons, 716 (95 percent) were interviewed (of the others, 16 declined to be interviewed, 5 did not complete the interview, and 15 could not be reached). A median of five months elapsed between the start of therapy for ESRD and the time of the interview.

The control subjects lived in the same area as the patients n9 and were selected by random-digit dialing so that their age distribution matched that of the case patients. We sought to enroll half as many control subjects as case patients. Of 1311 residences reached by telephone, 1259 (96 percent) were screened for eligible residents, and 402 were found to contain one or more eligible residents. Of the remaining 857 households, 846 contained no members in the required age group, 7 contained no English-speaking respondents, 3 contained respondents who had difficulty hearing, and 1 contained a respondent who had ESRD. When several eligible control subjects lived in the same household, one was selected at random. Of the eligible control subjects, 361 (90 percent) completed the interview.

## Data Collection

Trained interviewers contacted potential participants by telephone, explained the purpose of the study, provided a telephone number to call for additional information, obtained informed consent, and asked a set of standard questions. The interview lasted 24 minutes on average. People who initially declined to participate were contacted again after two weeks; about 40 percent agreed to participate when approached a second time.

## Exposure Variables

The participants were asked separately about their lifetime exposure to the following five types of analgesic drugs, referred to by their common brand names: single drugs or mixtures containing acetaminophen, but not aspirin or phenacetin; single drugs or mixtures containing aspirin, but not acetaminophen or phenacetin; mixtures containing acetaminophen and aspirin, but not phenacetin; single drugs or mixtures that contained phenacetin before its withdrawal from the market; and common NSAIDs containing ibuprofen, naproxen, or indomethacin.

The list of NSAIDs was based on a review of over-the-counter medications sold in Baltimore pharmacies in 1990; indomethacin was included because it was one of the first NSAIDs on the market. The other lists of medications were based on an update of the information used by Sandler et al in their studies n7 n8. Phenacetin-based medications were identified in order to adjust the analysis for exposure to this substance known to be nephrotoxic.

For each type of analgesic drug, the study participants were asked whether they had taken one or more brands more than 10 times in their lives (before starting dialysis, in the case of the case patients). Those who said they had done so were asked about the average frequency of their analgesic-drug use (days per week, month, or year), the age at which they began to take the drugs regularly, and the average number of pills consumed per day when they took the drugs. Average intake (in pills per year) and cumulative intake (in pills, calculated as the average intake multiplied by the number of years since the first regular use) were computed. In the case of mixtures containing both acetaminophen and aspirin, the total consumption was considered to include equal amounts of each primary drug. Average intake was categorized as light (0 to 104 pills per year, or 0 to 2 pills per week), moderate (105 to 365 pills per year, or up to 1 pill per day), or heavy (366 or more pills per year, or more than 1 pill per day), and cumulative intake was categorized as low (0 to 999 pills), medium (1000 to 4999 pills), or high (5000 or more pills).

## Statistical Analysis

The case patients and control subjects were compared by cross-tabulation and logistic-regression modeling n10. Odds ratios were used to estimate relative risks. Tests of linear trend were performed when appropriate. Population-attributable risks were computed to estimate the potential effect of withdrawing a given analgesic drug on the incidence of ESRD n11. To examine the association of analgesic-drug use with different types of kidney disease, we used a five-level categorical outcome variable, with one level assigned to the control subjects and four levels assigned to the case patients according to the ascribed cause of ESRD: diabetes mellitus, hypertension, other specified causes, or no definite origin. The presumed cause of renal failure was based on each patient's recall of the diagnosis by his or her nephrologist. Polychotomous logistic-regression analysis n10 was used to analyze multilevel outcomes. All statistical tests were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance. The analyses were conducted with Systat software n12.

## Results

The case patients and the control subjects differed significantly with respect to sex and race. Of the 716 case patients, 304 (42 percent) were women; 310 (43 percent) were white, 384 (54 percent) were black, and 22 (3 percent) were of other races. Of the 361 control subjects, 235 (65 percent) were women; 303 (84 percent) were white, 51 (14 percent) were black, and 7 (2 percent) were

of other races. The age distributions were similar in the two groups (mean +/- SD , 47 +/- 12 years in both), indicating successful matching.

A majority of the study participants had taken analgesic drugs either sporadically or regularly. Of the case patients, 77 percent had taken acetaminophen, 77 percent had taken aspirin, and 31 percent had taken NSAIDs more than 10 times in their lives. Among the control subjects, the rates were 75 percent for acetaminophen, 86 percent for aspirin, and 46 percent for NSAIDs. Similar proportions of case patients (15 percent) and control subjects (17 percent) had taken analgesics that may have contained phenacetin.

## Frequency of Use

In the univariate analysis, heavy users of acetaminophen (more than 365 pills per year) had an increased risk of ESRD, whereas moderate users (105 to 365 pills per year) did not (Table 1). No statistically significant associations were noted for aspirin and NSAIDs. Adjustment for age, sex, race, and the use of other analgesic drugs strengthened the odds ratios for acetaminophen use and revealed a significant dose-response relation (P for linear trend, 0.009). In contrast, this adjustment weakened the associations of ESRD with the use of aspirin and NSAIDs.

*Table 1. Average Annual Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD in Maryland, Virginia, West Virginia, and Washington, D.C., in 1991 *.

**TABLE OMITTED**

## Cumulative Intake

The odds of ESRD increased with increasing cumulative intake of acetaminophen (Table 2), whereas persons who had taken 1000 to 4999 pills containing aspirin had a lower risk of ESRD than those with a lower cumulative intake. In contrast to heavy average intake, a high lifetime intake of NSAIDs was associated with a fourfold increase in the odds of ESRD. Although the confidence intervals were wide, the odds of ESRD were lowest with moderate intake of aspirin or NSAIDs. Adjustment for age, sex, race, and the intake of other analgesic drugs strengthened the associations between the cumulative intake of acetaminophen and ESRD (P for linear trend, <0.001) and between high doses of NSAIDs and ESRD.

*Table 2. Cumulative Lifetime Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD in Maryland, Virginia, West Virginia, and Washington, D.C., in 1991 *.

**TABLE OMITTED**

## Effect of Race

Black subjects reported less use of analgesic drugs than white subjects, but the associations between the use of analgesic drugs and the risk of ESRD did not differ according to race (data not shown). In analyses of both average and cumulative intake, adjustment for race accounted for most of the difference between the unadjusted and the adjusted results; this was due to the large disparity between blacks and whites in the base-line risk of ESRD.

## Risk Factors According to Cause of ESRD

The pattern of risk associated with a person's average intake of analgesic drugs differed little according to the causes of ESRD that we studied: diabetes mellitus, hypertension, any other specified cause, or no known cause (Table 3). Since there were only 20 patients with ESRD who had underlying diagnoses of interstitial nephritis, no separate analysis of that subgroup was performed. The patterns of risk associated with cumulative intake of analgesic drugs were also similar in the various subgroups (Table 4): a high intake of acetaminophen or NSAIDs was apparently harmful, whereas a medium intake of aspirin appeared to be protective.

*Table 3. Adjusted Odds Ratios and 95 Percent Confidence Intervals for the Average Annual Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD According to the Ascribed Cause of ESRD *.

**TABLE OMITTED**

*Table 4. Adjusted Odds Ratios and 95 Percent Confidence Intervals for the Cumulative Lifetime Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD According to the Ascribed Cause of ESRD *.

**TABLE OMITTED**

## Population-Attributable Risks

Estimation of the population-attributable risk of ESRD suggested that if each participant consumed fewer than 105 pills containing acetaminophen per year (fewer than 2 pills per week), the incidence of ESRD would decrease by 7.7 percent (Table 5). Changes in the average intake of aspirin and NSAIDs would have negligible effects on the incidence of ESRD. A reduction in lifetime acetaminophen use to fewer than 1000 pills could potentially lower the incidence of ESRD by 10.5 percent. Reducing the intake of aspirin would have the opposite effect, resulting in an increase in ESRD. These inferences assume that the observed associations (harmful in the case of acetaminophen and protective in the case of aspirin) are causal and correctly estimated.

*Table 5. Population-Attributable Risk of ESRD According to Average Intake and Cumulative Life-time Intake of Acetaminophen, Aspirin, and NSAIDs *.

**TABLE OMITTED**

## Discussion

This study revealed several meaningful relations between analgesic-drug use and ESRD. The strength of these relations may have been underestimated, because drug use was measured rather imprecisely. These findings pertain only to adults 20 to 64 years of age who survived for about six months after the initiation of ESRD therapy.

Both heavy average intake (more than 1 pill per day) and medium-to-high cumulative intake (1000 or more pills in a lifetime) of acetaminophen appeared to double the odds of ESRD. These findings support those in two previous reports n6 n7. In our study, the estimated odds ratio of ESRD associated with daily use of acetaminophen was lower than that reported by Sandler et al n7; unlike them, we report a significant dose-response gradient. These discrepancies may be explained by differences in study methods: Sandler et al n7 measured analgesic use more precisely than we did, and they enrolled hospitalized case patients and control subjects drawn from the community, interviewed proxy respondents, and included patients at various stages of renal insufficiency.

Acetaminophen use apparently increased the odds of ESRD in patients with a variety of underlying renal diseases, including diabetic nephropathy. This may reflect the fact that tubulointerstitial changes (the typical analgesic-mediated injury) influence the progression of damage in a variety of renal diseases n13. Alternatively, acetaminophen can harm the kidney through several different pathogenic pathways n2. Because the diagnoses of underlying kidney disease were not validated in our study, misclassification may have obscured the differences between the effects of different diseases.

The potential effect of acetaminophen use on the overall incidence of ESRD is considerable. If our estimated odds ratios are valid and the association between acetaminophen use and ESRD is causal, reduced consumption of acetaminophen could decrease the overall incidence of ESRD by approximately 8 to 10 percent. This is 10 times more than would be inferred from the prevalence of analgesic nephropathy in patients with ESRD, as diagnosed by attending physicians (1 percent among patients 20 to 64 years of age in the United States from 1987 through 1990 n14). If our estimates could be extrapolated to the entire United States (which may not be possible, given the geographic variability in analgesic use n2) and to all age groups, such a reduction would represent a savings of $ 500 million to $ 700 million in costs for ESRD care each year. Because estimates of analgesic use based on recall by participants may be subject to misclassification, n15 the population-attributable risks provided by this study may underestimate the true potential benefits of reducing or stopping the consumption of acetaminophen.

Establishing the causality of the association between acetaminophen use and ESRD is critical. The association was dose-dependent, specific (i.e., unlike the

associations between other analgesics and ESRD), consistent with several previous reports, and biologically plausible, since acetaminophen is a metabolite of phenacetin. Thus, several criteria for causality were fulfilled. Nevertheless, the temporal precedence of the presumed cause still needs to be demonstrated, and experimental evidence for causality produced.

Unlike acetaminophen, aspirin did not increase the risk of ESRD. This confirms the results from some studies, n3 n7 but not others n5 n6. In our analysis, the risk of ESRD was slightly lower in persons taking an annual average of 105 to 365 pills and significantly lower in those who took 1000 to 4999 pills in their lifetime, as compared with persons who took aspirin less often. It is unlikely that aspirin has a true protective effect against renal failure. The J-shaped association, also observed for NSAIDs, may occur because persons with renal insufficiency (who are at high risk of ESRD) abstain from using aspirin. Heavy aspirin users may take analgesic drugs for serious indications, such as intense, protracted pain, and may be less concerned than moderate users about potential renal side effects. We cannot verify this hypothesis, because we did not investigate the reasons for analgesic use.

We detected no increase in the risk of renal failure among daily users of NSAIDs. An association of this type has been reported for men more than 65 years old, n8 but the age limits we used precluded verification of that finding. On the other hand, we found a steep increase in the odds of ESRD in persons who consumed 5000 or more pills containing NSAIDs during their lifetime. Although this finding is based on few observations (only 18 case patients and 2 control subjects reported taking NSAIDs in these quantities), it arouses concern about the safety of persons taking large quantities of NSAIDs. Our results may underestimate the toxicity of NSAIDs, because we did not thoroughly explore the use of preparations obtained by prescription and because patients with progressive kidney insufficiency may have been discouraged from using this class of drugs.

Previous research suggests that NSAIDs cause renal damage in persons with renal insufficiency by lowering the glomerular filtration rate through an anti-prostaglandin effect n16 n17. However, all NSAIDs may not have the same renal effects: ibuprofen may be more nephrotoxic than sulindac or other drugs n16 n17.

This study questions the safety of long-term acetaminophen use (more than 2 pills per day, or more than 1000 pills overall) and of consumption of large quantities of NSAIDs, but it suggests that aspirin use confers little or no excess risk of renal failure. Public health authorities should consider more careful oversight of the long-term use of acetaminophen in the general population. Possible options include using warning labels on packaging or requiring a prescription to purchase large amounts of acetaminophen. Any such decision must consider the substantial beneficial effects of this analgesic drug and the possible adverse effects of restricting access to it, such as a switch

by habitual acetaminophen users to other medicines, including NSAIDs, whose safety may also be questionable. Meanwhile, people requiring large quantities of analgesic medicines and those at high risk of renal failure may be best advised to use aspirin for pain control.

We are indebted to Ms. Tamra Myers for data-collection management; to Mrs. Shirley Kritt and Mrs. Jennifer Sykes for interviewing; to our collaborators at the Health Care Financing Administration (Dr. Zermain Breidenbaugh, Dr. Paul Eggers, Mrs. Pamela Frederick, Ms. Michael McMullan, Mr. Paul Mendelsohn, and Mr. Izzy Oppenheimer) and at the Mid-Atlantic Renal Coalition (Mrs. Nancy Armistead and Ms. Arlene Skinner); and to Dr. Dale P. Sandler, of the Epidemiology Branch, National Institute of Environmental Health Sciences, for kindly sharing information about analgesic medicines on the market in the past several decades.

REFERENCES:

[ n1 ]. Spuhler O, Zollinger HU. Die chronisch-interstitielle Nephritis. Z Klin Med 1953;151:1-50.

[ n2 ]. Stewart JH, ed. Analgesic and NSAID-induced kidney disease. Oxford, England: Oxford University Press, 1993.

[ n3 ]. Dubach UC, Rosner B, Sturmer T. An epidemiologic study of abuse of analgesic drugs

effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). N Engl J Med 1991;324:155-60.

[ n4 ]. Murray TG, Stolley PD, Anthony JC, Schinnar R, Hepler-Smith E, Jeffreys JL. Epidemiologic study of regular analgesic use and end-stage renal disease. Arch Intern Med 1983;143:1687-93.

[ n5 ]. Morlans M, Laporte JR, Vidal X, Cabeza D, Stolley PD. End-stage renal disease and non-narcotic analgesics: a case-control study. Br J Clin Pharmacol 1990;30:717-23.

[ n6 ]. Pommer W, Bronder E, Greiser E, et al. Regular analgesic intake and the risk of end-stage renal failure. Am J Nephrol 1989;9:403-12.

[ n7 ]. Sandler DP, Smith JC, Weinberg CR, et al. Analgesic use and chronic renal disease. N Engl J Med 1989;320:1238-43.

[ n8 ]. Sandler DP, Burr FR, Weinberg CR. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. Ann Intern Med 1991;115:165-72.

[ n9 ]. Perneger TV, Myers TL, Klag MJ, Whelton PK. Effectiveness of the Waksberg telephone sampling method for the selection of population controls. Am J Epidemiol 1993;138:574-84.

[ n10 ]. Hosmer DW Jr, Lemeshow S. Applied logistic regression. New York: John Wiley, 1989.

[ n11 ]. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904-14.

[ n12 ]. Wilkinson L. SYSTAT: the system for statistics. Evanston, Ill.: SYSTAT, 1990.

[ n13 ]. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. Am J Kidney Dis 1992;20:1-17.

[ n14 ]. United States Renal Data System. USRDS 1993 annual data report. Bethesda, Md.: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1993.

[ n15 ]. Schwarz A, Faber U, Borner K, Keller F, Offermann G, Molzahn M. Reliability of drug history in analgesic users. Lancet 1984;2:1163-4.

[ n16 ]. Ciabattoni G, Cinotti GA, Pierucci A, et al. Effects of sulindac and ibuprofen in patients with chronic glomerular disease: evidence for the dependence of renal function on prostacyclin. N Engl J Med 1984;310:279-83.

[ n17 ]. Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison. Ann Intern Med 1990;112:568-76.

EXHIBIT I

:D PAPER

# Analgesic Effect of Delta-9-Tetrahydrocannabinol

RUSSELL NOYES, JR., M.D., S. FRED BRUNK, M.D., DAVID A. BARAM, M.D., and ARTHUR CANTER, Ph.D. Iowa City, Iowa

CRUDE preparations of cannabis sativa were recommended for a variety of painful conditions toward the end of the 19th century.[1-3] As analgesics they were regarded as especially effective in conditions having a large functional or psychic contribution to the pain such as migraine, dysmenorrhea, and the pain of terminal illness. Yet they proved no match for the potent and rapid acting narcotics and eventually lost favor because their effects were milder and less predictable. In contrast to the narcotics, however, their toxicity was observed to be low, their disturbance of vegetative functions minimal, and their potential for addiction practically nonexistent. Recent identification and synthesis of delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient of cannabis, has made systematic administration of the compound possible and has rewakened interest in its therapeutic potential.[4,5]

This preliminary investigation was designed to demonstrate an analgesic effect of orally administered THC in patients suffering from cancer pain. Its specific purpose was the identification of a dosage range within which the drug might relieve pain without at the same time producing disturbing toxic effects. Placebo and randomly allocated, graded doses of THC were administered to hospitalized cancer patients who volunteered for a trial of this medication.

## Materials and Methods

Ten cooperative subjects, eight women and two men, were selected for participation in this study from among advanced cancer patients being followed at the University of Iowa Hospital. These patients, having a mean age of 51 years and a mean weight of 62 kg, reported continuous pain of moderate severity that was attributable to their disease. Five patients suffered from carcinoma of the breast, two from malignant lymphoma, one from carcinoma of the cervix, one from carcinoma of the colon, and one from lymphoepithelioma. Patients receiving large doses of narcotics were excluded from the study although seven had received methadone as part of their regular analgesic regimen. All were admitted to the University of Iowa Clinical Research Center where they were maintained on their usual analgesic program. Each was informed that, while on the study, he would receive varied doses of the active ingredient in marijuana. Each was further advised that doses would not be of equal strength and that the objective of the study was to determine which were the most effective in relieving pain. Informed consent was obtained in writing from all patients.

Regular analgesics were withheld after 4:00 A.M., and test medications were administered once daily at approximately

From the Departments of Psychiatry and Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242. This study was supported by Grant RR-59 from the General Clinical Research Centers Program Division of Research Resources, National Institutes of Health, U.S.P.H.S.

8:30 A.M., 1 hour after eating. On successive days, placebo and 5, 10, 15, and 20 mg THC, all identical in appearance, were administered double blind in a random sequence.* A full-time registered nurse assigned to the study administered test medications and interviewed subjects hourly regarding the severity of pain and the extent of relief experienced. The categories of slight, moderate, and severe pain all represented subjective judgments on the part of the patients at the time of being interviewed. The nurse's observations, including evident or reported side effects, were recorded on a pain chart designed for that purpose.[6,7] This observer also administered an 11-item subjective effects questionnaire hourly and a side effects inventory at the end of each 6-hour observation period. The subjective effects questionnaire consisted of the following seven-point scales: sleepy–awake, energetic–fatigued, sad–happy, quiet–restless, sociable–unsociable, dreamy–clear-headed, calm–uneasy, alert–dull, worried–peaceful, time slowed–time speeded up, and trouble thinking–thinking clearly. Hourly recordings of blood pressure and heart and respiration rates were also made.

Hourly ratings of the severity of pain (0=absent, 1=mild, 2=moderate, and 3=severe) were used to arrive at hourly pain *reduction* scores. These scores were obtained by subtracting the hourly ratings from that recorded prior to the drug's administration. If, for example, severe pain was reported before the drug was given, then mild pain 3 hours afterward would be assigned a reduction score of two. Pain *relief* scores were recorded as follows: 0=none, 1=slight, 2=moderate, 3=a lot, 4=complete. The sum of hourly pain reduction or relief scores for a given 6-hour observation period (total reduction or relief scores) were used as a basis for statistical analysis. Hourly scores on the subjective effects questionnaire were assigned to the number of points a subject moved away from a predrug reference on a particular scale.

## Results

Table I shows mean total pain reduction and relief scores for placebo and THC. Application of Edward's method of trend analysis of variance revealed a significant trend toward progressive relief of pain with increasing doses of the drug ($P<0.001$).[8] Since a comparison of pain relief scores between adjacent dose levels yielded no significant differences, scores for combined low dose levels (5 and 10 mg) were compared with scores for combined high dose levels (15 and 20 mg).

Here, a significant difference in the expected direction of greater pain relief with high doses of THC was demonstrated ($P<0.025$, paired observation method). Due to the small number of patients and the variability between them, further statistical analysis of these data did not seem appropriate. Mean hourly relief scores for placebo and 10, 15, and 20 mg THC are plotted in Fig. 1. They show that the analgesic effect of THC developed gradually and was prolonged. While the

**TABLE I**

**Total Pain Reduction and Relief Scores Following Oral THC**

| Dose | Scores (mean ± S.E.) | |
|---|---|---|
| | Pain reduction | Pain relief |
| Placebo | 0.9 ± 0.30 | 2.6 ± 0.61 |
| THC, 5 mg | 2.6 ± 0.53 | 4.7 ± 0.95 |
| THC, 10 mg | 1.4 ± 0.42 | 4.4 ± 0.98 |
| THC, 15 mg | 3.6 ± 0.65 | 5.8 ± 0.84 |
| THC, 20 mg | 4.6 ± 0.66 | 10.8 ± 1.19 |

* Delta-9-tetrahydrocannabinol in capsules containing a sesame oil vehicle was obtained from the National Institute of Mental Health.

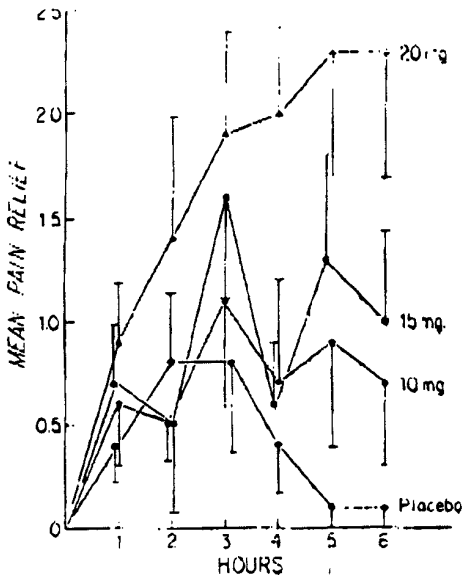


*Fig. 1. Mean (± standard error) hourly pain relief in ten patients following the administration of THC.*

peak effect occurred at 3 hours following 10 and 15 mg, it did not develop until 5 hours following a dose of 20 mg. A second peak observable at 5 hours after drug administration may have been the result of THC's mobilization from the gall bladder and reabsorption following food ingestion.[9] One patient with a lymphoepithelioma experienced no pain relief from THC at any dose. She differed from the others in having pain that was sharply localized, questionably related to her disease, and unresponsive to other analgesic medications. Five patients received substantial relief (total relief scores of greater than 6) from 15 mg and seven, from a dose of 20 mg.

Table II shows the frequency with which commonly experienced side effects were reported by the ten patients in this study. Patients receiving 20 mg THC were heavily sedated and even at 15 mg reported considerable drowsiness. This sedative effect was also apparent from responses on the subjective effects questionnaire. Table III shows total 6-hour change scores for three scales revealing a progressive reduction in arousal produced by the drug. Also shown in Table III is evidence of progressive mental clouding that made its appearance at 5 mg and became marked at 20 mg.

Other questionnaire scales showed no change. Euphoria was infrequently reported and was grossly evident in only two patients following the 15- and 20-mg doses. One of these was the only patient in the series giving a history of marijuana use. Several others reported minor elevations of mood when specific inquiry regarding such charges was made.

Both heart rate and blood pressure decreased following 15- and 20-mg doses of THC. The mean (± standard error) hourly decline in heart rate was 2.3± 1.93 beats per minute following 15 mg and 3.9±1.43 beats per minute following 20 mg. The mean hourly fall in blood pressure over the 6-hour observation was 11/7±1.48/1.31 mm Hg after 15 mg and 5/1±1.72/1.39 mm Hg following 20 mg. No change in respiration rate was observed.

## Discussion

This preliminary trial of THC on a limited number of patients has demonstrated an analgesic effect of the drug. Attempts to establish its potency relative to standard analgesics of mild to moderate strength such as aspirin and codeine appear warranted and are currently in progress. In a dose of 20 mg, the drug is highly sedating and, consequently, of limited value for most patients. Doses of 5 and 10 mg, which showed a trend toward pain relief greater than placebo, might or might not maintain their superiority in trials involving large numbers of patients.

In the setting of this experiment, THC demonstrated sedating effects in contrast

**TABLE II**

**Side Effects After Oral THC**

| Side effect | Number of patients experiencing side effects ($N=10$) | | | | |
|---|---|---|---|---|---|
| | 20 mg THC | 15 mg THC | 10 mg THC | 5 mg THC | Placebo |
| 1. Drowsiness | 10 | 7 | 5 | 7 | 3 |
| 2. Slurred speech | 8 | 8 | 4 | 4 | 2 |
| 3. Blurred vision | 7 | 7 | 4 | 2 | 0 |
| 4. Mental clouding | 6 | 7 | 4 | 5 | 2 |
| 5. Dizziness | 6 | 4 | 4 | 2 | 1 |
| 6. Headache | 4 | 3 | 5 | 5 | 2 |
| 7. Increased appetite | 4 | 5 | 5 | 2 | 0 |
| 8. Ataxia | 5 | 7 | 3 | 3 | 3 |
| 9. Dreaminess | 3 | 6 | 3 | 4 | 3 |
| 10. Disconnected thought | 5 | 1 | 2 | 2 | 0 |
| 11. Numbness | 4 | 3 | 2 | 1 | 0 |
| 12. Euphoria | 5 | 4 | 1 | 0 | 0 |
| 13. Visual hallucinations | 3 | 0 | 1 | 0 | 0 |
| 14. Tinnitus | 0 | 2 | 4 | 0 | 0 |

**TABLE III**

**Subjective Effects After Oral THC**

| Effect | Mean total deviations from predrug reference points on scales | | | | |
|---|---|---|---|---|---|
| | Placebo | 5 mg THC | 10 mg THC | 15 mg THC | 20 mg THC |
| Sedation | | | | | |
| 1. sleepy–awake | +6.5 | −4.4 | −4.9 | −6.8 | −9.8 |
| 2. fatigued–energetic | +1.6 | −2.1 | −2.2 | −6.9 | −7.0 |
| 3. dull–alert | +4.9 | −1.5 | −3.2 | −2.7 | −8.7 |
| Mental clouding | | | | | |
| 4. dreamy–clearheaded | +0.9 | −2.6 | −3.6 | −9.1 | −11.8 |
| 5. trouble thinking–thinking clearly | +2.2 | −3.3 | −3.8 | −6.7 | −6.7 |

to the stimulating ones commonly associated with its social use.[10] In place of heightened perception, numbness and pain reduction occurred; in place of euphoria and enhanced sociability, a dreamy social withdrawal developed. Associated with the latter, a fall in heart rate and blood pressure occurred in contrast to the increase in pulse which is typically reported.[11] Patients in this study were exposed to little stimulation, were relatively ill, and were, for the most part, socially isolated. These circumstances may well have been determinants of the drug's depressant effects.

Finally, the preliminary data reported here suggest that an association exists between the pain reduction caused by THC

and the reduction in arousal and attention produced by this drug. On the other hand, the reduction in pain appears to be independent of the compound's euphoric and antianxiety effects. Attempts to correlate physiologic measures of arousal and psychological assessments of attention with pain relief may provide clues to an understanding of the drug's mechanism of analgesic action.[12]

## Summary

A preliminary trial of oral delta-9-tetrahydrocannabinol (THC) demonstrated an analgesic effect of the drug in patients experiencing cancer pain. Placebo and 5, 10, 15, and 20 mg THC were administered double blind to ten patients. Pain relief significantly superior to placebo was demonstrated at high dose levels (15 and 20 mg). At these levels, substantial sedation and mental clouding were reported.

## References

1. Grinspoon, L.: Marihuana Reconsidered. Cambridge, Harvard University Press, 1971.
2. Mijuriya, T. H.: Historical aspects of cannabis sativa in western medicine. *New Physician* 18:902 (1969).
3. Synder, S. H.: Uses of Marihuana. New York, Oxford University Press, 1971.
4. Gaoni, Y., and Mechoulam, R.: Isolation, structure and partial synthesis of an active component of hashish. *J. Amer. Chem. Soc.* 86:1646 (1964).
5. Mechoulam, R., and Gaoni, Y.: A total synthesis of delta-9-tetrahydrocannabinol, the active constituent of hashish. *J. Amer. Chem. Soc.* 87:3273 (1965).
6. Houde, R. W., Wallenstein, S. L., and Beaver, W. T.: Evaluation analgesics in patients with cancer pain. *In* International Encyclopedia of Pharmacology and Therapeutics, Section 6, Volume 1, Lasagna, L., Ed., Clinical Pharmacology. New York, Pergamon Press, 1966.
7. Keele, K. D.: The pain chart. *Lancet* 2:6 (1948).
8. Edwards, A. L.: Experimental Design in Psychological Research. New York, Rinehart, 1960, pp. 224–227.
9. Dewey, W. L., and Turk, E. F.: The excretion and metabolism of 3H-delta-9-THC in intact and bile-duct cannulated rats. *Fed. Proc.* 31:506 (1972).
10. Hill, S. Y., Goodwin, D. W., Schwin, R., and Powell, B.: Marijuana: central nervous system depressant or excitant? *Amer. J. Psychiat.* 131:313 (1974).
11. Kiplinger, G. F., Manno, J. E., Roddan, B. E., and Forney, R. B.: Dose response analysis of the effects of tetrahydrocannabinol in man. *Clin. Pharmacol. Therap.* 12:650 (1971).
12. Paton, W. D. M., and Pertwee, R. G.: The actions of cannabis in man. *In* Marijuana, Mechoulam, R., Ed. New York, Academic Press, 1973, p. 329.

EXHIBIT J

Psychopharmacology 49, 79 – 84 (1976)

Psycho pharmacology


# Effects of Marihuana Use on Body Weight and Caloric Intake in Humans

ISAAC GREENBERG*, JOHN KUEHNLE, JACK H. MENDELSON, and JERROLD G. BERNSTEIN

Alcohol and Drug Abuse Research Center Harvard Medical School, McLean Hospital, Belmont, Massachusetts, U.S.A.

*Abstract.* Body weight and caloric intake were measured in a group of heavy and casual marihuana users prior to, during and following 21 days of marihuana smoking under research ward conditions. A group of control subjects were studied under identical conditions, but they did not smoke marihuana. Both heavy and casual marihuana users had a significant increase in caloric intake and gained weight during the marihuana smoking period. Heavy and casual users gained an average of 3.7 and 2.8 lbs respectively during the first 5 days of marihuana smoking. In contrast, control subjects gained only a small amount of weight (0.2 lbs) during the same time interval. Water retention did not appear to be a major factor in weight gain by the marihuana users. These findings are in agreement with both anecdotal reports and previous experimental data that marihuana use is associated with increased caloric intake and weight gain.

*Key words:* Marihuana smoking – Weight gain – Experimental setting – Caloric intake.

Marihuana is commonly believed to enhance food intake in man. Anecdotal accounts of increased food ingestion associated with marihuana smoking (Siler et al., 1933; Haines and Green, 1970; Snyder, 1971) have only recently been assessed in clinical studies (Hollister, 1971; Williams et al., 1946). Hollister (1971) found that subjects ingested more of a chocolate milkshake preparation after 0.5 mg/kg oral delta-9 THC than after placebo. When offered the milkshake 3 h post-drug, marihuana subjects consumed 731 ml vs. 503 ml ingested by the placebo group. Chronic exposure to marihuana (39 days) or pyrahexyl, a THC analogue, (28 days) was also associated with weight gain (Williams et al., 1946).

In a recent study, Regelson et al. (1974) administered delta-9 THC to patients with cancer to determine if the drug would retard chronic weight loss. In a preliminary communication, these investigators report the delta-9 THC appeared to stimulate appetite and the patients gained weight. However, no data concerning amount of weight gained or calories ingested was reported.

The present study was part of a larger group of experiments designed to assess the effects of chronic marihuana use on various biological and behavioral functions (Mendelson et al., 1974). This report focuses upon the influence of marihuana smoking on food intake and body weight.

## METHODS

*Subjects.* Male volunteers were recruited through advertisements placed in local newspapers. Psychiatric and medical examinations were carried out, and only those subjects in good physical and mental health were selected for participation in the study. Twelve 'casual' and fifteen 'heavy' marihuana users were studied compared with ten subjects who served as controls.

Casual users reported a mean duration of 5.3 years marihuana use with a monthly smoking frequency of 11.5 times. Heavy users reported a mean duration of marihuana use of 5.6 years and a monthly smoking frequency of 42 times. Both groups were matched as closely as possible with regard to socioeconomic background, intelligence and level of education. Further background information about the subjects is presented in Table 1.

Ten control subjects were exposed to identical ward conditions. These subjects had a past history of casual alcohol use and could work for money or alcohol on the research ward. Control subjects did not have access to marihuana or other drugs. As Table 1 indicates, the backgrounds of the control subjects were comparable to the casual marihuana users in all relevant respects. During the study they drank virtually no alcohol (average 1/5 oz. per day) and therefore qualify as drug-free controls.

*Marihuana.* All marihuana smoking had to be done at time of cigarette purchase, under the observation of a staff member.

* *Send offprint requests to:* Isaac Greenberg, Ph.D., Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill Street, Belmont, Mass. 02178, U.S.A.

Table 1. Background characteristics and previous drug-taking experience: casual and heavy marihuana smokers

| | Casual users ($N = 12$) | | Heavy users ($N = 15$) | | Controls ($N = 10$) | |
|---|---|---|---|---|---|---|
| | Mean | (SD) | Mean | (SD) | Mean | (SD) |
| Age | 23.3 | (1.1) | 23 | (1.6) | 23 | (1.5) |
| Years formal education | 14.5 | (1.4) | 13.6 | (1.5) | 15.1 | (1.6) |
| Years used marihuana | 5.3 | (1.1) | 5.6 | (1.9) | 6.4 | (2.3) |
| Marihuana use (times/mo) | 13.0 | (6.2) | 41.0 | (26.4) | 3.4 | (1.3) |
| Alcohol use (times/mo) | 9.3 | (8.0) | 19.9 | (10.0) | 6.9 | (4.1) |

A detailed report of the experimental analysis of marihuana acquisition and use has been presented elsewhere (Mendelson et al., 1972). Unused portions of smoked marihuana cigarettes were returned to the staff to insure that 'roaches' were not accumulated and smoked without staff knowledge. Since studies were carried out on an inpatient hospital research ward, staff were able to insure that subjects did not use drugs other than marihuana.

Cigarettes containing approximately 1 g of marihuana were obtained from the National Institute of Mental Health (NIMH) in lot standard dosage form. Each cigarette contained approximately 1.8–2.3% THC as assayed by the NIMH. Actual content analysis of the marihuana using ethanol-Soxhlet and Modified Lerner extraction procedures was as follows: cannabidiol, 0.18% ± 0.04%, $\Delta^8$THC, 0.002, $\Delta^9$THC, 2.06% ± 0.08%, cannabinol, 0.08% ± 0.012%.

*General Design.* The investigation was carried out on a four-bed clinical research ward of the Alcohol and Drug Abuse Research Center at the McLean Hospital. Each study consisted of three consecutive phases: (1) a pre-drug 5-day baseline, (2) a 21-day period during which marihuana (or alcohol for control subjects) was available, and (3) a post-drug period of 5 days duration. All other conditions were identical for the marihuana and for the alcohol control subjects.

Food was prepared in the cafeteria of McLean Hospital and was brought to the research ward and served by nurses or mental health workers. The type and amount of food eaten was recorded and caloric intake calculated. Subjects were also permitted to choose their favorite snack foods and both the cafeteria and snack foods were supplied free to the subjects. Body weight was recorded each morning at 8:00 a.m. Urine samples were collected on a 24-h basis for all the casual and 11 of the 15 heavy marihuana users.

## RESULTS

Daily body weight and caloric intake are reported for the heavy and casual users and the control group. Changes in body weight and caloric intake during successive 5-day periods of the study were analyzed with paired *t*-tests. Comparisons were made between the pre-drug control period and the first 5 drug days (study days 6–10) and also between the last five drug days (study days 22–26) and the post-drug phase. Body weights were obtained at 8:00 a.m. and represent food consumption during the previous day. Thus, post-drug body weights are plotted for a 4-day (days 28–31) rather than a 5-day (days 27–31) period in Figure 1.

Heavy marihuana users showed a significant ($P < 0.01$) increase in caloric intake and body weight following initiation of drug use (Fig. 1). Although body weight continued to increase during the drug phase, caloric intake decreased, but remained above baseline pre-drug levels. Upon termination of the smoking phase of day 26, both body weight and caloric intake decreased significantly ($P < 0.01$). The number of marihuana cigarettes smoked per day, displayed across the top of Figure 1, progressively increased during the 21-day drug phase; there was no clear relationship, however, between the number of marihuana cigarettes smoked by any single subject and the amount of food consumed. In fact, as Figure 1 indicates, the highest weight gains during the first five drug days corresponded to the least amount of marihuana use (4.29 cigarettes per day).

The casual user group (Fig. 2) also demonstrated increases in both body weight and caloric intake. Both measures increased significantly during drug availability and use ($P < 0.05$) and caloric intake decreased significantly following cessation of marihuana use ($P < 0.01$). However, body weight loss following cessation of marihuana use did not reach a statistically significant level. As with the heavy user group, no clear dose-weight relationship emerged for any subject. Once more, the high initial increases in body weight corresponded with relatively low levels of drug use (2.02 cigarettes per day).

Control subjects (Fig. 3) sustained monotonic increases in both body weight and caloric intake during the 30-day study. This pattern is in sharp contrast to the curvilinear changes seen in both marihuana groups. Further, the magnitude of weight and caloric intake changes in the control subjects was well below that seen in the marihuana groups. Weight gain comparisons between either marihuana group and the control group were statistically significant. (Casual users vs. control: $t = 4.13$, $P < 0.005$; heavy users vs. control: $t = 4.09$, $P < 0.005$.) The control sub-

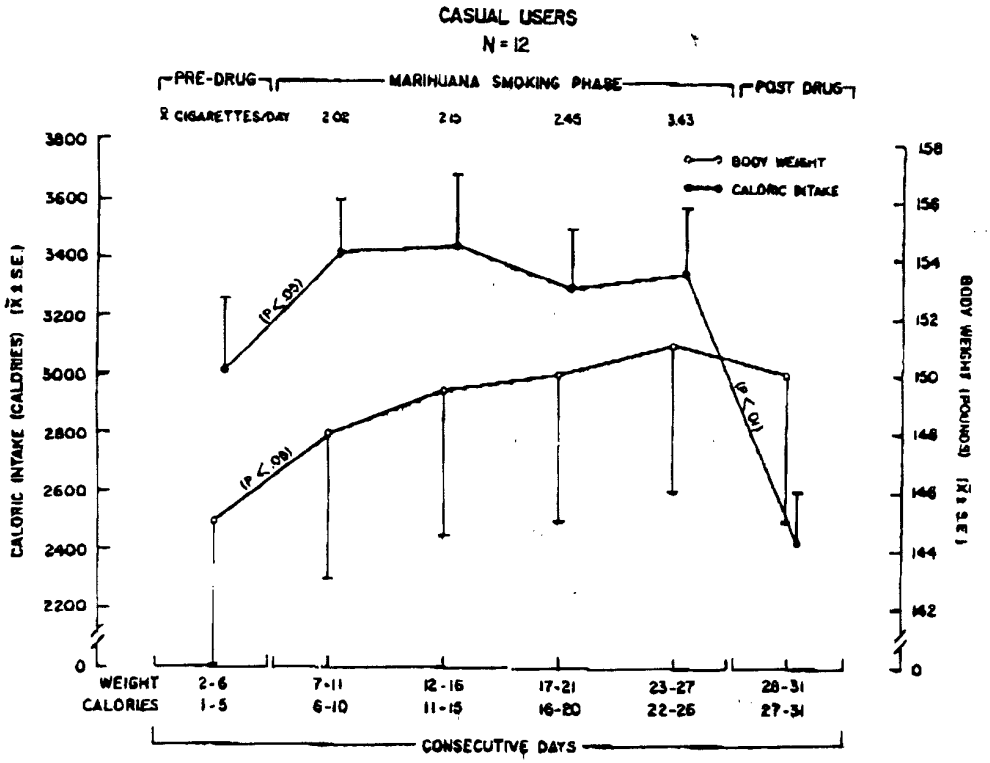


Fig. 1. Casual users ($N = 12$) patterns of body weight (O----O) and caloric intake (● ●) are shown for consecutive 5-day blocks (see text). All points are group means ± standard error of the mean. At top of figure, the mean daily number of marihuana cigarettes smoked is listed for each 5-day period

jects continued to ingest food in increasingly greater amounts during the last five days of the study, while both marihuana groups had significantly depressed food ingestion levels during this period of time.

To determine if fluctuations in body-weight might be due to water retention, urine volume output was plotted as a function of time and drug phase (Fig. 4). If water retention were a function of drug use, urine volume output should have decreased upon initiation of marihuana use and should have increased with cessation of marihuana use. However, the opposite phenomena was found in the twelve casual and eleven heavy users, indicating that increased fluid intake paralleled increased food intake.

## DISCUSSION

Results obtained in this study are in agreement with the findings of others on acute (Hollister, 1971) and chronic (Williams et al., 1946) effects of marihuana use on food ingestion. Hollister (1971) found that increased caloric consumption associated with acute delta-9 THC administration could be measured 3 h following drug administration. Williams et al. (1946) found that an increase in body weight occurred during a 39 day period of marihuana use. Caloric intake, however, only increased in a transient manner and then fell steadily to below pre-drug baseline levels. Evaluation of these data is difficult since the type, content and potency of the marihuana preparation smoked is not specified. Moreover, control groups were not studied to determine if non-drug related variables such as experimental setting, prison routine, type of food available, eating schedules, etc., had any influence on patterns of food ingestion. In the present study, high caloric intake was recorded throughout the smoking period for casual users, but showed a trend toward a sustained decrease below initial values for the heavy users. Since marihuana was available in our study for 21 days (vs. 39 days as described by Williams et al., 1946), it is possible that a longer period of marihuana availability would produce an initial increase followed by a depression of caloric intake.

A possible reason for a relative decrease in caloric intake after a significant initial increase at the onset of marihuana smoking may be related to gradual

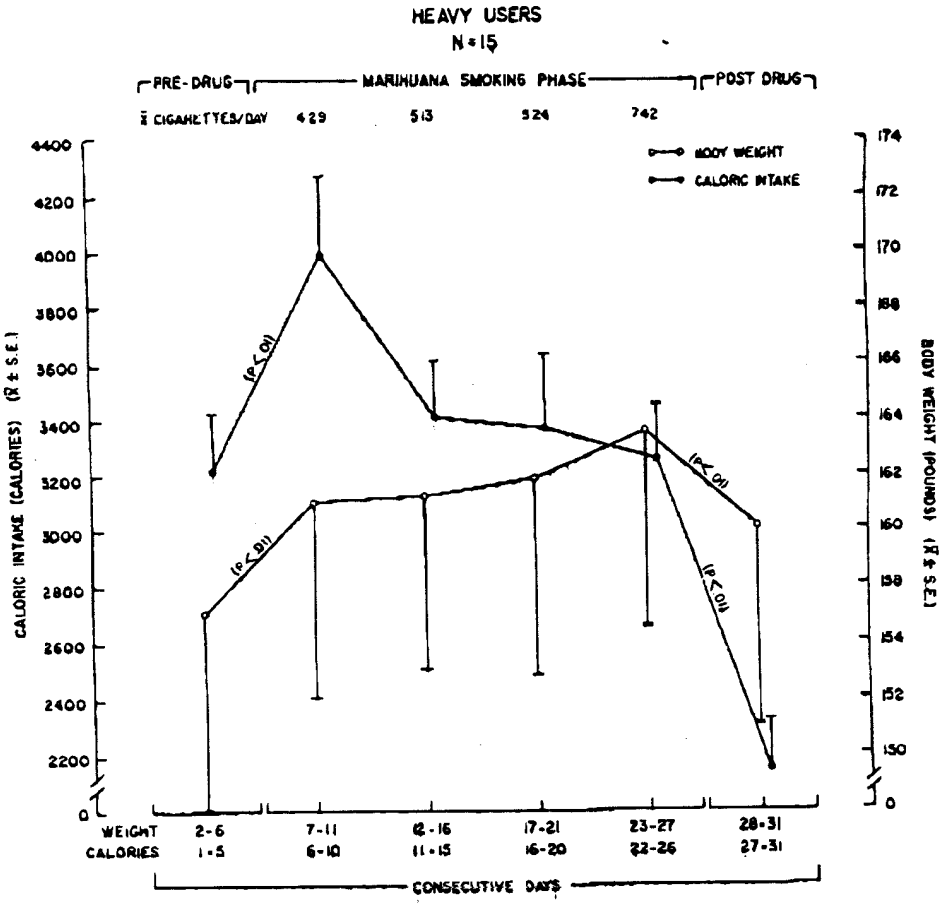


Fig. 2. Heavy users ($N = 15$) patterns of body weight (O O) and caloric intake (● ●) are shown for consecutive 5-day blocks (see text). All points are group means ± standard error of the mean. At top of the figure, the mean daily number of marihuana cigarettes smoked is listed for each 5-day period

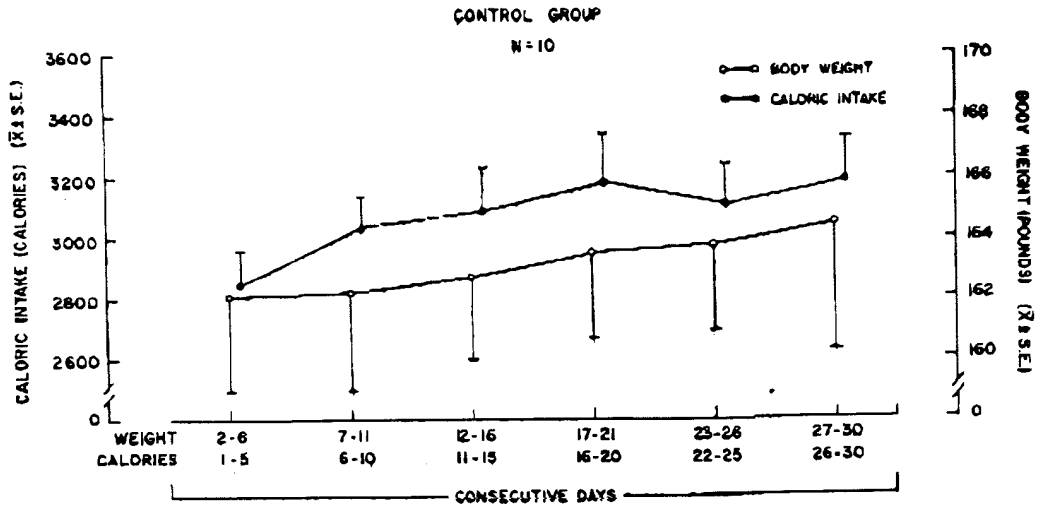


Fig. 3. Non-smoking controls ($N = 10$) patterns of body weight (O O) and caloric intake (● ●) are shown for consecutive 5-day blocks (see text). All points are group means ± standard error of the mean

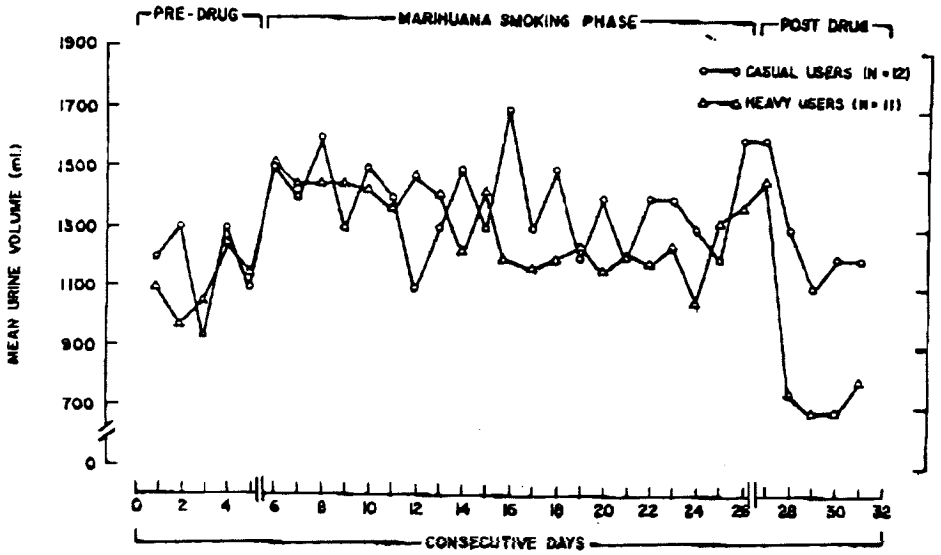


Fig. 4. Heavy (Δ——Δ) ($N$ = 10) and casual (O——O) ($N$ = 12) user urine volume output as a function of experimental phase

development of marihuana tolerance. It is also possible that the initial increase in food intake at the beginning of the marihuana smoking phase may have generated aversive consequences (e.g., fear of being overweight) and induced subjects to reduce food intake during subsequent marihuana smoking. In fact, subjects often verbalized their concern about gaining too much weight, but when overt dieting was reported, it began during the 5-day post-smoking period.

Control subjects gained very little weight as the study progressed. Increases averaged just over two pounds during 30 days and showed a linear trend. This phenomena might be expected considering restricted ward environment and the availability of free food.

Although there was no clear evidence that marihuana use resulted in marked fluid retention, this possiblity cannot be entirely ruled out. Benowitz and Jones (1975) have recently reported that weight gain in subjects administered daily $\Delta^9$ THC may have been due to fluid retention and plasma volume expansion. Caloric intake was not presented in their report. The subjects in the present study showed clear changes in caloric consumption accounting for at least part of the significant weight changes. More detailed studies of total body water content are now being conducted to determine how caloric intake and changes in body water influence the weight of marihuana users.

Following administration of either pyrahexyl or delta-9 THC, rats show a decrease in food intake and in body weight (Abel and Schiff, 1969; Manning et al., 1971; Sjoden et al., 1973; Sofia and Barry, 1974). Why marihuana administration depresses food intake in laboratory animals but elevates caloric intake in humans remains unknown. Dosage factors may be as important as species differences. Human subjects control the amount of marihuana they smoke, while animals are usually given dosages proportionately many times greater than those used by humans (Elsmore and Fletcher, 1972). In the single report of THC- or marihuana-related weight gain in animals, rats were first adapted to a deprivation schedula for 150 days and then given delta-9 THC (Gluck and Ferraro, 1974). Under these conditions, rats consumed food during their daily 1 h access period in contrast to non-drug conditions. Thus, long-term adaptation to limited food access may be a necessary prerequisite for marihuana-related enhanced food intake in animals. Humans are under no such deprivation schedule, and the seemingly contradictory results between humans and laboratory animals may due be to species differences or to variables which, to date, have not been identified.

*Acknowledgements.* This study was supported, in part, by Contract No. DADA17-73-C-3082 from the Department of the Army and Grant No. DA4RG010 from the National Institute on Drug Abuse, ADAMHA.

We wish to thank Miss Lorraine DeRubeis for her assistance in data analysis.

## REFERENCES

Abel, E. L., Schiff, B. B.: Effects of the marihuana homologue, pyrahexyl, on food and water intake, and curiosity in the rat. Psychon. Sci. 16, 38 (1969)

Benowitz, N. L., Jones, R. T.: Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. Clin. Pharmacol. Ther. 18, 287–297 (1975)

Elsmore, T. F., Fletcher, G. V.: Aversive effects in rat at high doses, $\Delta^9$-tetrahydrocannabinol. Science 175, 911–912 (1972)

Gluck, J. P., Ferraro, D. P.: Effects of $\Delta^9$ THC on food and water intake of deprivation experienced rats. Behav. Biol. 11, 395–401 (1974)

Haines, L., Green, W.: Marijuana use patterns. Brit. J. Addict. 65, 347–362 (1970)

Hollister, L. E.: Hunger and appetite after single doses of marihuana, alcohol, dextroamphetamine. Clin. Pharmacol. Ther. 12, 44–49 (1971)

Manning, F. J., McDonough, J. H., Jr., Elsmore, T. F., Suller, C., Sodetz, F. J.: Inhibition of normal growth by chronic administration of delta-9 tetrahydrocannabinol. Science 174, 424–426 (1971)

Mendelson, J. H., Meyer, R. E., Rossi, A. M., Bernstein, J. G., Patch, V. D., Babor, T. F., Reed, H., Salzman, C., Becker, D.: In: Marihuana: A signal of misunderstanding, Technical Papers 1, 68, U.S. Government Printing Office (1972)

Mendelson, J. H., Kuehnle, J. C., Ellingboe, J., Babor, T. F.: Plasma testosterone levels before, during and after chronic marihuana smoking. New Engl. J. Med. 291, 1051–1055 (1974)

Regelson, W., Butler, J. R., Schultz, J., Kirk, T., Peck, L., Green, M. L.: Delta-9 tetrahydrocannabinol (Delta 9-THC) as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. Paper read at International Conference on the Pharmacology of Cannabis, Savannah, Ga. (1974)

Siler, J. F., Sheep, W. L., Bates, L. B., Clark, G. F., Cook, G. W., Smith, W. A.: Marijuana smoking in Panama. Milit. Surg. 269–280 (1933)

Sjoden, P., Järbe, T., Henrikksson, B.: Influence of tetrahydrocannabinol ($\Delta^8$-THC and $\Delta^9$-THC) on body weight, food, and water intake in rats. Pharmacol., Biochem. Behav. 1, 395–399 (1973)

Snyder, S. H.: Uses of marijuana. New York: Oxford University Press 1971

Sofia, R. D., Barry, H.: Acute and chronic effects of $\Delta^9$-Tetrahydrocannabinol on food intake by rats. Psychopharmacologia (Berl.) 39, 213–222 (1974)

Williams, E. G., Himmelsbach, C. K., Wikler, A., Ruble, D. C.: Studies on marijuana and pyrahexyl compound. Publ. Hlth. Rep. (Wash.) 61, 1059–1083 (1946)

*Received February 2, 1976; Final Version April 15, 1976*

**EXHIBIT K**

**EXHIBIT K, *IN DRUGS BETWEEN RESEARCH AND REGULATIONS*, IS A BOOK. DEFENDANTS WILL PROVIDE A COPY OF THIS BOOK TO THE COURT UPON REQUEST**

**EXHIBIT L**

# Specialty Conference

## N-of-1 Clinical Trials

### A Technique for Improving Medical Therapeutics

*Discussant*
ERIC B. LARSON, MD, MPH, *Seattle*

*This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Paul G. Ramsey, MD, Associate Professor of Medicine, and Philip J. Fialkow, MD, Professor and Chair of the Department of Medicine.*

ERIC B. LARSON, MD*: Most clinicians have a keen interest in therapeutics and especially therapeutic efficacy. In fact, medical therapeutics can be viewed as a series of therapeutic experiments as follows:

| *A* | | | | *B* |
|---|---|---|---|---|
| Initial State | → | Therapy | → | Subsequent State |

The patient comes to the physician in an initial state, *A*, and is offered treatment. The patient then assumes a subsequent state, *B*.[1] If *B* is more desirable, we typically judge that therapy was effective. If *B* is no different or is less desirable, we judge that therapy made no difference or was ineffective. Although this account seems straightforward, such simple assertions may not be true because of confounding factors.[2]

Effectiveness may be overestimated because of several factors. First, a patient can recover spontaneously coincident with treatment, an especially well-known occurrence for self-limited conditions. Second, patients commonly present when their symptoms are worse, especially patients with a chronic disease. Coincidental treatment appears to cause the problem to subside when the patient has simply returned spontaneously to the average, so-called baseline state of a chronic disease. This has been referred to as "regression toward the mean."[3] A third factor that may lead to an overestimation of effectiveness is a placebo effect. For some therapies, as much as 30% or more of the benefits may be due to the well-known placebo effect.[4] Finally, the expectation of a beneficial response and a willingness-to-please effect[5] are related to the placebo effect. In many patients, the simple "expectation" that a treatment will be beneficial may often be sufficient to promote a beneficial effect. The willingness-to-please effect results from the so-called obsequiousness bias[5] in which a patient gets better to please an expectant physician.

Similar confounding forces can obscure therapeutic effectiveness. Coexistent illness can coincidentally exacerbate the underlying problem. Chronic diseases have spontaneous exacerbations, and when these occur coincident with treatment, it appears that therapy is ineffective. Malingering or a secondary gain in which the patient experiences benefit from not getting better can make a patient resistant to the true effect of treatment. An age-related (physiologic) decline superimposed on a beneficial treatment effect may combine to cancel each other. Finally, if an incorrect diagnosis has been made, treatment will appear to be ineffective. For example, if a patient's symptoms or signs represent the upper or lower limits of a normal variation, then the treatment received, although usually effective, is ineffective in the misdiagnosed case.

### Randomized Clinical Trials

Fortunately, randomized clinical trials (RCTs) have been used to evaluate medical therapeutics since the late 1940s.[6] Because such trials help eliminate the confounding factors outlined above, they have become the gold standard by which clinicians judge therapeutic efficacy. An RCT allocates consecutive patients to different treatments or randomly allocates the order of treatment in crossover experiments. When done carefully with enough patients, the randomization eliminates bias that might confuse the interpretation of the therapeutic experiment.

Unfortunately, many of a clinician's day-to-day treatment decisions cannot be based on the results of randomized trials. Table 1 shows examples of situations or problems in which RCTs may not be appropriate for making therapeutic choices. Unavailability of randomized clinical trials may be encountered in the case of a rare or unusual disease. Randomized trials may also not be available for some older treatments and for newer or novel treatments. Because RCTs have been widespread only since 1970, older treatments were often not evaluated by them. Newer or novel treatments, especially those devised by clinicians for single patients, are typically not subjected to randomized trials.

Even when there are good randomized trials showing efficacy, several factors limit their generalizability to a specific patient. For example, the patient might be outside the eligibility requirements for entry into an RCT. Eligibility criteria for most trials are so restrictive that less than 10% of patients with the disease in question may be accepted. Not surprisingly, the patients who are excluded are the ones in whom therapeutic dilemmas and an evaluation of therapeutics are often the most troublesome. Thus, their omission

*Professor of Medicine, Department of Medicine, and Medical Director, University of Washington School of Medicine, Seattle.

(Larson EB: N-of-1 clinical trials—A technique for improving medical therapeutics [Specialty Conference]. West J Med 1990 Jan; 152:52-56)

This work is supported by grant 1 RO3 HS 6006 from the National Center for Health Services Research and Health Care Technology Assessment.
Reprint requests to Department of Medicine, RG-20, University of Washington School of Medicine, Seattle, WA 98195.

TABLE 1.—*Limits of Randomized Clinical Trials (RCTs) for Care of Individual Patients*

| |
|---|
| RCT unavailable or impossible |
| Good RCTs show benefit but may not be generalizable |
| Eligibility criteria too restrictive |
| Some patients are nonresponders |
| Side effects |
| Good RCTs show *no* benefit but may not be generalizable |
| Atypical patients |
| Treatment response is idiosyncratic |

from RCTs allows investigators to assess efficacy with fewer complicating factors. Another problem arises from the fact that even though a randomized trial has shown efficacy, not all patients will benefit from treatment. In addition, some patients may experience enough side effects that the net effect of treatment is harmful. The single patient who does not have a beneficial response experiences that event with 100% certainty even when generalizations based on populations studied by RCTs indicate the net effects are likely to be beneficial.

There are also limits to the generalizability of RCTs that show no apparent benefit. Good randomized clinical trials may not show any net benefit, but an individual patient may still benefit from treatment, especially if the treatment has biologic plausibility. Some RCTs have inadequate sample sizes and, hence, inadequate statistical power to show efficacy.[7] An individual patient could also be an atypical responder, or responsiveness to treatment may be idiosyncratic and difficult to demonstrate by an RCT.

In summary, even though randomized clinical trials are widely used for assessing therapeutic efficacy, their results may not apply to single patients or they may be unavailable for certain treatments, thus leaving clinicians in a quandary about therapeutic efficacy. Because of this quandary, there is increasing interest in single-patient experiments. A number of terms have been used to describe single-patient experiments, including N-of-1 trials, single-patient clinical trials, single-case analysis, crossover and self-controlled research designs, and single-patient RCTs. The field has an interesting history and holds great promise for improving the science of medical therapeutics.

## Case Reports

Because case reports can be useful ways to illustrate valuable clinical lessons, I will present three single-case analyses in the order of my exposure to them. The first, a "case report" presented at the American Federation of Clinical Research meetings in 1985, was the case that piqued my interest in single-patient trials.[2] The second, a classic case that occurred at the interface of the developing science of statistics and popular culture, is intriguing for both its contents and the statistical power of its design.[8] The final case illustrates a single-case clinical trial that, although not random and only "single blinded," was convincing and influential.[9]

The first case was reported by Guyatt and co-workers from McMaster University, Hamilton, Ontario.[2] The patient, a 65-year-old man with uncontrolled asthmatic bronchitis, was becoming progressively more disabled by dyspnea with even simple daily activities. His therapeutic regimen eventually consisted of albuterol inhaler, ipratropium bromide, theophylline, and daily doses of prednisone. The clinician and the patient were uncertain whether the theophylline or ipratropium therapy was beneficial. Both suspected that theophylline was helpful and ipratropium was not. To optimize the therapeutic regimen, a single-patient trial was designed. Either theophylline or placebo, in a random order, was given for ten-day crossover periods. Three 10-day crossover pairs were planned. The end points included dyspnea, the need for albuterol inhaler, and the amount of sleep disturbance. During the first period, the patient did better than during the second ten days of the crossover trial. The same pattern then appeared during the second crossover period. The trial, which was originally scheduled to go for three crossover periods (about 60 days), now seemed too long to both the clinician and the patient. Both agreed that the trial should be terminated, presumably to allow the patient to resume taking theophylline. They were surprised when the placebo was associated with scores indicating increased well-being. Based on a review of the literature and the patient's course, it was determined that the seemingly anomalous results were most likely explained by gastroesophageal reflux (a xanthine side effect) and aspiration.[10] The theophylline therapy was stopped, and subsequently an N-of-1 trial of ipratropium revealed the beneficial therapeutic effects of its use. Eventually the patient was treated with a regimen of albuterol and ipratropium. He then tolerated a prednisone taper so that he could comfortably complete most of his activities of daily living on a regimen of 10 mg of prednisone every other day.

The second "case report" is not a medical case but represents a particularly famous single-case experiment. The case was an important one in the development of principles of experimentation and illustrates some useful points about randomization and statistical power. In 1935, R. A. Fisher, a British statistician whose name is most often linked with multiple-subject experiments, reported an example of how to conduct an experiment with a single subject and used that example to explain basic notions that underlie all experiments. This was the "lady tasting tea experiment."[8]

The case involved a tea-drinking English woman who claimed that she could tell whether the tea was added to the milk or the milk was added to the tea. Four cups of tea were prepared one way and four cups the other way, and the eight cups were then presented to her in a random sequence. She was told in advance that she was to identify the four cups that were prepared each way. The lady correctly identified all eight cups, and the $P$ value was determined by the randomization test procedure. The null hypothesis was that her response at any treatment time was the same as it would have been at that time if any of the other cups had been presented. There are $8!/4!4! = 70$ ways in which eight cups can be presented with respect to milk first or tea first, given that four cups were milk first and four tea first. Thus, Fisher computed the $P$ value as 1/70 because only 1 of the possible sequences of 4 *M*s and 4 *T*s correctly matched the woman's responses ($P = .014$).

An important feature of this experiment, in contrast to the first case report, is that the randomization occurred in blocks of eight treatments, not blocks of two as in the typical crossover experiment. Thus, the statistical power was considerably greater.

The third case report is a more primitive example of a single-patient trial.[9] Nonetheless, it also shows the value of single-patient experimentation. The report entitled "Inter-

nal-Mammary-Artery Ligation for Coronary Insufficiency—An Evaluation" was based on a presentation made in 1957 to the New England Surgical Society. This topic would later be investigated in a widely quoted article from the University of Washington describing a randomized, single-blind trial that compared a sham operation with internal mammary ligation.[11] Ralph Adams, MD, in the 1958 paper,[9] reported four cases, one of which was of a 60-year-old man admitted "three days after occurrence of his known episode of coronary thrombosis."

> His case was well known to the hospital because of previous attacks of deep thrombophlebitis, pulmonary embolism and hypercholesterolemia, and prior episodes of coronary occlusion. Precordial pain was intense and he was apprehensive that he would die. He was a highly educated man, well informed for a layman, on medical matters and in a position of considerable community responsibility. Admission was for the specific purpose of altering internal mammary circulation in the hope of giving him some cardiac protection. He was told . . . that this procedure was currently being widely discussed and, in some quarters, enthusiastically recommended. He was also informed that the hospital was in the process of evaluating the procedure as definitely as possible. These background facts led him to request that the operation be tried in the hope that he might be helped. . . .
>
> At operation, on the day of admission, a short incision was made in the second intercostal space lateral to each sternal border and each internal mammary artery was exposed. A silk ligature was placed about each artery but neither was tied. Thus, only a first-stage operation had been done, consisting of a skin incision and encirclement but not ligation of the internal mammary arteries.
>
> On awakening from the brief and light anesthetic, the patient reported that he was free of pain. He has had no pain since that date. An electrocardiogram on the day after operation showed no detectable change from preoperative tracing. Two days after the operation the ligatures from the internal mammary arteries were tied. Subsequent electrocardiographic tracings gave no evidence of improvement.

The author goes on to describe follow-up, which included no recurrence of symptoms, and states that

> in this case, there was not a fair chance to assay the relief of symptoms to be obtained by internal mammary artery ligation because the patient lost all symptoms after the first portion of a staged procedure that he believed to be the completed operation.

Adams reported what we would call a nonrandomized single-patient crossover experiment. A sham operation was followed by a real operation—dramatically showing what many might now call a placebo effect of internal mammary exposure.

## Formation of an N-of-1 Clinical Trial Service

Before establishing a single-patient trial service, we contacted Dr Gordon Guyatt, who has actively investigated single-patient trials. He provided us with great encouragement and a summary of the experience of an N-of-1-trials service at McMaster University.[2] Most of his trials had been in the subspecialties of pulmonary medicine and rheumatology. Of the first 42 trials done at the center, 29 gave definitive results. In 11, active treatment was found to be effective, in 17 it was ineffective, and in 1 it was harmful (the theophylline case). Eight other trials gave less definitive results. Five were judged unsuccessful, three because, despite definitive outcomes, the results did not lead to action (G. Guyatt, written communication, June 1987).

Based on this encouraging report, we submitted a small grant proposal to the National Center for Health Services Research. Our research group, which includes Allan Ellsworth, PharmD; Jim Nuovo, MD (family medicine); Ina Oppliger, MD (rheumatology); Gerald van Belle, PhD; and Alice Arnold, MS (biostatistics), is now funded to establish and evaluate a single-patient trial service. We have announced our intentions to workers in other specialties and are currently receiving patients.

Because the objective of the "N of 1" experiment is to find the best treatment for a particular patient, we and others believe that some of the ethical questions asked of the standard randomized trial no longer apply.[2] For example, does the potential benefit to other patients outweigh the possible risk to this patient? Nonetheless, three ethical requirements do apply. First, a patient's free and informed consent should be requested after the clinician has described every feature of the trial that would materially affect the patient's decision to take part, including the reported effectiveness and safety of alternative treatments, the treatment targets to be used, and the duration and number of treatment periods to be executed. The second ethical requirement is that a patient must be free to withdraw at any time without loss of care. The third is that the same degree of confidentiality applied in other clinical situations must apply to the study results. One of our first tasks as an N-of-1 clinical trial service was to approach the Human Subjects Committee (Institutional Review Board) and seek approval for pending single-patient trials. They have developed an expedited approval process that facilitates the prompt institution of clinical trials.

## When to Do a Clinical Trial

Perhaps the most germane issue in single-patient trials is when to do them. That is, when is a patient most likely to benefit from the results of a single-patient trial? The most important issue here is whether there is doubt about efficacy. Doubt may occur because neither the patient nor the physician is certain an existing treatment is working. In this setting, a patient with a chronic disease may be doing poorly or not improving on a medication regimen that could also be causing side effects, as exemplified by the theophylline case.

Another instance when efficacy may be in doubt is during the institution of a new treatment. Here the patient is being offered a new drug and the question is, "Will it work?" The clinician may be uncertain when the literature is equivocal about the drug, the risk-to-benefit ratio is less favorable, or the patient is reluctant to comply with presumably efficacious treatment.

For patients with rare or unusual conditions, the use of the single-patient trial may not only benefit the patient but also add to knowledge about the management of unusual conditions. The literature contains numerous examples of single-patient experiments where treatments of conditions like familial Mediterranean fever and narcolepsy were evaluated with N-of-1 trials.

Doubt about efficacy may be a motivating factor for a single-patient trial also when a patient insists on a treatment as necessary or effective in contradiction to medical advice or practice. The single-patient trial can be used when the physician is unable to convince the patient otherwise. In this case, a negative clinical trial should not surprise the physician but may be convincing to the patient.

After determining whether therapeutic efficacy is in doubt and deciding whether one wishes to demonstrate efficacy or a lack thereof, the clinician will need to consider other questions that affect the feasibility and worth of a single-patient trial. First is whether a treatment will likely be long term. Given the time required to conduct such a trial, single-patient trials of short-term therapies tend not to be

worth the effort required of the patient, and they are less likely to have value for the individual patient unless the patient will require the short-term treatment repeatedly.

Several questions related to the pharmacokinetics of a possible therapeutic agent affect the logistics and ease of doing single-patient trials.[12] The ideal treatment for single-patient trials is one that can be rapidly started and stopped. Thus, outcomes can be assessed starting relatively early in the trial, and there is little or no carryover between treatment periods. When these criteria are not met, carryover or period effects may complicate the interpretation.[13] These effects may require trials that are much more time consuming (for example, involving washout periods) or involve special design modifications. In general, single-patient trials are less likely to be useful for curative treatments (so-called period effects) or for long-acting treatments (due to carryover effects).

## How to Do a Clinical Trial

There are three critical components of the single-patient trial: randomization, blinding of patient and physician to treatment assignment, and defining and quantitating the outcomes. The last, establishing explicit criteria for evaluating the efficacy of treatment, is a feature of the single-patient trial that is also important for medical therapeutics in general.

Randomization is necessary to minimize systematic biases that will occur related to the order of treatment and to permit double blinding to occur. Randomization is usually accomplished in a crossover style, that is, in blocks of two. If, however, it is predetermined that four, six, or eight trials will be done, the statistical power of the trial is improved considerably by randomization in larger blocks.[13] For example, when six trials are planned, the possible $P$ values range from .125 for the paired experiment in which three crossover pairs occur ($[1/2]^3$) to .03 when all six trials are randomized independently ($[1/2]^6$). Intermediate values are possible when constraints are added.

Blinding is a key element to minimize observer-induced bias. In most single-patient trials, the patient records symptoms and, in some cases, signs. Ideally both patient and physician are blind to the treatment assignment. Records of assignment are kept with one of the trial service staff and, if a drug is involved, the pharmacist who has prepared the treatment packages.

Single-patient trials require that the goals of treatment be explicitly identified at the time the patient enters the trial. Ideally, three to five key variables are determined. The variables may reflect disease activity or symptom severity. Usually the most important variables measure patient functioning, reflecting the value of treatment for the patient. In the ideal case, outcomes would include the measurement of a physical sign, a subjective or objective rating of performance in conjunction with, for example, a laboratory measurement reflecting disease activity. The patient's goals must be assayed to be certain that the measures of performance are compatible with the patient's wishes, especially regarding quality of life.

Systematic measurement of a limited number of variables is important for a successful single-patient trial. We typically use self-administered questionnaires that rely on 7-point Likert scales or tabulate the frequency of events. We also teach patients to measure biologic variables like the forced expiratory volume in one second, peak flow, and walk time. We have found it easier to use 7-point Likert scales than visual analog scales. In the standard crossover design, the patient can be asked to state a preference for one treatment period compared with the other.

There are other issues that must be solved when designing a clinical trial. A critical question is the duration of treatment. In general, we believe the old adage, "shortest is easiest." Treatment often takes longer than expected, however, because time is required for peak effects to develop or for treatment effects to dissipate. For drug regimens that are rapidly started and stopped, treatments can be shorter and a random block design of six or eight trials of active drug and placebo can be evaluated in less than two weeks.

A special case occurs when a drug is being used to minimize or prevent attacks or exacerbations of a recurrent disease. To determine duration, the frequency of exacerbation needs to be estimated. Given a reasonable estimate of the frequency, the duration can be based on the "rule of 3s." This rule states that if an event occurs once every $x$ days, the duration of observation must be three times $x$ days to be 95% certain to observe one event. In the case of familial Mediterranean fever where an attack may occur once every two weeks, the treatment period would need to last six weeks to be reasonably certain to observe an effect.

Another question that affects the duration of the trial is how many pairs or trials are needed. The answer to this is the tautology, "as many as are needed." In some trials, we have recommended that a single pair may provide an adequate demonstration of efficacy. Such a demonstration lacks statistical power, but the demonstration of effect may be so compelling as to convince both patient and physician that efficacy is no longer in doubt. On the other hand, when the probability of a treatment being effective is about 50% before the

TABLE 2.—*Posterior Probabilities as Function of Prior Probabilities and Likelihood Ratio*

| Prior Belief Treatment Is Effective, P | Likelihood That Treatment Is Better Than Spontaneous | Patient Improves | Posterior Probability, P |
|---|---|---|---|
| .01 | 3 | Yes | .030 |
| | 5 | Yes | .051 |
| | 1/3 | No | .003 |
| | 1/5 | No | .002 |
| .10 | 3 | Yes | .25 |
| | 5 | Yes | .55 |
| | 1/3 | No | .032 |
| | 1/5 | No | .022 |
| .50 | 3 | Yes | .75 |
| | 5 | Yes | .83 |
| | 1/3 | No | .25 |
| | 1/5 | No | .17 |
| .80 | 3 | Yes | .92 |
| | 5 | Yes | .95 |
| | 1/3 | No | .57 |
| | 1/5 | No | .44 |
| .90 | 3 | Yes | .96 |
| | 5 | Yes | .98 |
| | 1/3 | No | .75 |
| | 1/5 | No | .64 |
| .95 | 3 | Yes | .98 |
| | 5 | Yes | .99 |
| | 1/3 | No | .86 |
| | 1/5 | No | .79 |

trial, and there are major risks of side effects, anything short of a statistical certainty may not be satisfactory. In the case of a paired crossover trial, the binomial distribution suggests that after four trials, the probability of treatment being repeatedly favored over placebo is .5 after the first trial, .25 after the second trial, .125 after the third trial, and .0625 after the fourth trial, which is $(1/2)^4$.

In general, the issue of "statistical" certainty—the mythical $P < .05$—is less critical in single-patient trials. An interesting perspective is added by assaying the clinician's estimate of the likelihood of success in that patient (the prior probability) and determining the estimated likelihood that the treatment is efficacious based on the literature. Using a Bayesian analysis, a posterior probability based on the patient outcome in a single-patient trial can be calculated as shown in Table 2 (G. van Belle, written communication, June 1987). These posterior probabilities show the effect that a single-patient trial can have on a clinician's level of certainty that treatment will be helpful for a patient.

## Conclusion

We formed the trial service to simultaneously establish, demonstrate, and determine the value of single-patient trials in clinical practice and to help do the clinical trials. Our involvement ranges from being limited consultants providing study drugs and simply reviewing the protocol, to providing detailed, in-depth consultation regarding the value of a clinical trial in a particular patient, developing a study design, interviewing the patient, developing target outcomes, printing forms, preparing placebo drug and outcome forms, and doing follow-up. In all cases, we provide an interpretation of the results of the trial and are anxious to learn how the trial was used in clinical decision making and practice.

In summary, single-patient clinical trials can be used to improve the efficacy of treatment—especially long-term treatments and treatments with uncertain efficacy or a risk of serious toxic effects. Examples of suitable conditions for study are numerous, including common problems such as chronic obstructive lung disease, osteoarthritis, recurrent headache and other chronic pain syndromes, "fibrositis" or fibromyalgia, and agitation in demented patients. We have done trials in these common conditions and have also investigated more unusual and complex problems such as progestational drug side effects, treatment of the "restless" leg syndrome, and treatments of orthostatic hypotension. The principal benefits are an increased certainty for patients and their physicians that a treatment is worth pursuing because it is effective or should be abandoned because of an absence of a net benefit.

### REFERENCES


1. Feinstein AR: Clinical biostatistics--II. Statistics versus science in the design of experiments. Clin Pharmacol Ther 1970; 11:282-292
2. Guyatt G, Sackett D, Taylor DW, et al: Determining optimal therapy—Randomized trials in individual patients. N Engl J Med 1986; 314:889-892
3. Sackett DL: Clinical diagnosis and the clinical laboratory. Clin Invest Med 1978; 1:37-43
4. Brody H: The lie that heals: The ethics of giving placebos. Ann Intern Med 1982; 97:112-118
5. Sackett DL: Bias in analytic research. J Chronic Dis 1979; 32:51-63
6. Cochrane AL: Effectiveness and Efficiency: Random Reflections on Health Service. London, Nuffield Hospitals Trust, 1972
7. Freiman JA, Chalmers TC, Smith H, et al: The importance of beta, the type II error, and sample size in the design and interpretation of clinical trials. N Engl J Med 1978; 299:690-695
8. Edgington ES: Statistics and single case analysis. Prog Behav Modif 1984; 16:83-119
9. Adams R: Internal-mammary-artery ligation for coronary insufficiency. N Engl J Med 1958; 258:113-116
10. Berquist WE, Rachelefsky GS, Kadden M, et al: Effect of theophylline on gastroesophageal reflux in normal adults. J Allergy Clin Immunol 1981; 67:407-411
11. Cobb LA, Thomas GI, Dillard DH, et al: An evaluation of the internal-mammary-artery ligation by a double-blind technique. N Engl J Med 1959; 260:1115-1118
12. Porta MS: The search for more clinically meaningful research designs: Single-patient randomized clinical trials. J Gen Intern Med 1986; 1:418-419
13. Kazdin AE: Single-Case Research Designs: Methods for Clinical and Applied Settings. New York, Oxford Press, 1982

# The *n*-of-1 Randomized Controlled Trial: Clinical Usefulness

## Our Three-Year Experience

Gordon H. Guyatt, MD; Jana L. Keller, BSc; Roman Jaeschke, MD; David Rosenbloom, DPharm; Jonathan D. Adachi, MD; and Michael T. Newhouse, MD

*Objective:* To review the feasibility and effectiveness of *n*-of-1 randomized controlled trials (*n*-of-1 trials) in clinical practice.

*Design:* Individual trials were double-blind, randomized, multiple crossover trials. The impact of *n*-of-1 trials was determined by eliciting physicians' plans of management and confidence in those plans before and after each trial.

*Setting:* Referral service doing *n*-of-1 trials at the requests of community and academic physicians.

*Object of Analysis:* All trials were planned, started, and completed by the *n*-of-1 service.

*Measures of Outcome:* The proportion of planned *n*-of-1 trials that were completed and the proportion that provided a definite clinical or statistical answer. A definite clinical answer was achieved if an *n*-of-1 trial resulted in a high level of physician's confidence in the management plan. Specific criteria were developed for classifying an *n*-of-1 trial as providing a definite statistical answer.

*Main Results:* Seventy-three *n*-of-1 trials were planned in various clinical situations. Of 70 *n*-of-1 trials begun, 57 were completed. The reasons for not completing *n*-of-1 trials were patients' or physicians' noncompliance or patients' concurrent illness. Of 57 *n*-of-1 trials completed, 50 provided a definite clinical or statistical answer. In 15 trials (39% of trials in which appropriate data were available), the results prompted physicians to change their "prior to the trial" plan of management (in 11 trials, the physicians stopped the drug therapy that they had planned to continue indefinitely).

*Conclusion:* We interpret the results as supporting the feasibility and usefulness of *n*-of-1 trials in clinical practice.

*Annals of Internal Medicine.* 1990;112:293-299.

From McMaster University, Hamilton, Ontario. For current author addresses, see end of text.

Randomized controlled trials are usually required to establish valid evidence of drug efficacy (1-3). However, there remain a number of clinical situations in which treatment decisions cannot be based on such trials. For example, guidance is unavailable for treating conditions that have not been investigated with randomized controlled trials; some conditions are so rare that even multicenter collaborative trials are not feasible. Further, even when a relevant randomized controlled trial generates a definite answer, its result may not apply to an individual patient. First, if the patient does not meet the eligibility criteria, extrapolation may not be appropriate; second, regardless of the overall trial results, some patients appear to benefit from the experimental therapy and some do not (4). To maintain the methodologic safeguards provided by randomized controlled trials and avoid the disadvantages of large-sample multicenter studies, we have developed a corresponding methodology for examining the intervention effect in individual patients.

Experimental studies (5-7) of single subjects have long been part of psychologic research. The methodology is known as single case or single subject research, $n = 1$, or, *n*-of-1 randomized controlled trials (hereafter referred to as *n*-of-1 trials). We have previously described how *n*-of-1 trials may be used in medical practice to determine the optimum treatment of an individual patient (4). More recently, we have provided detailed guidelines (8) for clinicians interested in conducting their own *n*-of-1 trials. Results pertaining directly to the patient involved are available immediately after the patient has completed the trial.

In 1985, we designed an *n*-of-1 service to facilitate clinicians' involvement with *n*-of-1 studies in our community (9). We have a formal referral service for *n*-of-1 studies and a tutorial service that teaches clinicians how to run their own trials. We describe our 3-year experience with providing the *n*-of-1 service in our community. We examined a spectrum of conditions and interventions in which *n*-of-1 trials were done and studied the outcome of each trial. The questions we asked were as follows: Are *n*-of-1 trials able to provide clinically useful information? Do clinicians change their management plans as a result of *n*-of-1 trials? Does physicians' confidence in management decisions change as a result of *n*-of-1 trials?

### Methods

#### Criteria for Doing an *n*-of-1 Trial

After a clinician and a patient expressed interest in conducting an *n*-of-1 trial, we assessed the suitability of the underly-

 

ing condition and potential therapeutic intervention. We have previously reported a set of criteria (8) that should be satisfied before an *n*-of-1 trial is attempted; these criteria were applied to patients' presentation to the *n*-of-1 service. In short, in addition to the effectiveness of treatment being in doubt, the disorder should be chronic and relatively stable. The treatment, if effective, should be continued long-term, and the patient should be eager to collaborate in designing and participating in the *n*-of-1 trial. In addition, the treatment or treatments must have a rapid onset and termination of action, and an optimal treatment duration should be known and practical. In each case, the choice of medication and the dosage were selected on the basis of the attending physician's clinical judgment.

## Conduct of Individual *n*-of-1 Trials

If our initial assessment of the clinical situation indicated that an *n*-of-1 trial was indicated, we prepared an individualized trial package. To assess drug efficacy, we administered individualized questionnaires that examined the severity of symptoms that were identified by patients as part of their disease and important in their daily life. These questionnaires consisted of four to seven items (symptoms), and severity of symptoms was usually measured on a 7-point scale. For example, if shortness of breath while shopping was a symptom identified as part of the illness and important in daily life, the patient was asked: Please indicate how short of breath you have been while shopping during the previous 2 or 3 days, by choosing one of the options from the scale below:

1. Extremely short of breath
2. Very short of breath
3. Quite a bit short of breath
4. Moderately short of breath
5. Mildly short of breath
6. A little short of breath
7. Not at all short of breath

Either the referring physician or a physician-member of the *n*-of-1 service saw the patient after each treatment period. The trial design was based on pairs of active drug and placebo, high dose and low dose, or first drug and alternate drug combinations; the order of administration within each pair was determined by random allocation. We recommended that at least three pairs of treatments be completed. Medication was prepared by one of the participating pharmacies. If active medication and matching placebo were available from the manufacturer, they were used; if not, the medication was crushed and put in capsules, and matching placebo capsules were prepared. The pharmacy held the code, and all other members of the team were blind to allocation. Treatment targets were monitored on a regular, predetermined schedule throughout the trial. If a patient felt much worse at any time during the trial, the current treatment period was terminated and, without breaking the code, the next treatment period was begun. The trial continued as long as the clinician and patient agreed that they needed more information to get a definite answer about the efficacy of the treatment or until the patient or clinician decided for any other reason to end the trial.

At the study's conclusion, the results were reported to the patient's physician. Mean values for all measures for each treatment period, the mean differences between treatment and control periods, the 90% confidence interval (CI) around the differences, and the probability of differences seen being due to chance (using a one-sided paired *t*-test of the difference in score) were reported (8). We also examined each treatment's magnitude of effect. Our previous experience with the symptom questionnaires that used a 7-point scale suggested that an improvement of 0.5 points per question corresponds to a noticeable improvement in the patient's well-being (10). For instance, if there were six questions, a total change of 3 or more points was considered clinically important.

To assess the impact of the *n*-of-1 trial on the physician's management plan, we asked each physician how he or she would treat the patient without an *n*-of-1 trial and, when *n*-of-1 trial results became available, how he or she intended to treat the patient. Management plan options included continuing the drug therapy, withdrawing the drug, or "other." We also investigated the level of the physician's confidence in his or her management plan, both before and after the *n*-of-1 trial, again using a 7-point scale. The physicians were asked the following: How comfortable do you feel now about your treatment plan?

1. Totally comfortable, certain it's the right thing for the patient
2. Almost totally comfortable, very likely it's the right thing for the patient
3. Quite comfortable, likely that the treatment plan is best for the patient
4. Not totally comfortable, but treatment plan is very likely to be as good as alternatives
5. Mildly uncomfortable, some uncertainty whether treatment plan is best for the patient
6. Moderately uncomfortable, feeling that the treatment plan may not be the best for the patient
7. Extremely uncomfortable, uncertain about treatment plan and, if wrong, patient may suffer

## Review of 73 *n*-of-1 Trials

Between October and December of 1988, we reviewed the files of all *n*-of-1 trials done in cooperation with our *n*-of-1 service. Trials were classified as complete when three pairs of treatment periods were completed or the trial was interrupted before completing three treatment pairs because of the clinician's and patient's belief that drug effectiveness had been established or refuted. The reasons for interruption were occurrence of intolerable symptoms compatible with side effects, perceived large treatment effect of the active medication, and such a low frequency of symptoms that the medication was judged not to be needed.

Trials not in either of these categories were classified as incomplete (interrupted before completing three pairs with no clinical conclusion reached before trial termination). Among completed trials, we examined the proportion that provided a definite clinical answer. These included trials that resulted in a high level of clinicians' confidence in their management decisions after an *n*-of-1 trial (1 or 2 on a 7-point scale); and trials that were interrupted before completing three treatment pairs because of the clinician's and patient's belief that drug effectiveness had been established or refuted. To classify such trials as providing definite answers, the clinical impression of drug efficacy (or its side effect) had to be confirmed after breaking the code.

For trials in which the primary outcome measure was the symptom questionnaire that used a 7-point scale, we have developed a set of statistical criteria to classify individual *n*-of-1 trials. Categories include providing a definite answer (either confirming drug or placebo superiority or indicating no difference), showing a trend in favor of active drug or placebo, or leaving the question of intervention efficacy unanswered (indefinite). These criteria use a combination of the clinical importance cut-off (0.5 points per question mean difference [D] in symptoms score) and statistical evaluation of the difference observed (one-tailed $P \leq 0.05$, narrow CI around the difference between active drug and placebo). The complete set of criteria is presented in Appendix 1.

## Examples of *n*-of-1 Trials

To show what is involved in doing an *n*-of-1 trial, we will describe a case in detail. A 23-year-old woman

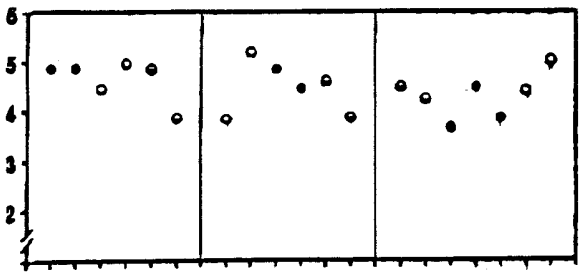

Figure 1. Results of *n*-of-1 trial, propranolol therapy for vasovagal syncope. Half-open circles represent weekly mean scores while receiving propranolol, 40 mg four times daily; open circles represent weekly mean scores while receiving propranolol, 20 mg four times daily; and closed circles represent weekly mean scores while receiving placebo.

presented in the autumn of 1987 with a history of recurrent vasovagal syncope of a year's duration. Associated symptoms included presyncope, nausea and vomiting, migrainous headaches, and flushing episodes. There was no obvious trigger to these symptoms. The syncopal episodes occurred as frequently as twice a week, the other symptoms on a more frequent basis, and the constellation of symptoms was adversely affecting the patient's quality of life. Extensive investigation showed no hormonal or autonomic nervous system abnormality. The patient was given nifedipine (for headaches) and amitriptyline as a vagolytic agent and her condition was initially judged to have improved somewhat; however, symptoms remained a major problem.

It has been hypothesized that a vasodepressor reaction (or common faint) can follow sympathetic nervous system stimulation, resulting in decreased left ventricular volume and stimulation of intracardiac receptors (11). This mechanism was thought to be playing a role in this patient's problems. A "tilt-table isoproterenol" test was abnormal; the patient developed significant bradycardia and hypotension when tilted to 60 deg and infused with 8 $\mu$g of isoproterenol (11). The patient's physician thought that propranolol might benefit (11) and contacted our *n*-of-1 service to conduct a trial.

The physician was uncertain of the optimal dosage, so the trial was set up with triplets of treatment periods instead of pairs. Each period lasted 2 weeks and, in each triplet, the patient received either placebo, 20 mg of propranolol four times daily, or 40 mg of propranolol four times daily. Treatment targets included daily rating of symptoms of lightheadedness and syncope, headaches, nausea or vomiting, feeling warm or sweating, and fatigue. Each symptom was rated on a 7-point scale. For instance, the patient was asked the following: How much trouble or distress as a result of lightheadedness or loss of consciousness have you had during the last day?

1. A very great deal of trouble or distress
2. A great deal of trouble or distress
3. A good deal of trouble or distress
4. A moderate amount of trouble or distress
5. Some trouble or distress
6. Very little trouble or distress
7. No trouble or distress

The results of the three triplets of treatment periods are summarized in Figure 1. Each data point in Figure 1 represents the mean of seven ratings of the five symptoms over a period of 1 week. The patient felt that there were no significant differences in how she felt over the 19 weeks of the trial, and this was confirmed by the symptom scores. It was concluded that propranolol was not effective.

Now uncertain about the benefit of amitriptyline in relieving symptoms, the attending physician wished to conduct a second trial before restarting the therapy. This trial was to have 4-week treatment periods, with the patient receiving placebo or 100 mg of amitriptyline at bedtime during each period. The same five symptoms were monitored, again on a daily basis. Before starting the trial, the physician replied to our questionnaire, stating that his a priori estimate of effectiveness was that the amitriptyline was of no benefit and that he was very confident of this assessment.

The patient felt much worse during the second period of the first pair than she had during the first period and, after 2 weeks of the second period, was convinced that she was receiving placebo. Without breaking the code, the period was terminated and the next pair begun. During the second period of the second pair, the patient again felt much worse and the period was terminated after the first week. After 1 week of the third pair, the patient again became convinced that she was receiving placebo and the second period of the third pair was begun early. The results are presented in Figure 2. The patient had been correct in each case about when she received placebo, and the large differences in symptom score reflect the magnitude of the differences she experienced between taking active drug and taking placebo. The mean differences in symptom score per question between active drug and placebo periods for the three pairs were 1.88, 1.81, and 2.08. A paired *t*-test with two degrees of freedom suggests that these results are very unlikely to have occurred by chance ($P < 0.001$). It was concluded that amitriptyline was effective, and the drug treatment has been continued to the present.

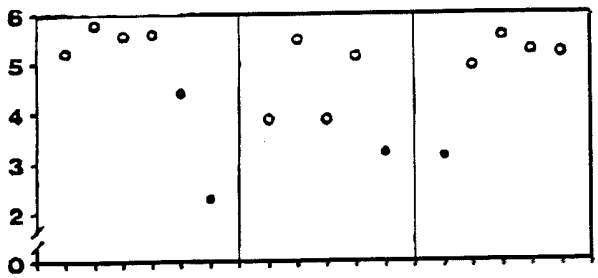

Figure 2. Results of *n*-of-1 trial, amitriptyline therapy for vasovagal syncope. Open circles represent weekly mean scores while receiving amitriptyline, and closed circles indicate weekly mean scores while receiving placebo.

**Table 1.** *Outcome of 73 n-of-1 Randomized Controlled Trials*

| |
|---|
| Planned *n*-of-1 trials, $n = 73$ |
| Three *n*-of-1 trials never started (1 because of death; 1, concurrent illness; and 1, consent withdrawn) |
| *n*-of-1 trials begun, $n = 70$ |
| Thirteen *n*-of-1 trials not completed (7 because of patients' noncompliance; 5, concurrent illness; and 1, physician noncompliance) |
| Completed *n*-of-1 trials, $n = 57$ |
| Nine *n*-of-1 trials with 3 pairs completed did not provide a definite clinical answer; 2 of the 9 provided a definite statistical answer |
| Definite *n*-of-1 trials, $n = 50$ |
| Forty-eight trials were clinically definite; 19, statistically definite |

## Results

### Spectrum of Use

We have not kept systematic track of inquiries about *n*-of-1 trials that were planned but deemed infeasible after preliminary discussion. Some examples include trials with patients with inflammatory bowel disease (in whom exacerbations occur too infrequently to make a trial feasible) and major changes in prednisone in patients with obstructive airway disease (in whom functional adrenal deficiency is likely to have developed). On several occasions, an open trial resulted in obvious benefit or obvious side effects before a formal trial was begun. In several instances, we were approached about patients with many unstable medical problems that made reliable ascertainment of the effect of a single medication impossible. Finally, *n*-of-1 trials were sometimes infeasible because of reservations about the patient's ability to keep a valid symptom diary.

Overall, our service participated directly in preparing 73 *n*-of-1 trials. Some results from 5 of these trials have been reported elsewhere (4, 8, 9, 12). Most of the trials tested a specific form of therapy in patients whose underlying condition was clearly defined (for example, amitriptyline therapy for fibrositis, ipratropium or theophylline for chronic airflow limitation). In three instances, the trial was used as a diagnostic tool: In a patient with inconclusive laboratory test results, the clinician investigated the efficacy of hydrocortisone in relieving symptoms possibly caused by Addison disease; in two trials, the clinician tested the efficacy of pyridostigmine bromide in ameliorating symptoms possibly caused by myasthenia gravis. In two other cases, different dose regimens of the same medication were used to determine the balance between the drug's efficacy and its side effects (prednisone therapy for chronic airflow limitation and propranolol for syncope).

The results of the 73 *n*-of-1 trials are presented in Table 1. Three trials were planned, but never started (1 because of concurrent illness; 1, consent withdrawn; and 1, patient's death). Of the 70 *n*-of-1 trials that began, 57 were completed. The reasons for suspension of 13 trials were patients' concurrent illness (5 trials) and lack of patients' (7 trials) or physicians' (1 trial) compliance with the study protocol. Among the 57 completed *n*-of-1 trials, the number of pairs were as follows: eight pairs, 1 trial; six pairs, 1; five pairs, 2; four pairs, 9; three pairs, 31; two pairs, 11; and one pair, 2. The duration of treatment periods varied widely, from 1.5 days to 6 weeks. The majority of trials lasted 1 to 4 weeks. Appendix 2 presents the spectrum of clinical conditions in which *n*-of-1 trials were done. One physician was involved in 19 trials; another, in 8. An additional four physicians participated in more than 1 completed trial.

### Results of Completed Trials

Forty-eight of 57 completed *n*-of-1 trials (84% of all completed and 66% of all planned) provided a definite clinical answer. These 48 trials included 39 that resulted in a high level of clinicians' confidence in the appropriateness of their management decisions after three pairs of treatment had been completed. An additional 9 *n*-of-1 trials were classified as complete despite trial interruption before completing three pairs. In 4 trials, differences between two treatment periods were so dramatic, the physician and patient decided to end the trial (ipratropium therapy for chronic airflow limitation on three occasions and haloperidol for psychosis on one). In each of these 4 trials, the clinical impression was confirmed after breaking the code; the clinician had guessed correctly when the patient was receiving active drug. On two additional occasions, occurrence of clinically important deleterious effects led to the termination of *n*-of-1 trials (theophylline therapy for chronic airflow limitation and clonidine for rheumatoid arthritis). Again, the clinical decision was substantiated after the code was broken. During 3 trials, the symptoms chosen as treatment targets did not occur within the first few treatment periods and the trial was terminated (propranolol therapy for syncope, dilantin for Meniere disease, and propantheline for abdominal pain). In each of the 9 *n*-of-1 trials classified as complete despite less than three pairs being done, active drug was compared with placebo.

Results of complete trials that used symptom questionnaires with responses on a 7-point scale as a primary outcome measure were reviewed according to criteria presented in Appendix 2. We had the data necessary to do this analysis in 44 *n*-of-1 trials. In 19 of 44 cases, the trial provided a definite statistical answer. In 15 trials, the beneficial role of the drug was confirmed; in 4, there was no difference between investigated therapy and placebo. None of the trials analyzed using these criteria indicated a harmful effect of a drug. All but 2 *n*-of-1 trials providing a definite statistical answer were classified as definite according to clinical criteria. In 1 of these 2 *n*-of-1 trials, the physician tested the efficacy of amitriptyline therapy for fibrositis—the impression of drug efficacy obtained during an earlier open trial was so strong that the results of the initial *n*-of-1 trial excluding drug benefit were questioned. A subsequent *n*-of-1 trial, with the same patient using a higher dosage of amitriptyline, confirmed the results of the first trial, and the physician discontinued the medication. In the second case, the physi-

cian questioned a patient's claim that pyridostigmine provided an improvement in weakness that was possibly related to myasthenia gravis. Despite a clearly positive *n*-of-1 result, failure by a neurologist to confirm the diagnosis of myasthenia led the attending physician to speculate that the patient might somehow have broken the blind, thus invalidating the results. The total number of *n*-of-1 trials providing definite clinical or statistical answer was, therefore, 50. Five *n*-of-1 trials had trends suggesting drug benefit, and, in two cases, trends favored placebo. Results of 18 completed trials were classified according to the statistical criteria as indefinite.

### Management Plans and Clinicians' Confidence

In 38 trials, the data on management decisions were available both before and after the trial. In 23 cases, the original decision was unchanged after the trial result became available. In the remaining 15 trials (39%), results of the *n*-of-1 trial prompted physicians to change the original decision (in 11 cases, to stop the drug treatment completely rather than continue; in 3 cases, to continue drug therapy indefinitely rather than stop; and, in 1 case, to conduct an additional *n*-of-1 trial). The level of confidence in the new management decision, measured on a 7-point scale, was 1.82 ± 1.05 (mean ± SD). Confidence in the original decision was 4.62 ± 1.36. This change in management confidence was similar to the increase seen in the *n*-of-1 trials that supported the original decision (from 4.53 ± 1.62 to 1.82 ± 1.07). The complete spectrum of changes in physicians' confidence after the 38 *n*-of-1 trials for which data are available for both before and after the trial is depicted in Figure 3. In most cases, physicians clearly were far more confident in their management after the *n*-of-1 trial.

In 44 *n*-of-1 trials, three pairs of treatment were completed. In 39 of these trials, physicians expressed total or very high confidence in their management decision (1 or 2 on a 7-point scale). In no case was this degree of confidence present before the *n*-of-1 trial. After these 44 *n*-of-1 trials, the average score on a 7-point management confidence scale was 1.77 ± 0.99.

In most of the trials we report, the attending clinicians had already conducted their own open trials and remained uncertain about treatment efficacy. In these instances, they would have managed the patients as described in the questionnaires we administered. In a few trials, physicians preferred to have the first exposure of patients to the experimental treatment as part of an *n*-of-1 trial. Although physicians may have considered options such as continuing the medication for a period and then testing response to withdrawal or conducting open trials of withdrawal and reinstitution, such plans were made explicit on only a few occasions.

## Discussion

We present our initial, 3-year experience in conducting *n*-of-1 trials and offering the *n*-of-1 service to community physicians. We tested this method of solving difficult therapeutic dilemmas in a broad spectrum of conditions and using different interventions. The clinical problem was most commonly clarification of the efficacy of a medication, generally recognized as useful, in an individual patient. In some cases, trials were used for the clarification of an optimal dosage of a medication or as an aid to diagnosis.

We were able to complete 81% of trials that were begun. The commonest reasons for not completing a trial were patients' noncompliance with the study protocol or emergence of a concurrent illness. In each trial, we tried to complete three pairs of treatments; achieving this goal was the commonest reason to categorize a trial as complete. Some trials were also categorized as complete despite the fact that three pairs of treatments had not been achieved. In all of these *n*-of-1 trials, the clinically relevant answer was reached at an earlier point. On three occasions, target end points occurred with an unexpectedly low frequency regardless of the treatment used. These *n*-of-1 trials were interrupted and classified not only as complete but also as providing a definite clinical answer: Indication for the use of a drug was refuted. These three *n*-of-1 trials dramatically show the necessity of assessing drug efficacy in a blind manner. Had the drug been tested in an open trial, the results would have been interpreted as showing the striking efficacy of the intervention.

To judge the clinical usefulness of *n*-of-1 trials, we developed a set of both clinical and statistical criteria. We felt that because the goal of an *n*-of-1 trial is to clarify a management decision, an *n*-of-1 trial can be considered definite only if this goal is achieved. A definite answer was obtained in 71% of all attempted *n*-of-1 trials. Clinicians were more liberal in their conclusions that a definite answer had been reached. When using rigorous statistical criteria for a definite answer, such an answer was attained in only 27% of trials that were begun (43% of the trials in which data required to make this assessment were present). On two occasions, physicians did not believe the statistical results; in both cases, two separate *n*-of-1 trials yielded the same results.

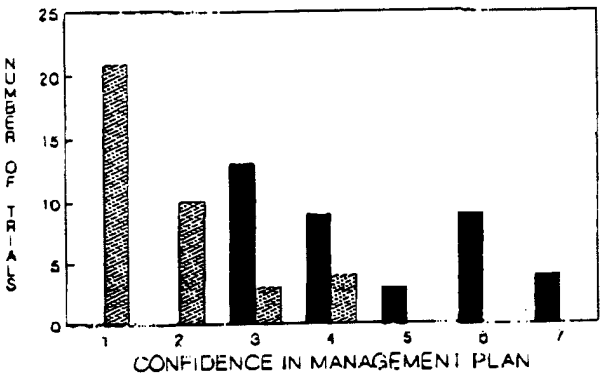


**Figure 3.** Impact of *n*-of-1 trials on clinicians' confidence in their management plans, data from 38 *n*-of-1 trials. The *y*-axis represents number of trials, and the *x*-axis indicates confidence in management plan. Closed bars represent confidence in management plan before trial, and open bars represent confidence in management plan after trial.

The relatively small proportion of trials in which statistical criteria for a definite result were obtained reflects to some extent the limited power of statistical tests when only three pairs have been conducted. The extent to which the clinicians were convinced of the results when statistical criteria were not met attests to the value of the method even without statistical analysis. Another limitation of statistical analysis is that the decision to continue with additional pairs can be driven by the results, potentially invalidating the nominal *P*-value obtained. Because of these limitations, we view the statistical analysis as an adjunct (but often very useful adjunct) for the interpretation of the results of *n*-of-1 trials.

The expense incurred by conducting *n*-of-1 trials will be an issue. Until now, our trials have been paid for by research funds. We have not, therefore, established a standard fee for the referral nor decided on how fees should be modified depending on the nature and length of the study. Although, in our experience, the research assistant time per trial was considerable, much of this time was spent on activities (such as administering questionnaires to physicians) that would not be part of *n*-of-1 trials once they are established in clinical practice. We believe that even without detailed information on costs, conducting *n*-of-1 trials is likely to be cost-effective. In our experience, a substantial proportion of trials result in discontinuation of medication that would otherwise have been continued for months or years. The cost savings from discontinuing medication and from reducing physician time spent in medication review and in treating adverse reactions to medication is likely to be considerable. Third-party payers may wish to consider these potential savings when developing policies on reimbursement of costs associated with *n*-of-1 trials.

We believe that our results show that *n*-of-1 trials are feasible to conduct in clinical practice and often result in clinically important changes in clinicians' confidence in their management decisions and in the management decisions themselves. We believe that most physicians try to be scientific in their approach to medication prescription and use some of the principles of the *n*-of-1 trial (such as observation of patients on and off medication) in their day-to-day practice. The methodology of the *n*-of-1 trial provides physicians with a set of tools that can further increase the scientific rigor of their clinical practice and increase the likelihood that the treatments they prescribe are indeed those that are best for the patient.

*Acknowledgments:* The authors thank Drs. Christopher Allen, Jennifer Blake, Dody Bienenstock, Ramona Carbotte, Clive Davis, Judah Denburg, Susan Denburg, Brian Hutchison, Jan Irvine, David Martin, Christopher Patterson, Michel Rothbone, Peter Rosenbaum, William Walsh, Robin Whyte, and the many other physicians who helped in the planning and conduct of individual trials; Professor Robin Roberts and Will Boyce and Drs. Dave Sackett, Murray Enkin, Stewart Pugsley, and John Chong, who contributed to the conceptual development of the *n*-of-1 approach; the pharmacy staff at McMaster University Medical Centre, particularly Iris Laschuck and Kathy Sussens, and at St. Joseph's Hospital, Hamilton, Ontario, particularly Doris Thompson, Betty Wong, and Nancy Giovinazzo for their help with preparation and management of medications.

*Requests for Reprints:* Gordon Guyatt, MD, Room 2C12, McMaster University Health Sciences Centre, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5 Canada.

*Current Author Addresses:* Dr. Guyatt: Room 2C12, McMaster University Health Sciences Centre, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5 Canada.
Ms. Keller: Room 2C3, McMaster University Health Sciences Centre, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5 Canada.
Dr. Jaeschke: Fontbonne Building, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario, L8N 4A6 Canada.
Dr. Rosenbloom: Pharmaceutical Services, McMaster University Health Sciences Centre, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5 Canada.
Dr. Adachi: 25 Charlton Avenue East, Hamilton, Ontario, L8N 1Y2 Canada.
Dr. Newhouse: Firestone Chest/Allergy Services, St. Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario, L8N 1Y2 Canada.

**Appendix 1.** Criteria for Assessing the Results of an *n*-of-1 Randomized Controlled Trial

Statistical criteria

| | |
|---|---|
| Definite answer | |
| Beneficial | $P \leq 0.05$ and $D \geq 0.5$ |
| Harmful | $P \leq 0.05$ and $D \leq -0.5$ |
| Neutral | $P > 0.05$ and $0.25 > D > -0.25$ and $\lvert CI \rvert$ not $\geq 0.5$ or $P > 0.05$ and $0.25 > D > -0.25$ and $\lvert D \rvert$ for each pair $\leq 0.5$ |
| No definite answer but trend seen | |
| Beneficial trend | $0.3 \leq D < 0.5$ and $P \leq 0.05$ and CI includes 0.5 or $D \geq 0.5$ and $P > 0.05$ |
| Harmful trend | $-0.3 > D > -0.5$ and $P < 0.05$ and CI includes $-0.5$ or $D \leq 0.5$ and $P > 0.05$ |
| No definite answer | |
| Not meeting criteria for either of the above categories. | |

Clinical criteria for definite trial

1. The clinician's high level of confidence in the appropriateness of the management decision after the *n*-of-1 trial (1 or 2 on a 7-point scale).
2. *n*-of-1 trial interruption before completing three treatment pairs because of the clinician's belief that drug effectiveness had been established or refuted (perceived large treatment effect or severe side effects, both confirmed after breaking the code, or low frequency of treatment endpoints).

**Appendix 2.** Spectrum of Clinical Conditions in Which *n*-of-1 Randomized Controlled Trials Were Used

Fifty-seven trials were completed. Twenty trials were done with 19 patients with fibrositis. In 18 of these trials, amitriptyline was tested; nitrazepam was tested in 2 trials. Sixteen trials were completed in patients with chronic airflow limitation. In 10 trials, inhaled ipratropium was tested; in 4, oral theophylline; and, in 2, inhaled salbutamol. Two other patients participated in 2 trials each. In a patient with suspected myasthenia

gravis, pyridostigmine was tested in 2 different trials. A patient with recurrent syncope participated in 1 trial testing propranolol, and 1 trial testing amitriptyline. Single trials were done in the following conditions, with the associated medication: chronic pain, maprotiline; anxiety, lorazepam; insomnia, lorazepam; suspected Addison disease, hydrocortisone; cryptosporidiosis, spiramycin; Raynaud disease, ketanserine; syncope, propranolol; coronary disease, diltiazem; familial, Mediterranean fever, colchicine; rheumatoid arthritis, clonidine; myositis, prednisone; abdominal pain, propantheline; Meniere disease, phenytoin; psychosis, haloperidol; and suspected polymyalgia rheumatica, prednisone.

Thirteen trials were begun but not completed. Eight of these trials involved patients with chronic airflow limitation. Five tested inhaled ipratropium; two, inhaled salbutamol; and one, oral theophylline. Single trials were started but not completed in the following conditions, with the associated medication: premenstrual syndrome, pyridoxine; spasticity in a paraplegic, clonidine; irritable bowel syndrome, trimebutine; idiopathic edema, captopril; and temporal lobe epilepsy, carbamazepine.

**References**


1. **Sackett DL.** Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest.* 1986;89:2S-3S.
2. **How to read clinical journals: V: To distinguish useful from useless or even harmful therapy.** *Can Med Assoc J.* 1981;124:1156-62.
3. **Deciding on the best therapy. In: Sackett DL, Haynes RB, Tugwell P.** *Clinical Epidemiology. A Basic Science for Clinical Medicine.* Boston: Little, Brown and Company; 1985. 171-97.
4. **Guyatt GH, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S.** Determining optimal therapy-randomized trials in individual patients. *N Engl J Med.* 1986;314:889-92.
5. **Kratochwill TR, ed.** *Single Subject Research: Strategies for Evaluating Change.* New York: Academic Press; 1978: 316.
6. **Hersen M, Barlow DH.** *Single Case Experimental Designs: Strategies for Studying Behaviour Change.* 2d ed. New York: Pergamon Press; 1984: 419.
7. **Kazdin AE.** *Single-Case Research Designs: Methods for Clinical and Applied Settings.* New York: Oxford University Press; 1982: 368.
8. **Guyatt GH, Sackett DL, Adachi JD, et al.** A clinician's guide for conducting randomized trials in individual patients. *Can Med Assoc J.* 1988;139:497-503.
9. **Keller JL, Guyatt GH, Roberts RS, Adachi JD, Rosenbloom D.** An N of 1 service: applying the scientific method in clinical practice. *Scand J Gastroenterol.* 1988; 23(Suppl 147):22-9.
10. **Jaeschke R, Singer J, Guyatt G.** Measurement of health status: ascertaining the minimal clinically important difference. *Controlled Clinical Trials.* [In press].
11. **Waxman MB, Yao L, Cameron DA, Wald RW, Roseman J.** Isoproterenol induction of vasodepressor-type reaction in vasodepressor-prone persons. *Am J Cardiol.* 1989;63:58-65.
12. **Woolf GM, Townsend M, Guyatt GH.** Treatment of cryptosporidiosis with spiramycin in AIDS. An "N of 1" trial. *J Clin Gastroenterol.* 1987;9:632-4.