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KEYWORDS. Cannabis, marijuana, THC, dronabinol, vomiting, spasticity, anorexia, pain, seizures, glaucoma, asthma, insomnia

Background. In 1999 the Institute of Medicine (IOM) issued a report entitled *Marijuana and Medicine* (Joy, Watson and Benson, 1999). It recommended the development of cannabinoid drug delivery systems which might be effective for nausea, vomiting and AIDS wasting syndrome, among other chronic disorders. The report went on to recognize that patients should be allowed to smoke marijuana if they failed to achieve relief from approved symptoms that could be relieved by cannabinoid drugs with rapid onset. Recommended criteria of the report included: access to marijuana within 24 hours of submission by a physician, supervision that allows for assessment of treatment effectiveness, and an oversight strategy comparable to an institutional review board. In this context a review of previously unpublished state-run clinical trials with *Cannabis sativa* (marijuana and/or ? 9-tetrahydrocannabinol capsules) to test efficacy in reducing nausea and vomiting following cancer chemotherapy is warranted. The impetus for these studies came from individual state legislatures responding to constituents' claims that smoking marijuana reduced or blocked nausea and vomiting.

Methods. Technical reports were obtained from 6 states which had conducted clinical trials. Each protocol was examined for the procedure used, the experimental design of the clinical trial and the results obtained. Data were available on 748 patients who smoked marijuana prior to and/or after cancer chemotherapy and 345 patients who used the oral THC capsule.

Results. Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief.

Conclusions. On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy.

The development of smokeless inhalation devices could certainly reduce the potential harm from smoking marijuana.

KEYWORDS. Cannabis, cannabinoid, marijuana, cancer, chemotherapy, nausea, vomiting, tetrahydrocannabinol

Receptors for ? 9-tetrahydrocannabinol (THC), cannabis' major psychoactive principle, have been identified in animal tissues. These proteins have a reason to exist because endogenous substances may bind to and functionally activate them, thereby producing pharmacological effects similar to those of THC. Such substances, named ''endocannabinoids,'' have been isolated and several studies have been performed on their pharmacological properties as well as on the molecular mechanisms for their biosynthesis, action and inactivation in animal cells. Within

The scheduling of cannabis under the Controlled Substances Act (CSA) has established legal precedents that determine how scientific evidence affects its regulation in the United States. This background challenges three common fallacies that make it seem marijuana prohibition is the only viable policy outcome. A contemporary effort to reschedule cannabis is based on recent findings that have established that marijuana lacks the high potential for abuse required for Schedule I or Schedule II status under the CSA. The primary policy issue is not, then, whether marijuana is the best medicine but instead whether people who use it medically should be treated as criminals.

KEYWORDS. Cannabis, cannabis use, cannabinoids, marijuana, marijuana use, tetrahydrocannabinol, dronabinol, drug control, drug policy, marijuana laws

Journal of Cannabis Therapeutics: An Editorial Introduction

It is with a great sense of anticipation and excitement that we present Volume 1, #1 of *Journal of Cannabis Therapeutics: Studies in Endogenous, Herbal & Synthetic Cannabinoids*.

This journal is devoted to the scientific examination of clinical cannabis, the biochemical mechanisms of endocannabinoids, and biosynthetic analogues that are based upon their cellular mechanisms.

We hope to educate and enlighten a broad-based readership of physicians, researchers and other health professionals as to the historical record of this controversial healing herb, its putative clinical applications in modern medicine, as well as the biochemical and pharmacological functions of cannabinoids in animals and humans. Topics pertaining to toxicology, psychology, social effects, and even pertinent political aspects of cannabis and cannabinoids will be presented in this forum.

Initially, the *JCT* will consist predominantly of review articles on the medical applications of cannabis and biochemical role of cannabinoids, whether ''endo'' or ''*nouveau*.'' We will also present editorials, abstract listings, pertinent book reviews, meeting notices, and Letters to the Editor, much as other journals. Where illustrative and meritorious, we will republish archival material and translations concerning cannabis research. In the near future, we hope that contributors will submit a greater proportion of original research in these areas, as well as double-blind controlled clinical trials that are the *sine qua non* of modern human research, but have been rarely pursued in the last generation due to governmental prohibitions.

Through peer review and high standards of scientific merit and scholarship, we hope to present a publication that is educational, enlightening and relevant, if occasionally provocative.

Our format is quarterly, but will consist of two standard issues plus

one double theme-related issue each year, so as to allow the in-depth treatment of particularly important topics.

We proudly initiate this inaugural issue with the latest contribution from the dean of American cannabis research, Leo Hollister. His legacy to our body of knowledge in this area of study is enormous, and he is well known for ''speaking his mind'' irrespective of the question on which side of the political fence his pronouncements may land. His review on clinical cannabis serves nicely as a point of departure on ''medical marijuana,'' focusing as it does on a foundation of peer-reviewed modern studies. Some among our readers are certain to criticize it as ''soft-pedaling'' possible clinical benefits of cannabis, while others will suggest he has been too supportive. Debate is only enhanced when the presentation promotes it through a solid discussion of the issues.

The contribution of Richard (Rik) Musty and Rita Rossi presents important new information on the clinical utility of cannabis and THC in the treatment of nausea and emesis in cancer chemotherapy. Their sources derive from state-sponsored studies, previously unpublished, or even politically suppressed. This paper was recently rejected by one of the premier medical journals in the USA based on the contention that its methods did not meet modern criteria of medical proof. Those of us who reviewed it for publication in *JCT* feel otherwise, and rather, that the information is relevant and compelling. Now a wider audience will have the ability to judge the material themselves.

Vincenzo Di Marzo presents a state-of-the-art review of endocannabinoids, and their possible application to clinical medicine. It is astounding to realize that this area of research has yet to exist for even one full decade. Despite its novelty, the discovery that our nervous and immune systems are regulated in part by endogenous mechanisms biochemically related to natural cannabinoids portends to be a fertile area of bench research and clinical investigation for many years to come. Dr. Di Marzo has done an admirable job in providing a suitable foundation for building a knowledge base on this topic for those of us to which it is new.

Indalecio Lozano is a name that will be new to most of our Anglophone readership. His background is quite distinct from our other authors, as an academic in the Humanities, and professor of Semitic Languages. His offering is one that deserves promotion on the subject of cannabis therapeutics, in that he brings to us a voice that is rarely

heard: that of the medical historian, who is able to restore lost knowledge and enable us to integrate it into the larger picture of our subject. In this instance, he provides an excellent review of the use of cannabis in the Arabic medical tradition. Heretofore, this body of knowledge has been poorly presented in the Western literature, whether due to inaccessibility, barriers of language, inadequate scholarship, or outright cultural myopia. In this journal, we hope to rectify some of these oversights, and fill a few of our historical and scientific lacunae.

John McPartland presents an interesting and thought-provoking examination of anti-inflammatory effects of cannabinoid and non-cannabinoid components. Representing as it does a ''hot topic'' in modern medicine, this review will provide a great deal of material worthy of further reflection for anyone who ponders the clinical implications of inflammation, or wishes to divine new approaches to its treatment.

In our effort to represent archival material on cannabis therapeutics, we will periodically feature a series titled ''Cognoscenti of Cannabis.'' The first pertains to Jacques-Joseph Moreau (de Tours), a French pioneer of psychopharmacology, and his attempts to treat a desperately ill patient, victim of ''lypemania,'' with an extract of cannabis. This article is presented in English for the first time.

Ultimately, Jon Gettman provides us a studied political and scientific analysis of perceived inconsistencies in the legislative classification of cannabis, natural tetrahydrocannabinol (THC), and its synthetic cousin, dronabinol (Marinol®). Serious issues are examined that remain open questions in the minds of many patients and their doctors who are seeking better tools in the battle against disease.

Reviews of two recent books, *The Science of Marijuana* by Leslie L. Iversen, and *Hashish!* by Robert Connell Clarke, round out the first issue.

Some parties will certainly question the scientific basis and therapeutic relevance of this journal. Skeptics as to its ultimate viability have even included members of its Editorial and Advisory Board. As this is written, legislation is under review in the US Congress that will challenge even its very legality. Any written or electronically published material that is perceived to encourage education and dissemination of knowledge pertaining to the promulgation of illicit drugs may be subject to legal proscription.

The editor's personal bias is that broader knowledge should not be

considered subversive until or unless it is absolutely clear that it purposely harms others. In *JCT,* we have no such intent. Rather we present the hope that our efforts will enhance the health and well-being of many individuals. We will raise the questions. It will only be through further examination of the issues, and the passage of time, that proof or refutation will occur. Consensus is a slowly evolutive process, and one that is rarely complete.

The history of cannabis is a fascinating example of knowledge gained and knowledge lost. The medical writings of the Ancient Sumerians and Chinese may yet offer us insights of clinical value to modern humanity. Cannabis prohibition has been previously attempted in other cultures, and failed to stem the human instinct to challenge ordinary consciousness, and seek relief from bodily and spiritual distress. If one may forgive an irresistible etymological pun, this resilient phytomedicinal has ''hit the canvas'' many times in the past, only to arise once more to attain medical utility, and popular usage in a sort of historical *cannabis interruptus*.

In closing, it would seem that a remarkable herb provides us with insights and challenges as to what constitutes medicine. With modern developments on endogenous cannabinoids, cannabis has led to a better understanding of our internal biochemical make-up, and pointed the way to possible synthetic therapies that may control many current afflictions. Cannabis, the herb, remains controversial. Beyond its psychoactivity, this plant offers greater opportunities. A renewable resource for fiber, food, and nature's greatest source of healthful essential fatty acids has been made a pariah. That this occurred on the basis of a political agenda, rather than on actual danger or clinical deficiencies, is an error that history and the scientific method demand be rectified. The truth about cannabis as a therapeutic tool should be sought expeditiously, and independently of the prejudice that has hindered the advancement of our knowledge of it for some sixty years.

Ethan Russo, MD
Missoula, MT
Spring 2000

Marijuana (Cannabis) as Medicine

Leo E. Hollister

ABSTRACT. The modern published literature on the therapeutic potentials of cannabis has been reviewed. A pure preparation of the major active component, delta-9-tetrahydrocannabinol (THC), Marinol® or dronabinol, is available for treating nausea and vomiting associated with cancer chemotherapy and as an adjunct to weight loss in patients with wasting syndrome associated with AIDS. Although such approval currently applies only to orally administered THC, for practical purposes smoked marijuana should also be expected to be equally effective.

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INTRODUCTION

Marijuana has been used medically for millennia and in the United States for over 150 years. It was in the US Pharmacopoeia until 1942 when it was removed because of federal legislation making the drug

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illegal. The number of potential indications ranged so widely as to rival those of patent medicines of the time (Table 1). Like the latter, all the proposed indications were based on anecdote and folklore. A few studies of the medical utility of a material thought to be similar to the active component of marijuana, synhexyl (parahexyl), were made during the 1940's and 1950's (Himmelsbach et al. 1994; Loewe, 1946; Stockings, 1947; Pond, 1948; Parker and Wrigley, 1950; Thompson and Proctor, 1953). However, it was not until the isolation and synthesis of delta-9-tetrahydrocannabinol (THC) as the active component during the mid 1960's that more formal pharmacologically based studies became possible (Gaoni and Mechoulam, 1964; Isbell et al. 1964). Nonetheless, a comparison of synhexl and THC revealed them virtually identical in clinical effects, except that synhexyl was less potent and slower in onset of action (Hollister et al. 1968). Curiously, almost all studies of medical marijuana have employed THC or its homologs rather than smoked marijuana. This oversight has created the current climate of controversy about the medical uses of marijuana.

During the past 25 years, a number of reviews have appeared touching upon the therapeutic aspects of marijuana (Nahas, 1973; Bhargava, 1978; Zinberg, 1979; AMA Council, 1980; AMA Council, 1981; Ungerleider and Andrysiak, 1985; Hollister, 1986; Hall et al., 1994; Grinspoon and Bakalar, 1995; Voth and Schwartz, 1997). As with

TABLE 1. Proposed Therapeutic Indications of Marijuana

*Antiemetic	Melancholia
*Appetite Stimulation	Neuralgia
*Antispasmodic, muscle relaxant	Antitussive
*Analgesic	Antineoplastic
*Bronchodilator	Antipyretic
*Anticonvulsant	Topical antibiotic
Sedative-hypnotic	Anti-inflammatory
Opiate, alcohol withdrawal	Obsessive-compulsive
Antihypertensive	Dysmenorrhea

*some suggestive evidence for efficacy

most issues surrounding use of marijuana, interpretation of the medical literature has been filled with controversy, ranging from those who believed it to be a panacea provided by Nature to alleviate the ills of mankind to those who believe that any acceptance of medical use will send the wrong message to young people, for whom marijuana is considered to be a menace and a stepping-stone to the use of more dangerous drugs. This reviewer will try assiduously to avoid bias as well as to place the possible medical uses of marijuana in the context of currently available alternative treatments for the same indication.

The present review will focus primarily on clinical studies evaluating proposed medical uses of marijuana published in refereed medical journals. The various indications will be discussed in the order of the amount of evidence currently available to support each. Readers may then form their own opinion regarding the overall quality of the evidence. Medical indications are divided into two categories, those with enough available evidence to merit further study and those for which evidence is so lacking or so poor as to merit little serious further consideration. Most studies will involve THC rather than smoked marijuana. The argument has been made that smoked marijuana, which contains almost 300 chemicals, few of which have been studied, might therefore have superior utility over the pure material. Although a number of cannabinoids have been found in marijuana, most with similar effects to those of THC itself, they are uniformly weaker and far less abundant than THC. Thus, customarily doses of raw marijuana have been calibrated to their THC content (Hollister 1974).

INDICATIONS WITH EVIDENCE FOR MEDICAL EFFICACY

Antiemetic Action

The antiemetic action of marijuana was not anticipated despite anecdotal reports over the years. The story is that a young patient being treated with chemotherapy for leukemia reported to his oncologists that smoking a marijuana cigarette before and during the chemotherapy ameliorated the nausea and vomiting which is routinely produced. These side effects of cancer chemotherapy are so noxious that patients may refuse life-saving treatment rather than endure them. Over time, repeated experiences of nausea and vomiting may be conditioned, so

that this adverse effect is evoked by the mere anticipation of a round of chemotherapy.

Although an antiemetic effect of THC had been suggested as early as 1972, the first report of a placebo-controlled trial came in 1975 from one of the top oncology centers in the USA. THC in the form of gelatin capsules, in which the drug was dissolved in sesame seed oil, was given in doses of 15 to 20 mg to 20 patients undergoing cancer chemotherapy. Three doses were given, 2 h before and 2 and 4 h after chemotherapy. Fourteen of the 20 patients in whom an evaluation could be made reported a definite antiemetic effect from the THC, while none was observed from placebo during 22 courses (Sallan et al. 1975).

Another comparison of THC with placebo was made in 15 patients with 11 acting as their own control. Fourteen of the 15 patients given THC obtained more relief of nausea and vomiting than from placebo during a course of high-dose methotrexate chemotherapy (Chang et al. 1979). Best results were obtained when plasma concentrations of THC were more than 12 mg/ml. Such concentrations would ordinarily be expected to produce rather definite mental effects (Hollister et al. 1981).

A larger uncontrolled study was done several years later confirming these results. Fifty-three patients refractory to other treatments were studied in an uncontrolled fashion. Ten had complete control of vomiting when THC was administered before chemotherapy and for 24 h thereafter. Twenty-eight had 50% or more reduction in vomiting, and only 15 patients showed no therapeutic effect whatsoever. However, four patients were dropped from the study because of adverse effects (Lucas et al. 1980).

In yet another comparison of THC and placebo, the former treatment was superior, but the side effects were so profound that the patients preferred avoiding treatment. However, doses were far in excess of what might be needed for efficacy, obtaining plasma concentration of 300 ng/ml of THC, several times those required (Kluin-Neleman et al. 1979).

Several studies followed with the next logical step, a comparison of THC with prochlorperazine, which was then the favored antiemetic. One of the first was by the group making the original controlled trial. Doses of 15 mg of THC were compared with 10 mg doses of prochlorperazine in a controlled crossover trial in 84 patients. THC produced

complete response in 36 of 79 courses, while prochlorperazine was effective in only 16 of 78 courses. Twenty-five patients received both drugs, of whom 20 preferred THC. Of the 36 courses of THC that resulted in complete antiemetic response, 32 were associated with mental effects characterized as a ‘‘high’’ (Sallan et al. 1979).

Another comparison between THC in 15 mg doses and prochlorperazine in 10 mg doses versus a placebo control was made in 116 patients who received oral doses 3 times a day. The THC regimen was equal to prochlorperazine, and both were superior to placebo. However, many patients who received THC found it unpleasant (Frytak et al. 1979). When THC was compared with prochlorperazine and placebo, the latter two treatments were found to differ, but THC was superior to either one (Orr et al. 1980). A controlled crossover design compared oral doses of THC 7.5 to 12 mg with oral doses of prochlorperazine in 214 patients and concluded that the two treatments were equal (Ungerleider et al. 1982).

Comparisons with other antiemetics have also been made. THC was found to be superior to either prochloperazine or metoclopramide in pediatric cancer patients. An increase in drowsiness, appetite and ‘‘high’’ were reported in patients treated with THC (Ekert et al. 1979). A crossover comparison of THC and haloperidol for treatment of 52 patients with nausea and vomiting from cancer chemotherapy compared oral doses of 10 mg/day of THC with 2 mg/day of haloperidol given alternately in two-week courses. Both drugs were equally effective. Some patients who did not respond to one drug responded to the other. Although no serious side effects were reported, THC toxicity was less well tolerated than that of haloperidol (Neidhart et al. 1981).

An uncontrolled study used 56 patients undergoing cancer chemotherapy that had not responded to standard treatment for prevention of nausea and vomiting. After being allowed four marijuana cigarettes daily during the course of chemotherapy, 78% benefited. Young age and previous experience with cannabis were predictors of good response. Sedation and dry mouth were the only side effects (Vinciguerra et al. 1988).

A review of dronabinol (oral THC) cancer chemotherapy patients treated for nausea and vomiting indicated that combination with prochloperazine was more effective than either drug alone. Among 750 courses of therapy with THC, about one-third each of patients had considerable response, partial response or no response. In open studies

of appetite stimulation among patients with either cancer or symptomatic HIV infections, doses of 2.5 mg twice daily were effective in stabilizing weight and improving appetite (Plasse et al. 1991).

Although smoked marijuana is often preferred, whether it is superior to orally administered THC has not been tested in controlled comparisons. It may very well be those pharmacokinetic differences between orally administered THC and smoked marijuana might explain the preference for the latter route. Orally administered THC is slow in onset of action though longer in duration. Smoked marijuana produces a THC concentration that mimics the pattern of intravenously administered THC (Agurell et al. 1986). This immediate effect might be perceived by patients as more desirable. For those patients who have this perception, smoked marijuana may be the drug of choice. Smoking marijuana cigarettes, even at street prices, would certainly be less expensive than using conventional antiemetic drugs.

An oral preparation of THC (Marinol®, dronabinol) has attained approval for two indications. Nausea and vomiting associated with cancer chemotherapy are still something of a problem with usual anti-nauseants and THC has been shown to be an effective treatment compared with prochlorperazine (Lane et al. 1991). Severe weight loss associated with the wasting syndrome experienced by patients with AIDS is another indication less well established. No comparisons have been made with other possible treatments, either 5-HT_3 receptor antagonists or anabolic steroids, such as testosterone.

A survey that questioned members of the American Society of Clinical Oncology obtained responses from 1,035 members. About 44% of the responders told of using illegal marijuana for the treatment of at least one patient and almost one-half would prescribe marijuana were it to be made legal. Respondents also were of the opinion that marijuana itself was more effective than THC or semisynthetic cannabinoids (Doblin and Kleiman 1991).

A later survey of oncologists in 1993 by means of questionnaire obtained replies from 141 physicians. The major question was how they would rank available antiemetics for such use (Schwartz 1994). The four favored drugs were metoclopramide, lorazepam, dexamethasone or other corticosteroids, and prochlorperazine or promethazine. Marijuana or oral THC (dronabinol) was rated sixth in preference. Of those oncologists who had prescribed marijuana or THC for their patients, the drug was considered efficacious in about 50% of patients.

However, one in four patients complained of bothersome side effects. By the time of the survey, prescriptions for marijuana had declined. Few oncologists reckoned that they would prescribe the drug more frequently were it made legal and freely available. This survey was completed before the availability of 5-HT_3 antagonists, such as ondansetron, which would currently be the first choice in treatment. Neither did it consider the efficacy of combinations of antiemetics, which have often surpassed the efficacy of single drugs.

In summary, one can conclude that marijuana, both taken orally as THC or smoked, is effective in controlling nausea and vomiting associated with cancer chemotherapy being comparable in efficacy to some currently used antiemetics. As this indication is already approved for the oral form, and as no evidence indicates that the effects from smoking are qualitatively different, one might accept the use of smoked marijuana for the same indication. The choice of dosage form could then be made based on whether a rapid-acting short-lived effect was preferable to a slow-onset, longer duration of action. One might even imagine scenarios in which both dosage forms might be used together. Although evidence for efficacy of the smoked form is less than optimal, in part due to less opportunity for such studies, it is now at least as convincing as was the evidence for orally administered THC. The admission of smoked marijuana as an acceptable treatment for this specific indication would be justified on the basis of present knowledge and would save both much effort and expense by avoiding the need for their elegant proof of efficacy demanded for drugs with the less well-known efficacy and safety.

Very likely, the major drawback would be the psychoactive effects, which, while sought out by those who use marijuana socially, are unwanted effects when the drug is used therapeutically. This difficulty might be met if one could find a cannabinoid that retained the antiemetic action without causing any mental changes. As isomer of the synthetic cannabinoid, 7-hydroxy-delta-6-tetrahydrocannabinol, is devoid of psychoactivity. Yet, in pigeons treated with the anticancer drug cisplatin, a drug most likely to cause vomiting, it showed antiemetic effects (Feigenbaum et al. 1989). Thus, the goal of separating these effects may be within reach. However, the number of drugs now shown useful for control of vomiting has increased greatly since cannabinoids were first considered as useful. The issue may have become

moot, unless such cost considerations prevail more in the future than they have in the past.

Appetite Stimulation

Frequent anecdotal reports by users of cannabis testify to the development of a ravenous appetite with a craving for sweets, especially chocolate. An experimental study, using a standardized chocolate milkshake, tested this idea. Subjects were treated with oral doses of THC 0.5 mk/kg, as well as placebo, alcohol and dextroamphetamine as a negative control. Of 12 fasted subjects, 7 who received THC increased their intake, 2 showed no change and three consumed less as compared with placebo. As expected, dextroamphetamine decreased intake. Alcohol, despite the calories provided, produced little change. When 12 subjects were fed before the test, 7 increased food intake, and 5 showed no change. Results were inconstant, both within and between subjects (Hollister 1971).

After 21 days of inpatient marijuana smoking, both body weight gain and caloric consumption were higher in casual and heavy users than in the control subjects (Greenberg et al. 1976). The psychological toxicological effects of chronic administration (0.1-0.34 mg/kg po qid) of THC were studied in cancer patients on in-and-out patient bases. The clinical observations demonstrated that THC slows or reverses weight loss and possesses some antiemetic and analgesic properties (Regelson et al. 1976).

The wasting syndrome associated with AIDS has made the search for drugs that might stimulate appetite more meaningful. THC in the form of dronabinol has been most often studied. An open pilot study of dronabinol in patients with AIDS-associated cachexia showed it effective in increasing weight as well as being well tolerated. Ten men received doses of 2.5 mg three times daily for periods of 4 to 20 weeks. Eight patients gained weight an average of 0.6 kg/month while 2 showed no gain. Initially, patients had been losing weight at the rate of 0.93 kg/month. Increasing the dose to 5 mg three times daily did not enhance weight gain (Plasse 1991).

A randomized double-blind comparison of dronabinol 2.5 mg twice daily with placebo over a 6 week period was completed in 88 patients. Before the study, patients were at least 2.3 kg below their ideal weight. Among the dronobinol-treated patients, the mean weight gain was 0.1 kg from baseline compared with a loss of 0.4 kg among the placebo

group. Side effects were not severe enough to merit discontinuation of treatment (Beal et al. 1995). Following the controlled study, patients entered an open study of one year's duration. Doses could vary between 2.5 and 20 mg/day according to response. A weight gain of 2 kg was found in those patients who completed three months of treatment. No evidence of the development of tolerance was noted. Side effects were not a major problem.

A phase 2 study of dronabinol in patients with cancer-associated anorexia and weight loss, revealed that low doses (2.5 mg twice daily after meals) improved appetite. Despite the low dose, 22% of patients withdrew from therapy because of side effects (Nelson et al. 1994). In a letter concerning this subject, the authors responded that dronabinol was safe and effective for appetite stimulation during chemotherapy, but that they considered metoclopramide, megestrol and dexamethasone better (Nelson and Walsh 1995). As the latter drugs are mainly used as antiemetics, one wonders whether whatever weight gain they might have provided was due to that action.

Four studies explored the role of age, gender, satiety state, and route of drug administration and dose on appetite stimulation in normal men. Increased food intake was found only after chronic dosing with rectally administered THC 2.5 mg three times daily for 3 days. Orally administered THC in the same dose did not increase appetite. Nor did inhalation of marijuana smoke. The conclusion was that appetite stimulation from cannabinoids was highly variable (Mattes et al. 1994).

An experimental approach to determine the effect of marijuana smoking on appetite used 7 men who were sequestered during observation. A single marijuana cigarette smoked during a period of isolation and work had no effect. However, 2-3 cigarettes smoked during a period of socialization increased caloric intake. The intake was largely in the form of snacks rather than increased consumption at mealtime (Foltin et al. 1986).

Testosterone enanthate, a long-acting injectable form, given in doses of 200 mg IM every 3 weeks, increased weight gain in AIDS patients, most particularly in the form of increased lean body mass. It should be noted that all these patients showed a low serum testosterone level at baseline, which may limit this beneficial effect to such patients (Grinspoon et al. 1998). Nonetheless, testosterone, other anabolic steroids, and human growth hormone might be reasonable competitors of THC for this indication.

Spasticity

It is said around our hospital if you want to know what marijuana smoke smells like, you should drop by the spinal cord injury ward. Such patients think that marijuana is helpful for relieving the pain and muscle spasm secondary to spinal cord injuries.

Ten patients who admitted using marijuana after spinal cord injury perceived a decrease in pain and spasticity as reported on a questionnaire (Dunn and Davis 1974). Another questionnaire given to 43 patients also with spinal cord injury reported decreased spasticity following marijuana use. Current use was related to past use and to use by peers, suggesting some possible bias in reporting (Hanigan et al. 1986).

The effects of oral THC 35 mg/day on muscle resistance, deep tendon reflexes and spasticity was evaluated in 5 patients with traumatic paraplegia. Two patients showed beneficial effects of THC, two had no real benefit and the fifth withdrew from the study because of the mental side effects (Malec et al. 1990).

A double-blind study was performed comparing 5 mg of THC orally, 50 mg codeine orally, and placebo in a patient with spasticity and pain due to spinal cord injury. The three conditions were applied 18 times each in a randomized and balanced order. THC and codeine both had an analgesic effect in comparison with placebo. Only THC showed a significant beneficial effect on spasticity. In the dosage used, no altered consciousness occurred (Maurer et al. 1990).

An antispastic action of THC was confirmed by the first clinical study. Oral doses of 5 and 10 mg of THC were compared with placebo in patients multiple sclerosis. The 10 mg dose reduced spasticity by clinical measurement (Petro and Ellenberger 1989).

A short-term trial of oral THC in 13 patients with multiple sclerosis and spasticity refractory to standard drugs revealed that a dose of 7.5 mg/day was the minimally effective dose. At this dose, subjective spasticity scores were less for THC than placebo. However, on objective measurements, there were no differences. A dose of 7.5 g/day was also highest tolerated; none of the patients in the trial requested continuation after the blind condition was abandoned (Meinck et al. 1989). A study of one patient with multiple sclerosis and another with spinal cord injury showed that doses of 5 mg/day of THC produced some relief of symptoms. Improvement in a 30-year-old man with multiple

sclerosis after smoking a marijuana cigarette was confirmed by electromyography of the flexor muscles of the leg and measurement of hand action tremor (Ungerleider et al. 1987). Administration of oral THC 5 to 10 mg to eight severely disabled multiple sclerosis patients yielded mild subjective improvement in tremor and sense of well being among two patients (Clifford 1983). The overall impression is that THC has some beneficial effect on spasticity, but tolerance to the side effects of the drug may be idiosyncratic.

On the other hand, a group that started with the premise that marijuana would reduce the spasticity of patients with multiple sclerosis and permit better postural control found the opposite. Ten adult patients with that disease were compared with 10 normal volunteers after smoking a marijuana cigarette. Both groups suffered a decrease in posture and balance as measured by a computer-controlled dynamic posturographic platform. No differences were observed between them (Greenberg et al. 1994). The medical treatment of spasticity with drugs such as diazepam, cyclobenzaprine, baclofen and dantrolene leaves much to be desired. In this case, smoking marijuana, which produces a sudden rise of THC levels, might not be the best route of administration. Further studies with oral dosing are required before this indication is written off.

A questionnaire concerning the effects of marijuana in 122 patients with multiple sclerosis revealed a generally beneficial profile of perceived effects. In descending order, the following symptoms were reported as being relieved: spasticity (97%), chronic pain in extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue, double vision, sexual, bowel and bladder dysfunction, and visual dimness (30%). Thus, we are faced with a substantial conflict between patients' perceptions and objective studies (Consroe et al. 1997).

Cannabidiol, another naturally occurring cannabinoid, was given in doses increasing from 100 to 600 mg/day to five patients with idiopathic dystonias, along with previously administered treatments. Dose-related improvement ranging from 20% to 50% was noted in all patients. However, in two patients with coexisting Parkinson syndromes, doses of over 300 mg/day exacerbated the hypokinesia and resting tremor, indicating an aggravating action in such patients (Consroe et al. 1986).

Analgesic Effects

Preclinical evidence of an analgesic effect of cannabinoids is strong. THC and the synthetic homologues, nantradol, and nabilone, shared some properties with morphine in the chronic spinal dog model. Latency of the skin twitch reflex was increased, and withdrawal abstinence was suppressed. Naltrexone did not antagonize these actions, suggesting that they are not mediated through opiate receptors which might suggest the eventual combination of opiate and cannabinoids (Gilbert 1981).

Both THC and a synthetic cannabinoid induced an antinociceptive effect in spinally transected rats, indicating a supraspinal mechanism of analgesia. Previously the same investigators had found evidence of a spinal site mediated through spinal alpha-adrenergic receptors (Lichtman and Martin 1991).

There is clinical support for an analgesic action as well. Single oral doses of 10 mg and 20 mg of THC compared with codeine (60 mg and 120 mg) in patients with cancer pain. A 20 mg dose of THC was comparable to both doses of codeine. The 10 mg dose, which was better tolerated, was less effective than either dose of codeine (Noyes et al. 1975). THC given IV in doses of 44 ng/kg to patients undergoing dental extraction produced an analgesic effect, which was less than that achieved from intravenous doses of 157 μg of diazepam. Several of these patients actually preferred placebo to the dose of 22 μg of THC per kg because of anxiety and dysphoria from the latter drug (Raft et al. 1977). Intramuscular levonantradol was compared with placebo in postoperative pain, and a significant analgesic action was confirmed. No dose-response relationship was observed, and the number of side effects from levonantradol was rather high (Jain et al. 1981).

Paradoxically, smoking of material estimated to deliver 12 mg of THC increased sensitivity to an electric shock applied to the skin of normal volunteers (Hill et al. 1974). The apparent paradox is that the biphasic action of THC (initial stimulation followed by sedation) both increases and decreases pain. Traditionally, aspirin-like drugs, which work peripherally by inhibiting the synthesis of prostaglandins, are used to treat pain derived from the integument. The initial mental stimulation from THC might increase sensitivity to this kind of pain. Visceral pain, such as that of cancer patients, is usually treated by

opiates having both peripheral and central sites of action. Recent evidence suggests that opiates may act directly on pain pathways in the spinal cord as well as reducing the affective response that accompanies pain. Thus, when the two types of pain are distinguished from each other and viewed in the context of the sequential biphasic action the apparent paradox is solved.

Because THC and other cannabinoids seem to be relatively safe (no deaths from overdose) and produce at best only a mild form of dependence, the notion of producing a synthetic cannabinoid with few other actions than analgesia has stimulated a great deal of interest on the part of various pharmaceutical companies. While it seems unlikely that THC itself will ever be used as an analgesic, synthetics may ultimately fulfill this role. Such drugs might be expected to act primarily on peripheral cannabinoid receptors rather than on those abundant in the CNS.

INDICATIONS WITH SPARSE EVIDENCE OF EFFICACY

Glaucoma

Discovery of the ability of cannabis to lower intraocular pressure (IOP) was more or less fortuitous. Intraocular pressure was measured as part of a multifaceted study of the effects of chronic smoking of large amounts of cannabis. IOP was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking (Hepler and Frank 1971). Lowered intraocular pressure lasted 4 to 5 h after smoking a single cigarette. Its magnitude was unrelated to the total number of cigarettes smoked. The maximal effect on IOP was produced by the amount of THC absorbed in a single cigarette containing 19 mg of THC. When patients with ocular hypertension or glaucoma were tested, 7 of 11 showed a fall of intraocular pressure of 30%. Confirmatory evidence was obtained from a trial in which intravenous injection of THC in doses of 22 □g/kg and 44 □g/kg produced an average fall in IOP of 37%, with some decreases as much as 51% (Cooler and Gregg 1977).

The effects of intravenously administered cannabinoids on IOP were measured in 12 normal volunteers. Half received intravenous doses of THC, cannabidiol and cannabinol, the other half received doses of delta-8-THC, 11-hydroxy-THC, and 8-beta-hydroxy-del-

ta-9-THC. Total dose of THC and its 11-hydroxy metabolite was 3 mg; delta-8-THC was given in total dose of 6 mg, 8-beta-hydroxy-THC to a total of 9 mg, cannabinol and cannabidiol to total of 20 mg. Significant reductions in IOP were produced by the THC, delta-8-THC, and 11-hydroxy-THC, all of which are psychoactive compounds while the other cannabinoids had little or no such activity. Thus, it seemed impossible to separate mental effects, which were considerable for the effective drugs, from lowering of IOP (Perez-Reyes et al. 1976).

Orally administered THC (20 or 25 mg) lowered IOP about 8 mm Hg among 17 patients with heterologous glaucomas. No such lowering was found in patients who received only 5 or 10 mg doses. All patients who received the higher doses experienced severe mental effects. One patient, who received only a 5 mg dose, experienced severe tachycardia and orthostatic hypotension (Merritt et al. 1980).

Similar findings were reported from the same group after having 16 patients smoke marijuana cigarettes weighing 900 mg (amount of THC unspecified). Compared with placebo, IOP was lowered for 3-4 hours following the smoke. However, rapid heart rate and lowering of blood pressure which preceded this action were quite large and would not be tolerated by many patients among the age group who suffer glaucoma (Merritt et al. 1980).

As treatment for glaucoma is a lifetime proposition, systemic therapy has never been seriously considered. Topical therapy, properly used, has been generally satisfactory. Unfortunately, attempts to make a tolerable topical preparation of THC or other cannabinoids have been impossible to date. One hears tales of patients with glaucoma whose vision is spared only by smoking marijuana cigarettes; remarkably, no case reports, along with objective measurements, even of a few such patients, have appeared. As glaucoma occurs most often in older patients, one has difficulty imagining such patients embracing a lifetime of possible marijuana intoxication. This possible indication has elicited no literature during the past 12 years.

Anticonvulsant

One of the therapeutic uses suggested for cannabis was as an anticonvulsant. Such an effect was documented experimentally many years ago (Loewe and Goodman 1947). Studies in various animal species have shown cannabidiol effective in many animal-screening tests for anticonvulsants (Wada et al. 1973; Turkanis et al. 1974).

Clinical testing has been rare, despite all these various lines of evidence supporting an anticonvulsant effect of cannabinoids. Better control of seizures following regular marijuana smoking was reported in a not very convincing single case (Consroe et al. 1975).

Cannabidiol (CBD), a non-psychoactive cannabinoid, was tested in 15 epileptic patients poorly controlled by usual drugs. Patients were randomly assigned to a dose of 300 mg of CBD or placebo and treated for as long as 4 1/2 months, while continuing their past anticonvulsant drugs. Of 8 CBD-treated patients, 4 remained free of seizures, 3 showed partial improvements and 1 showed no response. Of 7 placebo-treated patients, only 1 showed improvement. The drug was well tolerated (Cunha et al. 1980). As cannabidiol has little if any psychoactivity, it is a good candidate for this use.

The number of effective anticonvulsants has increased since the original interest in cannabidiol. Consequently, no further clinical studies have been reported.

Bronchial Asthma

A general study of the effects of marijuana on respiration revealed a bronchodilating action in normal volunteer subjects. Marijuana smoke delivered by smoking cigarettes containing 2.6% THC caused fall of 38% in airway resistance and an increase of 44% in airway conductance, with less change when a 1% THC cigarette was smoked. The low-dose group showed lesser changes, but they were still significant as compared with baseline (Vachon et al. 1973).

Asthma was deliberately induced by either inhalation or methacholine or exercise in asthmatic patients. They were then treated with inhalation of placebo marijuana, of saline, of isoproterenol, or of smoke derived from 500 mg of marijuana containing 2% THC. Both marijuana smoke and isoproterenol aerosol effectively reversed both methacholine- and exercise-induced asthma while saline and placebo marijuana had no effect (Tashkin et al. 1975).

Aerosols of placebo-ethanol, THC (200 μg) in ethanol, or of salbutamol (100 μg) were tested in another study of 10 stable asthmatic patients. Forced expiratory volume in 1 s, forced vital capacity, and peak flow rates were measured on each occasion. Both salbutamol and THC significantly improved ventilatory function. Improvement was more rapid with salbutamol, but two treatments were equally effective at the end of 1 h (Williams et al. 1972).

While it is conceivable that an aerosol preparation could be made, those currently used (corticosteroids and beta-adrenergic agonists) are well established. Although treatment of asthma in the past has employed smoked drugs (stramonium [*Datura* spp.] cigarettes known as cubebs were used until 60-70 years ago), it seems intuitively wrong to treat a pulmonary condition with a method of drug administration that increases inflammation. As treatment of bronchial asthma has shifted towards emphasis on alleviating the inflammatory aspects, there is little support for using smoked marijuana. Consequently, interest in the indication is currently non-existent.

Insomnia

THC does not differ from conventional hypnotics in reducing rapid eye movement (REM) sleep (Pivik et al. 1972). THC in doses ranging from 61 to 258 μg/kg produces in normal subjects increments in stage four sleep and decrements in REM sleep, but without the characteristic REM rebound which follows chronic treatment with an hypnotic. When THC was administered orally as a hydroalcoholic solution in doses of 10, 20, and 30 mg, subjects fell asleep faster after having mood alterations consistent with a ''high.'' Some degree of ''hangover'' the day following was noted from larger doses (Cousens and Dimascio 1973). Another sleep laboratory study showed that a dose of 2 mg of THC given orally decreased REM sleep. After 4-6 nights of use, abrupt discontinuation of THC produced a mild insomnia but not marked REM rebound (Freemon 1974). REM rebound may not be apparent after low doses of THC; however, very high doses (70 to 210 mg) reduced REM sleep during treatment and were followed by marked REM rebound after withdrawal (Feinberg et al. 1976). The sleep produced by THC does not seem to differ much from that of most currently used hypnotics. Side effects before sleep induction as well as hangover effects make the drug less acceptable than currently popular benzodiazepines. No further studies have been reported.

Early on, synthetic cannabinoids were tried as antianxiety and antidepressant drugs. Diazepam 5 mg was superior to the synthetic cannabinoid nabilone 2 mg for treating experimentally induced anxiety in highly anxious people. Thus, even aside from the marijuana-like effects of nabilone, it was not acceptable (Nakano et al. 1978). Following a favorable report from use of synexyl for treatment of depression, a further study found it to be of no benefit (Parker and Wrigley 1950).

Again, cannabinoid-like drugs were of little use in these psychiatric conditions. Nor has there been any attempt to exploit them in this fashion over the succeeding decades.

DISCUSSION

Among the many possible therapeutic uses of marijuana, a few have enough supporting evidence to justify further studies. Greatest support has been elicited for using the drug, mainly in the form of orally administered THC, for the control of nausea and vomiting. This use has been further legalized by the switch of synthetic oral THC to Schedule III of the Controlled Substances Act. Capsules (Marinol® or dronabinol) containing THC dissolved in oil have been marketed for this purpose. Demand for such preparations has not been great, however, probably because of the reluctance of physicians to prescribe a drug that so recently was considered illegal and possibly also to the fact that many other antiemetics have been developed during the past decade which obviate the mental side effects of THC. The remaining issue is whether smoked marijuana might be superior, as such administration permits rapid and close titration of dose. This issue has not been resolved and would take a large, expensive clinical trial to settle. Thus far, no support has been offered for such a trial.

As appetite stimulants are not very effective, this possible action of marijuana is certainly worth consideration. Data suggest that stimulation is inconstant and mild. All of the studies have involved oral THC, which would seem to be the most appropriate route for this purpose, its slower but more prolonged duration of action being consonant with the aims of treatment. Anabolic steroids offer another approach to this indication. Comparisons between these and THC would be required.

Available medications to relieve muscle spasticity are generally somewhat disappointing. Whether the few reports of benefit from marijuana improve the situation is questionable. The incoordinating effects of this drug might aggravate the underlying neurological condition.

Development of cannabinoids as analgesics is attractive, but it seems obvious that neither oral THC nor smoked marijuana is the best approach. If synthetic cannabinoids could be developed which retain the analgesic action but minimize the mental effects, this indication would be more promising.

Other potential medical uses, such as treatment for glaucoma, asthma, seizures and insomnia or anxiety, not only have very little experimental support but also would seem adequately treated with existing drugs. During the past dozen years, little interest in exploring these is apparent in the medical literature.

A major unresolved issue is the comparison between orally administered THC and smoked marijuana. Many users aver that smoke marijuana may have active ingredients other than THC, as perhaps 300 or so chemicals are present in the plant or in the smoke. As few of these have ever been studied alone (nor will they be), the argument cannot be settled directly. On the other hand, except for some THC-like structures, which are present in marijuana in much smaller amounts, and with far less potency than that of THC, no other active material has been found. Thus, it appears unlikely that some panacea is being missed. As for the kinetic advantages of smoking, immediate effects might be desirable for situations in which immediate action is preferable; most drugs are used for longer-lived conditions in which sustained effects are more essential.

CONCLUSION

It is surprising that more than 35 years after the synthesis of THC, and the resulting capability of clinical pharmacological studies, little published literature has tested various potential therapeutic uses of the drug. Earliest studies were more concerned with the actions of the drug on various organ systems and were not concerned with therapeutic actions. For part of the past 15 years, an increasing literature explored this aspect but has recently dropped off. Therapeutic use has become entwined with the political and legal moves that have polarized investigators. The consequence is that legal steps have been taken which are poorly supported by medical evidence.

For those of us who like to have new treatments accepted on the basis of evidence rather than plebiscite, it has been a discouraging period. The solutions proposed by the recent Institute of Medicine Report would seem to be even more discouraging than those which were obtained before. In view of the fact that marijuana and its constituents may be among the safest materials one can be exposed to, it would seem reasonable to make its testing less, rather than more difficult.

Meanwhile, we must ponder the question, ‘‘Are we missing a therapeutic advance or is the lore of the past only folklore that has no place in modern science?’’ Innovation is desperately needed if we are to settle the question before all chances for proper appraisals are lost.

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Effects of Smoked Cannabis and Oral Δ^9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials

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ABSTRACT. Background. In 1999 the Institute of Medicine (IOM) issued a report entitled *Marijuana and Medicine* (Joy, Watson and Benson, 1999). It recommended the development of cannabinoid drug delivery systems which might be effective for nausea, vomiting and AIDS wasting syndrome, among other chronic disorders. The report went on to recognize that patients should be allowed to smoke marijuana if they failed to achieve relief from approved symptoms that could be relieved by cannabinoid drugs with rapid onset. Recommended criteria of the report included: access to marijuana within 24 hours of submission by a physician, supervision that allows for assessment of treatment effectiveness, and an oversight strategy comparable to an institutional review board. In this context a review of previously unpublished state-run clinical trials with *Cannabis sativa* (marijuana and/or Δ^9-tetrahydrocannabinol capsules) to test efficacy in reducing nausea and vomiting following cancer chemotherapy is warranted. The impetus for these studies came from individual state legislatures responding to constituents' claims that smoking marijuana reduced or blocked nausea and vomiting.

Methods. Technical reports were obtained from 6 states which had

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conducted clinical trials. Each protocol was examined for the procedure used, the experimental design of the clinical trial and the results obtained. Data were available on 748 patients who smoked marijuana prior to and/or after cancer chemotherapy and 345 patients who used the oral THC capsule.

Results. Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief.

Conclusions. On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy.

The development of smokeless inhalation devices could certainly reduce the potential harm from smoking marijuana.

KEYWORDS. Cannabis, cannabinoid, marijuana, cancer, chemotherapy, nausea, vomiting, tetrahydrocannabinol

The first study comparing oral Δ^9-tetrahydrocannabinol (THC) to placebo capsules and marijuana to marijuana placebo cigarettes was published by Chang et al. (1979). In this study 15 patients were given oral doses of THC over several courses of chemotherapy. Each subject received a 10 mg THC capsule beginning two hours prior to chemotherapy and every three hours subsequently. In the event of a breakthrough vomiting episode, those patients were given marijuana cigarettes to smoke for the remaining administrations rather than oral THC. When measured THC blood levels were < 5 ng/ml, 44% of subjects vomited, between 5 ng/ml and 10 ng/ml, 21% vomited, and > 10 ng/ml, 6% vomited. After smoking marijuana, the incidence of vomiting for the same blood levels ranges were 83%, 38% and 0%. Vomiting rates after placebo capsules or smoked placebo marijuana were 72% and 96%, respectively.

In a marijuana-only trial, Vinciguerra et al. (1988) tested 56 patients, non-randomized, who acted as their own controls. Patients rated themselves via subjective assessment of nausea and vomiting. Thirty-four percent of the patients rated smoked marijuana as being very effective, 44% moderately effective, and 22% ineffective. The authors did not report the frequency of nausea and vomiting when marijuana was not smoked.

Technical reports were obtained from 6 states, in which inhaled marijuana was used in patients undergoing cancer chemotherapy. The states had passed legislation to make these studies legal. Usually, studies were designed by researchers in collaboration with State Departments of Health. Each state was required to write a protocol for the research (which was submitted to the Food and Drug Administration (FDA) for approval). Subsequently, a Schedule I license was obtained from the Drug Enforcement Administration (DEA). Finally, rolled marijuana cigarettes and capsules of THC (in sesame oil) were obtained from the National Institute on Drug Abuse (NIDA). These studies will be reviewed individually in this article.

In 1999, the Institute of Medicine (IOM) recommended that marijuana be made available for patients refractory to other medications (Joy, Watson and Benson, 1999). This review provides further support to the Chang and Vinciguerra studies.

TENNESSEE

Background. The State of Tennessee conducted this trial after legislative action in April of 1981 (Board of Pharmacy, 1983).

Treatment Method. Patients (all of whom were refractory to other anti-emetics) were referred for treatment by the patient's personal physician. Patient records were reviewed by a Patient Qualification Review Board of the State of Tennessee. Those approved were randomized to 3 age groups: less than 20 years old, 20-40 years old, and over 40 years old. Those not having conditions precluding oral administration were administered the THC capsule and those unable to ingest capsules were treated with smoked marijuana cigarettes. Most of the patients had previously been treated with the THC capsule. Thus the report focused on the effects of use of marijuana cigarettes.

Measures. A patient treatment evaluation form was completed for each day of treatment. Recording forms included a record of dose and notes, the patient's assessment of nausea and vomiting, appetite and food intake, physical state, and (marijuana) ''high.'' Forty-three patients were enrolled in the study. Sixteen patients were excluded for various reasons: missing data, abusive drug use, premature death, those who could not tolerate smoking, or patients who declined treatment.

Results. The results of the study are shown in Table 1. Treatment

TABLE 1. Tennessee trial: Patient assessment of the effects of smoked marijuana on nausea and vomiting, side effects and appetite

Marijuana Effect		Side Effects		Appetite	
	n %		n %		n %
Very Effective	11 (40.1%)	Mild	23 (85%)	Above Average	5 (18.5%)
Moderately Effective	11 (40.1%)	Moderate	3 (11.1%)	Normal	16 (59.3%)
Partially Effective	1 (0.04%)	Severe	1 (0.04%)	Below Normal	5 (18.5%)
Slightly Effective	4 (15%)				
Poor	1 (.04%)				

success by method was also discussed. Success was defined as partially, moderately, or very effective. For those under age 40 years of age, 100% success was achieved with marijuana cigarettes. For those over 40, 83.3% success was achieved. Only 6 patients used the THC capsule alone and 100% success occurred in those under 40 years of age, and in 33% for those over 40. Side effects were predominantly mild, and appetite improved in about 1 out of 5 patients.

MICHIGAN

Background. Michigan conducted a study under the direction of the Michigan Department of Public Health after legislative action in 1979. John. R. Ingall of the Detroit Metropolitan Comprehensive Cancer Center was the study coordinator, and the report was complied by the Michigan Cancer Foundation (Department of Social Oncology, Evaluation Unit 1982).

Treatment Method. In order to be eligible for the trial, patients had to meet these criteria: be under active cancer chemotherapy treatment, have a satisfactory medical status such that potential side effects of marijuana or a phenothiazine derivative, thiethylperazine (Torecan®), were not life-threatening or likely to evoke serious mental/behavioral effects, and be free of serious mental or organic disease. Patients were randomly assigned to a marijuana cigarette or thiethylperazine therapy group. If the treatment failed in a 24 hour trial, patients were then crossed over to the other treatment group. For the marijuana group,

patients took one puff per minute until they felt ‘‘high’’ 30 minutes prior to chemotherapy. The smoking procedure continued until sometime after chemotherapy was completed. One hundred sixty-five patients completed this trial (78 male and 86 female).

Measures. Measures were recorded by patient self-report as well as physician/nurse observations.

Results. The results for this study are shown in Table 2. Marijuana was marginally more effective as compared to thiethylperazine in controlling nausea and vomiting/retching. As in the previous study, reported side effects were mild.

GEORGIA

Background. The State of Georgia and Emory University collaborated to conduct this trial after legislative action in 1980 (Kutner 1983).

Treatment Method. Cancer patients who were unresponsive to usual anti-emetics, but who were able to employ the oral route of administration were eligible for this trial. Patients were randomly assigned to one

TABLE 2. Michigan Trial: Frequency of Nausea, Vomiting/Retching and Side Effects

	Nausea			Vomiting/Retching After Chemotherapy	
	Marijuana	Torecan*		Marijuana	Torecan*
None	14 (15.0%)	8 (15.7%)	None	19 (18.1%)	10 (14.9%)
Mild	31 (33.3%)	16 (31.4%)	Less than 4 h	25 (23.8%)	19 (28.4%)
Moderate	22 (23.7%)	14 (27.5%)	Between 4-12 h	25 (23.8%)	19 (28.4%)
Severe	19 (20%)	12 (23.5%)	Between 12-24 h	14 (13.3%)	10 (14.9%)
Unknown	7 (7.5%)	1 (0.02%)	Over 24 h	9 (8.6%)	4 (6.0%)
			Unknown	13 (12.4%)	5 (7.5%)

Side Effects of Marijuana Smoking

Sleepiness	21/113 (18.5%)
Sore Throat	13/113 (11.5%)
Headache	7/113 (6.2%)

* Thiethylperazine (Torecan®)

of three treatment groups by age: less than 20 years old, 20-40 years old, and over 40. The treatment groups were: oral THC capsules, standardized cannabis smoking, or patient controlled smoking.

Measures. At each treatment a form was completed containing information on effectiveness of treatment, side effects and the patient's assessment of nausea, vomiting, appetite, physical status, mood and ''high.'' One hundred nineteen patients completed the study.

Observations included patient self-reports and physician summaries. Patient satisfaction was assessed for each treatment. Success was judged by the patient reporting as to whether he/she was satisfied, or very satisfied with the treatment. If the patient was not sure of effectiveness on the first cycle of treatment, but was satisfied or very satisfied on subsequent cycles, this was also considered to be a success. Failure was defined when the patient was dissatisfied on the initial cycle, the patient dropped out of the study, or changed treatment method.

Results. The overall results are shown in Table 3 and by age group in Table 4. Examining the data (in percentages) by age groups reveals success rates were very similar across age groups. These data show success rates were about the same for oral THC and patient controlled

TABLE 3. Georgia Trial: Overall Success with All Treatments by Age

	Age			
	< 20	20-40	> 40	Total
Success	10 (71.4%)	30 (75%)	47 (72.3%)	87 (73.1%)
Failure	4 (28.6%)	10 (25%)	18 (27.7%)	32 (26.9%)
Total	14	40	65	119

TABLE 4. Georgia Trial: Success by Treatment Oral THC (PO), Standardized Smoking (SS) and Patient Controlled Smoking (PCS) of Marijuana

	PO	SS	PCS	Total
Success	57 (76%)	17 (65.4%)	13 (72.2%)	87 (73.1%)
Failure	18 (24%)	9 (34.6%)	5 (27.8%)	32 (26.9%)
Total	14	40	65	119

smoking, but standardized smoking yielded somewhat inferior outcomes.

Reasons for failure in patients who failed treatment with oral THC were as follows: 8 patients experienced severe nausea and vomiting, 6 had adverse reactions, 2 were dissatisfied, 1 had breakthrough vomiting, and 1 had no effect. For those who smoked marijuana, 6 patients experienced smoking intolerance, 1 had an adverse reaction, 1 had severe nausea and vomiting, 2 had breakthrough vomiting, and 4 had other side effects.

NEW MEXICO (1983)

Background. This program of Research was conducted by the Lynn Pierson Therapeutic Research Program for the New Mexico Health and Environment Department after authorization by the legislature in 1978 (Behavioral Science Division, 1983).

Treatment Method. Patients enrolled in the program were randomly assigned to one of two treatments: THC capsule or marijuana cigarettes. Doses were matched so that each patient received approximately 15 mg of THC. Patients were administered the treatment before a cycle of chemotherapy. After chemotherapy, patients could continue taking the marijuana or THC for 5 days. Forty female patients and 27 male patients received marijuana cigarettes, while 50 female patients and 25 male patients received THC capsules.

Measures. Observations were made by patients with a self-report scale called the Target Problem Rating Scale. For nausea and vomiting, improvement was defined when patients reported less nausea or vomiting compared with previous anti-emetics. No improvement was defined as no change compared with previous anti-emetics.

Results. The data are shown in Table 5. Patients who smoked marijuana achieved improvement overprevious antiemetic drugs, with those smoking the drug exceeding 90% success.

TABLE 5. New Mexico Trial (1983)

Group	Oral THC	Inhaled Marijuana
Improvement	57 (74.83%)	58 (90.39%)
No Improvement	9 (25.17%)	3 (9.6%)

NEW MEXICO (1984)

Background. The Lynn Pierson Therapeutic Research Program continued in 1984 (Behavioral Science Division 1984).

Treatment Method. The program was similar to that in 1983, with the exception that some patients received only one treatment and others received an average of six treatments after chemotherapy. Patients were randomly assigned to the same treatment groups as in the 1983 protocol. The protocol also allowed patients options to begin in one treatment group and switch to another, to refuse to be in the smoking group, or to try both routes of administration sequentially. Success was defined as a reduction in nausea and vomiting, and failure was defined as no reduction. Table 6 shows the results. It is important to note that few patients continued with the oral THC treatment, while those who smoked marijuana achieved over 90% success. Summarizing side effects of both THC and marijuana reported over the two years, treated patients often fell asleep. Of those who did not (approximately 90 patients), 50% reported sleepiness and 45% felt ''high.'' No other side effects were noted in the report.

CALIFORNIA

Background. After legislation passed by the State of California Legislature in 1979, a Cannabis Therapeutic Program was carried out between 1983 and 1989 under the supervision of the California Research Advisory Panel (1989).

Treatment Method. Over the years, several protocols were used. Essentially, the early protocols were conservative, e.g., patients were required to have failed treatment with conventional anti-emetic drugs. Later, a more relaxed protocol was used in which the patient and the physician decided whether or not to try the THC capsule or smoke marijuana.

TABLE 6. New Mexico Trial (1984): Treatment Success After the First Treatment with Inhaled Marijuana or Oral THC

Group	Oral THC	Inhaled Marijuana	Combined
Success	6 (54.5%)	79 (95.2%)	79 (98.8%)
Failure	5 (45.5%)	4 (4.8%)	1 (1.2%)

Measures. Physicians used 5 point rating scales to record nausea and vomiting.

Results. Table 7 shows the combined results of the various protocols combined. In this study, smoked marijuana was consistently more effective than oral THC in blocking vomiting except in the most severe cases (> 6 times). Control of nausea was about the same for both groups. The pattern of side effects did not differ, to any extent, between smoked marijuana and oral THC.

NEW YORK

Background. The New York Department of Health study conducted a large scale (Phase III type) cooperative clinical trial (Randall, 1990).

Treatment Method. The central question addressed was how effective inhaled marijuana was in preventing nausea and vomiting due to chemotherapy in patients who failed to respond to previous anti-emetic therapy. Patients undergoing chemotherapy were allowed to use marijuana distributed through three centers: North Shore Hospital (NSH), Columbia Memorial Hospital (CMH), and a triad of the Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital (JGH). By 1985, the New York program provided marijuana therapy to 208 patients through 55 practitioners. Of those, data on 199 patients were evaluated. These patients had received a total of 6,044 NIDA-

TABLE 7. California Trials: Ratings of Nausea and Vomiting for Smoked Marijuana or the THC Capsule.

	Smoked Marijuana	THC Capsule		Smoked Marijuana	THC Capsule
Nausea			Vomiting		
None	9 (9.2%)	38 (15.1%)	None	19 (19.4%)	89 (35.3%)
Mild	34 (34.7%)	85 (33.9%)	1-3 times	36 (36.7%)	69 (27.4%)
Moderate	36 (36.7%)	73 (29.1%)	4-6 times	18 (18.4%)	35 (13.9%)
Severe	17 (17.3%)	55 (21.9%)	> 6 times	24 (24.5%)	59 (23.4%)
Missing	2 (2%)	6 (2.3%)	Missing	1 (1%)	5 (2.3%)

Side Effects (combined ratings from mild to severe are shown Table 8).

TABLE 8. California Trials: Side Effects Reported by Patients

	Smoked Marijuana n = 98	Smoked Marijuana %	THC Alone n = 257	THC Alone %
Dry Mouth	53	56.5	112	44.8
Tachycardia	6	6.4	25	10.0
Ataxia	16	27.1	31	12.8
Dizziness	31	33.1	67	26.8
Orthostatic	7	7.5	32	12.8
Anxiety	19	20.2	47	18.8
Sedation	49	52.1	160	64.0
Elated Mood	25	26.6	61	24.4
Confusion	23	26.6	79	31.6
Perceptual	15	15.9	57	22.8
Fantasizing	10	10.7	29	11.6
Depressed	17	18.1	33	13.2
Panic/Fear	7	7.5	9	7.6

supplied marijuana cigarettes provided to patients during 514 treatment episodes.

Measures. Observations were made by patient self-report.

Results. North Shore Hospital reported marijuana was effective at reducing emesis 92.9% of the time; Columbia Memorial Hospital reported efficacy of 89.7%; the triad of Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital reported 100% of the patients smoking marijuana gained significant benefit.

Analyzing patient evaluations, the report concluded that approximately 93% of marijuana inhalation treatment episodes were effective or highly effective when compared with other anti-emetics. The New York study reported no serious adverse side effects. No patient receiving marijuana required hospitalization or any other form of medical intervention.

DISCUSSION

Even though slightly different methods and different research designs were used in these studies, it is clear that inhaled marijuana was

effective in reducing or eliminating nausea and vomiting following cancer chemotherapy. In those studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration. In almost all of these studies, patients were admitted only after they failed treatment with standard anti-emetics, suggesting the patients may have been under fairly aggressive treatment for their cancers.

With regard to side effects, short term use of marijuana leads to sedation, a high, and smoke intolerance in some patients. At this point in time there is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy, Watson and Benson, 1999).

In a 1991 survey, Doblin and Kleiman (1991) reported that more than 70% responding oncologists (n = 1035) reported at least one of their patients had used marijuana as an anti-emetic, and that they had also either observed or discussed the patients' use. In addition, 44% of the respondents reported recommending marijuana to at least one patient. Two hundred seventy-seven respondents felt they had clinical experience with both marijuana and Marinol™ (oral THC): (44% thought marijuana was more effective, 43% thought they were about equally effective, and 13% thought Marinol™ was more effective). These data suggest that physicians at that time continued to discuss or recommend marijuana use to some patients. In this sample of oncologists, it seems they understood the potential efficacy of marijuana use. Whether this situation has changed since 1991 is unknown, but one might argue that the introduction of the anti-emetics of the selective serotonin-3 antagonist class, may have changed this practice.

While there have been no studies which have compared smoked marijuana or Marinol™ with the serotonin receptor type-3 antagonists (granisetron or ondansetron), it is instructive to review published clinical trials with these compounds for the sake of comparison. In 9 clinical trials with ondansetron, anti-emesis was obtained in 40%-81% (mean 63.5%) of patients (Beck et al. 1993; Buser et al. 1993; Crucitt et al. 1994; Hainsworth et al. 1991; Herrstedt et al. 1993; Kaasa et al. 1990; Marty et al. 1980; Olver et al. 1996; Roila et al. 1991). In 5 clinical trials with granisetron, 37.7%-93% (mean 56.6%) anti-emesis was reported (Italian Group for Antiemetic Research 1995; Markman et al. 1996; Perez et al. 1997; Ritter Jr. et al. 1998; Sekine et al. 1996). It is generally known that combining anti-emetic drugs with different

mechanisms of action often improves efficacy (Jones et al. 1991). This suggests that future research should consider combining cannabinoids with other anti-emetics.

The data reviewed here suggest that the inhalation of THC appears to be more effective than the oral route. In order to achieve the IOM recommendation to allow patients access to marijuana, both state and Federal Governments would need to reschedule marijuana from Schedule I to Schedule II, or reinstate the Compassionate Use Program. The development of smokeless inhalation devices would certainly be an advance in the use of THC as an anti-emetic medication. Finally, a large number of synthetic cannabinoid and endocannabinoid agonist analogs have been developed. It would seem that testing of these compounds as potential anti-emetics would also be worthwhile.

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Methods. Technical reports were obtained from 6 states which had conducted clinical trials. Each protocol was examined for the procedure used, the experimental design of the clinical trial and the results obtained. Data were available on 748 patients who smoked marijuana

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Slightly Effective	4 (15%)				
Poor	1 (.04%)				

100% success was achieved with marijuana cigarettes. For those over 40, 83.3% success was achieved. Only 6 patients used the THC capsule alone and 100% success occurred in those under 40 years of age, and in 33% for those over 40. Side effects were predominantly mild, and appetite improved in about 1 out of 5 patients.

MICHIGAN

Background. Michigan conducted a study under the direction of the Michigan Department of Public Health after legislative action in 1979. John. R. Ingall of the Detroit Metropolitan Comprehensive Cancer Center was the study coordinator, and the report was complied by the Michigan Cancer Foundation (Department of Social Oncology, Evaluation Unit 1982).

Treatment Method. In order to be eligible for the trial, patients had to meet these criteria: be under active cancer chemotherapy treatment, have a satisfactory medical status such that potential side effects of marijuana or a phenothiazine derivative, thiethylperazine (Torecan®), were not life-threatening or likely to evoke serious mental/behavioral effects, and be free of serious mental or organic disease. Patients were randomly assigned to a marijuana cigarette or thiethylperazine therapy group. If the treatment failed in a 24 hour trial, patients were then crossed over to the other treatment group. For the marijuana group, patients took one puff per minute until they felt ‘‘high’’ 30 minutes prior to chemotherapy. The smoking procedure continued until some-

time after chemotherapy was completed. One hundred sixty-five patients completed this trial (78 male and 86 female).

Measures. Measures were recorded by patient self-report as well as physician/nurse observations.

Results. The results for this study are shown in Table 2. Marijuana was marginally more effective as compared to thiethylperazine in controlling nausea and vomiting/retching. As in the previous study, reported side effects were mild.

GEORGIA

Background. The State of Georgia and Emory University collaborated to conduct this trial after legislative action in 1980 (Kutner 1983).

Treatment Method. Cancer patients who were unresponsive to usual anti-emetics, but who were able to employ the oral route of administration were eligible for this trial. Patients were randomly assigned to one of three treatment groups by age: less than 20 years old, 20-40 years

TABLE 2. Michigan Trial: Frequency of Nausea, Vomiting/Retching and Side Effects

	Nausea			Vomiting/Retching After Chemotherapy	
	Marijuana	Torecan*		Marijuana	Torecan*
None	14 (15.0%)	8 (15.7%)	None	19 (18.1%)	10 (14.9%)
Mild	31 (33.3%)	16 (31.4%)	Less than 4 h	25 (23.8%)	19 (28.4%)
Moderate	22 (23.7%)	14 (27.5%)	Between 4-12 h	25 (23.8%)	19 (28.4%)
Severe	19 (20%)	12 (23.5%)	Between 12-24 h	14 (13.3%)	10 (14.9%)
Unknown	7 (7.5%)	1 (0.02%)	Over 24 h	9 (8.6%)	4 (6.0%)
			Unknown	13 (12.4%)	5 (7.5%)

Side Effects of Marijuana Smoking

Sleepiness	21/113 (18.5%)
Sore Throat	13/113 (11.5%)
Headache	7/113 (6.2%)

* Thiethylperazine (Torecan®)

old, and over 40. The treatment groups were: oral THC capsules, standardized cannabis smoking, or patient controlled smoking.

Measures. At each treatment a form was completed containing information on effectiveness of treatment, side effects and the patient's assessment of nausea, vomiting, appetite, physical status, mood and ''high.'' One hundred nineteen patients completed the study.

Observations included patient self-reports and physician summaries. Patient satisfaction was assessed for each treatment. Success was judged by the patient reporting as to whether he/she was satisfied, or very satisfied with the treatment. If the patient was not sure of effectiveness on the first cycle of treatment, but was satisfied or very satisfied on subsequent cycles, this was also considered to be a success. Failure was defined when the patient was dissatisfied on the initial cycle, the patient dropped out of the study, or changed treatment method.

Results. The overall results are shown in Table 3 and by age group in Table 4. Examining the data (in percentages) by age groups reveals success rates were very similar across age groups. These data show success rates were about the same for oral THC and patient controlled smoking, but standardized smoking yielded somewhat inferior outcomes.

TABLE 3. Georgia Trial: Overall Success with All Treatments by Age

	Age			
	< 20	20-40	> 40	Total
Success	10 (71.4%)	30 (75%)	47 (72.3%)	87 (73.1%)
Failure	4 (28.6%)	10 (25%)	18 (27.7%)	32 (26.9%)
Total	14	40	65	119

TABLE 4. Georgia Trial: Success by Treatment Oral THC (PO), Standardized Smoking (SS) and Patient Controlled Smoking (PCS) of Marijuana

	PO	SS	PCS	Total
Success	57 (76%)	17 (65.4%)	13 (72.2%)	87 (73.1%)
Failure	18 (24%)	9 (34.6%)	5 (27.8%)	32 (26.9%)
Total	14	40	65	119

Reasons for failure in patients who failed treatment with oral THC were as follows: 8 patients experienced severe nausea and vomiting, 6 had adverse reactions, 2 were dissatisfied, 1 had breakthrough vomiting, and 1 had no effect. For those who smoked marijuana, 6 patients experienced smoking intolerance, 1 had an adverse reaction, 1 had severe nausea and vomiting, 2 had breakthrough vomiting, and 4 had other side effects.

NEW MEXICO (1983)

Background. This program of Research was conducted by the Lynn Pierson Therapeutic Research Program for the New Mexico Health and Environment Department after authorization by the legislature in 1978 (Behavioral Science Division, 1983).

Treatment Method. Patients enrolled in the program were randomly assigned to one of two treatments: THC capsule or marijuana cigarettes. Doses were matched so that each patient received approximately 15 mg of THC. Patients were administered the treatment before a cycle of chemotherapy. After chemotherapy, patients could continue taking the marijuana or THC for 5 days. Forty female patients and 27 male patients received marijuana cigarettes, while 50 female patients and 25 male patients received THC capsules.

Measures. Observations were made by patients with a self-report scale called the Target Problem Rating Scale. For nausea and vomiting, improvement was defined when patients reported less nausea or vomiting compared with previous anti-emetics. No improvement was defined as no change compared with previous anti-emetics.

Results. The data are shown in Table 5. Patients who smoked marijuana achieved improvement overprevious antiemetic drugs, with those smoking the drug exceeding 90% success.

TABLE 5. New Mexico Trial (1983)

Group	Oral THC	Inhaled Marijuana
Improvement	57 (74.83%)	58 (90.39%)
No Improvement	9 (25.17%)	3 (9.6%)

NEW MEXICO (1984)

Background. The Lynn Pierson Therapeutic Research Program continued in 1984 (Behavioral Science Division 1984).

Treatment Method. The program was similar to that in 1983, with the exception that some patients received only one treatment and others received an average of six treatments after chemotherapy. Patients were randomly assigned to the same treatment groups as in the 1983 protocol. The protocol also allowed patients options to begin in one treatment group and switch to another, to refuse to be in the smoking group, or to try both routes of administration sequentially. Success was defined as a reduction in nausea and vomiting, and failure was defined as no reduction. Table 6 shows the results. It is important to note that few patients continued with the oral THC treatment, while those who smoked marijuana achieved over 90% success. Summarizing side effects of both THC and marijuana reported over the two years, treated patients often fell asleep. Of those who did not (approximately 90 patients), 50% reported sleepiness and 45% felt ''high.'' No other side effects were noted in the report.

CALIFORNIA

Background. After legislation passed by the State of California Legislature in 1979, a Cannabis Therapeutic Program was carried out between 1983 and 1989 under the supervision of the California Research Advisory Panel (1989).

Treatment Method. Over the years, several protocols were used. Essentially, the early protocols were conservative, e.g., patients were required to have failed treatment with conventional anti-emetic drugs. Later, a more relaxed protocol was used in which the patient and the physician decided whether or not to try the THC capsule or smoke marijuana.

TABLE 6. New Mexico Trial (1984): Treatment Success After the First Treatment with Inhaled Marijuana or Oral THC

Group	Oral THC	Inhaled Marijuana	Combined
Success	6 (54.5%)	79 (95.2%)	79 (98.8%)
Failure	5 (45.5%)	4 (4.8%)	1 (1.2%)

Measures. Physicians used 5 point rating scales to record nausea and vomiting.

Results. Table 7 shows the combined results of the various protocols combined. In this study, smoked marijuana was consistently more effective than oral THC in blocking vomiting except in the most severe cases (> 6 times). Control of nausea was about the same for both groups. The pattern of side effects did not differ, to any extent, between smoked marijuana and oral THC.

NEW YORK

Background. The New York Department of Health study conducted a large scale (Phase III type) cooperative clinical trial (Randall, 1990).

Treatment Method. The central question addressed was how effective inhaled marijuana was in preventing nausea and vomiting due to chemotherapy in patients who failed to respond to previous anti-emetic therapy. Patients undergoing chemotherapy were allowed to use marijuana distributed through three centers: North Shore Hospital (NSH), Columbia Memorial Hospital (CMH), and a triad of the Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital (JGH). By 1985, the New York program provided marijuana therapy to 208 patients through 55 practitioners. Of those, data on 199 patients were evaluated. These patients had received a total of 6,044 NIDA-

TABLE 7. California Trials: Ratings of Nausea and Vomiting for Smoked Marijuana or the THC Capsule.

	Smoked Marijuana	THC Capsule		Smoked Marijuana	THC Capsule
Nausea			Vomiting		
None	9 (9.2%)	38 (15.1%)	None	19 (19.4%)	89 (35.3%)
Mild	34 (34.7%)	85 (33.9%)	1-3 times	36 (36.7%)	69 (27.4%)
Moderate	36 (36.7%)	73 (29.1%)	4-6 times	18 (18.4%)	35 (13.9%)
Severe	17 (17.3%)	55 (21.9%)	> 6 times	24 (24.5%)	59 (23.4%)
Missing	2 (2%)	6 (2.3%)	Missing	1 (1%)	5 (2.3%)

Side Effects (combined ratings from mild to severe are shown Table 8).

TABLE 8. California Trials: Side Effects Reported by Patients

	Smoked Marijuana n = 98	Smoked Marijuana %	THC Alone n = 257	THC Alone %
Dry Mouth	53	56.5	112	44.8
Tachycardia	6	6.4	25	10.0
Ataxia	16	27.1	31	12.8
Dizziness	31	33.1	67	26.8
Orthostatic	7	7.5	32	12.8
Anxiety	19	20.2	47	18.8
Sedation	49	52.1	160	64.0
Elated Mood	25	26.6	61	24.4
Confusion	23	26.6	79	31.6
Perceptual	15	15.9	57	22.8
Fantasizing	10	10.7	29	11.6
Depressed	17	18.1	33	13.2
Panic/Fear	7	7.5	9	7.6

supplied marijuana cigarettes provided to patients during 514 treatment episodes.

Measures. Observations were made by patient self-report.

Results. North Shore Hospital reported marijuana was effective at reducing emesis 92.9% of the time; Columbia Memorial Hospital reported efficacy of 89.7%; the triad of Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital reported 100% of the patients smoking marijuana gained significant benefit.

Analyzing patient evaluations, the report concluded that approximately 93% of marijuana inhalation treatment episodes were effective or highly effective when compared with other anti-emetics. The New York study reported no serious adverse side effects. No patient receiving marijuana required hospitalization or any other form of medical intervention.

DISCUSSION

Even though slightly different methods and different research designs were used in these studies, it is clear that inhaled marijuana was

effective in reducing or eliminating nausea and vomiting following cancer chemotherapy. In those studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration. In almost all of these studies, patients were admitted only after they failed treatment with standard anti-emetics, suggesting the patients may have been under fairly aggressive treatment for their cancers.

With regard to side effects, short term use of marijuana leads to sedation, a high, and smoke intolerance in some patients. At this point in time there is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy, Watson and Benson, 1999).

In a 1991 survey, Doblin and Kleiman (1991) reported that more than 70% responding oncologists (n = 1035) reported at least one of their patients had used marijuana as an anti-emetic, and that they had also either observed or discussed the patients' use. In addition, 44% of the respondents reported recommending marijuana to at least one patient. Two hundred seventy-seven respondents felt they had clinical experience with both marijuana and Marinol™ (oral THC): (44% thought marijuana was more effective, 43% thought they were about equally effective, and 13% thought Marinol™ was more effective). These data suggest that physicians at that time continued to discuss or recommend marijuana use to some patients. In this sample of oncologists, it seems they understood the potential efficacy of marijuana use. Whether this situation has changed since 1991 is unknown, but one might argue that the introduction of the anti-emetics of the selective serotonin-3 antagonist class, may have changed this practice.

While there have been no studies which have compared smoked marijuana or Marinol™ with the serotonin receptor type-3 antagonists (granisetron or ondansetron), it is instructive to review published clinical trials with these compounds for the sake of comparison. In 9 clinical trials with ondansetron, anti-emesis was obtained in 40%-81% (mean 63.5%) of patients (Beck et al. 1993; Buser et al. 1993; Crucitt et al. 1994; Hainsworth et al. 1991; Herrstedt et al. 1993; Kaasa et al. 1990; Marty et al. 1980; Olver et al. 1996; Roila et al. 1991). In 5 clinical trials with granisetron, 37.7%-93% (mean 56.6%) anti-emesis was reported (Italian Group for Antiemetic Research 1995; Markman et al. 1996; Perez et al. 1997; Ritter Jr. et al. 1998; Sekine et al. 1996). It is generally known that combining anti-emetic drugs with different

mechanisms of action often improves efficacy (Jones et al. 1991). This suggests that future research should consider combining cannabinoids with other anti-emetics.

The data reviewed here suggest that the inhalation of THC appears to be more effective than the oral route. In order to achieve the IOM recommendation to allow patients access to marijuana, both state and Federal Governments would need to reschedule marijuana from Schedule I to Schedule II, or reinstate the Compassionate Use Program. The development of smokeless inhalation devices would certainly be an advance in the use of THC as an anti-emetic medication. Finally, a large number of synthetic cannabinoid and endocannabinoid agonist analogs have been developed. It would seem that testing of these compounds as potential anti-emetics would also be worthwhile.

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The Endocannabinoid System: Can It Contribute to Cannabis Therapeutics?

Vincenzo Di Marzo

ABSTRACT. Receptors for ? ^{9}-tetrahydrocannabinol (THC), cannabis' major psychoactive principle, have been identified in animal tissues. These proteins have a reason to exist because endogenous substances may bind to and functionally activate them, thereby producing pharmacological effects similar to those of THC. Such substances, named ''endocannabinoids,'' have been isolated and several studies have been performed on their pharmacological properties as well as on the molecular mechanisms for their biosynthesis, action and inactivation in animal cells. Within the framework of the ongoing debate on the therapeutic potential of cannabinoid receptor agonists and antagonists, the present article addresses the possibility that our knowledge of the endocannabinoid system may result in the development of new drugs for the treatment of illnesses as diverse as nervous and immune disorders, pain, inflammation and cancer. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>*

KEYWORDS. Cannabinoids, endocannabinoids, endogenous cannabinoids, anandamide, 2-arachidonoyl glycerol, receptors

THE ENDOCANNABINOID SYSTEM

Research on the mechanism of action of the psychoactive components of *Cannabis sativa*, the cannabinoids, culminated in the early

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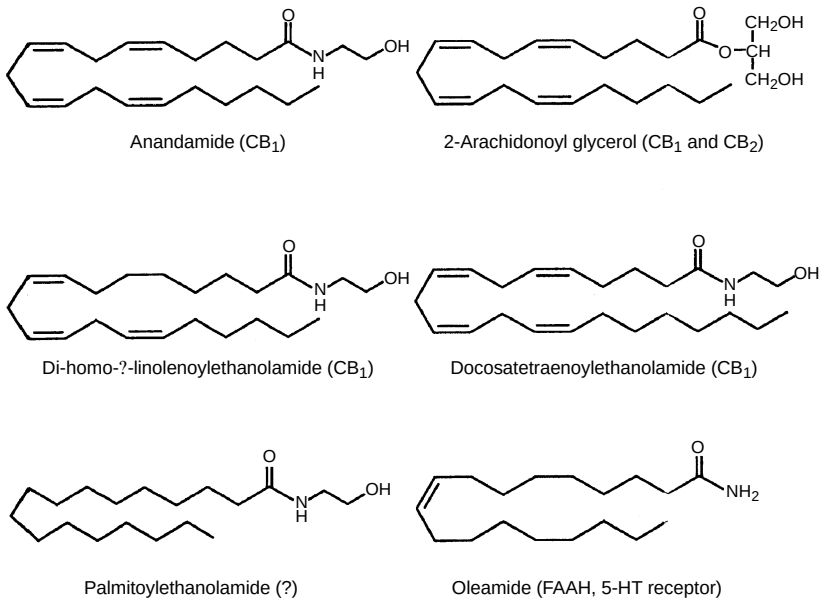
1990's with the finding of cannabinoid receptors and of their possible endogenous agonists (see Matsuda 1997 and Di Marzo 1998 for reviews) (Figure 1). These molecules, together with the proteins that regulate their activity and/or levels, constitute the ''endocannabinoid system.'' The first subtype of cannabinoid receptors, named CB_1, is widely distributed in both nervous and non-nervous tissues, and is responsible for most of the 'central' actions, and also for some of the peripheral ones, of plant and synthetic cannabinoids. The second subtype of cannabinoid receptors, named CB_2, has been found to date in high levels only in immune tissues and cells and may mediate some of the immune-modulatory effects of the cannabinoids, although little direct evidence for this possibility has been found so far. Evidence for CB_2-like receptors in peripheral nerves has been also described (Griffin et al. 1997). The finding of selective CB_1 and, more recently, CB_2 receptor antagonists (Rinaldi-Carmona et al. 1994, 1998; Felder et al. 1998), and the development of cannabinoid receptor knockout mice (Ledent et al. 1999; Zimmer et al. 1999; Buckley et al., 1999) will

FIGURE 1. Chemical structures and likely molecular targets of the endocannabinoids and other cannabimimetic fatty acid derivatives.



soon provide a definitive answer as to which of the typical pharmacological actions of cannabinoids are mediated by either receptor subtype, and may even support the hypothetical presence of further molecular targets for these compounds. As to the possible endogenous counterparts of the cannabinoids, over the last seven years several fatty acid derivatives have been found to mimic the properties of ? ^{9}-tetrahydrocannabinol (THC), cannabis' major psychoactive principle. Not all of these substances, however, have the capability to displace high affinity cannabinoid ligands from selective binding sites in membrane preparations containing the CB_1 or the CB_2 receptor. Anandamide (Devane et al. 1992), the amide of arachidonic acid with ethanolamine, was the first of such compounds to be isolated and received its name from the Sanskrit word for ''internal bliss,'' *ananda*. Next came two polyunsaturated congeners of anandamide (Hanus et al. 1993), and a glycerol ester, 2-arachidonoyl glycerol (2-AG) (Mechoulam et al. 1995; Sugiura et al. 1995). These compounds share the ability to bind to and activate CB_1 and (particularly in the case of 2-AG) CB_2 receptors. Therefore, they induce a series of pharmacological effects *in vitro* and *in vivo* that are, to some extent, similar to those exerted by THC (Hillard and Campbell 1997; Di Marzo 1998; Mechoulam et al. 1998). Hence the name of ''endocannabinoids'' was proposed for anandamide and 2-AG. Other fatty acid derivatives (Figure 1), such as palmitoylethanolamide and *cis*-9-octadecenoamide (oleamide), do not have high affinity for either of the two cannabinoid receptor subtypes discovered so far, and yet they exhibit pharmacological actions that in some cases are cannabis-like (see Lambert and Di Marzo 1999 for review). The molecular mode of action of these latter compounds, that cannot be referred to as ''endocannabinoids,'' is currently being debated and is possibly due in part to the modulation of either the action or the metabolism of anandamide and 2-AG (Mechoulam et al. 1997; Lambert and Di Marzo 1999).

The study of the pharmacological properties of the endocannabinoids was not limited to confirm for these compounds the same spectrum of activities previously described for THC. Indeed, qualitative and quantitative differences between the action of classical and endogenous cannabinoids became evident since the first studies on these new metabolites (Hillard and Campbell 1997; Di Marzo 1998; Mechoulam et al. 1998). The chemical structure of anandamide and 2-AG (Figure 1), with the presence of hydrolysable amide or ester bonds and

of an arachidonate moiety, raises the possibility that these substances may be metabolized to other bioactive compounds through the several oxidizing enzymes of the arachidonate cascade (Burstein et al. 2000). Moreover, the lack of chiral centers contributes to making these molecules capable, in principle, of interaction with many molecular targets. The endocannabinoids, therefore, are ideal templates for the development of new drugs. Three different pieces of information are necessary in order to understand whether an endogenous substance can represent the starting point for the design of therapeutic agents. First, its pharmacologically activity *in vitro* and *in vivo* needs to be thoroughly assessed. Next, the biochemical bases for the biosynthesis, action and degradation of the substance need to be fully understood. Finally, a correlation between the occurrence of particular physiological and pathological conditions and the levels of this metabolite in tissues must be investigated. In this article, I will briefly describe the landmarks in these three aspects of the research on endocannabinoids. I will also provide a few examples of how endocannabinoid-derived molecules might turn out to be useful in the alleviation and cure not only of those illnesses traditionally treated with cannabis preparations, such as inflammation, nausea, diarrhea, and chronic pain, but also for cancer, mental disorders and immune diseases.

ENDOCANNABINOID PHARMACOLOGY: MORE THAN MEETS THE EYE

As mentioned above, anandamide, in some cases, exhibits effects qualitatively and quantitatively different from those of the classical cannabinoids. This may be partly due to the rapid metabolism of this compound both *in vitro* and *in vivo* (Deutsch and Chin 1993; Willoughby et al. 1997), but also to the fact that anandamide is a partial agonist in some functional assays of CB_1 and CB_2 activity (Mackie et al. 1993; Breivogel et al. 1998). Moreover, recent studies seem to suggest that this compound is able to adapt to binding sites within other receptors (Hampson et al. 1998; Kimura et al. 1998; Zygmunt et al. 1999). The selective antagonists developed so far for cannabinoid receptors (Rinaldi-Carmona et al. 1994, 1998) have been and still are useful tools to understand when and where anandamide effects are mediated by these proteins. It is still difficult at this stage to distinguish, among these effects, those with a physiological or therapeutic

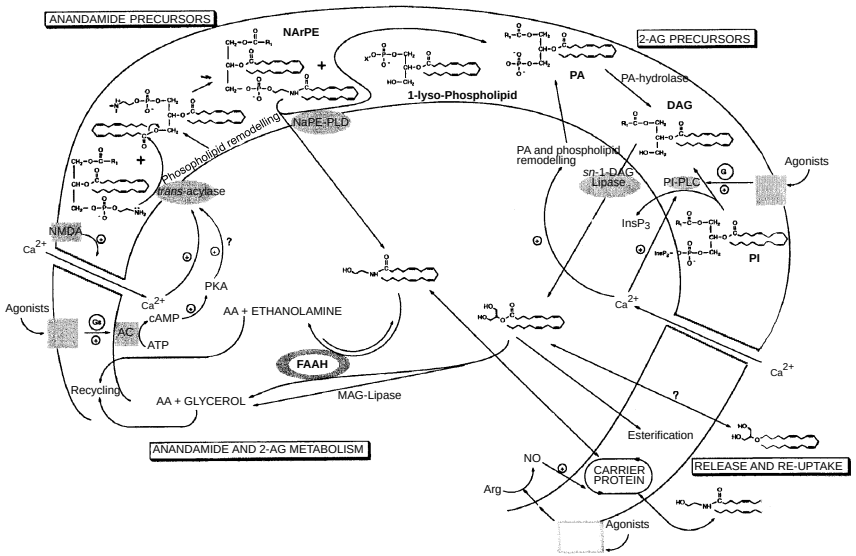
relevance. However, it is possible to speculate based on the range of concentrations necessary to observe a certain effect as compared to the usually low tissue concentrations of anandamide. Thus, in the brain, this metabolite was shown to exert inhibitory actions on learning and memory (Mallet and Beninger 1996; Castellano et al. 1997), to modulate the extra-pyramidal control of motor behavior (Romero et al. 1995), and to protect astrocytes against inflammatory stress (Molina-Holgado et al. 1997). These effects are probably due to the capability of anandamide to induce, via activation of CB_1 receptors, a series of intracellular events resulting in the modulation of neurotransmitter release, action and re-uptake (see Di Marzo et al. 1998b for review). This neuromodulatory action may also underlie anandamide regulation of hormone release at the level of the hypothalamus/pituitary/adrenal axis (Fernandez-Ruiz et al. 1997), as well as the anti-nociceptive effects of the compound through both spinal and supra-spinal mechanisms (reviewed by Martin and Lichtman 1998). In peripheral tissues, anandamide regulates the heartbeat and vascular blood pressure and produces vasodilator effects through several possible mechanisms (recently reviewed by Kunos et al. 2000). The endocannabinoid also relaxes smooth muscle in the gastrointestinal system and reproductive/urinary tract (Pertwee and Fernando 1996; Izzo et al. 1999). Regulation of reproduction also occurs at the level of the sperm acrosome reaction (Schuel et al. 1994) and embryo development and implantation (Paria et al. 1995, 1998). As most of these findings were obtained after the development of the CB_1 receptor antagonist SR141716A (Rinaldi-Carmona et al. 1994), it was possible to demonstrate the intermediacy of this receptor in most of the above effects. Conversely, the involvement of CB_2 receptors in the immune-regulatory effects of anandamide is yet to be fully established (for a recent review see Parolaro 1999), probably due to the only very recent availability of a selective antagonist for these receptors, SR144528 (Rinaldi-Carmona et al. 1998). Finally, anandamide was also found to regulate some key cell functions such as cell proliferation and energy metabolism (De Petrocellis et al. 1998, Guzman and Sanchez 1999), but only in the first case by activating CB_1 receptors. As to 2-AG, only a few pharmacological studies have been performed to date on this compound, possibly because of its limited commercial availability until recently. Apart from its activity in the mouse ‘‘tetrad’’ of tests for cannabimimetic compounds (i.e., analgesia in the ‘‘hot-plate’’ or ‘‘tail-

flick'' test, immobility on a ring, hypothermia and inhibition of spontaneous activity in an open field [Mechoulam et al. 1995]), this compound shares with THC an immune-modulatory action (Ouyang et al. 1998) and an inhibitory effect on embryo development (Paria et al. 1998) and breast and prostate cancer cell proliferation (De Petrocellis et al. 1998; Melck et al. 2000). 2-AG also induces calcium transients in neuroblastoma × glioma cells and HL-60 cells (via CB_1 and CB_2 receptors, respectively), an effect that is not efficaciously exerted by anandamide (Sugiura et al. 1999, 2000). Therefore, different pharmacological actions can be observed not only for *endo*cannabinoids and *exo*cannabinoids, but also for anandamide and 2-AG.

LEVELS OF ENDOCANNABINOIDS IN TISSUES: PHYSIOLOGY AND PATHOLOGY

Biochemical pathways for anandamide and 2-AG biosynthesis and inactivation by intact cells have been identified (see [Hillard and Campbell 1997; Di Marzo 1998; Di Marzo et al. 1998] for reviews) (Figure 2). Mechanisms for the regulation by both physiological and pathological stimuli of the enzymes involved in these pathways have also been found. On stimulation with calcium ionophores, or other calcium mobilizing stimuli, anandamide is produced by neurons and leukocytes from the hydrolysis of a membrane phospholipid precursor, *N*-arachidonoyl phosphatidyl ethanolamine (NArPE). The reaction is catalyzed by a phospholipase D specific for NArPE and other homologous phospholipids. Notably, phospholipase D enzymes are known to be subject to regulation by intracellular mediators (e.g., the diacylglycerols). NArPE, in turn, is produced by the transfer of arachidonic acid from the *sn*-1 position of phospholipids onto phosphatidylethanolamine. The enzyme involved in this case is a *trans*-acylase regulated by calcium and cAMP-induced protein phosphorylation. 2-AG is produced in intact neurons from the hydrolysis of diacylglycerols catalyzed by the *sn*-1 selective diacylglycerol lipase. Diacylglycerols serving as 2-AG precursors are in turn formed from the hydrolysis of either phosphatidylinositol or phosphatidic acid. The enzymes catalyzing these two reactions are a phospholipase C and a phosphatidic acid hydrolase, respectively. There is no evidence that these two enzymes are different from enzymes of the same type responsible for

FIGURE 2. Schematic representation of endocannabinoid biosynthetic and metabolic pathways describes so far in intact cells. Adapted from Di Marzo et al., 1998b. Abbreviations: NMDA, N-Methyl-D-Aspartate; NaPE-PLD, N-acyl-phosphatidylethanolamine-selective phospholipase D; PI-PLC, phosphatidylinositol-selective phospholipase C; PA, phospatidic acid; DAG, diacylglycerol; AC, adenylyl cyclase; PKA, protein kinase A; MAG, mono-acylglycerol; NO, nitric oxide; AA, arachidonic acid; FAAH, fatty acid amide hydrolase.



the formation of intracellular mediators, and therefore it is likely that they are subject to several regulative mechanisms.

Also the routes leading to endocannabinoid degradation are likely to be tightly regulated (Hillard and Campbell 1997; Di Marzo 1998; Di Marzo et al. 1998b). The major enzyme responsible for anandamide hydrolysis, fatty acid amide hydrolase (FAAH), has been cloned from four species (Cravatt et al. 1996; Giang and Cravatt 1997; Goparaju et al. 1999) and found to contain a proline-rich domain necessary for enzymatic activity (Arreaza and Deutsch, 1999). This domain contains a consensus sequence for recognition by regulatory proteins that may target FAAH to its subcellular location, thereby regulating its activity. FAAH also recognizes as a substrate 2-AG (Goparaju et al. 1998), for which, however, other hydrolytic enzymes have been described. One of these hydrolases, present in rat platelets and macro-

phages, is down-regulated by lipopolysaccharides (LPS) exposed by bacterial walls (Di Marzo et al. 1999).

As the hydrolytic enzymes responsible for the degradation of endocannabinoids seem to be located in intracellular sites (Giang and Cravatt 1997), the internalization of these compounds is necessary for their degradation to occur. A mechanism for the facilitated diffusion of anandamide across the cell membrane has been identified in several cell types. This ''carrier'' is temperature-dependent, saturable, quite selective for anandamide and some of its analogues, and sensitive to specific inhibitors (Beltramo et al. 1997; Hillard et al. 1997; Di Marzo et al. 1998a; Melck et al. 1999). More importantly, the anandamide carrier is activated by nitric oxide (Maccarrone et al. 1998, 2000), a finding that creates the possibility of regulatory loops between the action of some mediators or pathological stimuli and anandamide inactivation.

The observations described above suggest that the levels of pharmacologically active endocannabinoids in tissues may change during a certain physiological or pathological response and, therefore, that substances interfering with anandamide or 2-AG biosynthesis, action and metabolism may be used as therapeutic agents. However, over the last six years, only a few studies have attempted to correlate endocannabinoid levels with particular physiopathological conditions. Pioneering studies have been carried out in peripheral tissues. Anandamide was produced in the highest levels in the mouse uterus when this tissue is least receptive to the embryo (Schmid et al. 1997). This finding and the observation that anandamide inhibits embryo implantation (Paria et al. 1995, 1998) suggest that a defective regulation of endocannabinoid levels in the uterus may underlie early pregnancy failures. If this is proven to be the case, inhibitors of anandamide synthesis, or CB_1 receptor antagonists, could be used to prevent this clinical problem. Formation of 2-AG in platelets and of both 2-AG and anandamide in macrophages was correlated with septic shock-induced hypotension in rats (Varga et al. 1998). In fact, macrophages and platelets from rats treated with LPS were shown to induce CB_1-mediated hypotension in untreated rats. Likewise, macrophages from rats undergoing hemorrhagic shock produce anandamide and induce hypotension in untreated rats in a fashion sensitive to the CB_1 antagonist SR141716A (Wagner et al. 1997). In this case, THC treatment was found to improve the chances of survival of rats after hemorrhagic shock, whereas

SR141716A appeared to rescue the animals from septic shock. These data underlie the importance of studies on the endogenous cannabinoid system for the development of alternative therapeutic approaches.

In the brain, anandamide, but not 2-AG, was found to be released from the dorsal striatum of freely moving rats and shown to counteract the motor-inducing action of the dopamine D2 receptor agonist quinpirole (Giuffrida et al. 1999). This finding is in agreement with data suggesting for anandamide a role in the extra-pyramidal control of locomotion, possibly at the level of dopamine action (Romero et al. 1995). A more recent study showed that endocannabinoid levels in the external layer of the globus pallidus are inversely correlated with spontaneous motor activity in the reserpine-treated rat, an animal model of Parkinson's disease (Di Marzo et al. 2000a). Out of the six brain regions analyzed, only the globus pallidus–an area which receives CB_1–containing GABAergic terminals from the striatum, and where both classical and endogenous cannabinoids potentiate GABA inhibitory action on movement (Wickens and Pertwee 1993)–was found to contain *increased* amounts of 2-AG concomitantly to the akinesia induced by reserpine-mediated catecholamine depletion in the striatum. Both anandamide and 2-AG levels in the globus pallidus were *reduced* concomitantly to the administration to reserpine-treated rats of dopamine receptor agonists and the subsequent partial recovery of motor behavior. Finally, co-administration to rats of quinpirole and the CB_1-antagonist SR141716A almost totally restored normal locomotion. On the other hand, it was also found that the dyskinesia induced in MTPT-treated monkeys after prolonged treatment with L-dopa, a typical consequence of curing Parkinson's disease in humans with this drug, was alleviated by SR141716A (Fox et al. 1999). These studies suggest that agonists and antagonists of CB_1 receptors may be used advantageously in the future for the treatment of parkinsonian patients. Furthermore, these data reveal the existence of a complex regulatory interplay between the dopaminergic and endocannabinoid systems, according to which activation of dopamine receptors may either activate or inhibit endocannabinoid signaling, and endocannabinoids would either counteract or reinforce dopamine action, depending on the brain region and the pathophysiological situation. Indeed, this interplay may occur also at the level of the limbic system and underlie a role of endocannabinoids in the reinforcement of, or the recovery from, the effects of prolonged drug abuse. In fact, a recent

study showed that chronic treatment of rats with THC results in the down-regulation of cannabinoid receptor binding and signaling in all brain regions analyzed except for the limbic forebrain, where these two parameters were not altered (Di Marzo et al. 2000c). This region was also the only one exhibiting higher amounts of anandamide with respect to vehicle-treated rats. It is possible that dopamine released in the nucleus accumbens following chronic administration with THC (or more potent drugs of abuse, such as morphine and alcohol) (Tanda et al. 1997) stimulates the formation of anandamide in this region, by analogy to what was previously found for the dorsal striatum (Giuffrida et al. 1999). In any event, this finding may suggest the involvement of the endocannabinoid system in motivation and reward, thus opening the way also to the possibility that drugs derived from anandamide and 2-AG be used in the treatment of depression, and related nervous disturbances.

The finding of anandamide and 2-AG in the hypothalamus of rats (Gonzales et al. 1999) and of CB_1 receptors in some nuclei such as the arcuate nucleus and the medial preoptic area (Fernandez-Ruiz et al. 1997) supports the notion, based on the well known appetite-stimulating, anti-emetic and hypothermic properties of THC, that the endocannabinoid system may be involved in the control of hypothalamic functions. Further studies are now required to understand whether endocannabinoid levels can be associated with hyperphagia or anorexia, and be tuned by the several transmitter systems that intervene in the regulation of food intake.

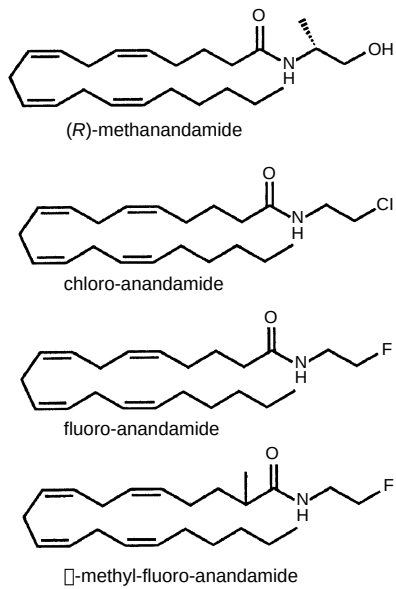
Finally, a possible correlation between anandamide release from neurons of the periaqueductal grey (PAG), a region of the brainstem, and anti-nociception was recently described (Walker et al. 1999). Electrical stimulation of the PAG results in CB_1-mediated analgesia and the release of anandamide in micro-dialysates from this region. Small amounts of the endocannabinoid were released from the PAG also following a nociceptive stimulus such as the injection of formalin into the hindpaw (Walker et al. 1999). The same stimulus does not lead to the local formation of anandamide, 2-AG or palmitoylethanolamide in the hindpaw (Beaulieu et al. 2000). Therefore, it is possible that anti-nociceptive endocannabinoids are formed at a supraspinal level following noxious stimuli. However, it is not clear how the low concentration of anandamide found in PAG microdialysates (~180 pM) can be consistent with the weak analgesic effect observed with this

compound following intrathecal, systemic and, particularly, intra-cerebroventricular administration (Calignano et al., 1998; Martin and Lichtman 1998), or with the high nM concentrations required for this compound to activate CB_1 receptors (Hillard and Campbell 1997).

NEW DRUGS FROM THE ENDOCANNABINOID SYSTEM. CURATIVE OR PALLIATIVE?

From the findings described in the previous sections, it is clear that the discovery of endocannabinoids opens several unprecedented possibilities for the development of new drugs. Firstly, the finding that a novel class of compounds derived from fatty acids and different from classical cannabinoids and aminoalkyl-indoles could activate the cannabinoid receptors stimulated the synthesis of several new endocannabinoid-based compounds (see Martin et al. 1999, for a comprehensive review). Some of these compounds (Figure 3) are several-fold more potent than anandamide and 2-AG at CB_1 receptors, while others are

FIGURE 3. Chemical structures of potent synthetic anandamide analogues with high affinity for CB_1 receptors and/or enhanced metabolic stability.

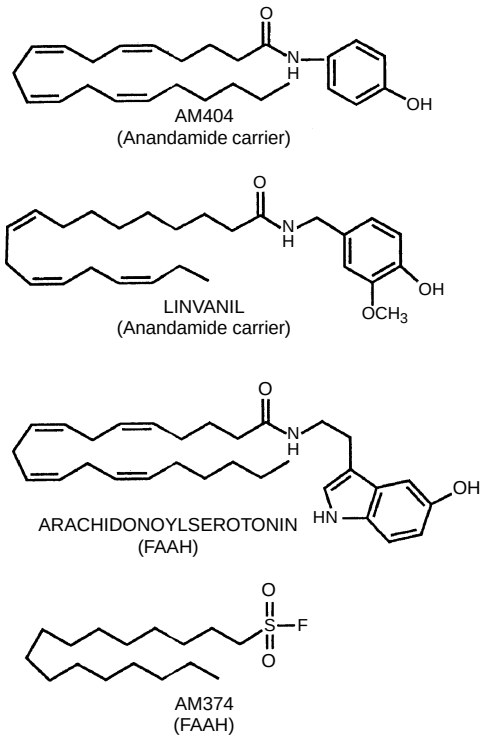


more resistant to enzymatic hydrolysis and can exert longer-lasting pharmacological actions. Secondly, when a cause and effect relationship is established between certain pathological conditions and the levels of endocannabinoids (measured by sensitive analytical techniques as in some of the studies described in the previous section), the application of endocannabinoid-based drugs for the cure of these disorders will be possible. In fact, these studies should provide indispensable hints as to what pathological state can be treated with CB_1 and CB_2 agonists or antagonists. Thirdly, our knowledge of the enzymes regulating endocannabinoid levels will allow us to develop selective inhibitors to be used for those disorders for which a correlation with defective endocannabinoid synthesis or inactivation is clearly demonstrated. Indeed, a few such substances are already available, as in the case of the rather selective inhibitors of FAAH and the anandamide carrier shown in Figure 4. Some of these compounds, such as AM404 and linvanil (two carrier inhibitors) and AM374 (a FAAH inhibitor) have been shown to lower the concentration threshold for anandamide activity both *in vivo* and *in vitro* (Beltramo et al. 1997; Gifford et al. 1999; Maccarrone et al. 2000). These compounds may be useful for those yet-to-be discovered pathological states arising from excessive degradation of endogenous anandamide. Moreover, if ways to target them selectively to peripheral tissues are devised, these compounds may render locally active doses of exogenous anandamide analogues that are devoid of undesired psychotropic activity.

Indeed, the development of new therapeutic agents from the endocannabinoids may provide a way out of the social and legal implications arising from the prescription of medical cannabis, at the center of heated debates in the UK and USA. In fact, given the numerous differences found so far between the pharmacological effects of the endogenous compounds and THC, it is likely that endocannabinoid-like drugs may have beneficial effects by simply compensating for possible malfunctions in the endogenous system, without causing the ''high'' typical of marijuana intoxication. Indeed, a recent study showed that both anandamide and its metabolically stable analogue (*R*)-methanandamide (Figure 3) do not cause dependence in rats (Aceto et al. 1998).

Finally, one last issue that should be addressed in the future is whether these putative therapeutic agents will be used simply as palliatives, as the history of medicinal cannabis would suggest, or instead

FIGURE 4. Chemical structures of synthetic inhibitors of anandamide inactivation (i.e., facilitated transport into cells or fatty acid amide hydrolase-catalyzed hydrolysis).

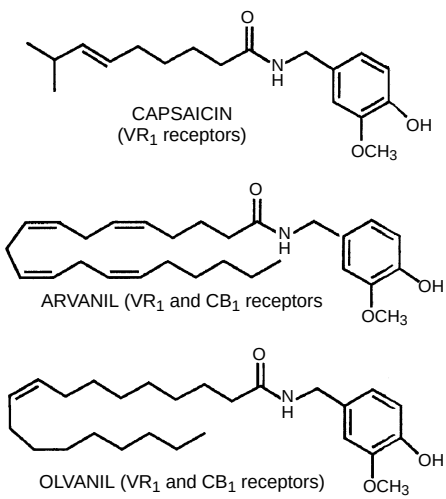


as curative drugs. The answer to this question may come from studies attempting to establish a causative role of a defective endocannabinoid system in some disorders such as, for example, those arising from exaggerated or disrupted immune responses (inflammation, allergy, auto-immune diseases), or from the hyper- or hypo-activity of the dopaminergic or other neurotransmitter systems (schizophrenia, Tourette's syndrome, anorexia, depression) (Consroe 1998). Were such a causative role to be found, metabolically stable endocannabinoids analogues and/or inhibitors of endocannabinoid degradation may contribute to the cure of these diseases. On the other hand, there may be a case for the use of exogenous endocannabinoids also in the treatment of those pathological states that are not necessarily related

to altered endocannabinoid levels and action. One example may be the recent finding of anandamide derivatives with potent anti-proliferative activity against growth factor-dependent breast and prostate cancer cell proliferation (De Petrocellis et al. 1998; Melck et al. 2000; Di Marzo et al. 2000b). One of these compounds, arvanil (Figure 5 and [Melck et al. 1999]) is a structural ''hybrid'' between anandamide and the widely used pharmacological tool capsaicin (the active principle of hot chiles), and exerts also very potent analgesic actions (Di Marzo et al. submitted). Last, but not least, the capability of endocannabinoids to synergize with opioids and opiates in the treatment of hyperalgesia and chronic pain is being debated (Manzanares et al. 1999).

In conclusion, the road to novel drugs from the endocannabinoid system is still long and unpaved. Although much progress has been done towards the understanding of the chemical bases underlying anandamide molecular recognition by cannabinoid receptors and inactivating proteins, thus leading to new pharmacologically active substances (Figures 3-5), a multi-disciplinary effort will be now required from biochemists, physiologists, pharmacologists and clinicians in order to understand whether and for what disorders these new chemicals can be used as therapeutic agents.

FIGURE 5. Chemical structures and properties of cannabinoid-vanilloid "hybrids."



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The Therapeutic Use of *Cannabis sativa* (L.) in Arabic Medicine

Indalecio Lozano

ABSTRACT. Arab scientists were several centuries ahead of our current knowledge of the curative power of hemp (*Cannabis sativa* L., Cannabaceae). Modern Western scientific literature ignores their contribution on the subject. We review in this paper the therapeutic uses of the plant in Arabic medicine from the 8th to the 18th century. Arab physicians knew and used its diuretic, anti-emetic, anti-epileptic, anti-inflammatory, painkilling and antipyretic properties, among others.

KEYWORDS. *Cannabis sativa* L., Cannabaceae, therapeutic uses, Arabic medicine

INTRODUCTION

The modern medical and pharmacological literature which deals with the therapeutic properties of hemp (*Cannabis sativa* L., Cannabaceae) tends to ignore the valuable contributions of Arabic scientists on the subject. The tradition of the plant's medicinal use was adopted by these scientists from the cultures of the Ancient World, having been used for over a thousand years as a textile and medicine in Arabia, Mesopotamia, Persia, Egypt, China, India and extensive areas of Eu-

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rope (Levey 1979; Escohotado 1989-1990). The role played by the medical, pharmacological and botanical literature of the Greeks in this regard is well-known, dominating medical circles in Asia Minor, Syria, Egypt and their neighbouring regions right up until the arrival of Islam in the 7th century. The *Materia medica* of Dioscorides (1st century), translated into Arabic by Istifān b. Bāsīl in the days of the caliph al-Mutawakkil (d. 861 A.D.), and the *De Simplicium medicamentorum temperamentis ac facultatibus liber VII* of Galen (d. 199 A.D.) similarly translated by Ḥunayn b. Isḥāq (d. 873 A.D.), were by far the most important sources for Arabic physicians, and were a decisive stimulus in the development of their knowledge of the plant.

To date, there are only a few works that deal with the history of the therapeutic use of hemp in Arabic medicine (Hamarneh 1972; Levey 1979; Lorano 1990), and even these only tangentially. The current renewed interest in research into the curative potential of the plant justifies a review of the subject in the light of new Arabic documental sources.

MATERIALS AND METHODS

Medical, pharmacological and botanical literature written in Arabic has been systematically and exhaustively consulted, as far as possible, from the 8th to the 18th century. Over the same period, lexicographical, agricultural, literary, legal, historical and geographical sources, which were likely to contain data on *Cannabis sativa* (L.), were also examined. The great majority were published texts, though some manuscripts were also examined. Of all the texts reviewed, more than fifty contain information on the plant, although due to limited space not all of them are mentioned in the bibliography.

In the results, we have focused our attention on the discoverer or pioneer of each therapeutic use, and only the most significant contributions of later authors have been cited. Thus, not all the sources that mention these uses have been included.

This paper arises out of a background of historical philological studies on Arabic-Islamic medicine and thus it neither can nor seeks to tackle any debate on the pharmacological mechanisms involved in the therapeutic uses documented here.

RESULTS

"Temperament" of the Plant, Parts Used, Modes of Preparation and Administration

Arab scientists explained the curative properties of hemp according to the principles of the humoral theory they learned from the Greeks. As is well-known, this theory assumes that each simple possesses a characteristic, ''temperament,'' determined by its degrees of ''heat,'' ''cold,'' ''wetness'' and ''dryness.'' Similarly, they largely accepted the opinion of Galen (1821-1833, VI pp. 549 f. and XII, p. 8), who talks of the desiccating and warming power of hemp. However, there is no lack of prestigious authorities who had quite the opposite opinion, stating that cannabis is naturally cold (al-Ṭabarī 1928, p. 376), or composed of hot and cold parts (al-Anṭākī, n.d., I, p. 219; al-Qūṣūnī 1979-80, I, pp. 56 f.). There is even greater controversy over the definition of the degree of heat and dryness possessed by the plant, Arab physicians citing properties from the first to the third degree. This is not surprising, if one takes into account that they could find no reference to help them in the works by Galen and Dioscorides, and that the concept of temperament and its degrees do not permit empiric proof in the sense understood by current scientific methods.

The part of the plant that was most used in therapeutic treatments was the seeds, and to a lesser extent the leaves. Methods of preparation differ according to the ailment to be treated, using the oil obtained from the seeds and the juice from the leaves and green seeds.

It was administered externally in the form of ointment in the nose, orally or in drops into the ears. Only very rarely is the actual dose which should be used in each treatment mentioned. It seems that it was commonly used as a simple medicament.

Treatment of Ear Diseases

The first mention of the curative power of hemp in Arabic literature was by Ibn Māsawayh (al-Rāzī 1968, XXI i, p. 124) (d. 857 A.D.), who refers to the oil obtained from hemp seeds and applied in drops into the ear as having the virtue of drying out the ''moisture'' (*ruṭūba*) generated by this organ, a curative property which later physicians attribute to the juice of these seeds. In the period in which Ibn Māsa-

wayh lived, the works of Galen and Dioscorides were translated. From them, Arabic physicians learned the use of the juice of green hemp seeds in the treatment of earache caused by an obstruction in the ear (Galen 1821-1833, VI pp. 549 ff.; Dioscorides 1957, p. 304). Continuing this tradition, in the 10th century Ishāq b. Sulaymān (1986, II, p. 133) stated that hemp seed oil relieved earache caused by the ''cold'' (*bard*) and the moisture in the organ, and also talked, for the first time, of its power to unblock any obstructions there. In the 13th century, the botanist from Malaga, Ibn al-Bayṭār (1291 A.H., II, pp. 115 f.) prescribed hemp seed oil to cure ''gases'' (*rīḥ*) in the ear. In the 14th century, Ibn al-Jaṭīb (1972, p. 69) from Granada recommended the use of this oil mixed with gum resin of *Ferula galbaniflua* to relieve ''hot pain'' (*al-waǿ ḥārr*) associated with *tinnitus aurium*. In the 16th century, al-Anṭākī talks of how the leaves of ''Anatolian hemp,'' as he calls it (*al-qinnab al-rūmī*) (Lozano 1996, pp. 152 ff.), kill the ''worms'' which develop in the ear, and adds that they have unblocking properties, as if you fill the ear with them, all the foreign material which is lodged there will be expelled.

Vernucide and Vermifuge

In the 9th century al-Dimaǿ ¯ (Ibn al-Bayṭār 1291 A.H., IV, p. 39) is the first author who mentions the vermicidal and vermifugal properties of the plant, saying that it has the power of killing the ''worms'' (*al-dīdān*) that grow in the body. Between the 11th and 12th centuries, the anonymous author of the '*Umdat al-ṭabīb* (1990, Il, n° 2149) asserted that anyone who has tapeworms should eat hemp seeds, as their shells fill up with the parasites and are then expelled with them in the feces. Between the 14th and 15th centuries al-Firūzābādī (1952, I, p. 203) states that if the seeds of the plant are ingested or applied in the form of ointment over the stomach, this kills ascaris (*ḥabb al-qar'*).

Treatment of Skin Diseases

Ibn Māsawayh (al-Rāzī 1968, XXI i, p. 124) is the first author who refers to the use of hemp in the treatment of pityriasis (*ibriya*) and lichen (*ḥazāz*), and suggests that the affected part of the body should be washed with the juice from the leaves. In the 11th century Avicenna

(1294 A.H., I, p. 434) recommends oil from the seeds for the same purpose. Al-Fīrūzābādī (1952, I, p. 203) asserts that hemp seeds can be used to treat vitiligo (*al-bahaq*) and leprosy (*al-baraṣ*).

With regard to the treatment of skin diseases, and halfway between dermatology and cosmetics, al-Rāzī (al-Bīrūnī 1973, I, p. 33) (d. 925 A.D.) was the first to prescribe the use of hemp leaves as a substitute for *Melia azedarach* (L.) (Meliaceae) to stimulate hair growth. According to Ibn ¿ 100 A.D.) the leaves should be macerated in water and then applied to the roots of the hair.

Purging Qualities

The first reference to the purging properties of hemp is made by al-Dima¿ ¯ (Ibn al-Bayṭār 1291 A.H., IV, p. 39), who states that the juice from hemp seeds, administered through the nose, purges the brain. In the 9th century this use is also cited by Ṯābit b. Qurra (1928, p. 21, 97), who includes hemp among the simples that can purge the upper part of the liver and eliminate any obstruction produced in this organ. He prescribes that the hemp seeds should be taken with honey mixed with vinegar.

Diuretic Properties

The pioneer of the diuretic power of hemp seeds is Isḥāq b. ‘Imrān (Ibn al-Bayṭār 1291 A.H., IV, p. 39) (d. 907 A.D.). In the opinion of Isḥāq b. Sulaymān (1986, II, p. 133), this property is due to their warming power.

Antiepileptic Properties

Between the 10th and 11th centuries al-Ma¿ ¯sī (1877, II, p. 116) talks for the first time of the use of hemp in the treatment of epilepsy and prescribes that the patient should be given the juice of the leaves through the nose. In the 15th century, al-Badrī (Lozano 1989-90, p. 174 f.) provides us with a spurious tale in which hemp leaves are presented as a remedy that gives an immediate cure to epilepsy.

Carminative Properties

The carminative properties of hemp seeds, already known by Galen, are mentioned for the first time by Isḥāq b. Sulaymān. Al-Maسī (1877, II, p. 116) writes that the leaves have the same property and adds that they can be used to treat gases generated in the uterus, intestines and stomach.

Treatment of Abscesses and Tumours

Between the 11th and 12th centuries Ibn Bukārī° 679) prescribes the juice from hemp leaves to cure abscesses (*juraت*) occurring in the head. One century later, Ibn al-Bayṭār states that if an ''oily wax'' made with hemp seed oil is applied to hardened tumours (*al-awrām al-سiya*), they dissolve.

Liquification and Purging of Humors

Isḥāq b. Sulaymān mentions for the first time that hemp seeds increase the liquidity of the corporal humors. Al-Maısī (1877, II p. 116) attributes the same property to the leaves of the plant and says that they can be used to purge phlegmatic excretions from the stomach. Ibn Habal (1362 A.H. II, p. 185) (d. 1213 A.D.) indicates that hemp seeds are good for evacuating bile and phlegm.

Treatment of the Hardening and Contraction of the Uterus

Ibn al-Bayṭār (1291 A.H., II, p. 116) prescribes hemp seed oil for treating these ailments.

Pain-Killing Properties

The use of hemp as a pain-killer was not limited to the treatment of earache. Ibn al-Bayṭār (1291 A.H., II, p. 116) recommends hemp seed oil for soothing neurological pains (*waṣab*). Around the same time, al-Qazwīnī (1849, p. 293) (d. 1283 A.D.) says that the juice can be used to soothe ophthalmia.

Antipyretic Properties

Al-Fīrūzābādī (1952, I, p. 203) sustains that hemp seeds are an effective remedy in curing *febris quartana (hummà l-rib‘).*

Antiparasitic Properties

Al-Anṭākī says that the boiled leaves from ‘‘Anatolian hemp’’ kill lice and nits if used to wash the part of the body where these parasites are.

Antiemetic Properties

The same al-Anṭākī attributes anti-emetic properties to the seeds from ‘‘Anatolian hemp.’’

CONCLUSION

Arab scientists were several centuries ahead of our current knowledge of the curative power of *Cannabis sativa* (L.). They knew and used its diuretic, anti-emetic, anti-epileptic, anti-inflammatory and pain-killing virtues, among others. For this reason, it seems reasonable to suggest that the data to be found in Arabic literature could be considered as a possible basis for future research on the therapeutic potential of cannabis and hemp seeds. This would seem to be particularly necessary if we take into account that currently, the traditional use of the plant among Arab Islamic peoples of the world has almost completely disappeared due to the legal restrictions which prohibit its cultivation and use.

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Cannabis and Eicosanoids: A Review of Molecular Pharmacology

John M. McPartland

ABSTRACT. Many constituents of cannabis exhibit beneficial anti-inflammatory properties, such as ? ^{9}-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil. The effects of these cannabis constituents on eicosanoid metabolism is reviewed. THC and GLA modulate the arachidonic acid cascade, inhibiting the production of series 2 prostaglandins and series 4 leukotrienes. Cannabinoid receptor- as well as non-receptor-mediated signal transduction pathways appear to be involved. It is proposed that THC acts as a selective cyclooxygenase-2 (COX-2) inhibitor. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>*

KEYWORDS. Cannabis, cannabinoids, tetrahydrocannabinol, marijuana, anandamide, prostaglandins, thromboxanes, leukotrienes, phospholipase, cyclooxygenase, lipooxygenase

INTRODUCTION

Eicosanoids are bioactive compounds derived from C_{20} polyunsaturated fatty acids, and include the prostaglandins, thromboxanes, and leukotrienes. Many of these compounds originate from arachidonic

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acid (AA), via a series of enzymatic transformations. Eicosanoids play roles in the regulation of immunity, inflammation, and neurotransmission (Zurier 1993).

The AA cascade is circumfused by the metabolism of endogenous cannabimimetic ligands, including anandamide (ANA) and 2-arachidonyl glycerol (2-AG). Coincidentally, the AA cascade is modulated by many exogenous cannabis compounds, such as ? ^{9}-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil.

Many studies concerning cannabis and eicosanoids report contradictory data. One fact seems certain: the release of AA from membrane phospholipids is stimulated by THC (Burstein and Hunter 1977) and by ANA (Wartman et al. 1995). The mechanism of this release may or may not involve cannabinoid (CB) receptors. CB receptors are proteins associated with cell membranes, consisting of single serpentine chains of amino acids, approximately 53 kiloDaltons (kDa) in size. The N-terminus of the protein is extracellular, the carboxyl terminus is intracellular, and the rest of the chain winds into seven transmembrane helices, with interconnecting loops of amino acids extending extra- and intracellularly (reviewed by Felder and Glass 1998). Two CB receptors have been identified. CB_1 receptors arise in neurons and some glial cells, primarily in the central nervous system, as well as in cells of the gut, uterus, and elsewhere. CB_2 receptors are found in immune cells (B-cells, monocytes, T-cells, etc.) and immune tissues (tonsils, spleen, etc.).

CB_1 receptors may mediate AA release, according to Hunter and Burstein (1997). These researchers attenuated THC-stimulated AA release by treating N18 mouse neuroblastoma cells with either CB_1 antisense probes or the CB_1 antagonist SR141716A. Contrarily, Felder et al. (1992,1993) reported that activated CB_1 receptors did not induce AA release. Felder and colleagues proposed that THC induced AA release by increasing intracellular calcium, a non-CB receptor effect. Increased intracellular calcium, in turn, induced AA release. Hunter and Burstein (1997) argued that Felder's transfected CHO cells may not express the signaling components required for AA release via receptors. Most recently, Pestonjamasp and Burstein (1998) decreased THC-stimulated AA release by treating murine monocyte cells with the CB_2 antagonist SR144528, suggesting the possible involvement of CB_2 receptors in THC-stimulated AA release.

Non-receptor mechanisms must be responsible for the activity promoted by cannabidiol (CBD). CBD is non-psychoactive and does not bind to CB receptors, yet it potently stimulated AA release, more so than THC (White and Tansik 1980). Similarly, cannabinol (CBN) and cannabigerol (CBG), with little receptor affinity, also stimulated AA release, at lower EC_{50} concentrations than THC (Evans et al. 1987).

AA release from membrane phospholipids is catalyzed by three enzymes, phospholipases A, C, and D. Each of these enzymes will be reviewed.

PHOSPHOLIPASE A_2

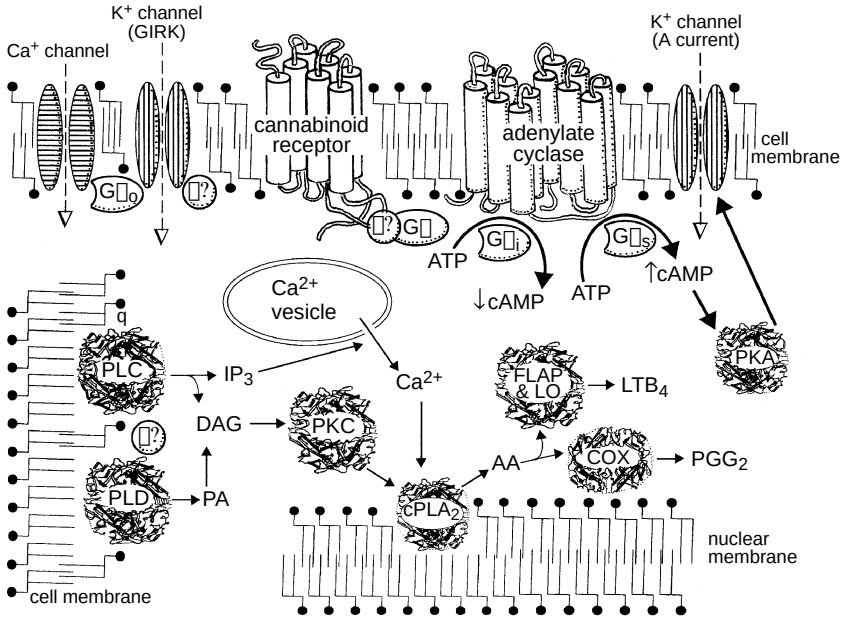
Phospholipase A_2 ($P1A_2$) activity increases in cells exposed to THC (Evans et al. 1987) and ANA (Wartmann et al. 1995). This enzyme hydrolyzes membrane phospholipids, particularly phosphatidylcholine and phosphatidylethanolamine, into two products–a lysophospholipid and a free fatty acid. If the fatty acid at the *sn* (stereospecific numbering)-2 position is AA, then $P1A_2$ releases AA in a single-step reaction. Various forms of $P1A_2$ have been identified. One $P1A_2$ specifically implicated in AA release is cytosolic $P1A_2$ ($cP1A_2$), a soluble 85 kDa protein. Upon activation, $cP1A_2$ translocates from the cytoplasm to the nuclear membrane, where it hydrolyzes phospholipids.

Felder et al. (1992) reported that cannabinoid-enhanced $P1A_2$ activity was not a receptor-mediated event. Felder et al. (1993) repeated their results using ANA. A nonreceptor mechanism must also be responsible for the potent stimulation of $P1A_2$ activity by CBD (White and Tansik 1980), and CBN and CBG (Evans et al. 1987).

Although currently unproven, CB receptors could indirectly enhance $P1A_2$ activity via G-proteins. G-proteins couple to many kinds of receptors, including those for cannabinoids, eicosanoids, opioids, epinephrine (- and -adrenergic receptors), acetylcholine (muscarinic but not nicotinic receptors), serotonin, dopamine, ACTH, CCK, VIP, FSH, LH, TSH, parathyroid hormone, calcitonin, somatostatin, glucagon, angiotensin II, oxytocin, vasopressin, and substance P.

G-proteins are composed of three subunits: an subunit and a ? subunit complex (Figure 1). At least three families of G-proteins are associated with CB receptors–Gi, Go, and Gs (Glass and Felder 1997).

FIGURE 1



When a cannabinoid agonist binds to the extracellular face of a CB receptor, there is a change in the conformation of the intracellular domain of the receptor, which permits coupling of the G-protein. Coupling activates the G-protein, which quickly uncouples from the receptor and splits into its G and G? subunits. Each goes its own way, thus bifurcating the receptor signal; the signal is further amplified by the fact that each CB receptor can activate many G-proteins. Uncoupled subunits diffuse along cell membranes and influence multiple effector systems (Figure 1). G and G? subunits directly regulate ion channels, such as N-, Q-, and L-type Ca^{2+} channels, and G-protein-coupled inwardly rectifying K+ (GIRK) channels. G subunits also interact with adenylate cyclase, thus modulating the rate of cyclic AMP (cAMP) synthesis. By this mechanism, G subunits regulate the activity of cAMP-dependent protein kinase A (PKA). PKA in turn modulates the activity of transcription factors in the CREB protein family, and the transcription of genes in the nucleus.

CB receptor activation decreases cAMP production (Devane et al.

1988). Since cAMP inhibits $cP1A_2$, a CB receptor-mediated decrease in cAMP may result in a net release of AA (Di Marzo et al. 1997). Alternatively, CB receptors may act through ras and mitogen-activated protein kinase (MAPK), which phosphorylates and activates $cPlA_2$ (Wartmann et al. 1995, Di Marzo et al. 1997). Lastly, diacylglycerol (DAG), a product of other CB-receptor-mediated pathways, may activate $cP1A_2$ via protein kinase C (PKC) and MAPK.

THC actually modulates $P1A_2$ in a biphasic manner (Evans et al. 1987); low concentrations stimulate enzyme activity (EC_{50} range of 2-6 □g/ml), whereas high concentrations inhibit the enzyme (IC_{50} range of 17-48 □g/ml). To explain biphasic activity, Sulcova et al. (1998) proposed that different concentrations of ANA and THC may invoke CB receptors to couple to different G-proteins–low concentrations may activate Gs proteins (stimulatory), whereas high concentrations activate Gi proteins (inhibitory). Glass and Northup (1999) demonstrated that different agonists (THC, ANA, HU-210, and WIN 55,212-2) induced different G-protein coupling of CB receptors (Gi versus Go).

PHOSPHOLIPASE C

One type of phospholipase C (PLC) hydrolyzes a specific phospholipid, phosphatidylinositol 4,5-biphosphate, into two products that serve as second messengers: diacylglycerol (DAG) and inositol 1,4, 5-triphosphate (IP_3). DAG activates PKC, as mentioned previously, whereas IP_3 releases Ca^{2+} from intracellular stores (Figure 1). DAG can subsequently be hydrolyzed into AA and monoacylglycerol.

Felder et al. (1992) did not find CB receptors had any effect on PLC activity. This was corroborated by Glass and Northup (1999), who found CB receptors did not couple with G□q subunits; G□q subunits normally stimulate PLC□ activity.

PHOSPHOLIPASE D

Phospholipase D (PLD), a 100 kDa protein, hydrolyzes phospholipids into phosphatidic acid and a polar head. Phosphatidic acid is subsequently hydrolized by a phosphatase enzyme into DAG plus

phosphate. DAG can subsequently enter the DAG lipase pathway described above. Burstein et al. (1994) reported THC activated PLD, as measured by increased levels of phosphatidic acid, and they suggested the activation may be a receptor-mediated process.

AA released by phospholipase enzymes does not have a long half-life. It quickly becomes metabolized or becomes reincorporated back into phospholipids. THC, however, inhibits the reuptake of free AA into phospholipids (Reichman et al. 1991); this does not appear to be a CB-receptor-mediated phenomenon (Felder et al. 1993).

AA may be metabolized into a variety of oxygenated products via several enzymes, including (1) cycloxygenases, (2) lipoxygenases, (3) cytochrome P450 enzymes, and perhaps (4) fatty acid amide hydrolase (FAAH). Only the first two enzymes will be addressed in this review. For reviews of the latter two enzymes, see Bornheim et al. (1993) and Felder and Glass (1998), respectively.

CYCLOXYGENASE

Cycloxygenase (COX) enzymes are globular, 72 kDa proteins that associate with membrane surfaces. AA released from membranes enters a channel within COX that leads to the active catalytic site. When AA reaches the catalytic site, COX inserts two oxygen molecules and extracts a free radical from AA, resulting in the five-carbon ring that characterizes prostaglandin G_2 (PGG_2). PGG_2 is subsequently metabolized to other prostaglandins (e.g., PGE_2), prostacyclins (e.g., PGI_2), and thromboxanes (e.g., TXB_2). Note that prostaglandins derived from AA have two double bonds, indicated by the subscript 2. Prostagiandins with one or three double bonds are derived from other fatty acids (e.g., PGE_1 from dihomo-gamma-linolenic acid, and PGE_3 from eicosapentaenoic acid).

THC blocks the conversion of AA to PGE_2, presumably by inhibiting COX activity (Burstein and Raz 1972). But in subsequent studies, THC exhibited a biphasic, dose-related effect on PGE_2 release, namely, inhibition at doses of 0.016-0.16 □M and stimulation at 1.6 □M (Burstein and Hunter 1977). This biphasic activity was probably due to the release of AA by THC; i.e., increased substrate overcame COX inhibition.

Cannabinoid structures that do not activate CB_1 receptors also in-

hibit the metabolism of AA to PGE_2, including CBD, CBN, and CBC (Burstein et al. 1973). Even noncannabinoid constituents in marijuana can inhibit COX activity and PGE_2 synthesis, such as essential oils (Burstein et al. 1975), phenols (Burstein et al. 1976), and flavonoids (Evans et al. 1987). The flavonoid cannflavin A was more potent an inhibitor than THC or CBD, with an IC_{50} of 7.0 mg/ml (Evans et al. 1987). But on a weight basis, crude marijuana extracts were more inhibitory than any single constituent, suggesting that synergy occurs with individual compounds (Evans et al. 1987).

The mechanism by which cannabinoids inhibit COX remains unclear. Pro-inflammatory cytokines may be involved, such as interferon ? (INF?), interleukin-1 (IL-1), and tumor necrosis factor a (TNF). COX is activated by these cytokines, and cannabinoids are known to inhibit INF? production (Klein et al. 1998a), and inhibit IL-1 and TNF (Zurier et al. 1998). Inhibition of INF? by THC appears to be mediated by CB_2 receptors rather than CB_1 receptors (Klein et al. 1998a). Whereas and IL-1 and TNF are inhibited by a cannabinoid without receptor affinity (Zurier et al. 1998). TNF is also inhibited by noncannabinoids present in cannabis, such as apigenin, a flavonoid (McPartland and Pruitt 1999).

The modulation of cytokines by cannabinoids is complex, and biphasic effects are seen (Klein et al. 1998b). Evidence suggests that cannabinoids may directly inhibit COX without involving the cytokine network.

COX ISOFORMS

Two COX isoforms exist, dubbed COX-1 and COX-2. Although they both synthesize prostaglandins, they appear to serve different functions. COX-1 is constitutively expressed, localized in the endoplasmic reticulum, and it produces prostaglandins that protect the gastric mucosa, renal parenchyma, vascular endothelium, and platelet function COX-2 is found on the nuclear envelope, it is activated during inflammatory reactions, and by proinflammatory cytokines. COX-2 activation potentiates the pain and inflammation caused by bradykinin, histamine, and leukotrienes. Lastly, COX-2 prostaglandins are manufactured by malignant cells in the colon (Sheehan et al. 1999).

The obvious goal, at least as far as pain and inflammation is concerned, is to develop drugs that block COX-2 without affecting COX-1. Standard non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, inhibit COX-2 and COX-1. Thus, NSAIDs inhibit inflammation but also predispose people to stomach ulcers and renal disease. Recently, however, ''selective COX-2 inhibitors'' have become available, such as celecoxib (Celebrex®) and rofecoxib (Vioxx®).

NSAIDs inhibit COX by a simple blockade of the channel that leads to the active catalytic site within COX. Selective COX-2 inhibitors exploit small differences in the shapes of COX-1 and COX-2 tunnels (Hawkey 1999). The difference between the COX isoforms is a single amino acid substitution, which produces a sidepocket in the channel of COX-2. Selective COX-2 inhibitors are bulky molecules; they fit in the COX-2 channel sidepocket, but cannot fit in the narrower channel of COX-1.

Zurier et al. (1998) studied COX inhibition by THC-11-oic acid, a metabolite of THC that is non-psychoactive and has little affinity for CB receptors. Zurier and coworkers substituted the pentyl side chain of THC-11-oic acid for a dimethylheptyl side chain. The synthetic product, termed ajulemic acid, demonstrated highly selective COX-2 activity.

It is proposed here that the bulky tricyclic ring structure of THC, like that of ajulemic acid, may provide selective COX-2 inhibition, assuming THC can gain access to cytoplasmic COX enzymes. Mechanical blockade of the COX-2 channel would not be a CB-receptor-mediated event. The hypothesis that THC and perhaps all cannabinoids selectively inhibit COX-2 is supported by the clinical observation that chronic marijuana use does not damage the gastric mucosa, unlike NSAIDs which inhibit COX-1 as well as COX-2.

Lack of gastric toxicity by cannabinoids, however, may be due to enhanced production of nitric oxide (NO). NO protects the gastric mucosa by stimulating COX-1 enzymes (Hawkey 1999), and some researchers report that cannabinoids stimulate release of NO (Stefano et al. 1996), although stimulation is not observed in all cell lines (Waksman et al. 1999).

LIPOXYGENASE

AA released by $cP1A_2$ can also be metabolized by lipoxygenase (LO) enzymes. Three types of LO enzymes, 5-LO, 12-LO, and 15-LO, are known in humans; they are associated with membranes and weigh about 75 kDa.

The 5-LO enzyme catalyzes the insertion of an oxygen molecule into AA at carbon 5, forming 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), an unstable intermediate which can be further metabolized into a series of leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4). Leukotrienes cause epithelial inflammation, mucus secretion, smooth muscle contraction, and bronchoconstriction, leading to symptoms of asthma and ulcerative colitis (Drazen et al. 1999). The 15-LO enzyme converts AA into 15-HPETE, which is further metabolized to 15-hydroxy-eicosatetraenoic acid (15-HETE) or a series of lipoxins (LX_A, LX_b, etc.). These products are potential mediators of airway inflammation, and they induce hyperalgesia by increasing the sensitivity of pain fibers in the skin (Riccio et al. 1997). The 12-LO enzyme converts AA into 12-HPETE, which is subsequently reduced to 12-HETE. These products modulate neurotransmission and may have neuroprotecuve properties, as well as cardioprotective ‘‘ischemic preconditioning’’ effects, but 12-HETE also promotes tumor cell adhesion, an important factor in metastasis (Chen et al. 1997).

In a noncellular soybean LO assay, THC and CBD inhibited 15-LO activity, with IC_{50} values around 3 μM (Evans et al. 1987). Noncannabinoid constituents of cannabis, such as cannflavin, did not inhibit LO at pharmacologically relevant concentrations. Subsequently, the same research group studied the effects of THC and CBD on the 5-LO enzyme. CBD produced a 100% inhibition of LTB_4 production in human polymorphonuclear (PMN) cells, with an IC_{50} = 5.4 μM; THC was only capable of producing a 90% inhibition, with an IC_{50} = 8.2 μM (Formukong et al. 1991). This degree of inhibition is comparable to the new pharmaceutical drug zileuton (Zyflo®); a single 800 mg dose blocks LTB_4 production by 80%, although the IC_{50} = 0.5 μM (McGill and Busse 1996).

THE HEMP CONNECTION

Not all prostaglandins and leukotrienes are derived from AA. One

group of non-AA-derived eicosanoids utilizes dihomo-?-linolenic acid (DGLA) as a substrate. Prostaglandins derived directly from DGLA have one double bond, and carry the subscript 1, such as PGE_1. Another group of prostaglandins, with three double bonds, carries the subscript 3, such as PGE_3.

PGE_1 and PGE_3, unlike their PGE_2 cohorts, actually provide antiinflammatory benefits. They shift the prostaglandin cascade away from series 2 products (e.g., PGE_2), suppress monocyte production of inflammatory cytokines, suppress synovial cell hyperplasia, decrease platelet aggregation, and protect the gastric mucosa against NSAID-induced injury (reviewed by DeLuca et al. 1995).

PGE_1 synthesis can be enhanced by consuming ?-linolenic acid (GLA), the precursor to DGLA. GLA is derived from the seed oil of evening primrose (*Oenothera biennis*, with 7-9% GLA), borage (*Borago officinalis*, 17-23% GLA), black currant (*Ribes nigrum*, 15-19% GLA), and hemp (*Cannabis sativa*, 2-6% GLA).

PGE_3 synthesis is enhanced by consuming omega-3 fatty acids: eicosapentaenoic acid and docosahexaenoic acid are found in fish oils (especially cold water fish like sardines, mackerel, salmon, bluefish, herring, and, to a lesser extent, tuna); □-linolenic acid (ALA) is found in the seed oil of certain plants, such as flax (*Linum usitatissimum*, containing 58% ALA), hemp (*C. sativa*, containing 15-25% ALA), and black currant (*R. nigrum*, containing 12-15% ALA).

Only hemp oil and black currant oil contain the precursors to both PGE_1 and PGE_3. Hemp oil alone has the added benefit of containing the precursors in a 3:1 ratio, the optimal ratio for human nutrition (Pate 1999).

CONCLUSIONS

This review of eicosanoids and cannabis has been limited to molecular pharmacology. Taken together, *in vitro* studies suggest that cannabinoids act as antiinflammatory agents, inhibiting the AA cascade at several levels. Antiinflammatory activity is mediated by both CB-receptor and non-receptor mechanisms.

Clinical trials concerning eicosanoids and cannabis will be surveyed in a future review. Extracts of cannabis have long been known to decrease pain and inflammation in experimental animal models and

human subjects (O'Shaugnessy 1839). Traditional healers from Eurasian cultures have used cannabis to alleviate pain and inflammation for a very long time (Mechoulam 1986). For the same purposes, cannabis tinctures were prescribed by European and North American physicians, from O'Shaugnessy's era until Anslinger's era. Modern research has documented the molecular efficacy of cannabis products. As Graham (1976) predicted, ''The drug has been frowned upon, officially banned . . . but the interest of the medical profession is slowly reviving. It is not impossible that a limited but respectable niche will be established for it in therapeutics by the end of the century.''

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Cognoscenti of Cannabis I: Jacques-Joseph Moreau (1804-1884)

Ethan Russo

Portrait of Moreau in 1845, by N.E. Maurin, Library of the Academy of Medicine, Paris, France.

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Jacques-Joseph Moreau (de Tours) was one of the earliest pioneers of modern psychopharmacology. Born in 1804 in Montrésor, France, Moreau pursued medical studies in Tours and Paris, subsequently studying psychiatry under the tutelage of Jean Étienne Dominique Esquirol, whose eclectic approach to healing of the mind included the prescription of therapeutic travel. As part of his duties, Moreau accompanied patients to the Orient, where he was able to observe the effects of, and partake himself of hashish, the resinous by-product of cannabis (Holmstedt 1973).

Upon his return to France, Moreau investigated the therapeutic possibilities of this substance. He likely is the character known as ''Dr. X'' who provided hashish in the form of an electuary called *dawamesk* to literary illuminati such as Théophile Gautier, Charles Baudelaire, Alexandre Dumas and Honoré de Balzac of *Le Club des Hachichins* at the *Hôtel Pimodan* in Paris.

Moreau was among the first to apply herbal pharmacology systematically to the treatment of mental illness, using the dissociative hallucinogen, *Datura stramonium* L. Solonaceae (Moreau 1841). Moreau espoused a theory that such compounds mirrored effects of insanity, and from them, physicians might gain insight into psychopathological conditions, and even their amelioration. He then applied this concept to cannabis. His 1845 book, *Du Hachisch et de l'Alientation Mentale. Études Psychologiques.* (Moreau 1845) is a classic in the field. Unfortunately, it is a document that few have actually viewed themselves. It had a limited press run, and was never reprinted until a 1980 facsimile edition was issued by Ressources of Paris and Geneva. On the infrequent occasions that original copies appear on the rare book market, prices in the thousands of dollars are obtained.

The book was not translated into English until 1973, as *Hashish and Mental Illness* (Moreau 1973), but this volume, too, is out of print. In an early passage, Moreau observes (p. 211):

> One of the effects of hashish that struck me most forcefully and which generally gets the most attention is that manic excitement always accompanied by a feeling of gaiety and joy inconceivable to those who have never experienced it. I saw in it a mean of effectively combatting the fixed ideas of depressives, disrupting the chain of their ideas, of unfocusing their attention on such and such a subject.

In his early efforts to apply this knowledge of cannabis to patients, Moreau observed mixed results, and himself questioned its utility. However, he persisted in his efforts. Subsequently, some years later, Moreau reported an in-depth case study of a man with intractable lypemania, a type of obsessive melancholia (Moreau de Tours 1857), and its apparent resolution with cannabis therapy. Spontaneous cure might be surmised, but subsequent evidence supports a rational basis for its efficacy with the work of Muller-Vahl on obsessive-compulsive disorder (Muller-Vahl et al. 1998; Muller-Vahl et al. 1999).

Close examination reveals that this article, presented here in English for the for the first time, was apparently written by one *"Homo, interne provisoire,"* but obviously under the close direction and supervision of Moreau at the *Hospice de Bicètre.* It presents an important insight into 19th century medicine, psychopharmacology and cannabis usage.

According to Bo Holmstedt (Efron 1967) (p. 7), one of Moreau's favorite pronouncements was, ''Insanity is the dream of the man who is awake.'' Moreau died in 1884 at the age of 80.

In the intervening century, many have judged Moreau's efforts to apply cannabis therapeutically as a failure. This view is not universal, however. Professor E. Perrot of the *Faculté de Pharmacie de Paris* stated in 1926 (Rouhier 1975) (p. IX):

> The Indian hemp, to take but one example, quite cheated the hopes of Moreau de Tours, but it would be imprudent to affirm that it will not be better utilized by the psychiatry of tomorrow! [translation EBR]

This sentiment is a useful one to consider in the modern age, as the search for better pharmacotherapeutic agents continues.

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Lypemania with Stupor; Tendency to Dementia.– Treatment by the Extract (Resinous Principle) of *Cannabis indica*.– Cure. Bicètre Hospice

M. Moreau (de Tours)
(Moreau de Tours 1857)

Following the doctrine that we have heard professed numerous times by Monsieur Doctor Moreau, it is with madness as with most of the great neuroses: the type of medicine that best suits in the prodromal period or initial phase of this illness loses all or almost all its efficacy once the chronic state is declared.

At the time this medication (internal or external derivatives, baths, affusions, etc.) must be abandoned, and resumed only in the cases, happily fairly frequent, where the affliction recovers momentarily a certain acuity.

In the confirmed chronic state, the physician must have recourse, above all, if not exclusively, to the employ of medicaments capable of profoundly modifying the vitality of the organ first injured, that is to say, the brain. The opiates (useful particularly in chronic alcoholism), the extract of Indian hemp, etc., achieve this objective perfectly. The observation which follows here is an example; we have thought that this title will acutely interest our readers.

The so mentioned Louis Suzung, 18 years of age, a typesetting worker, enters the hospital for the insane (secondary section) the 5th of January 1857.

The admission document is thus composed:

Translated from French by Ethan Russo, MD.

> Ill for only one month; febrile condition, tremors; state of stupor; melancholy; refuses almost absolutely to respond. (He had had typhoid fever?)

Nevertheless, one sees, this last piece of information from the certificate is provided with some doubt; in effect, if we ask his mother, she tells us from the start that her son had had typhoid fever; but pressed to respond to the symptoms that he had presented in the course of this illness, it is no longer possible to recognize a foundation there, and furthermore, although one would admit the possibility, one could not invoke it as a point of departure for the metal affliction. For here is what his mother reported to us: ‘‘Before having taken to his sickbed, my son was getting lost in the streets; he could not find his way, he had lost his habitual reasoning. This state lasted eight days until he was obligated to take to his bed, and he remained down for three weeks, complaining of a pain in the pit of his stomach, of an intense headache, fever, etc.; but without abdominal pains properly speaking, without diarrhea, without ringing in the ears, without epistaxis.’’–He himself, when he had recovered his wits, and interrogated on this point, confirms completely that which his mother recounted, and in addition, he added to us that it was at the time of a quarrel in the attic that he became obliged to take to bed, a quarrel which serve as a point of departure of a futile motive, and due evidently to his mental state.

The father and mother of Suzung are still living, the father, being young, is graying; once married, he stood by this habit, and would drink only a few drops with a friend from time to time, but speaking of his mother, he would renew at times to the point of gaiety. He had during those times sciatic pains, and had suffered an attack of apoplexy.

The mother had suffered a typhoid fever in her youth; in 1833, an enteritis. From the age of fourteen she had been prone to neuralgic pains in the head, which in the last year had taken on an unaccustomed intensity. What is more, she had a paralyzed arm. She had from her marriage four children: two boys and two girls. One of the girls died at the age of three, during convulsions; the other was well, and presented nothing remarkable; she much resembles her father. As to the boys, who are simply the portrait of the mother, the elder became insane at the age of eighteen, at the same age accordingly as he who occupies us at this instance, and, according to the file, we see that the form of the

insanity is the same: state of stupidity, refusal to respond, lypemania, a few moments of agitation, etc. He remained in the hospital from the 11th of August to the 23rd of November, 1849. At times, he presents again with a few delirious ideas, his mother says; he becomes intoxicated, and since his departure from the hospital, he has had a sciatica.

As to Suzung, who is the subject of this observation, the day of his entry, we found him seated on his bed. His physiognomy expresses down-heartedness, anxiety; he regards everyone with fear; he complains continually; he utters a few words that he interrupts with groans, and in which there is question of *God, of offenses to Divinity, of deserved chastisements, of earthworms,* etc. He does not respond to questions to which one addresses him; he repeats a few words that he hears spoken.

The second day, a flesh wound was placed on the nape of his neck. ‘‘In good time,’’ he says during the operation, ‘‘my God, punish me, I am well to blame.’’ The wound modified nothing in his state. He is agitated, and also has a few moments of violence during which he seeks to strike out, and one is obliged to restrain him on the couch. There, he takes on extraordinary poses, tries to strike himself against the posts of the chair that he occupies, or the iron of the bed nearby, and if he succeeds: ‘‘There’s another one killed!’’ he says with each blow he gives himself. Then the resumes his moaning, his incoherent words, and recites his imaginary supplications. He refuses nourishment, and it is not until after a long debate that one may make him take a bit of broth. At last, one morning, being unbound, and having evaded the surveillance of the boy, one finds him mounted on a window, and it is probable that his intention was bad.

After twenty days, the wound having produced no result, one omitted it, and the ill one was submitted to hashish, which was given to him in pills, a the dosage of 5 centigrams to start. One half-hour after the pill was taken, he was given a cup of black coffee. The administration of this medicament was continued for fifteen days, at a progressively increasing dose, and one succeeded at giving him up to 30 centigrams.

This method of treatment seemed at first to produce no change in the state of the patient. His complaints, his remarks, the form of his hallucinations did not change; he was only more dejected, he would close his eyes in a spasmodic manner; the psychic manifestations of the hashish became mingled with those of the illness, and the state of Suzung seemed considerably aggravated.

One was forced to maintain him perpetually restrained on his couch. He did not wish to accept food but from one sole service boy, who managed to make him swallow a few spoons of broth; from every other hand, he obstinately refused the food that one presented to him. He thinned down a great deal, wide eschars formed on his sacrum, on the trochanters, his elbows; but they had the aspect of sores of good nature; the general state was very grave, and inspired serious fears. He remained continually tormented by his visions, but the words by which he expressed his supplications changed: ‘‘The screw, hello! the screw, the kneading-trough, the cuts of five hundred blades, etc.’’ Whatever the remarks he whispered, he then resumes his continual groaning. The patient was submitted to tonics.

This state perpetuated itself all the way to the month of April, the epoch in which his wounds commenced to scar. He accepted aliments more voluntarily, whoever was the person who offered them. His thinness was extreme, but in sum, his general state was less severe.

After a fortnight, the eschars were completely closed; his frailness was less marked, and because still continually prey to the same ideas, one was obliged to maintain him with the strait-jacket, but one could, on nice days, take him in the courtyard. Little by little, one saw this serious general state ameliorate; his thinness was a little less. At the same time as this physical improvement was produced, almost imperceptibly so to speak, one observed some improvements in the mental state. Thus, one was no longer obliged to retain the strait-jacket; he ate a bit on his own; but that represented all the stated progress.

More often he remained in the courtyard propped against a tree, and taking extremely grotesque poses; he made a hunchback, arranged his arms in a bizarre fashion, resting half bent on his legs, one would say that he was going to collapse on himself; he urinated in his pants, he neglected to wipe his nose, even when the nasal mucus passed his nasal orifices. In a word, he was a veritable infant of a few months for whom it was necessary to care, to dress, to clean, etc. The groans were the same, and if one spoke to him, or better, if he repeated a few of the words that he heard, or else he whispered: The screw, the trough, etc. His ideas had not changed. At diverse occasions, Monsieur Doctor Moreau compared him to these *santons* (idiots from the abuse of hashish) that the Arabs parade in Egypt. After this medicine, the primitive illness found itself almost completely effaced by the symp-

toms germane to the action of hashish. From there, it was believed possible to harbor a favorable prognosis.

This state lasted through the final days of April and almost the entire month of May. At times, one could remark that his general health was better. The thinness had disappeared, and in this physical respect, Suzung was very well. His face, so thin a few months before, was full, and likewise, this rapid passage from the state of inanition which inspired such fears.

But here in the first days of June I remarked at the evening visit that while I approached Suzung with caution, and without him seeing me, he was no longer complaining; and that as soon as I presented myself to him, the moaning commenced. Finally, one evening, the 5th of June, I was able to obtain a direct response to the question to which I addressed him. Asked about his imaginary fears, he responded to me that with respect to Monsieur Moreau he was afraid.

The following day, I was able to follow a conversation that I did not seek to prolong, and the morning of the 7th, a bit of the fear he experienced returned, it was to Monsieur Moreau that he responded. It was an immense step.

The 8th, his responses were perfectly exact to questions addressed. Asked about his past life, he gave a very good account of his profession, the attics where he had worked, of that which he had experienced during his entry to the hospital, his bed number where he resided in the infirmary, etc., etc. The memory returned for all, except for that which transpired during the time that the had been sick confined to bed in his mother's house. Nevertheless, in the midst of this return to reason, he retained a few lypemaniacal ideas, and repeated in some moments the word guillotine. As there was a concert that day, one asked if he would like to attend; he went, but complained after a few moments that the music gave him a headache, and he asked permission to retire.

The 9th, we found him in the morning occupied with reading an article that a patient had lent him, and at the evening visit, he complained of cephalalgia, perfectly explainable by the assiduousness which he had given to his reading (from 8 o'clock in the morning to 5 o'clock in the evening).–Foot bath with mustard.

The 10th, his head was yet a bit heavy, but his reason had returned completely. For him, that which had passed in these last months was nothing but a long dream of which he was very exactly aware. The guillotine, of which he had talked again a few days before, was a

ridiculous idea, he said it himself; the memory of his illness at his mother's home had returned to him. He was completely cured.

From this day, Suzung presented no remarkable phenomena, if this is not a perfect conservation of his mental faculties, and the 18th of June he was able to be returned to his family.

Homo, Provisional Intern

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Cannabis and the U.S. Controlled Substances Act

Jon Gettman

ABSTRACT. The scheduling of cannabis under the Controlled Substances Act (CSA) has established legal precedents that determine how scientific evidence affects its regulation in the United States. This background challenges three common fallacies that make it seem marijuana prohibition is the only viable policy outcome. A contemporary effort to reschedule cannabis is based on recent findings that have established that marijuana lacks the high potential for abuse required for Schedule I or Schedule II status under the CSA. The primary policy issue is not, then, whether marijuana is the best medicine but instead whether people who use it medically should be treated as criminals. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>*

KEYWORDS. Cannabis, cannabis use, cannabinoids, marijuana, marijuana use, tetrahydrocannabinol, dronabinol, drug control, drug policy, marijuana laws

INTRODUCTION

The United States Congress established the present system of regulating drugs according to their supposed harmfulness in 1970 (US Code Cong, Adm News 1970). The Controlled Substances Act (CSA)

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created five regulatory schedules with which to classify drugs and substances (21 USC 812) according to legal and scientific criteria specified in the legislation (21 USC 812 (b); 21 USC 811 (c)). The interpretation of these statutes was subsequently clarified by the US Court of Appeals in NORML v. Ingersoll (497 F.2d 654 (1974)) and NORML v. Drug Enforcement Administration, (559 F.2d 735 (1977)). While the initial placement and scheduling of substances was set forth in the Act, Congress also provided a mechanism for making changes in the schedules. Drugs and substances can be added, rescheduled, or removed from regulation under the CSA as justified by scientific evidence and according to federal rulemaking procedures. Rescheduling proceedings require the filing of a petition by the Justice Department, the Department of Health and Human Services (DHHS), or any interested party (21 USC 811 (b)).

Schedule I drugs are subject to a near complete prohibition and are only legally available for research under the tightest controls. *The CSA states that a drug may not be placed in Schedule I unless three findings are established. The drug must have a high potential for abuse relative to other controlled substances, no currently accepted medical use in the United States, and lack accepted safety for use of the drug under medical supervision* (21 USC 812 (b)(1)).

Cannabis was placed as marijuana in Schedule I by Congress despite clear evidence it failed to meet these criteria. The Nixon Administration acknowledged that cannabis lacked the dependence liability required for either Schedule I or Schedule II status, but requested that marijuana be placed in Schedule I anyway pending the then-forthcoming work of a national commission on marihuana and drug abuse (Egeberg 1970, 4629):

> Some question has been raised whether the use of the plant itself produces ‘‘severe psychological or physical dependence’’ as required by a Schedule I or even Schedule II criterion. Since there is still a considerable void in our knowledge of the plant and its effects of the active drug contained in it, our recommendation is that marihuana be retained within Schedule I at least until the completion of certain studies now underway to resolve this issue.

‘‘Certain studies’’ refers to a then forthcoming Commission on Marihuana and Drug Abuse that was mandated with the passage of the Controlled Substances Act (21 USC 801; P.L. 91-513; P.L. 92-13).

This commission eventually recommended the decriminalization of marijuana (National Commission on Marihuana and Drug Abuse 1971).

The National Organization for the Reform of Marijuana Laws (NORML) filed a rescheduling petition in 1972 arguing that marijuana lacked the high potential for abuse required for Schedule I status. The US government refused to accept the petition until so ordered by the US Court of Appeals in NORML v. Ingersoll (497 F.2d 654 (1974)). Subsequently the Court ordered the Drug Enforcement Administration (NORML v. DEA, (559 F.2d 735 (1977)) and the Department of Health and Human Services (NORML v. DEA et al. (1982)) to adequately process the petition. Fourteen years after the petition was filed public proceedings before an Administrative Law Judge (ALJ) were held. By this time the proceedings had narrowed to the single issue of whether cannabis had an accepted medical use (DEA 1986). The ALJ determined that marijuana did have an accepted medical use in the United States and recommended its rescheduling to Schedule II (Young 1988).

Administrative Law Judge Francis Young based his determination that cannabis had an accepted medical use in the United States on a standard adopted from litigation of medical malpractice suits. The burden of proof used in this determination was whether the therapeutic use of cannabis was recognized by a respected minority of the medical community, and Young found convincing evidence in the record that contemporary therapeutic use of cannabis was indeed so recognized (Young 1988).

The DEA rejected Judge Young's standard for evaluating accepted medical use, instituted their own, and declined to accept the ALJ's recommendation; DEA adopted their own standards which relied heavily on journal publication and other commonly utilized scientific criteria (Lawn 1989; Bonner 1992). The Court of Appeals ruled in ACT v. DEA (930 F.2d 936 (1991)) and reaffirmed its decision in ACT v. DEA (15 F.3d 1131; (1994)), twenty two years after the original petition was filed, that DEA's own standards and decision were neither unreasonable, arbitrary, or capricious.

The scientific record in these original rescheduling proceedings closed in early 1989. Later that year a scientific revolution in understanding the effects of marijuana and cannabinoid drugs occurred. Before this time, the scientific basis of marijuana's characteristic ef-

fects was not known. Marijuana's actions have subsequently been elucidated to occur through an endogenous cannabinoid receptor system which has subsequently revolutionized scientific understanding (Howlett et al. 1990; Herkenham 1992; IOM 1999).

The CSA establishes the scope of the scientific inquiry that should be used to determine if a substance meets the requirements of any of the five schedules. The DEA is required to ask DHHS for scientific and medical reviews, and DHHS must consider eight factors in their evaluation. These factors include: (a) the actual or relative potential for abuse, (b) pharmacology, (c) other scientific knowledge of effects, (d) the history and pattern of abuse, (e) the scope and significance of abuse, (f) whether there is a risk to public health, (g) psychic or physiological dependence liability, and (h) whether the substance is a precursor to a controlled substance (21 USC 822 (c)).

As a private citizen the author filed a new petition for marijuana's rescheduling in 1995. This petition argued that the discovery of the cannabinoid receptor system and contemporary findings in each of the eight areas listed above clarified that marijuana does not meet the required criteria for Schedule I or Schedule II status. The petition consisted of an extensive literature review of cannabinoid research findings published between 1988 and 1994. The DEA accepted the petition for filing on July 17, 1995 (Greene 1995) and after extensive review determined that it provided sufficient grounds for removal and rescheduling. In December, 1997 the DEA formally referred the petition to the DHHS for a binding scientific and medical review (Whalen 1997), currently underway.

The results of this review may also require the United States to amend international treaties regarding cannabis in addition to rescheduling marijuana under the CSA. With respect to the scheduling of THC, the active ingredient in marijuana, the US government recognized that the DHHS review process could conceivably require amendment of international treaties (Memorandum of Federal Respondents, NORML v. DEA 1982, 19):

> It is prudent for DDHHS to provide a complete scientific and medical evaluation on THC at this time, because even if the ultimate DHHS recommendation is found to be inconsistent with current treaty obligations, the United States could petition for international rescheduling.

This recognition cites a Court of Appeals Ruling on a prior marijuana rescheduling petition which makes reference to (NORML v. Ingersoll 1974, 658):

> . . . a subsidiary contention that even if there are current treaty obligations, the executive officials have a duty to consider the petition toward the objective of possible treaty modification of legislative or treaty action.

COMMON MISCONCEPTIONS ABOUT MARIJUANA AND THE CONTROLLED SUBSTANCES ACT

The preceding policy context for evaluating marijuana's scheduling under the CSA is frequently misunderstood. Three pervasive fallacies about national marijuana policy in the United States inhibit discussion of the relevance of recent scientific findings. All derive from a failure in the application of the standards for regulating drugs under the Controlled Substances Act. These fallacies make it seem that marijuana prohibition, the status quo, is the only viable policy outcome.

The first fallacy is that any indication that marijuana has a dependence liability justifies its placement in Schedule I of the CSA. The Controlled Substances Act distinguishes the relative abuse potentials of drugs. Schedule IV was added during the legislative process to distinguish the abuse potential of benzodiazepines from that of the barbiturates placed in Schedule III, which in turn are distinguished from drugs such as cocaine in Schedule II, or heroin in Schedule I.

The second fallacy is that marijuana must remain in Schedule I if it has no accepted medical use, and is restricted to Schedule II if it does. In NORML v. DEA (1977) the Court of Appeals held that all three requirements are necessary to justify Schedule I status, and that a drug or substance's potential for abuse is the most important criterion. The highest potential for abuse is also a requirement for Schedule II status. If marijuana does not have the highest abuse potential relative to other drugs it can not be properly scheduled in either Schedule I or II.

In other words court rulings have established that Schedule I is not the default classification for drugs or substances without ''accepted medical use in the United States.'' If it were, the third fallacy would instead be valid, which is that marijuana must remain in Schedule I unless it can be proven to provide optimum results relative to other drugs.

These three fallacies establish artificial standards for evaluating the significance of marijuana research. The first fallacy is the basis for claims that any evidence of dependence liability justifies marijuana's Schedule I status. The second is the basis for assertions that ''accepted medical use'' is the primary basis for scheduling under the CSA. The third fallacy is the basis for claims that marijuana should be held to a different and higher standard than any other drug in establishing ''accepted medical use.'' All three ignore existing court rulings.

MARIJUANA'S ABUSE POTENTIAL

In the January 1998 edition of the *American Journal of Public Health* Joseph Califano wrote (Califano 1998, 8):

> Recent neuroscientific studies have demonstrated in stunning detail the changes in brain chemistry that marijuana and cocaine cause, opening up possibilities for new treatments. They also challenge old beliefs about the supposed ''safety'' of marijuana use. The evidence indicates a biomedical link between use of alcohol, nicotine, marijuana, cocaine, and heroin, because all of these substances affect dopamine levels in the brain through common pathways. (Tanda et al. 1998; Rodriguez de Foncesa et al. 1998) Recent research also demonstrates that cessation of marijuana use brings on withdrawal symptoms, which may encourage a user to resume marijuana use or to try other drugs such as cocaine or heroin. (Tanda et al. 1998; Rodriguez de Foncesa et al. 1998)

It has long been recognized that some individuals' use of marijuana is characterized by dependence and that the dependence liability of marijuana is relatively less addictive than alcohol or tobacco, and certainly not comparable to the dependence liability of cocaine or heroin. Despite the importance of the recent scientific breakthroughs in describing how cannabis produces its characteristic effects little has emerged to challenge the conclusions of a frequently cited 1986 literature review by Leo Hollister in the *Pharmacological Review* (Hollister 1986, 17):

> Physical dependence is rarely encountered in the usual patterns of social use, despite some degree of tolerance that may develop . . .

> Compared with other licit social drugs, such as alcohol, tobacco, and caffeine, marijuana does not pose greater risks. One would wonder, however, if society were given a choice based on current knowledge, whether these drugs would have been granted their present status of acceptance. Marijuana may prove to have greater therapeutic potential than these other social drugs, but many questions still need to be answered.

With respect to marijuana, Califano makes a case for CSA control of cannabis but not its Schedule I status. According to Hollister's observation many, though not all, of those questions have indeed been answered by research subsequent to the discovery of the cannabinoid receptor system (see below). It has been long reported that heavy marijuana use followed by abstinence produces a mild withdrawal syndrome characterized by irritability and sleeplessness (Hollister 1986; Abood and Martin 1992; Aceto et al. 1996). Corticotropin-Releasing Factor (CRF) is a chemical released in the amygdala associated with stress and negative consequences of withdrawal from alcohol, cocaine, and opiates (Koob 1996). Rodriguez de Foncesa, Koob, and colleagues have demonstrated that withdrawal from cannabinoids, induced by use of an antagonist to shut down cannabinoid receptor sites in animal subjects, results in the production of CRF (Rodriguez de Foncesa et al. 1998). Billy Martin and colleagues have also used a cannabinoid receptor agonist to produce withdrawal symptoms in animal subjects (Aceto et al. 1996).

This and other research is discussed in a 1998 article in the *Annual Review of Pharmacology and Toxicology* by Christian Felder and Michelle Glass. These authors reach a different conclusion than Califano above (Felder and Glass 1998, 192):

> Much of the political and public objection to the use of ? ^{9} THC or marijuana as a therapy centers around its abuse potential and the belief by some that it serves as a ''gateway'' drug leading users to ''harder'' drugs of abuse. Many therapeutic drugs have abuse potential, yet this does not invalidate their role in current therapies. While there is some preliminary evidence for cannabinoids activating the reward pathways in the brain (Tanda et al. 1998), most investigators have failed to find addictive or reinforcing effects of cannabinoids in animal models. Unlike cocaine or heroin, cannabinoid agonists produce conditioned place aver-

> sion even at low doses (McGregor et al. 1996; Parker and Gilles 1995) and anxiogenic effects (Onavi et al. 1990). Furthermore, animals will not self-administer cannabinoids (Harris et al. 1974; Leite and Carlina 1974; Cocoran and Amit 1974), and a lack of cross-sensitization between cocaine (McGregor et al. 1995) or amphetamines (Takahashi and Singer 1981) and cannabinoids has also been demonstrated.

These statements do not describe a drug with a high potential for abuse comparable to Schedule I or II drugs such as cocaine and heroin. The review of Felder and Glass suggests both that marijuana does not belong in either Schedules I or II, and that it has sufficient therapeutic potential to provide acceptable medical usage. Their analysis confirms what was widely known at the time the CSA was passed and elucidated in the wake of the receptor system discovery.

MARIJUANA'S SAFETY FOR USE

During the 1970's and early 1980's mechanisms by which marijuana caused its characteristic effects were not yet known. According to Miles Herkenham of the National Institute of Mental Health (NIMH) (Herkenham 1992, 19):

> Because the cellular and biochemical mechanisms of action of psychoactive cannabinoids were not understood, neuroscientists were allowed great breadth to speculate upon the influence that these compounds might have on the neurons of the brain.

These speculations were often presented as the latest scientific evidence or as what scientists now believe about cannabis. The perception that marijuana is inherently unsafe for use has a historical basis in this uncertainty about its mechanism of action.

Much speculation was previously based on a theory that cannabis produced its characteristic effects by way of cell membrane perturbation (Paton 1976; Paton 1979; Harvey and Paton 1985), as if the sticky characteristics of marijuana resin actually clogged up circuits in the brain. The persistent yet inconsistent viscosity of cannabinoid resin hampered the experiments. The characteristics of the emulsifiers and the potencies of the tested solutions flawed the research designs in

ways that made their external validity suspect and difficult to interpret (Nahas 1984; Martin 1986; Herkenham 1992).

In 1988 Allyn Howlett and her research team made a key breakthrough thanks to the graduate work of William Devane. Using CP55, 940, a high potency synthetic cannabinoid developed by Pfizer, they were able to establish that cannabinoid effects are mediated by a previously undiscovered endogenous receptor system in the brain (Devane et al. 1989). In the labs of NIMH Miles Herkenham and his research teams mapped cannabinoid receptor locations in the human brain and in several other mammalian species (Herkenham et al. 1990), discovered that tolerance to cannabinoids results from down-regulation of receptor sites (Oviedo et al. 1993), and established binding sites in peripheral rat tissues important to understanding cannabinoids' effects on the immune system (Lynn and Herkenham 1992). Rather, cannabinoids produce their action like benzodiazepines and other modern pharmaceuticals that activate or moderate endogenous receptor systems.

Claims that marijuana is a safe drug in terms of accidental overdose were also confirmed by ''the paucity of receptors in medullary nuclei that mediate respiratory and cardiovascular functions'' (Herkenham et al. 1990, 1936).

THERAPEUTIC POTENTIAL

The distribution of cannabinoid receptor sites provides explanations for many of the therapeutic effects claimed by marijuana users. For example (Herkenham et al. 1990, 1936), ''dense binding in the basal ganglia and cerebellum suggests cannabinoid involvement in movement control . . . beneficial for some forms of dystonia, tremor, and spasticity.'' Yet patients' anecdotes of these and other therapeutic effects were dismissed by the Drug Enforcement Administration (DEA) in 1989 and attributed not to the motor control effects but to the presumed high potential for abuse of Schedule I drugs (Lawn, 1989).

The potential of cannabinoids to relieve pain has been the basis for the development of several synthetic cannabinoid analogs (Segal 1987; Johnson and Melvin 1987; Melvin and Johnson 1987). Recent cannabinoid research findings also report analgesic effects of a cannabinoid agonist on neuropathic pain (Herzberg et al. 1997), relief from migraine symptoms (Russo 1998), significant antinociception from

injected cannabinoids (Smith et al. 1998), antioxidant properties useful as neuroprotective agents (Hampson et al. 1998), pain control resulting from the endogenous cannabinoid anandamide (Calignano et al. 1998), and activation of a brainstem circuit also involved in opioid analgesia (Meng et al. 1998; Martin, W.J. et al. 1998).

The contemporary and historical use of cannabis in a therapeutic and medical context is well documented (Mathre 1997). Contemporary therapeutic use of marijuana is extensively portrayed in *Marihuana the Forbidden Medicine* by Lester Grinspoon and James Bakalar (1997), which includes many case histories of patients discredited by the DEA, and recently vindicated by receptor-related discoveries. The therapeutic potential of marijuana and cannabinoid drugs has been recognized for glaucoma, nausea and vomiting, analgesia, spasticity, multiple sclerosis, AIDS wasting syndrome and several other areas (IOM 1982; Hollister 1986; Howlett et al. 1990; Grinspoon and Bakalar 1997; Mathre 1997; Taylor 1998; Felder and Glass 1998).

The legislative history used by the Court of Appeals to interpret the CSA instructs that the ''social, economic, and ecological characteristics of the segments of the population involved'' be considered, along with the ''economics of regulation and enforcement attendant to such a decision.'' Also, one ''should be aware of the social significance and impact of such a decision upon those people, especially the young, that would be affected by it'' (US Code Cong. Adm News 1970, 4603). Therapeutic marijuana use is relevant in assessing the intent of some users and the social costs of prohibition on those that it affects. These considerations can not be omitted from cost/benefit considerations.

The underlying basis for legislative perpetuation of marijuana prohibition under current US law purports that marijuana is too dangerous for individuals to use on the basis of informed consent, and that all marijuana use is the result of risky thrill seeking and drug dependency. It is now evident not only that a majority of people use marijuana on the basis of informed consent but that a considerable number use cannabis in order to utilize its pharmacological effects in therapy for a diverse number of clinical conditions.

CONCLUSION–POLICY RAMIFICATIONS

The Controlled Substances Act was passed with recognition that (21 USC 801 (1)):

> Many of the drugs included within this [Act] have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people.

Of the many policy issues that stem from the Schedule I status of cannabis it is medical access that remains a paramount concern for the public interest. While state law is beginning to provide some protections for medical users of cannabis in several states, medical access is difficult if not impossible without changes in federal scheduling. One purpose of the CSA was to balance the public interest in controlling dangerous drugs with its interest in having the greatest possible access to drugs with useful and legitimate medical purposes.

Acknowledgement that marijuana is not as dangerous as the law once claimed may lead to reconsideration of other marijuana-related laws and policies. It is a betrayal of the public trust to treat cannabis as if it has the same potential for abuse as heroin and cocaine. The substantiation of the scientific basis for US marijuana laws can also enhance the integrity of law enforcement and public health activities and otherwise contribute to their increased effectiveness.

While pharmacological sources for cannabinoids are available now and maybe improved in the future, this matter is irrelevant to the legal issues presented by any individual's marijuana use. In the case of medical use of cannabis the primary public policy issue is whether the state wishes to criminally prosecute individuals whose use of this substance is for therapeutic reasons and a matter of informed consent. Science has established a rational basis for such therapeutic use and clarified marijuana's abuse potential sufficiently to support the ability of individual patients to exercise informed consent about its use. The question is not whether marijuana is the best medicine but whether people who use it medically should be treated as criminals.

Scientific standards provide the best guide to drug control regardless of where they may lead in terms of policy outcomes, because they provide a consistent and reliable basis for rational evaluation and analysis. This was, indeed, the intention of the Congress when it passed the CSA and designated the DHHS as the preeminent judge of scientific fact. Congress intended for the scheduling of drugs to remain consistent with contemporary scientific knowledge. In the case of cannabis, contemporary scientific knowledge does not support its current placement in Schedule I as a drug with the highest potential for abuse.

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BOOK REVIEWS

THE SCIENCE OF MARIJUANA. Iversen, Leslie L. *Oxford: Oxford Press, 2000, 283 pp., $29.95, hardcover.*

This book represents the latest entry in popular texts on cannabis, and is a well-written, inexpensive and accessible review of the important topics. After a brief but insightful foreword by Solomon Snyder, Dr. Iversen, a fellow psychopharmacologist, guides us through discussions of the plant, the pharmacology of THC, and its CNS and peripheral effects. Chapters on medical uses of cannabis, its safety issues, recreational use and future prospects follow subsequently. Iversen presents all topics, including more technical aspects of the endocannabinoids in a clear, measured narrative. In fact, one of the primary strengths of this tome is its thoughtful and well-considered moderate tone in pursuit of controversial topics.

The book is well researched and documented. The references, though not exhaustive, include important representative books and articles on selected topics. The index, in contrast, is somewhat limited.

Other criticisms worthy of mention are very few. A couple of errors rankle: a consistent misspelling of *sinsemilla* (modern term for *ganja*, the unfertilized female cannabis flowering tops, ''without seed'') as ''sensemilla''; multiple citations of Abel's seminal review of cannabis history, *Marihuana: The First Twelve Thousand Years*, as published in 1943 instead of 1973. These are not substantive complaints. More importantly, the wealth of current data on the role of cannabis, endocannabinoids and synthetics on mechanisms and treatment of pain are given a more superficial discussion than this reader would desire. Some clinicians may take issue with Iversen's contention that the

current armamentarium of anti-anxiety agents and hypnotics, particularly benzodiazepines, has rendered ''obsolete'' these debated indications for cannabis.

Iversen emphasizes that dangers of smoked cannabis have been exaggerated. Unfortunately, he succumbs to the traditional pitfall of Western pharmacology that dictates that marijuana merely represents a crude vehicle for THC administration. An exploration of cannabis' other important terpenoid and flavonoid components and their interactions with the cannabinoids would be welcome. The German concept of phytochemical synergy is not applied herein to this most complicated herbal medicinal.

Lest anyone consider passing up this fine offering on the basis of these criticisms, they would making a serious error. Iversen's ability to present complex topics in an understandable and compelling fashion is noteworthy. It is truly refreshing to see a thorough airing of the controversies surrounding cannabis in a manner that appears free from any apparent political agenda. Rather, the scientific facts are weighed on their respective merits. In closing, *The Science of Marijuana* is a finely penned and documented effort that deserves a wide reading by scientists, clinicians, politicians and the public.

Ethan Russo, MD

HASHISH! Clarke, Robert Connell. *Los Angeles: Red Eye Press, 1998, 387 pp., $29.95, softcover.*

Rob Clarke, a cannabis researcher with HortaPharm in Holland, and projects manager of the International Hemp Association has written an exclamatory book on hashish, that peculiar Middle Eastern crude extract of cannabis.

Clarke presents an in-depth history and analysis of the topic pertaining to its people, places and techniques. Stunning photos accompany the text, which is well-written, lively and sometimes humorous. Although this book will be of greatest interest to past and present *aficionados* of recreational cannabis, who wish to investigate the THC content of that Afghani hashish that invaded their dorm rooms in the '70's, there is much here of scientific value.

Clarke devotes a great deal of attention to the methods of cannabis processing including rubbing and sieving that concentrate THC and terpenoid cannabis components. A most complete analysis of water extraction techniques, and vaporization methods for smoking cannabis are also included. Medical application is treated briefly.

There is no doubt that some will see this book as subversive and exploitive, the kind of material that many federal legislators would like to render illegal. In this age where some dare to speak about ''harm reduction'' as applied to cannabis and other illicit drugs, however, Clarke's treatise has much to teach clinical cannabis patients and clinicians, while offering a challenge to interested scientists to further investigate the topic.

Ethan Russo, MD