# A STUDY OF MARIJUANA'S THERAPEUTIC POTENTIAL

Prepared by:

The Hawaiian School of Public Health

Marijuana Task Force

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TABLE OF CONTENTS

## FOREWORD

In 1977, the Hawaiian Senate requested the Hawaiian Public Health Service to survey and evaluate the existing scientific literature on the medicinal uses of marijuana and report these findings to the Ninth Legislature (Senate Resolution 323, SD-1). That report, prepared by the School of Public Health's Marijuana Task Force, was completed on October 26, 1977, and presented to the legislature during hearings in January of 1978.

As a result of the Report, Hawaii became the first state to introduce legislation designed to legalize marijuana for medicinal purposes. Although that legislation failed to pass, four states succeeded in passing therapeutic legislation during the 1978 sessions. As a result of this and other events in recent years, public interest in marijuana's medical properties has rapidly expanded and the demand for information on this topic has been great.

As part of its continuing effort to educate the public on marijuana's effects, The Center for the Study of Non-Medical Drug Use has reprinted the Hawaiian Marijuana Task Force Report, excerpting only those sections which deal with Hawaiian Law.

The Center wishes to extend its appreciation to the Hawaiian School of Public Health for its excellent work in compiling this report. The members of the Marijuana Task Force were: Carol Arnold, Virginia Ching, Rosemary DeSanna, and Patricia Ann Sexton. They were assisted by Dr. Russell Hicks. Jerrold M. Michael is the Dean and Professor of Public Health at the University of Hawaii.

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This publication is part of The Issue Series, a public information project of The Center for the Study of Non-Medical Drug Use.

The Center is a non-profit educational foundation established in 1972 to provide an informed perspective on marijuana and other drugs. The Center's activities include public education, legal programs, and policy evaluation.

Larry A. Schott
Director

## Introduction

Cannabis, one of the oldest healing drugs, has been used for therapeutic purposes among cultures throughout the world and for a variety of ailments. Folk medicine shows the use of the drug in India, Southeast Asia, China, Russia and Poland to name a few areas in the world where the drug was traditionally used as a medicinal herb. Cannabis was thought to have antibiotic and analgesic properties and was also used as a curative for rheumatism, allergies, depression and insomnia, and numerous other diseases.

More recently, interest in the therapeutic potentials of cannabis was revived in the 19th Century with the drug being further investigated as an anticonvulsant and muscle relaxant. While scientific investigation did not occur under laboratory conditions, reports concerning the efficacy of marijuana as a therapeutic drug tended to be favorable. Nevertheless, due to a number of circumstances, the medical use of the drug began to decline. The potency of the drug was not uniform. Marijuana is not water soluble, and, therefore, was difficult to administer in a medically effective manner. Furthermore, the tendency of delta-9-tetrahydrocannabinol (THC), the active ingredient of marijuana, to break down when exposed to air or sunlight gave the drug a very short shelf-life. Other medications were being synthesized which had the same medicinal effects as marijuana but which were more predictable. And finally, the Tax Act of 1937 classified the drug as a narcotic and therefore unsuitable as a medication.[1]

As recently as ten years ago, the controversy and fear surrounding marijuana made it almost impossible for researchers to study the drug. University officials dissuaded researchers from the study of marijuana, and obtaining the drug for research purposes involved overcoming a number of legal obstacles. Furthermore, once obtained, the potency of the drug was unknown and hardly uniform because the drug came from various confiscated sources, thus making it difficult to use in a comparative manner for research purposes.

In 1967, the U.S. Government began subsidizing the investigation of marijuana. The objective of the investigations at that time was the development of marijuana as a uniform drug of known potency for pharmacological use. In 1968, the British government published the first contemporary report concerning the status of scientific knowledge with respect to marijuana. And in 1971, the Department of Health, Education and Welfare published the first of what was to become an annual report on marijuana. Examining the drug in an objective scientific manner, these reports served to diminish the horror stories that had once surrounded the use of the drug.

In view of the fact that marijuana has been under research for approximately a decade and has been investigated as a therapeutic drug for only six or seven years, there does not exist a vast quantity of data or scientific research on the efficacy of marijuana as a medicinal drug. However, what evidence does exist suggests that the active ingredient of cannabis, delta-9-THC, along with some of its metabolites is effective in certain medical areas. The following report surveys the major areas in which cannabis has been and is continuing to undergo study as a therapeutic agent. These includes glaucoma, asthma, cancer, epilepsy, psychological action.

## References

1. Marihuana and Health, Fifth Annual Report to the U.S. Congress from the Secretary of Health, Education and Welfare, 1975. National Institute of Drug Abuse, Rockville, Maryland. P. 119.

## I. Glaucoma

At present, glaucoma is responsible for 14% of all new cases of blindness and is the second leading cause of blindness in the United States. While different types of glaucoma exist, a common characteristic among all varieties is an abnormally high intraocular pressure (IOP) which eventually damages the optic nerve and results in blindness. According to Dr. R.S. Hepler of the Jules Stein Eye Institute at U.C.L.A. School of Medicine, there is no clear understanding as to how an elevated IOP affects the optic nerve, however, it is believed that an elevated IOP interferes with the blood supply to the optic nerve thus causing the latter to atrophy. Peripheral vision is initially lost and later the loss of central vision also occurs. "Vision once lost to glaucomatous optic atrophy can never be regained." (Emphasis added.) (Hepler, Petrus, 1976).

Currently, glaucoma, which is incurable, is controlled through the use of conventional medications. However, many glaucoma patients experience little or no relief and others experience potentially serious side effects from conventional medications.* Surgical therapy, another alternative for controlling glaucoma, is generally looked to as a last resort as there is both a high incidence of cases where surgery fails to control glaucoma and a significant amount of risk involved. Serious complications may occur as a result of surgery. (Hepler, Petrus, 1976).

The possibility of using marijuana as a means of controlling open-angle glaucoma first came to light in 1971 when Hepler and Frank discovered that smoking marijuana reduced intraocular pressure. A series of studies testing the effects of marijuana and its derivatives on IOP have since followed. All have indicated that the active ingredient of marijuana, delta-9-THC, and other marijuana derivatives do indeed reduce IOP. Green and Podos (1974) and Purnell and Gregg (1973) among others have confirmed the IOP reducing effects of cannabinoids.

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*The following medications have been conventionally used for the treatment of glaucoma and may have the following side effects:

1) Miotics: Can cause blurred vision during the day and impaired vision at night. They are suspected of contributing to the development of cataracts, and may pre-dispose a patient to uveitis and retinal detachment.

2) Epinephrine: Causes local ocular irritation and chronic redness of the eyes. May create cardiac arrhythmias and hypertension.

3) Carbonic Anyhydrase Inhibitors: Causes electrolyte imbalance, fatigue, anorexia, weight loss and renal stones. (Hepler, Petrus, 1976).

Dr. Hepler, in a study conducted in 1974, tested for the ocular effects of smoking marijuana, and concluded that there are "no indications of any deleterious effects of smoking marijuana on visual function or ocular structure." (Hepler, et al., 1972). More specifically, while reducing IOP on an average of 4-5 hours (in the Hepler, Frank and Petrus study), marijuana had no cumulative effects on visual function and ocular structures. Further study by Hepler, Frank and Ungerleider indicated that while the pupils actually constricted (rather than dilating as is commonly believed) after smoking marijuana, normal responsiveness to light was not affected. Other visual function tests concluded that visual acuity, refraction, peripheral visual fields, binocular fusion and color vision were not altered significantly. Dr. Hepler concludes that marijuana may be more useful than other conventional medications and furthermore may reduce IOP in a way that conventional medications do not, thus making marijuana a potential additive. (Hepler, et al., 1972.)

Cooler and Gregg, while noting the effects of IOP reduction by the administration of marijuana to glaucoma patients, conducted studies to further describe the effects of marijuana administered intravenously to subjects with normal IOP. They discovered an average reduction in IOP of 37% and 29% among subjects receiving approximately 3.0 mg. and 1.5 mg. respectively. They also observed that there were no statistically significant changes in respiration or blood pressure and no appreciable analgesic properties. There was a significant increase in anxiety among subjects receiving both dosages of delta-9-THC. (Cooler, Gregg, 1976.)

The remaining obstacles to overcome where the use of marijuana for controlling glaucoma is concerned appear to be in the manner in which the drug is administered and in determining dosage. The National Institute of Drug Abuse (NIDA) is currently experimenting with administering delta-9-THC in oral tablet form, and studies using marijuana in eyedrop form have successfully been conducted on rabbits.

It should be noted that in November, 1976, the Washington, DC, Superior Court handed down an unprecedented decision allowing Robert Randall to smoke marijuana as a means of controlling his glaucoma. Mr. Randall's condition was first treated in 1972 with conventional medications which eventually became ineffective as he developed a tolerance to these drugs. By 1974, he had suffered complete loss of vision in his right eye and vision in his left eye was severely impaired. Mr. Randall sought relief for his glaucoma condition by smoking marijuana. His subsequent arrest for possession of the drug led to his participation in experimental studies which indicated that smoking marijuana did indeed normalize Mr. Randall's IOP and lessened visual distortion. Mr. Randall was eventually acquitted by reason of medical necessity. For fourteen months, Mr. Randall participated in another research program at Howard University in Washington, DC. Following termination of that program in January, 1978, the federal government denied Mr. Randall access to marijuana for nearly five months. After filing suit in federal court, Mr. Randall once again received medical supplies of marijuana, this time in a conventional physician-patient-pharmacy relationship.

## Bibliography

### Glaucoma


1. Cooler, P.; Gregg, J.M. The Effect of Delta-9-Tetrahydrocannabinol on Intraocular Pressure in Humans. The Therapeutic Potentials of Marijuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book (1976).

   Purpose of study: to describe further the effects of intravenous delta-9-THC on IOP in subjects with normal IOP.

   Study population: 10 males, 20-30 years old. Double blind study using:

   1) Delta-9-THC average 3.0 mg. total dosage
   2) Delta-9-THC average 1.5 mg. total dosage
   3) Diazepam sodium (valium) avg. 10 mg. total dosage
   4) Placebo: human serum albumin

   Delta-9-THC solubilized and administered intravenously. Results:

   1) At higher dosage of delta-9-THC, IOP reduced in all nine subjects receiving higher dose average 37% reduction.
   2) At lower dosage, delta-9-THC, 9 of 10 subjects IOP reduced average 29% reduction.
   3) Valium reduced IOP in 6 of 10 subjects average 10% reduction.
   4) Placebo reduced IOP in 3 of 10 subjects average 2% reduction.

   Other observations:
   1) No statistically significant change in respiration or blood pressure.
   2) No appreciable analgesic properties with either cutaneous or periosteal stimulation.
   3) Anxiety levels increased markedly in subjects receiving both levels of delta-9-THC and only slightly in subjects receiving placebo and valium.

2. Hepler, R.S.; Petreus, R. Ocular Effects of Marihuana Smoking. Pharmacology of Marihuana. Vol. II, pp. 815-828 (1976).

   Purpose of study: to determine the effects of smoking marijuana on the eye. The study population included normal human studies, glaucoma patients and rabbits. A double-blind study was conducted using:
   1) natural marijuana with standard delta-9-THC content.
   2) synthetic delta-9-THC blended into placebo marijuana material (THC spiked placebo).
   3) oral THC -- synthetic delta-9-THC dissolved in sesame oil and administered in capsules.
   4) placebo -- marijuana without THC.

Results: Humans with normal IOP

Pupils: There was a statistically non-significant constriction in the pupils at five minutes after drugs were administered in groups using the first three drugs.

IOP: There was a statistically significant reduction of intraocular pressure after smoking or ingesting marijuana or THC. IOP dropped on an average of 30% among those smoking natural marijuana and 2% THC. Those smoking the placebo also experienced an average 10% reduction in IOP indicating that marijuana without THC may contain other cannabinoids which may have caused the reduction.

Chronic and Cumulative Effects: Pupils showed no sign of chronic or cumulative effects resulting from marijuana. The reduction in IOP lasted four-five hours and showed no indication of cumulative effects.

Results: Glaucoma patient studies

Of eleven patients studied, seven experienced substantial drop in IOP averaging 30%.

Results: Animal studies

There were insufficient observations to draw statistical conclusions.

3. Hepler, R.S.; Petreus, R. Experiences with Administration of Marihuana to Glaucoma Patients. The Therapeutic Potential of Marihuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book. pp. 63-77 (1976).

Purpose of study: to determine what if any effects marijuana might have on glaucoma.

The patient population consisted of 12 persons with open-angle glaucoma. Those with mild or moderate glaucoma discontinued their customary medications 24-48 hours prior to receiving marijuana. Those with severe glaucoma continued using medications until their arrival at the research centers. The patients received marijuana either in smoked form or orally during three sessions. They were observed for four hours following the administering of marijuana and their intraocular pressure measured repeatedly.

Results: 10 of 12 patients experienced a reduction in IOP of 30% (on the average) and lasting 4-5 hours. There is no explanation for lack of effect on the remaining two patients.

Marijuana appears to be additive to the effects of conventional medications.

4. Hepler, R.S.; Frank, I.M.; Ungerleider, J.T. Pupillary Constriction After Marihuana Smoking. American Journal of Ophthamology. pp. 1185-1190. December (1972).

Purpose of study: to determine ocular effects of marijuana especially with respects to pupillary effects.

Results: Indicated that the size of the pupils actually decrease after smoking marijuana while maintaining normal responsiveness to light. There were decreases in tear secretion, intraocular pressure, and conjunctival hyperemia. Tests measuring any change in visual function were applied, specifically, tests for visual acuity, refraction, peripheral visual fields, binocular fusion and color vision, and indicated no significant alteration in visual function.

5. Perez-Reyes, W.D.; Wall, M.D.; Davis, K.H. Intravenous Administration of Cannabinoids and Intraocular Pressure. Pharmacology of Marihuana. Vol. II, pp. 829-832.

Purpose of study: to determine whether cannabinoids other than delta-9-THC reduce intraocular pressure significantly and have less intense psychological and cardiovascular effects than delta-9-THC.

Six cannabinoids were intravenously administered into subjects with normal intraocular pressure. The six cannabinoids were: 1) delta-9-THC, 2) cannabinol, 3) cannabidiol, 4) 11-hydroxy-delta-9-THC, 5) delta-8-THC, 6) 8-hydroxy-delta-9-THC.

Results:

1) Delta-9-THC and 11-hydroxy-delta-9-THC decreased intraocular pressure but also resulted in intense psychological and cardiovascular effects although doses administered were moderate.
2) Delta-8-THC decreased intraocular pressure more than any of the other cannabinoids and produced only moderate psychological and cardiovascular effects.
3) The remaining drugs had only a moderate effect on intraocular pressure, and cannabidiol had a placebo effect.

Conclusion:
Delta-8-THC is the least expensive and most abundant synthetic cannabinoid. Its intraocular pressure reducing properties and the fact that it produces psychological and cardiovascular effects that are less intense than delta-9-THC may indicate that it is the most appropriate cannabinoid for treatment of glaucoma.

## II. Mental Functioning

This section of the report deals with the potentially therapeutic uses of marijuana in the treatment of mental dysfunction. These uses includes sedative-hypnotic action, coping behavior and anti-depressant activity.

Although marijuana has often been accused of creating mental dysfunction, there is evidence which points to some beneficial applications. Walter Bromberg (1939), Senior Psychiatrist at Bellevue Hospital commented, "The relationship between cannabis and the onset of a functional psychosis is not always clear . . . what role did the drug play? Could the psychosis have begun without the drug? Was the use of cannabis the patient's attempt to cure his developing psychosis?" This questioning was in 1939. Experts in the area cannot agree, as demonstrated by Lowinger (1971) in a survey of participants at the 1968 meeting of the American Psychiatric Association. There was no consensus among the group on the relationship between cannabis and psychopathology.

Such contradictions and disagreements should not discourage further efforts. The therapeutic potential of cannabis must be weighed against the probability of adverse behavioral effects, but it is felt that research which balanced the behavioral effects to the advantage of the patient and/or eliminated the adverse effects altogether could be carried out.

The findings in this area are necessarily vague and difficult to measure and therefore may tend to be contradictory on the basis of studies done to date. Weil and Zinberg (1968) carried out the first adequately controlled experiment which attempted to document the psychological effects of cannabis in man. Their findings offer the groundwork from which further investigations may proceed.

1. It is safe and feasible to study the effects of marijuana on human volunteers who smoke it in a laboratory.

2. In a neutral setting, persons who are naive to marijuana do not have strong subjective experiences after smoking low or high doses of the drug, and the effects they do report are not the same as those described by regular users of marijuana who take the drug in the same neutral setting.

3. Marijuana naive persons do demonstrate impaired performance on simple intellectual and psycho-motor tests after smoking marijuana; the impairment is dose-related in some cases.

4. Regular users of marijuana do get high after smoking marijuana in a neutral setting but do not show the same degree of impairment of performance on the tests as do naive subjects. In some cases their performance improves.

With these findings, researchers began to investigate the psychological effects in a more systematic fashion. Some basic principles had been established.

A. Sedative-Hypnotic

Cousens and DiMacio (1973) used physically healthy insomniacs as subjects to investigate the potential of delta-9-THC as a clinically useful hypnotic. Oral doses of 10-30 mg. were found to decrease significantly the total time required to fall asleep.

Sofia and Knobloch (1973) demonstrated that pretreatment of laboratory mice with delta-9-THC decreased both the time required to fall asleep and the duration of total sleep time.

Neu (1976) performed two studies to investigate the relaxing and sedating effects of cannabis. In a double-blind study using 10-30 mg. delta-9-THC or placebo, the drug significantly reduced the time of sleep onset when compared to the placebo. Side effects were noticed. The second study used 5-15 mg. delta-9-THC compared with 500 mg. chloral hydrate and placebo. Neither drug, when compared with the placebo, facilitated sleep onset nor extended duration of sleep. The investigators suggested that the winter cold in the room used as a laboratory may have sufficiently altered the outcome of the experiment by interfering with sleep. Further investigation should be conducted.

Freemon (1974) demonstrated that delta-9-THC (20 mg.) reduced REM time. This finding confirms findings in earlier studies. Withdrawal does not produce increased REM sleep (rebound).

Feinberg (1975) using marijuana extract and delta-9-THC (70-120 mg.) found reduced REM activity. Withdrawal, however, led to considerably increased REM sleep. Tassinari (1976) reported increased total sleep time and reduced REM sleep. Variation in amounts administered to test subjects may explain the differences between Feinberg and Freemon.

Although side effects do occur, the role of cannabis in the treatment of insomnia remains to be determined. Low lethality and the absence of serious toxic effects make it worthy of investigation as a medical resource.

B. Hypnotizability

Bilash (1972) and Franzini (1973) both suggested that cannabis may heighten hypnotic suggestibility. In follow-up studies by Fisher (1972) and Beahrs(1974) neither group showed a change in hypnotic susceptibility. The data support the contention that hypnotizability as measured by standardized scales is a stable character trait resistant to experimental manipulation.

C. Anti-depressant

Kotin (1973) attempted to assess the anti-depressant effect of delta-9-THC in hospitalized patients diagnosed as moderately to severely depressed. Administration for seven days failed to produce significant euphoria or anti-depressant effects.

Regelson (1976), however, in his work with cancer patients, noted that delta-9-THC acted as a mood elevator and tranquilizer producing significant improvement on a standard depression scale.

These findings suggest the possible effectiveness of delta-9-THC as an antidepressant. A longer period of drug administration may be needed for chronic depressive states before improvement is noted.

D. Coping Behavior

Since the precise action of marijuana and the mind is still unknown, the question of whether cannabis promotes or inhibits psychopathology still remains.

Casarett and Baselt (1974) report that "THC in single or multiple doses produces an alteration of biogenic amines in the brain. Of chief interest is the fact that the changes are consonant with an increased level of dopamine which has been demonstrated in both animals and man to produce a unique kind of loss of aggression." This loss of aggression may be labeled "amotivational syndrome" by some. For others, it may offer a way to deal with stress and ego deficiencies.

Bey (1969) studied twenty soldiers with psychotic symptoms associated with marijuana use and concluded that cannabis had helped the subjects achieve a balance in their lives.

Melges (1971) found that cannabis produced dose-related isolation of present from past and future and interfered with goal-directed behavior. They questioned the evil of this and proposed that such effects may contribute to the functioning of certain persons.

In a study of women college students, Rouse (1973) found that cannabis served as a way for some of the subjects to deal with anxiety and depression.

So we return to the questioning of Bromberg with more questions, and emphasize that only through further research will these questions be answered.

## Bibliography

### Mental Functioning

1. Beahrs, J.O.; Carlin, A.S.; and Shehorn, J. Impact of Psychoactive Drugs on Hypnotizability. The American Journal of Clinical Hypnosis. 16(4): 267-269 (1974).

Eleven adult male marijuana smokers who were pre-tested for hypnotic susceptibility were later tested for hypnotic susceptibility under four experimental conditions: 1) after smoking a cannabis cigarette containing 7.5 mg. of THC and receiving placebo IM injection; 2) after smoking a placebo cannabis cigarette and receiving 2 mg. of haloperidol IM; 3) after a combination of both drugs; and 4) after placebo smoke and placebo injection. The drugs had no systematic impact on hypnotizability as measured by a modified version of the Harvard Group Scale of Hypnotizability.

2. Bey, D.R.; and Zecchinelli, V.A. Marijuana as a Coping Device in Vietnam. USARV, 40(22):21-28 (1969).

The authors studied twenty soldiers with diagnosed psychotic symptoms associated with marijuana use. They conclude that instead of causing such symptoms, marijuana served to help the patients achieve balance in their efforts to cope with identity diffusion, ego weakness, low self-esteem and shallow object relationships.

3. Bilashi, I.S.; Arnold, M.; and Zeil, C. Marijuana and Suggestibility. Canadian Psychiatric Association. 17(4), 327-329 (1972).

Alterations of the marijuana "high" with "set" and "setting" may be related to suggestibility as measured by the Stanford Hypnotic Susceptibility Scale. In addition, marijuana may itself heighten suggestibility.

4. Bromberg, Walter. Marihuana: A Psychiatric Study. JAMA. 113(1): 412 (1939).

5. Casarett, L.J.; and Baselt, R.C. A Toxicologic View of Marijuana. Hawaii Medical Journal. 30(4): 262-263 (1971).

6. Cousens, K.; and DiMascio, A. Delta-9-THC as an Hypnotic, An Experimental Study of Three Dose Levels. Psychopharmacologia. 33:355-364 (1973).

Either a placebo or 10 to 30 mg. of delta-9-THC were administered orally in double blind fashion to nine mild insomniacs. The tests were conducted once per week for six weeks. The results showed that THC effectively decreased the time required to fall asleep. According to this study, marijuana has hypnotic actions of short duration. During the pre-sleep phase, the side effects were those of mood alteration and temporal disintegration. After waking, some subjects had a "hangover", some had a "high". A few had residuals of the temporal disintegration, the duration of which was dose related.

7. Feinberg, I.; Jones, R.T.; Walder, J.M.; Cavness,C.; and March, J. Effects of High Dosage Delta-9-Tetrahydrocannabinol on Sleep Patterns in Man. Clinical Pharmacology and Therapeutics. 17(6):458-464 (1975).

Using both marijuana extract and delta-9-THC (70-210 mg.), it was found that both drugs reduced REM activity and increased Stage IV sleep. Withdrawal produced increased amounts of REM sleep and a temporary decrease in Stage IV sleep.

8. Fisher, S.; Pillard, R.C.; and Botto, R.W. Hypnotic Susceptibility During Cannabis Intoxication. Psychopharmacologia. 26 (Supplement) 126 (1972).

Twenty male volunteers showed no change in hypnotic susceptibility under ad libitum marijuana smoking compared to control conditions.

9. Franzini, L.R.; and McDonald, R.D. Marijuana Usage and Hypnotic Suggestibility. Journal of Consulting Clinical Psychologists. 40(2):176 (1973).

Psychology students were administered the Harvard Group Scale of Hypnotic Susceptibility test and completed questionnaire asking for demographic data and drug experience. Frequent marijuana use was correlated with greater susceptibility to hypnosis.

10. Freemon, F.R. The Effect of Delta-9-Tetrahydrocannabinol on Sleep. Psychopharmacologia. 35:39-44 (1974).

Twenty mg. of delta-9-THC was administered orally at bedtime to five volunteers. A decrease in REM sleep occurred. After four to six consecutive nights of administration of the drug, it was abruptly stopped. This withdrawal failed to produce a REM rebound, although mild insomnia was observed.

11. Kotin, J.; Post, R.M.; and Goodwin, F.K. Delta-9-Tetrahydrocannabinol in Depressed Patients. Archives on General Psychiatry. 28:345-48 (1973).

Eight hospitalized in-patients with moderate to severe depression were given 0.3 mg./kg. delta-9-THC or a matching placebo regularly for seven days. No evidence of a significant mood elevating and/or antidepressant effect could be demonstrated.

12. Lowinger, P. Psychiatrists' Attitudes about Marijuana. American Journal of Psychiatry. 127(7),196-97.

13. Melges, F.T.; Tinklenberg, J.R.; Hollister, L.E.; and Gillespie, H.K. Marihuana and the Temporal Span of Awareness. Archives of General Psychiatry. 24:564-567 (1971).

Marijuana extract administered orally to volunteers caused dose-related isolation of present from past and future and interference with goal-directed thinking. These changes were associated, in general, with euphoria. One of the possible reasons for marijuana use is that some persons find loss of awareness of past and future problems pleasant.

14. Neu, C.; DeMascio, A.; and Zwilling, G. Hypnotic Properties of THC: Experimental Comparison of THC, Chloral Hydrate and Placebo. The Therapeutic Potential of Marijuana. New York. Plenum Medical Book Co. (1976).

In the first study, nine subjects with sleep difficulties were given 10, 20 or 30 mg. of delta-9-THC or a placebo at weekly intervals using a double blind method. The drug, as compared to the placebo, significantly reduced sleep onset. Furthermore, sleep was less interrupted during the drug nights. Side effects were dose related. The chief complaint was a hangover the next day. In the second study, the delta-9-THC doses were reduced to 5, 10, and 15 mg. in order to avoid side effects. These were compared to a placebo and to 500 mg. chloral hydrate. Neither the chloral hydrate nor the delta-9-THC facilitated sleep induction or extended the duration of sleep as compared with the placebo. A few complaints of hangover were noted. Difficulties in controlling the room temperature during the winter may have sufficiently interfered with sleep to invalidate the results of the studies.

15. Regelson, W.; Butler, J.R.; Schulz, J.; Kirk, T.; Peek, L.; Green, M.L.; and Zalis, M.O. Delta-9-Tetrahydrocannabinol as an Effective Antidepressant and Appetite Stimulating Agent in Advanced Cancer Patients. Pharmacology of Marijuana. Braude, M. and Szara, S. (eds.). New York: Raven Press (1976).

A double-blind study with cancer patients receiving chemotherapy. An initial starting dose of 0.1 mg./kg. was raised only if previous doses were well tolerated. Cannabis was self-administered by subjects. Based on a battery of standardized tests, delta-9-THC acted as a mood elevator and tranquilizer. Cognitive functioning was unimpaired and appetite enhancement and retardation of weight loss were noted from clinical records. The need for narcotics was decreased and patients reported relief from pain.

16. Rouse, B.A.; and Ewing, J.A. Marijuana and Other Drug Use by Women College Students: Associated Risk Taking and Coping Activities. American Journal of Psychiatry. 130(4):486-490 (1973).

Use of marijuana was correlated with certain reported data (high socio-economic background, rejection of religion, use of alcohol, tobacco, birth control pills and prescribed psychotropic drugs). Users coped with anxiety or depression with a drug or sexual activity. Nonusers engaged in religious and physical activity. Users expressed more willingness to take all kinds of risks.

17. Sofia, R.D., and Knobloch, L.C. The Interaction of Delta-9-Tetrahydrocannabinol Pretreatment with Various Sedative-Hypnotic Drugs. Psychopharmacologia. 30:185-194 (1973).

The purpose of the investigation was to determine the effects of THC, following acute pretreatment, on the occurrence, onset and duration of the loss of righting reflex induced by several widely used sedative-hypnotic drugs. Pretreatment with a fixed dose of delta-9-THC produced a significant increase in the duration of action and number of mice exhibiting loss of the righting reflex after administration of several different sedative-hypnotic drugs. Moreover, pretreatment with various doses of THC caused a significant reduction in the onset to and duration of sleeping time of most of the sedative-hypnotic drugs tested.

18. Tassinari, C.A.; Ambrosetto, G.; and Gastaut, H. Clinical and Polygraphic Studies During Wakefulness and Sleep of High Doses of Marihuana and Delta-9-THC in Man. Pharmacology of Marihuana. Braude, M. and Szara, S. (eds.). New York: Raven Press (1976).

Eight volunteer subjects were given delta-9-THC (0.7-1.0 mg./kg.). Total sleep time as well as Stage II sleep were increased. REM sleep was reduced.

19. Weil, Andrew T.; Zinberg, N.E.; Nelsen, J.M. Clinical and Psychological Effects of Marihuana in Man. Science. 162:1234-1242 (1968).

A series of pilot experiments on acute marijuana intoxication in human subjects. The primary section of the study is concerned with effects on nine subjects who were inexperienced with cannabis. Two different doses of marijuana (0.5 and 1.0 gm. of 0.9% THC) and an inactive placebo were administered in a controlled double-blind study. In addition to the naive subjects, eight chronic marijuana users were tested with the high dose only. Subjects took either the drug or placebo by a standard and uniform inhalation method designed to minimize practice effects and individual differences in smoking technique. Subjects were then tested on a battery of standard psychological and psychomotor tests, and certain physiological measurements were taken in a neutral laboratory setting.

## III. Pulmonary and Pre-Anesthetic

### A. Bronchodilation

One of the most promising areas in marijuana research for therapeutic potential is the treatment of asthmatic patients. There have been several studies within the past few years which have shown that delta-9-THC acts as a bronchodilator in both asthmatic and normal subjects. Delta-9-THC causes acute bronchodilation both in healthy young men and in subjects with either chronic, stable bronchial asthma or experimentally induced bronchospasm.

Vachon and Tashkin and their collaborators are the main investigators who have conducted research in this area since 1972 and have helped to clarify a number of questions about the effects of marijuana on the diameter of airway conducting passages.

In 1973, these two groups published studies referring to the bronchodilator effects of marijuana. Vachon (1973) and his colleagues at Boston University School of Medicine studied the effects of a single administration of smoked marijuana on normal subjects and on asthmatic patients. In the normal group they found that airway resistance decreased significantly permitting an increase in specific airway conductance and mean expiratory flow rates. In the asthmatic patients there was a significant and prolonged reversal of bronchoconstriction.

Tashkin and his associates (1973) at the School of Medicine, UCLA, conducted a double blind study of 32 non-naive, male subjects randomly assigned to three groups, one of which smoked a placebo, the second receiving a 1% dose of delta-9-THC and the third using a 2% dose of delta-9-THC. They found that both dosages of delta-9-THC decreased airway resistance with a peak occurring at 15 minutes after administration and with activity still remaining after an hour. In a subsequent study, they (Tashkin, et al., 1974) examined dose response curves with oral placebo, and with 10, 15 and 20 mg. of delta-9-THC. THC dosages exhibited peak effects at three hours with persisting effects evident for six hours.

Tashkin and his investigators (1975) studied the effects of smoking marijuana after inducing bronchspasm in asthmatics with methacholine or exercise. In a single blind method 10 mg. of smoked delta-9-THC was compared with 1.25 mg. of inhaled isoproternol (Isuprel), both drugs placebo controlled. Bronchospasm was relieved promptly by both active drugs but not by their placebos. The isoproternol had a faster and higher peak effect, but the delta-9-THC had a longer duration of activity.

Smoking marijuana would not be an appropriate route of administration of cannabis since the smoke is irritating to the lung tissues. Other side effects which are manifested in smoking cannabis are tachycardia and the "high" associated with smoking.

Several other modes of administration have been and are being studied. Abboud and Sanders (1976) administered oral delta-9-THC in 10 mg. doses to six asthmatics and six control patients in a double blind study. They found that oral administration of delta-9-THC is unlikely to be of therapeutic value in asthma since its bronchodilator action was mild and inconstant and was associated with unwanted psychotropic and cardiovascular effects.

The use of aerosols to deliver delta-9-THC to the bronchioles has been studied by both Vachon and Tashkin in separate studies. Tashkin, et al., (1976,1977; Olsen, et al., 1976), in two phases of their study administered in random double blind fashion, several doses of delta-9-THC to both healthy men and asthmatic subjects and compared the effects of aerosolized delta-9-THC with those produced by smoking or ingesting comparable quantities of delta-9-THC. Their findings in healthy subjects showed possible therapeutic advantages of aerosolized delta-9-THC particularly in low doses of 5-10 mg. as compared to the smoked or orally administered THC with respect to a greater speed of onset and duration of bronchodilation. Furthermore, there was less cardiac and psychotropic effects.

However, the asthmatic subjects exhibited throat and chest discomfort associated with inhalation of aerosolized delta-9-THC. Vachon and his associates (1976A, 1976B) have minimized this bronchial irritation by using a micro-aerosolized delta-9-THC spray in 10 asthmatics. By using this method a much smaller total dose of the drug is delivered locally to the receptor sites with the presumed effect of limiting the amount of the drug available for systemic absorption. This micro-aerosol produced significant and prolonged bronchodilation, that is, it decreased airway resistance by an average of 16% at 90 minutes and increased flow rates without any adverse side effects. Both researchers indicate that further studies must be done on the aerosol to refine this mode of administration and determine its feasibility as a potential therapeutic for asthmatic patients.

## Bibliography

### Bronchodilation

1. Abboud, R.T.; Sanders, H.D. Effect of Oral Administration of Delta-9-THC on Airway Mechanics in Normal and Asthmatic Subjects. Chest. 70:4, 480-483 (1976).

Six asthmatic and six control subjects were used in a double blind study on the effect of oral administration of 10 mg. of delta-9-THC on airway mechanics. After oral administration of delta-9-THC in the control subjects, there was a slight but statistically significant increase in specific airway conductance, but no significant increase in the maximal expiratory flow at 50% of vital capacity. In 5 of the 6 asthmatic patients, there were variable changes in airway mechanics, but

the mean changes were not significant. The sixth asthmatic patient developed severe bronchconstriction after receiving the 10 mg. dose of THC. The results showed a mild and inconstant bronchodilator effect of delta-9-THC, with associated significant effects on the central nervous system in some subjects. The study concludes that oral administration of delta-9-THC is unlikely to be of therapeutic value in asthma since its bronchodilator action was mild and inconstant and unless a derivative with more effective bronchodilation action and minimized center nervous system effects can be developed.

2. Olsen, J.L.; Lodge, J.W.; Shapiro, B.J.; Tashkin, D.P. An Inhalation Aerosol of Delta-9-Tetrahydrocannabinol. Journal of Pharmacy and Pharmacology. 28:86 (1976).

3. Tashkin, D.P.; Shapiro, B.J.; Frank, I.A. Acute Pulmonary Physiologic Effects of Smoked Marijuana and Oral Delta-9-Tetrahydrocannabinol in Healthy Young Men. The New England Journal of Medicine. 289: 336-341 (1973).

Thirty-two healthy experienced male marijuana smokers were used in this study to determine the acute pulmonary physiologic effects of smoked marijuana and oral delta-9-THC on specific airway conductance. Results showed that in subjects smoking marijuana in 1 or 2 percent concentrations of delta-9-THC, specific airway conductance was increased, reached peak levels at 15 minutes and remained significantly elevated at 60 minutes. Smoking tobacco and deep breathing maneuvers simulating marijuana smoking decreased specific airway conductance. Twelve subjects were administered oral doses of delta-9-THC in 10, 15 and 20 mg. Specific airway conductance was significantly increased attaining peak levels at 3 hours after ingestion and remaining elevated 4-6 hours. The results of this study suggest that both smoked marijuana and oral delta-9-THC cause significant dilation of the airways lasting as long as 60 minutes and 6 hours respectively.

4. Tashkin, D.P.; Shapiro, B.J.; Frank, I.M. Acute Effects of Smoked Marijuana and Oral Delta-9-THC on Specific Airway Conductance in Asthmatic Subjects. American Review of Respiratory Diseases. 109:420-428 (1974).

Using a double blind crossover technique in ten stable bronchial asthma subjects, the acute effects of smoking natural marijuana at 2% concentration and 15 mg. of oral delta-9-THC on plethysmographically determined airway resistance and specific airway conductance were compared with effects of placebo. Specific airway conductance increased immediately and remained elevated at least two hours, after smoking marijuana; however, there were no changes after the placebo. After ingesting 15 mg. of THC specific airway conductance was significantly elevated at one and two hours and the airway resistance was reduced significantly at one to four hours. No changes occurred after placebo. The findings suggest that smoked marijuana and oral THC caused significant bronchodilation of at minimum two hours duration in asthmatic subjects.

5. Tashkin, D.P.; Shapiro, B.J.; Lee, Y.E.; Harper, C.E. Effects of Smoked Marijuana in Experimentally Induced Asthma. American Review of Respiratory Disease. 112:377-386 (1975).

The effects of smoked marijuana on bronchomotor tone were evaluated in eight subjects, aged 19 to 39 years of age, with clinically stable bronchial asthma after experimental induction of acute bronchospasm by inhalation of methacholine or by exercise.

Bronchospasm was induced by inhalation of methacholine and placebo marijuana was then administered in smoked form. This produced minimal changes in specific airway conductance and thoracic gas volume. The administration of 2.0% smoked marijuana and aerosolized isoproterenol after methacholine-induced bronchospasm caused prompt correction of bronchospasm and hyperinflation.

Exercise induced bronchospasm was produced by using a bicycle ergometer or treadmill. On these occasions placebo marijuana and aerosolized saline were adminstered after bronchospasm and recovery occurred gradually over a period of 30-60 minutes. When 2.0% of smoked marijuana and isoproterenol were each administered, they also caused a prompt return of specific airways conductance and thoracic gas volume to pre-exercise values.

The results of this study show significant bronchodilation and reduction in hyperinflation in resting patients with stable bronchial asthma after smoking marijuana, after experimentally induced bronchoconstriction and hyperinflation.

6. Tashkin, D.P.; Shapiro, B.J.; Reiss, S.; Olsen, J.L.; Lodge,J.W. Bronchial Effects of Aerosolized Delta-9-THC. The Therapeutic Potential of Marijuana by S. Cohen and R.C. Stillman (eds.). Plenum Press, New York. pp. 97-107 (1976).

Seven male experienced marijuana smokers, ages 22-23 years, were used in a pilot study to evaluate the cardio-pulmonary and psychotropic effects of varied doses of delta-9-THC which were administered by aerosol inhalation. These effects were compared with those produced by smoking or ingesting comparable quantities of delta-9-THC. The subjects were studied for seven days separated by at least 48 hours. On the first day, isoproterenol was adminstered, and on subsequent study days the subjects received 5, 10 or 20 mg. of synthetic delta-9-THC as an aerosol, smoked a cigarette containing 900 mg. of marijuana at 2.2% delta-9-THC, ingested 20 mg. synthetic delta-9-THC in sesame oil within gelatine capsules. After administration of the aerosolized THC significant changes occurred in specific airway conductance, heart rate and psychic "high" which appeared dose-related. The 5 mg. dose of aerosolized THC resulted in peak bronchodilation effects which was longer lasting than the dose of isoproterenol (5 hours vs. 30 minutes). The side effects from the 5 mg. dose of aerosolized THC was modest and short-lived compared to the effects of the higher 10 and 20 mg. doses of aerosolized THC.

The results of the study suggest that aerosolized delta-9-THC in lower doses of 5-10 mg. may have more therapeutic benefits than smoked and oral routes of administration with respect to speed of onset and duration of bronchodilation and with less cardiac and central nervous system effects.

7. Tashkin, D.P.; Reiss, S.; Shapiro, B.J.; Calvarese, B.; Olsen, J.L.; Lodge, J.W. Bronchial Effects of Aerosolized Delta-9-Tetrahydrocannabinol in Healthy and Asthmatic Subjects. American Review of Respiratory Disease. 115:57-65 (1977).

The purpose of this study was to determine the cardiopulmonary side effects and the intoxicating influence of different doses of aerosolized delta-9-THC in healthy and asthmatic subjects, and to compare the effects of aerosolized delta-9-THC with those of a comparable quantity of smoked or ingested delta-9-THC.

The healthy subjects were 11 male experienced marijuana smokers between the ages of 22-33. The asthmatic subjects were five clinically stable bronchial asthmatic patients, 3 men and 2 women between the ages of 31 to 64 years. Varied doses of delta-9-THC administered in random double blind fashion were evaluated for effects on airway dynamics, heart rate and central nervous system, and compared with aerosolized placebo, isoproterenol, and 20 mg. of oral and smoked delta-9-THC. The results showed significant physiological changes after inhalation of aerosolized delta-9-THC, and in healthy subjects suggests the possible therapeutic advantages of aerosolized delta-9-THC in low doses (5 mg.) over the smoked and orally administered delta-9-THC. The aerosolized delta-9-THC exhibited greater magnitude, speed of onset and duration of bronchodilation and lesser cardiac and central nervous system side effects. The investigators concluded that in asthmatic subjects aerosolized delta-9-THC, which created throat and chest discomfort may not be suitable for therapeutic use in bronchospastic patients.

8. Vachon, L.; Fitzgerald, M.X.; Solliday, N.H.; Gould, I.A.; Gaensler, E.A. Single Dose Effect of Marijuana Smoke: Bronchial Dynamics and Respiratory Center Sensitivity in Normal Subjects. New England Journal of Medicine. 288:19, 983-989 (1973).

Seventeen normal subjects, 18 to 26 years old with previous marijuana smoking experience, were used to study the acute effects of marijuana smoke on the normal tracheobronchial tree and on respiratory control. Marijuana was administered randomly to 9 subjects in a high dose (2.6 percent) concentration of delta-9-THC and to 8 subjects in a low dose (1.0 percent) concentration. Physiologic variables were monitored before smoking and for 20 minutes after. Results in the high dose group showed increase in heart rate of 28%, a decrease in airway resistance of 38% and an increase of 44% in specific airway conductance. The low dose group exhibited no increase in heart rate although there was a significant but lesser change in airways dynamics than the high dose group. The results of the study show that marijuana smoke causes bronchodilation rather than bronchoconstriction and does not cause central respiratory depression.

9. Vachon, L.; Robins, A.; Gaensler, E.A. Airways Response to Aerosolized Delta-9-THC: Preliminary Report. The Therapeutic Potential of Marijuana. Stillman and Cohen (eds.). Plenum Medical Book, New York (1976A).

The purpose of this study was to improve the therapeutic effectiveness of marijuana by refining the delivery system and delivering the drug locally in much smaller total dose. The results suggest that THC administered as a microaerosol in a dose of 0.5 mg., as compared to 5 mg. in other studies, produces a significant and prolonged bronchodilation while avoiding the adverse side effects which are usually exhibited in larger doses.

10. Vachon, L.; Mikus, P.; Morrissey, W.; Fitzgerald, M.; Gaensler, E. Bronchial Effects of Marijuana Smoke in Asthma. Pharmacology of Marijuanas: A Monograph of the National Institute on Drug Abuse (Volume II). M.C. Brande and S. Szara (eds.). Raven Press, New York (1976).

This is a repeat of Vachon, et al.'s 1973 study but conducted with asthmatic subjects. The investigators studied the effects of a single administration of marijuana smoke on bronchial mechanics in seventeen adult males with asthma. The subjects were between 18 and 30 years of age. Two groups were administered a high, 1.9%, and low, 0.9%, dose concentration of delta-9-THC. The asthmatic subjects responded to both concentrations showing a significant and prolonged reversal of the bronchoconstriction, and exhibiting a significant but shorter duration tachycardia. The marijuana smoke seemed to have an irritating effect on asthmatic subjects by causing more coughing than in normal subjects. The implication of this study is that very low concentrations of THC could act as a potential bronchodilator for reversible airway obstruction.

11. Vachon, L.; Robins, A.G.; Gaensler, E.A. Airways Response to Micro-Aerosolized Delta-9-THC. Chest. 70:444. Sept. (1976B).

A micro-aerosol of THC in 0.7 mg. dose was administered to seven normal subjects and 10 asthmatic patients. THC decreased airway resistance in asthmatics and increased flow rates; adverse side effects of tachycardia and "high" were insignificant. They conclude that low dose micro-aerosolized THC is an effective bronchodilator.

An undesirable feature of the activity of marijuana is the adverse effects on cardiovascular functions and related drug interactions. Gregg, et al., (1976b) conducted clinical studies to determine the cardiovascular effects of cannibinols combined with stressful oral surgery. Intravenous administration of THC caused classic dose-related tachycardia, and a transient syncopal hypotension following the pre-medication. Patients given general anesthesia within 72 hours of smoking marijuana sustained abnormal heart rate increases when compared with control non-smokers. This could have resulted from an interaction between stored cannabinol metabolites and atropine which was administered as part of the anesthetic technic. They concluded that THC has no advantage over diazepam or placebo as a pre-medicant, and interacted undesirably with other anesthetic medications.

From the studies thus far conducted and herein reviewed, it appears that contrary to initial expectation, THC does not have therapeutic advantages as a pre-anesthetic sedative.

## Bibliography


Pre-Anesthetic

1. Gregg, J.M.; Small, E.W.; Moore, R.; Raft, D.; Toomey, T. Emotional Response to Intravenous Delta-9-THC During Oral Surgery. Journal of Oral Surgery, 34:301-313 (1976a).

Delta-9-THC was administered intravenously as a pre-medicant to oral surgery patients in various doses. The patients exhibited pronounced elevations of anxiety states, dysphoric mood response, more frequent and intense psychotic-like thought in comparison to control placebo or diazepam responses. There were no major qualitative or quantitative differences observed between low and high doses of delta-9-THC. The authors conclude that a "surgical environment, containing even the mild stress of out-patient oral surgery appears to have the potential to precipitate undesirable emotional responses among cannabinol-intoxicated patients".

2. Gregg, J.M.; Campbell, R.L.; Levin,K.L.; Ghia, J.A.; Elliott, R.A. Cardiovascular Effects of Cannabinol During Oral Surgery. Anesthesia and Analgesia, 55:203-213 (1976b).

Fifty-five clinical trials were conducted to determine the cardiovascular effects of cannabinols. The two-part study compared the cardiovascular effects of premedicant intravenous doses of THC, diazepam and placebo, and did a restrospective study of the cardiovascular effects of outpatient general anesthesia

in patients who had smoked marijuana within 72 hours before anesthesia. When delta-9-THC was given intravenously as a premedicant and compared with diazepam and a placebo, a classic dose-related tachycardia followed the THC injection. Syncopal hypotension followed THC premedication and antiarrhythmic effects were observed after large doses. Patients given general anesthesia within 72 hours after smoking marijuana exhibited sustained abnormal postoperative tachycardia when compared with control nonsmokers.

It was concluded that delta-9-THC has no particular advantage over diazepam or placebo as a premedicant. THC altered the patients' adaptivity to stress and interacted undesirably with other anesthetic medications.

3. Johnstone, R.E.; Lief, P.L.; Kulp, R.A.; Smith, T.C. Combination of Delta-9-THC With Oxymorphone or Pentobarbital: Effects on Ventilatory Control and Cardiovascular Dynamics. Anesthesiology, 42:674-684 (1975).

The psychologic, respiratory and cardiovascular effects of delta-9-THC combined with oxymorphone (OXM) or with pentobarbital (PBL) were studied in 15 healthy volunteers. OXM caused sedation and ventilatory depression in 8 volunteers; THC in combination increased sedation and also increased respiratory depression with each THC dose. The combination of PBL and THC produced an unacceptably high incidence of anxiety and induced hallucinations. The study concluded that neither the combination of THC with OXM nor with PBL appears more desirable for anesthetic pre-medication than currently available agents.

4. Smith, T.C.; Kulp, R.A. Respiratory and Cardiovascular Effects of Delta-9-THC Alone and in Combination With Oxymorphone, Pentobarbital and Diazepam. From The Therapeutic Potential of Marihuana by S. Cohen and R.C. Stillman, eds. Plenum Medical Book Co., New York (1976) pp. 123-132.

## IV. Anticonvulsant

Although marijuana was used in the 19th Century fairly widely as an anticonvulsant, there has been very little clinical research done in this area in recent years. Most of the investigative studies on the use of delta-9-THC as an anticonvulsant have been conducted on animals. Consroe and his associates (Consroe, et al., 1973; Consroe & Man, 1973) studied the effects of delta-8-THC and delta-9-THC on animal seizures experimentally induced by pentylentetrazol, audiogenic stimulation and maximal electroshock stimulation. They found that both cannabinols blocked all three types of seizures in a dose-related manner. Both drugs appear to be qualitatively similar to diphenylhydantoin in their spectrum of anticonvulsant activity.

Wada, et al., (1975) examined the antiepileptic effects of cannabis in animals predisposed genetically to epilepsy. They administered delta-8-THC and delta-9-THC on Senegalese baboons and found that both isomers failed to affect the myoclonic response to photic stimulation. However, both isomers of THC exerted dose-related antiepileptic effects upon established kindled convulsions provoked by electrical stimulation of the amygdala. In terms of both antiepileptic effects and general toxicity delta-9-THC was more potent than delta-8-THC. The antiepileptic effects of the two THC isomers appears to be due to the suppression of propagation of the induced after-discharge to distant cerebral structures, although high doses also seem to suppress the after-discharge at the site of stimulation.

Feeney, et al., (1976) evaluated the effects of marijuana on epilepsy in 15 naturally epileptic Beagle dogs who were given either placebo or various dosages of delta-9-THC or cannabidiol on 20 consecutive days. Results in this study indicated that delta-9-THC, the psychoactive component of marijuana can activate existing epileptic pathology.

The clinical studies of anticonvulsant properties of cannabis on humans have been minimal. Davis and Ramsey (1949) conducted a pilot study to examine the effect of THC in five epileptic, hospitalized children who had been receiving treatments of diphenylhydantoin or mephenytoin. Two children showed improvement on one cannabinoid, with one becoming seizure-free, however, transfer to a second cannabinoid gave mixed results. Perez-Reyes and Wingfield (1974) reported on the single case of a 24 year old man with centricephalic epilepsy. Intravenously infused cannabidiol did not reduce, and perhaps increased, the abnormal EEG activity.

In another case report, Consroe, et al., (1975) reported on a 24 year old man with grand mal epilepsy whose epileptic seizures were controlled by smoking marijuana in conjunction with taking routine doses of phenobarbital and diphenylhydatoin. This suggests that smoked marijuana may have a beneficial action in some types of human epilepsy.

## Bibliography

Anticonvulsant

1. Consroe, P.F.; and Man, D.P. Effects of Delta-8- and Delta-9-THC on Experimentally Induced Seizures. Life Sciences. 13:429-439 (1973A).

A comparative study on the anticonvulsant effects of delta-8- and delta-9-THC on experimentally induced seizure models, i.e. audiogenic seizure (AS0 test, maximal electroshock seizure (MES) test, and pentylenetetrazol (PTZ) in audiogenic rats. Both delta-8- and delta-9-THC were effective in blocking the 3 types of convulsive seizures in a dose-related manner. Delta-8-THC is 3 times more neurotoxic than delta-9-THC. The investigators conclude that delta-8-and delta-9-THC may have poor therapeutic potentials as antiepileptic drugs due to the low protective indexes determined in the study.

2. Consroe, P.F.; Man, D.P.; Chin, L.; Picchioni, A.L. Reduction of Audiogenic Seizure by Delta-8- and Delta-9-Tetrahydrocannabinols. Journal of Pharmacy and Pharmacology. 25:764-765 (1973B).

A study on female rats showed that delta-8-THC doses of 1.25, 2.5 and 5 mg. $kg.^{-1}$ produced antiseizure activity against sound induced convulsions.

3. Consroe, P.R.; Wood, G.C.; Buchsbaum, H. Anticonvulsant Nature of Marihuana Smoking. Journal of the American Medical Association. 234:306-307 (1975).

A 24 year old epileptic patient who received daily therapeutic doses of diphenylhydantoin and phenobarbital to control epileptic seizures reported this regimen inadequate as he continued to have regular attacks. At age 22, the patient began smoking marijuana while continuing the prescribed anticonvulsant drug therapy, and was able to control the attacks as long as he continued to take the combination of all three drugs.

4. Consroe, P.; Jones, B.; Laird, H.; Reinking, J. Anticonvulsant-Convulsant Effects of Delta-9-Tetrahydrocannabinol. The Therapeutic Potential of Marihuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book Co. pp. 363-382 (1976).

In this anticonvulsant study, experiments were designed to obtain data on delta-9-THC's activity in rats against some well-known chemical convulsants and to further quantitate and compare its properties in electric seizure models. The resultant data clearly shows that the cannabinoid significantly protects animals against maximal seizures over the full range of PTZ doses used.

In the convulsant study, experiments were designed to obtain basic pharmacological data on the convulsant effects of delta-9-THC in specially bred rabbits. Conclusions from the data indicate that tolerance to delta-9-THC induced convulsions is highly subject and dose dependent.

The present data confirm and extend findings of both an anticonvulsant and convulsant effect of delta-9-THC, "a truly unique drug." These divergent properties underscore the extremely complex pharmacological profile of this major psychoactive component of marijuana. Sixty-three references are appended to this report.

5. Davis, J.P.; and Ramsey, H.H. Antiepileptic Action of Marihuana Active Substances. Federation Proceedings. 8:282-285 (1949).

6. Feeney, D.M.; Spiker, M.; and Weiss, G.K. Marihuana and Epilepsy: Activation of Symptoms by Delta-9-THC. The Therapeutic Potential of Marihuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book. pp. 343-362 (1976).

To evaluate the effects of marijuana on epilepsy, fifteen naturally epileptic Beagle dogs were given either placebo or various dosages of delta-9-THC or cannabidiol on twenty consecutive days. Myoclonic jerks and generalized seizures were observed in those dogs receiving high dosages of delta-9-THC. In six epileptic Beagles implanted with cortical and subcortical electrodes, delta-9-THC reliably evoked myoclonus and temporal lobe seizures. Additionally, low dosages of delta-9-THC activated epileptiform activity from quiescent alumina cream motor cortex foci in three chronic cats. These results indicate that delta-9-THC a psychoactive component of marijuana, can activate existing epileptic pathology. This report includes 40 references.

7. Karler, R.; and Turkanis, S.A. The Antiepileptic Potential of the Cannabinoids. The Therapeutic Potential of Marihuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book. pp. 383-397 (1976).

The objective of this research was to determine the clinical potential of the cannabinoids as antiepileptics. On the basis of laboratory data in animals and on clinical data, cannabidiol (CBD) appears to have a good potential for this purpose. In animals it has a relatively high protective index; that is, its anticonvulsant activity manifests itself at lower doses than does its neurotoxicity. The protective index for CBD is similar to that for the well-established antiepileptic PB. Furthermore, in humans, CBD is devoid of the psychotoxicity and of the cardiac effects of delta-9-THC and its 11-hydroxy metabolite.

The combination of these properties suggests that this cannabinoid may be an acceptable agent for human trial; however, any further assessment of the clinical potential of CBD must be deferred, because it has not been extensively studied and little is known about its general pharmacological and toxicological properties. Such data are necessary before any serious consideration can be given to the use of CBD or any other cannabinoid in humans. 27 references are appended to this report.

8. Perez-Reyes, M.; and Wingfield, M. Cannabidiol and Electroencephalographic Epileptic Activity. Journal of the American Medical Association. 230:1635 (1974).

9. Wada, J.A.; Asawa, T.; Corcoran, M.E. Effects of Tetrahydrocannabinols on Kindled Amygdaloid Seizures and Photogenic Seizures in Senegalese Baboons, Papio, Papio. Epilepsia. 16:439-448 (1975).

This study was conducted to examine the antiepileptic effects of cannabis in animals predisposed genetically to epilepsy and to observe the effects of THC on photo myoclonic response and on kindled amygdaloid convulsions in Senegalese baboons, a species with marked susceptibility to photic seizures.

Injections of delta-8-THC and delta-9-THC failed to affect myoclonic response to photic stimulation in the Senegalese baboons.

The results of the study indicate that both isomers of THC exerted dose-related antiepileptic effects upon established kindled convulsions provoked by electrical stimulation of amygdala. Delta-9-THC was more potent than delta-8-THC in terms of antiepileptic effects and general toxicity.

## V. Analgesic

When tincture of hemp was introduced into Western medicine in 1839, it was claimed to be an effective analgesic. Despite the enthusiastic endorsement of numerous 19th Century clinicians, cannabis preparations fell from favor as more potent and predictable drugs were introduced.

Recently, there has been a renewed interest in the analgesic effect of the psychoactive ingredient of cannabis (THC). Numerous animal studies, including Kaymakcolon (1974) and Sofia (1973), have demonstrated mild analgesic effects of THC suggesting both a peripheral action via the inhibition of prostaglandin $E_2$ biosynthesis and a central action via the stimulation of pituitary-adrenal axis and the elevation of serum corticosterone levels.

The difficulty of animal studies is in the separation of the euphoric or sedative effects of THC from its analgesic effect.

Noyes (1975) and his colleagues at the University of Iowa College of Medicine have published two articles on the effect of orally administered THC to terminal cancer patients suffering moderately severe pain. They show a definite analgesic effect coupled with sedation, altered perception of time and a sense of detachment and loss of control. While the patients appeared peaceful, they expressed displeasure with the behavioral side-effects.

Further studies on larger scales are definitely indicated specifically to evaluate the use of THC as an adjunct to well-known effective analgesic agents.

## Bibliography


Analgesic

1. Kaymakcalan, S.; Tucker, R.K.; and Turker, M.N. Analgesic Effect of Delta-9-Tetrahydrocannabinol and Development of Tolerance to this Effect in the Dog. Psychopharmacologia. 33:123-128 (1974).


This report studied the effect of THC on dogs subjected to electrical stimulation of tooth pulp. The animals received relatively high doses of THC (0.1 mg/kg and 0.5 mg/kg). Pain was measured by tremors in jaw muscles and crying. Unfortunately, no data on controls is presented for evaluation. Their data appears to show an approximate increase in pain threshold by 400% with the gradual development of tolerance over a 12 day period. The analgesic effect lasted four days and peaked at one hour. The lack of controls makes this data extremely difficult to assess.

2. Noyes, Russell, Jr., et al. The Analgesic Properties of Delta-9-Tetrahydrocannabinol and Codeine. Clinical Pharmacology and Therapeutics. 18:84-89 (1975).

Thirty-six patients with advanced cancer and continuous pain of moderate severity, attributable to their disease, received (on successive days) placebo, 10 and 20 mg. of THC and 60 and 120 mg. of codeine orally in identical capsules in a random double blind pattern. Pain relief and subjective effects were followed closely over a seven hour period. Significant differences were observed between placebo and 20 mg. THC and between placebo and 120 mg. codeine. Other differences did not reach significance. Patients receiving 20 mg. of THC were heavily sedated. With few exceptions, patients voiced dislike for the sedation and accompanying altered perception of time, sense of detachment and loss of control. The authors concluded that the analgesic properties of THC appear to be mild and for that reason should be studied among patients experiencing mild pain since all their patients appeared exceptionally peaceful while at the same time reporting little pain relief.

3. Noyes, Russell Jr.,; Brunk, Fred; Baram, David A.; and Canter, Arthur. Analgsic Effect of Delta-9-Tetrahydrocannabinol. The Pharmacology ofMarijuana, Braude, M. and S. Szara (eds.). New York: Raven Press (1976).

This report is based on a study of 10 patients with pain secondary to terminal cancer who received 5, 10, 15 and 20 mg. of THC orally in a double blind random sequence on successive days. The study was well documented as to pain relief and side effects. Pain relief significantly superior to placebo was demonstrated at high dose levels. They also showed that with increasing doses the drug was highly sedating and a dreamy social withdrawal developed which was unpleasant for a majority of their patients.

4. Sofia, R.D.; et al. Anti-Edema and Analgesic Properties of Delta-9-Tetrahydrocannabinol. Journal of Pharmacology and Experimental Therapeutics. 186:646-654 (1973).

This report contains studies on the use of THC in mice with experimental edema, arthritis and a variety of pain producing tests. The results support the conclusions that THC is an effective anti-inflammatory agent mediated in some way by the pituitary-adrenal axis. Other studies support the conclusion that THC increases plasma corticosterone levels. In their studies, the analgesic activity for THC is substantially greater than aspirin with possibly a central rather than peripheral action as with aspirin.

## VI. Cancer

Delta-9-THC is currently being used experimentally in three areas of cancer treatment: as an antinauseant, antiemetic agent; as an analgesic agent; and as a tumor growth retardant.

The use of delta-9-THC as a means of reducing or eliminating the nausea, vomiting and loss of appetite following chemotherapy shows definite promise. Since present antiemetics are often unsuccessful in controlling such symptoms in these patients, an improved treatment for this purpose is desirable. Sallan (1976) reports on the administration of two oral courses of delta-9-THC or a placebo to a small number of cancer patients in chemotherapy who were not responding well to conventional antiemetics. Nausea and vomiting were brought under control with delta-9-THC significantly more often than with the placebo. In response to the Sallan report, a letter to the editor of The New England Journal of Medicine about cancer patient and poet, Ted Rosenthal (Allen 1976) reported that the smoking of marijuana, which was directed by his physician, permitted him to eat when previous drugs had had no effect in relieving his nausea and vomiting caused by chemotherapy. Butler and Regelson (1976) in their study on treatment effects of delta-9-THC in an advanced cancer population provide limited evidence that the drug has a beneficial effect on the symptoms of "depression, pain, nausea, and vomiting, and show an attenuation of the cachexia of cancer patients."

In studying the psychological effects of oral delta-9-THC in advanced cancer patients, Noyes (1976) reports that the drug is an effective, mild analgesic producing relaxation, mild mood elevation, appetite stimulation, and a degree of analgesia. Adverse reactions in 9% of patients included complaints of dizziness, blurred vision, and impaired thinking. In another letter to the editor of The New England Journal of Medicine in response to the Sallan report (Nieburg, 1976), it was reported that two cancer patients who smoked marijuana, which does not necessarily have the same properties as delta-9-THC taken by mouth, suffered increased pain after smoking and had to stop. In another study of analgesic and antitumor potential of the cannabinoids, Harris (1976) reports that delta-9-THC proved inactive in standard analgesic test procedures on rats and mice at doses below those that produced severe behavioral and psychomotor impairments. The researchers expressed hope, however, that a non-dependence producing strong analgesic may emerge from the cannabis field.

The action of delta-9-THC on the inhibition of tumor growths is also reported. Studies by Harris (1976) indicate that mice inoculated with Lewis lung adenocarcinoma materials showed reductions of tumor size from 25% to 82% depending upon the dose and duration of treatment, with subsequent administrations of oral delta-9-THC, delta-8-THC and cannabinol. Friend leukemia virus growth was also inhibited by delta-9-THC, but L1210 murine leukemia was not. In vitro experiments confirmed the animal inhibition of growth, leading the authors to conclude that certain cannabinoids possess antineoplastic properties by virtue of their interference with RNA and DNA synthesis. Similar studies and results are also reported by Munson. In another study by Johnson and Wiersema (1974), delta-9-THC was found to inhibit bone marrow leukopoiesis when injected intravenously into rats. These results suggest that certain types of leukemia may also be responsive to therapeutic use of delta-9-THC.

## Bibliography

### Cancer

1. Allen, Terence. Tetrahydrocannabinol and Chemotherapy: A Letter to the Editor. New England Journal of Medicine, Vol. 294, No. 3, January 15, 1976. pp. 168

A brief letter to the editor describes the antiemetic effects of cannabis as described in the book, How Could I Not Be Among You?, by its author and poet, Ted Rosenthal, who died of leukemia in 1972. Rosenthal smoked marijuana when he became nauseated after ingesting asparaginase, a chemotherapeutic drug, upon the recommendation and direction of his physician.

2. Butler, Joel R.; and Regelson, William. Treatment Effects of Delta-9-THC in an Advanced Cancer Population. The Therapeutic Potential of Marihuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book. pp. 313-328 (1976).

The purposes of this study were 1) to test the acute and chronic psychological and physiological correlates of delta-9-THC on a selected population of 54 subjects with limited life expectancy to establish dosage and toxicity; and, 2) to evaluate the beneficial effects, for example reverse depressive trends and anxious behavior, and to determine analgesic, antiemetic, and appetite-stimulating effects, on cancer patients.

The dosage of delta-9-THC supplied by the National Institute of Mental Health in 5 mg. capsules was computed according to subjects' weight. Five psychological tests were routinely administered prior to study and at the end of each treatment condition.

The results, including both significant findings and trends, suggest that delta-9-THC, when administered as a "general tonic" to medically ill patients and within the context of their specific medical treatments (cancer chemotherapy) acts as both a mild tranquilizer and euphoriant. The results of this study also provide limited evidence that delta-9-THC has a beneficial effect on the symptoms of depression, pain, nausea, and vomiting, and show an attenuation of the cachexia in cancer patients.

Thirty-seven references are included in this report.

3. Harris, Louis S. Analgesic and Antitumor Potential of the Cannabinoids. The Therapeutic Potential of Marihuana. S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book. pp. 299-312 (1976).

The author reports that delta-9-THC proved inactive in standard analgesic procedures on rats and mice at doses below those that produced severe behavioral and psychomotor impairments. Results of cross-tolerance tests between morphine

and B-hexahydrocannabinol are described and give hope that a non-dependence-producing strong analgesic may emerge from the cannabis field.

Harris also reports that mice inoculated with Lewis lung adenocarcinoma materials showed reductions of tumor size from 25% to 82%, depending upon the dose and duration of treatment, with subsequent administrations of oral delta-9-THC, delta-8-THC, and cannabinol, but these investigators did not find such an effect with cannabidiol. Cannabinoids increased survival time by a quarter to a third compared to an increase of about 50% for cyclophosphamide. Friend leukemia virus growth was also inhibited by delta-9-THC, but L1210 murine leukemia was not. In vitro experiments confirmed that certain cannabinoids possess antineoplastic properties by virtue of their interference with RNA and DNA synthesis.

Twenty-six references are included in this research paper.

4. Johnson, R.J.; and Wiersma, V. Repression of Bone Marrow Leukopoiesis by Delta-9-Tetrahydrocannabinol (delta-9-THC). Research Communications in Chemical Pathology and Pharmacology, Vol. 7, No. 3, March, 1974. pp. 613-616.

Delta-9-THC was found to inhibit bone marrow leukopoiesis when injected intravenously in the rat.

Reduction of metamyelocytes and an increase of mature lymphocytes was noted in the THC-treated animals. No significant difference in erythropoiesis was noted between control and THC-treated animals.

These results suggest that certain types of leukemia may be responsive to therapeutic use of delta-9-THC.

3. Munson, A.E.; Harris, L.S.; Friedman, M.A.; Dewey, W.L.; and Carchman, R.A. Antineoplastic Activity of Cannabinoids. Journal of the National Cancer Institute, Vol. 55, No. 3, September, 1975. pp. 597-602.

Lewis lung adenocarcinoma growth was retarded by the oral administration of delta-9-THC, delta-8-THC, and cannabinol (CBN), but not cannabidiol (CBD). Animals treated for 10 consecutive days with delta-9-THC, beginning the day after tumor implantation, demonstrated a dose-dependent action of retarded tumor growth. Mice treated for 20 consecutive days with delta-8-THC and CBN had reduced primary tumor size. CBD showed no inhibitory effect on tumor growth at 14, 21 or 28 days. Delta-9-THC, delta-8-THC and CBN increased the mean survival time, whereas CBD did not. Delta-9-THC administered orally daily until death in doses of 50, 100 or 200 mg/kg did not increase the life-spans of mice hosting the L1210 murine leukemia. However, delta-9-THC administered daily for 10 days significantly inhibited Friend leukemia virus-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for actinomycin D. Experiments with bone marrow and isolated Lewis lung cells incubated in vitro with delta-9-THC and delta-8-THC showed a dose-dependent inhibition (30-20%, respectively) of tritiated thymidine and $^{14}$C-uridine uptake into these cells. CBD was active only in high concentrations.

6. Nieburg, Herbert A.; Margolina, Francine; and Seligman, Barbara. Tetrahydrocannabinol and Chemotherapy: A Letter to the Editor. New England Journal of Medicine, Vol. 294, No. 3, January 15, 1976. pp. 168.

An article by Sallan et al., which described the value of cannabis derivatives in preventing nausea in cancer patients receiving chemotherapy, prompted this letter of caution in response. The authors state that two of their cancer patients who had been smoking marijuana for a number of years and who were presently receiving chemotherapy, experienced increased pain while "high" on the drug and reached a point where they had to cease smoking marijuana altogether.

7. Noyes, Russell; Brunk, Fred S.; Avery, David; and Carter, Arthur. Psychologic Effects of Oral Delta-9-Tetrahydrocannabinol in Advanced Cancer Patients. Comprehensive Psychiatry, Vol. 17, September/October 1976. pp. 641-646.

The primary purpose of this study was to compare the analgesic properties of THC and codeine. THC was shown to be a mild analgesic in patients with cancer pain. In light of THC's therapeutic potential in this and a variety of other indications, it became important to identify its side effects in a treatment setting and establish the limits of its safety. In a dose of 20 mg., this drug was not only prohibitively sedating, but was severely intoxicating as well. In addition, 9% of the patients experienced adverse reactions despite the controlled and supportive environment in which the drug was administered. The 10 mg. dose rarely presented such problems, however, it was also sedating and yielded complaints of dizziness, blurred vision, and impaired thinking. On the positive side, the drug produced relaxation, mild mood elevation, appetite stimulation and a degree of analgesia, effects which could prove useful in cancer patients.

8. Sallan, Stephen; Zinberg, Norman; and Frei, Emil. Antiemetic Effects of Delta-9-Tetrahydrocannabinol in Patients Receiving Cancer Chemotherapy. The Therapeutic Potential of Marihuana, S. Cohen and R.C. Stillman (eds.). New York, Plenum Medical Book, 1976. pp. 329-335.

Oral delta-9-THC 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 THC 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 THC courses and in none of the 22 placebo courses. For patients completing the study, response occurred in 12 out of 15 courses of THC and in none of the 14 courses of placebo. No patients vomited while experiencing a subjective "high". Oral THC has antiemetic properties and is significantly better than a placebo in reducing vomiting caused by chemotherapeutic agents.

## VII. Anti-bacterial

The antibacterial properties of cannabis have often been mentioned in the literature pertaining to the ancient and folk medicine of various cultures. The efficacy of cannabis in promoting healing for external afflictions has been consistently reported up to the present time.

The first systematic investigation of these properties was carried out in 1937. This work was not followed up until the 1970's.

Kabelik, Krejci and Santavy (1960) investigated the active substances of cannabis from the bacteriological and chemical viewpoint and from the standpoint of the eventual applicability of the effective substances in clinical practice. They found evidence of the bactericide effect of the substances upon certain gram-positive microorganisms, including those resistant to penicillin. They cite clinical trials which stand in support of the results obtained in vitro. One example of a clinical trial is recounted below:

> ...Of great interest was the follow-up of a physician and pathologist, who was treated with the IRC (bilogically active substances) for a severe infection of the thumb of the right hand, an injury he suffered in the dissecting room. The severe condition, threatening amputation, and the absolute resistance of the microflora to available antiobiotics were overcome by substances from cannabis.

Further work in this area was carried out by van Klingeren and ten Ham (1976). They tested the antibacterial activity of delta-9-THC and cannabidiol. They, too, documented the effectiveness of these substances against gram positive microorganisms.

Since the anti-bacterial effect of cannabis is significantly reduced in the presence of blood, plasma and serum, it is unlikely that cannabis derivatives will be used internally. However, its effectiveness as a topical preparation should be investigated further, particularly noting the ability of the substances to inhibit the growth of penicillin-resistant strains. Kabelik also mentions the results achieved, though unpublished, toward the possible application of cannabis in veterinary medicine, particularly as a preventive to veterinary workers for those diseases which are passed from animals to man.

## Bibliography

### Anti-bacterial

1. Kabelik, J.; Krejci, Z.; and Santavy, F. Cannabis as a Medicament. Bulletin of Narcotics. pp. 5-23. July-Sept. (1960).

A systematic investigation of the mid-European flora carried out in order to establish the presence of antibacterially effective substances. A high content of remarkably active substances found present in Cannabis sativa var. indica and in Cannabis sativa has been investigated in detail from the bacteriological and chemical viewpoints and from the standpoint of the eventual applicability of the effective substances in clinical practice. Experimental evidence showed the bactericide effect of the substances from cannabis in vitro upon the following gram-positive microorganisms: Staphylococcus aureus hemolytic, Staphylococcus aureus – resistant to penicillin, Streptococcus alpha, Streptococcus beta hemolytic, Pneumococcus, Enterococcus, Corynebacterium diphtheria, Bacillus anthracis, Erysipelothrix rhusiopath. A significant antibacterial effect upon the Mycobacterium tuberculosis in vitro could be observed up to a dilution of 1:150,000. The gram negative microorganisms proved to be resistant. Blood, plasma and serum partially inactivate and decrease the antibacterial effect.

2. van Klingeran and ten Ham, M. Antibackterial Activity of Delta-9-Tetrahydrocannabinol and Cannabidiol. Antonie van Leeuwenhoek. 42:9-12 (1976).

Both cultures of staphylococci and streptococci were innoculated with varying concentrations of delta-9-THC and cannabidiol. Findings were that both substances were bacteriostatic and bactericidal, but were ineffective against gram negative bacilli. When horse serum was incorporated, the antibacterial effect was greatly reduced.

## VIII. Conclusions and Recommendations

Twelve years ago there was very little research being conducted on marijuana and those investigators interested in studying the drug were fearful of possible legal recriminations. The socio-political controversy surrounding marijuana prevented the scientific/medical communities of this country from investigating the potential medical applications of the drug. During the past ten years considerable publicity and government supported research have proven many of the existing fears unwarranted and exaggerated.[1] In fact, as a pharmaceutical cannabis has an extremely low biological toxicity, which is a highly desirable property of the drug.[2] It is, therefore, relatively safe to use in conducting clinical research on human subjects. Other findings have shown that there is no physical dependence and minimal autonomic disturbance.[3]

There are two undesirable reactions which need to be controlled if marijuana were to be used as a medication, i.e., its psychotropic activities and its tendency to accelerate heart rate (tachycardia). However, with continued research and experimentation, these properties will eventually be removed. Marijuana is a complex mixture of over a dozen cannabinoids, and other substances whose molecular structures can be modified in a manner that will eliminate its undesired psychological effects, make the drug water soluble and stabilize the drug for a longer shelf life.[4] Additionally, synthetic cannabinoids are being developed which are designed to provide the desired action for a particular condition. As the government reports indicate, however, cannabis must continue to undergo further testing before the Federal Drug Administration can approve the drug for therapeutic application.

There are several areas in which therapeutic applications of marijuana appear to be most promising. In the treatment of glaucoma, cannabis reduces intraocular pressure in either its smoked or oral form. THC is as potent as, and in some cases, more effective than antiglaucoma preparations currently available, and a preparation which can be topically applied is now being investigated. A second area where marijuana is showing promise as a therapeutic drug is in the management of asthmatics. Several studies have shown that THC dilates the pulmonary air passages and decreases airway resistance. Asthmatic patients have responded to oral, smoked or aerosolized THC with bronchodilation, and several researchers are working on developing an aerosolized THC which eliminates the lung irritant properties of the smoked marijuana and the psychotropic properties of the oral THC. Administering THC to cancer patients undergoing chemotherapy has produced encouraging results. THC reduces or eliminates the nausea, vomiting and loss of appetite associated with chemotherapy. The standard antiemetic drugs now available have not been very successful in mitigating these adverse side effects whereas THC has been most effective in its action.[5,6]

Studies determining the anticonvulsant effects of THC have thus far proven inconclusive. There are a few isolated cases where cannabis was used to treat epileptic patients, but no clinical research has been done recently on human subjects. The effectiveness of delta-9-THC as an anti-tumor agent, an anti-depressant, a sedative-hypnotic, an analgesic, a pre-anesthetic, an antiobiotic requires further study.

It is evident that further research must be conducted in the medicinal properties of marijuana and the drug's effectiveness as a therapeutic fully demonstrated before it is rescheduled as a prescriptive drug. The following must first be resolved:

1) the elements in THC producing undesirable side effects, such as psychoactivity and tachycardia, should be removed;

2) effective and safe forms of administration need to be developed in modes suitable to its particular therapeutic application, e.g., a topical preparation for glaucoma, an aerosolized spray for asthmatics;

3) development of THC in synthetic form or parent-altered compounds requires testing for toxicity; and,

4) the question of development of tolerance when used as a drug in chronic disorders, as well as reverse tolerance must be addressed.[8, 9]

The National Institute of Drug Abuse (NIDA) promotes and supports research investigating the therapeutic applications of cannabis. NIDA supplies research materials to investigators, and funds research.

At present, very little if any, research on the medicinal uses of marijuana is being conducted in Hawaii. The task force believes further investigation into the therapeutic potentials of marijuana is worthwhile and, therefore, recommends the following:

1. The Hawaii State Legislature should advocate increased research in the area of the therapeutic effects of marijuana. This can be accomplished through:

   a) financially supporting such research;
   b) removing the social stigma attached to marijuana by educating both the public and scientific/medical communities as to the therapeutic potentials of marijuana; and,
   c) informing investigators in the scientific/medical communities of the relative ease in conducting research using marijuana.

2. Studies have suggested that marijuana may be useful as an anti-emetic and an anti-nauseant drug for patients undergoing chemotherapy for control of cancer. We strongly recommend that immediate investigative research proceed in this area in Hawaii.

3. Because glaucoma eventually results in blindness, the task force further recommends that persons suffering from glaucoma who are unresponsive to conventional medications not be prohibited from using marijuana to control their disease.

## References


1. DuPont, R.L., Marihuana: An Issue Comes of Age, from Pharmacology of Marijuana by M.C. Braude and S. Szara, eds. Raven Press, New York, 1976, pp. 3-8.

2. Marihuana and Health: In Perspective. Summary and Comments on Fifth Annual Report of the U.S. Congress from the Secretary of Health, Education, and Welfare, 1975. National Institute on Drug Abuse, Rockville, Maryland (1976).

3. Mikuriya, T., ed. Marihuana Medical Papers 1839-1972. Medi-Comp Press, Oakland, California, 1973, pp. XIII, XVII.

4. Cohen, S. Therapeutic Aspects in Marihuana Research Findings: 1976. NIDA Research Monograph 14. by R.C. Peterson, ed. National Institute on Drug Abuse, USDHEW, Rockville, Maryland. 1977.

5. Cohen, Conclusions of the Conference in The Therapeutic Potential of Marihuana, by S. Cohen and R.C. Stillman, eds. Plenum Medical Book Company. New York, 1976, pp. 399-430.

6. Marihuana and Health. Sixth Annual Report to the U.S. Congress. From the Secretary of Health, Education and Welfare 1976. National Institute on Drug Abuse, Rockville, Maryland, 1977, pp. 25-26.

7. Marihuana and Health. Fifth Annual Report to the U.S. Congress from the Secretary of Health, Education and Welfare 1975. National Institute on Drug Abuse, Rockville, Maryland. 1976, pp. 117-127.

8. Marihuana and Health op. cit.

9. Szara, S. Clinical Pharmacology of Cannabis: Scientific and Nonscientific Constraints. From Pharmacology of Marijuana by M.C. Braude and S. Szara, eds. Vol. I. Raven Press, New York, 1976, pp. 29.

## Glossary

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| afterdischarge | the portion of the response to stimulation in a sensory nerve which persists after the stimulus has ceased. |
| amygdala | a term used in anatomical nomenclature to designate an almond-shaped structure, such as the amygdala of the brain. |
| analgesic | an agent that alleviates pain without causing loss of consciousness. |
| anesthetic | a drug or agent that is used to abolish the sensation of pain. |
| antibacterial | a substance that destroys bacteria or suppresses their growth or reproduction. |
| antidepressant | an agent that stimulates the mood of a depressed patient. |
| antiemetic | an agent that prevents or alleviates nausea and vomiting. |
| antineoplastic | an agent which inhibits or prevents the development of neoplasms (any new and abnormal growth, specifically a new growth of tissue in which the growth is uncontrolled and progressive); checking the maturation and proliferation of malignant cells. |
| audiogenic | produced by sound. |
| autonomic | functionally independent. |
| biosynthesis | the building up of a chemical compound in the physiologic processes of a living organism. |
| bronchodilator | an agent that causes expansion of the lumina of the air passages of the lungs. |
| cachexia | a profound and marked state of constitutional disorder; general ill health and malnutrition. |
| cannabidiol | chemical derivative of cannabis. |
| cannabinoids | chemical derivative of cannabis. |
| cannabinols | chemical derivative of cannabis. |
| cannabis | the dried flowering tops of hemp plants, Cannabis sativa L. which contains the euphoric principles delta-one-3,4-trans (delta-9-) and delta-six-3,4-trans (delta-8-) tetrahydrocannabinol. It is classified as a hallucinogenic and is prepared as bhang, ganja, hashish, and marijuana. |

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| corticosterone | a crystalline steroid found in the adrenal cortex. It possesses life-maintaining properties in adrenalectomized animals and several other activities ascribed to the adrenal cortex. |
| derivative | a chemical substance derived from another substance. |
| diphenylhydantoin | a white, odorless powder used as an anti-convulsant in grand mal epilepsy. Brand name: Dilantin. |
| epinephrine | a hormone secreted by the adrenal medulla in response to splanchnic stimulation. It is a potent stimulator of the sympathetic nervous system. It is used pharmaceutically as a sympathomimetic, a cardiac stimulant, a pressor substance, and to relax bronchial smooth muscles. |
| hypnotic | a drug that acts to produce sleep. |
| in vitro | within a glass; observable in a test tube; in an artificial environment. |
| isomers | any compound exhibiting, or capable of exhibiting isomerism (the possession by two or more distinct compounds of the same molecular formula, each molecule possessing the identical number of atoms of each element, but in different arrangement). |
| leukopoiesis | production of white blood cells or corpuscles. |
| mephenytoin | an anticonvulsant. |
| metabolites | any substance produced by metabolism or by a metabolic process. |
| miotics | an agent that causes the pupil to contract. |
| myoclonic | relating to or marked by myoclonus (shocklike contractions of a portion of a muscle, an entire muscle, or a group of muscle, restricted to one area of the body or appearing synchronously or asynchronously in several areas. |
| pentylentetrazol | white, odorless crystals used as a convulsant analeptic (a drug which restores health, vigor or consciousness). |
| photic | pertaining to light. |
| placebo | an inactive substance or preparation given to satisfy the patient's symbolic need for drug therapy, and used in controlled studies to determine the efficacy of medicinal substances. |

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| prostaglandin | a group of naturally occurring, chemically related, long-chain hydroxy fatty acids that stimualte contractility of the uterine and other smooth muscles and have the ability to lower blood pressure and to affect the action of certain hormones. |
| psychopathology | the pathology of mental disorders; the branch of medicine which deals with the causes and nature of mental disease. |
| psychosis | a general term of any major mental disorder of organic and/or emotional origin characterized by derangement of the personality and loss of contact with reality, often with delusions, hallucinations, or illusions. |
| psychotropic | exerting an effect upon the mind; capable of modifying mental activity; usually applied to drugs that affect the mental state. |
| pulmonary | pertaining to the lungs. |
| REM sleep | the stage of sleep in which dreaming is associated with mild involuntary muscle jerks and rapid eye movements (REM). It usually occurs three to four times each night at intervals of 80 to 120 minutes, each occurrance lasting from five minutes to more than an hour. In adults, about 20% is REM sleep. |
| REM rebound | the phenomenon in which a subject deprived of REM sleep for a prolonged period will, on being permitted to sleep undisturbed, compensate by having about 60% more REM sleep than he normally would. |
| sedative | an agent that allays excitement. |
| synthetic | produced by synthesis, the artificial building up of a chemical compound by the union of its elements or from some other suitable starting materials. |
| tachycardia | excessive rapidity in the action of the heart. |
| tetrahydrocannabinol | the active principle of cannabis occurring in two isomeric forms: delta-one-3,4-trans (delta-9-) and delta-six-3,4-trans (delta-8-) tetrahydrocannabinol, both considered psychomimetically active. |
| tolerance | the ability to endure without ill effect, unusually large doses of a drug, and to exhibit decreasing effect to continued use of the same dose of a drug. Drug tolerance: progressive diminution of susceptibility to the effects of a drug, resulting from its continued administration. |
| uveitis | inflammation of the uvea (the iris, ciliacy body and choroid considered together). |