

Cannabis and the U.S. Controlled Substances Act

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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>> © 2001 by The Haworth Press, Inc. All rights reserved.]*

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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 marijuana 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 marijuana 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 Marijuana 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 Fonseca 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 Fonseca 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 Fonseca, 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 Fonseca 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 Δ^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.

REFERENCES

- Abood, Mary E., and Billy R. Martin. 1992. Neurobiology of marijuana abuse. *Trends Pharmacol Sci* 13:201-206.
- Aceto, Mario D., Susan M. Scates, John A. Lowe and Billy R. Martin. 1996. Dependence on Δ^9 -tetrahydrocannabinol: Studies on precipitated and abrupt withdrawal. *J Pharmacol Exp Ther* 278(3):1290-1295.
- Alliance for Cannabis Therapeutics (ACT) v. Drug Enforcement Administration (DEA), 15 F.3d 1131 (1994).
- Alliance for Cannabis Therapeutics (ACT) v. Drug Enforcement Administration (DEA); National Organization for the Reform of Marijuana Laws (NORML) v. DEA, 930 F.2d 936 (1991).
- Bonner, Robert. 1992. Marijuana scheduling petition; denial of petition. *Fed Reg* 57, (26 March):10,499.
- Califano, Joseph. 1998. Editorial: Substance abuse and addiction—the need to know. *Amer J Pub Health* 88(1):9-10.
- Calignano, Antonio, Giovanna La Rana, Andrea Giuffrida, and Daniele Piomelli. 1998. Control of pain initiation by endogenous cannabinoids. *Nature* 394:277-281.
- Cocoran, M.E. and Z. Amit. 1974. Reluctance of rats to drink hashish suspensions: free choice and forced consumption, and the effects of hypothalamic stimulation. *Psychopharmacologia* 35:129-47. Cited in Felder and Glass 1998.
- Devane, William A., Francis A. Dysarz III, M. Ross Johnson, Lawrence S. Melvin and Allyn C. Howlett. 1989. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 34:605-613.
- Drug Enforcement Administration (DEA). 1986. “Schedules of Controlled Substances; Hearing on Petition to reschedule Marijuana and Its Components.” *Fed Reg* 51, no. 121 (24 June): 22, 946.
- Egeberg, Roger. 1970. HEW Letter to Congress, 8 August. *United States Code Congressional and Administrative News, 91st Congress—Second Session, Volume 3*. St. Paul, MN: West Publishing Co. 1970. Pg. 4629.
- Felder, Christian, and Michelle Glass. 1998. Cannabinoid receptors and their endogenous agonists. *Annu Rev Pharmacol Toxicol* 38:179-200.
- Greene, Steven (Drug Enforcement Administration). 1995. Letter to author, 27 July.
- Grinspoon, Lester and James Bakalar. 1997. *Marihuana, The Forbidden Medicine*. rev. ed. New Haven, CT: Yale University Press.
- Hampson, A.J., M. Grimaldi, J Axelrod, and D. Wink. 1998. Cannabidiol and Δ^9 -tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA*. 95:8268-8273..
- Harris, R.T., W. Waters and D. McLendon. 1974. Evaluation of reinforcing capability of Δ^9 -tetrahydrocannabinol in rhesus monkeys. *Psychopharmacologia* 37:23-29. Cited in Felder & Glass, 1998.
- Harvey, D.J. and W.D.M. Paton. (1985) Marihuana '84, final summary. In *Marihuana '84. Proceedings of the Oxford Symposium on Cannabis*. Oxford: IRL Press Limited. Pg. 734-735.
- Herkenham, Miles 1992. Cannabinoid receptor localization in brain: relationship to motor and reward systems. In *The Neurobiology of Drug and Alcohol Addiction*. Annals of the American Academy of Sciences. 654:19-32.

- Herkenham, Miles, Allison B. Lynn, Mark D. Little, M. Ross Johnson, Lawrence S. Melvin, Brian R. De Costa, and Kenner C. Rice. 1990. Cannabinoid receptor localization in brain. *Proc Natl Acad Sci USA* 87:1932-1936.
- Herzberg, U., E. Eliav, G.J. Bennett, and Irwin J. Kopin. 1997. The analgesic effects of R(+)-WIN 55, 212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neurosci Lett* 221: 157-160.
- Hollister, Leo E. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38(1):1-20.
- Howlett, Allyn C., Michelle Bidaut-Russell, William Devane, Lawrence S. Melvin, M Ross Johnson and Miles Herkenham. 1990. The cannabinoid receptor: biochemical, anatomical, and behavioral characterization. *Trends Neurosci* 13(10): 420-423.
- Institute of Medicine. 1982. *Marijuana and Health*. Arnold Relman (ed.). Washington, D.C.: National Academy Press.
- Institute of Medicine. 1999. *Marijuana and Medicine: Assessing the Science Base*. Joy, Janet, Stanley Watson, and John Benson (eds.) Washington, DC: National Academy Press.
- Johnson, M. Ross and Lawrence S. Melvin. 1987. Chapter 7. The discovery of nonclassical cannabinoids. In *Cannabinoids as Therapeutic Agents*. 1986. Raphael Mechoulam (ed.) Boca Raton, FL: CRC Press. pg. 121-145.
- Koob, George. 1996. Drug addiction: the yin and yang of hedonic homeostasis. *Neuron* 16: 893-896.
- Lawn, John. 1989. "Marijuana scheduling petition; denial of petition." *Fed Reg* 54, no. 249 (29 December):53, 773.
- Leite, J.R. and E.A. Carlina. 1974. Failure to obtain cannabis-directed behavior and abstinence syndrome in rats chronically treated with *Cannabis sativa* extracts. *Psychopharmacologia* 36:133-45. Cited in Felder and Glass 1998.
- Lynn, Allison.B., and Miles Herkenham. 1993. Localization of cannabinoid receptors and nonsaturable high-density cannabinoid binding sites in peripheral tissues of the rat: implications for receptor-mediated immune modulation by cannabinoids. *J Pharmacol Exp Ther* 268(3):1612-1623.
- Martin, Billy R. 1986. Cellular effects of cannabinoids. *Pharmacol Rev* 38(1):45-74.
- Martin, William J., Kang Tsou, and J.M. Walker. 1998. Cannabinoid receptor-mediated inhibition of the rat tail-flick reflex after microinjection into the rostral ventromedial medulla. *Neurosci Lett* 242:33-36.
- Mathre, Mary Lynn. 1997. *Cannabis in Medical Practice: A Legal, Historical, and Pharmacological Overview of the Therapeutic Use of Marijuana*. Jefferson, NC.: McFarland & Co.
- McGregor, I.S., P.A. Bryant, and J. Arnold. 1995. CP55,940, a synthetic cannabinoid, does not sensitize locomotor activity or cocaine responsivity with intermittent administration in Wistar rats. *Soc Neurosci Abstr* 21:726. Cited in Felder and Glass 1998.
- McGregor, I.S., C.N. Issakidis, and G. Prior. 1996. Adverse effects of the synthetic cannabinoid CP55,940 in rats. *Pharmacol Biochem Behav* 53:657-64. Cited in Felder and Glass 1998.
- Melvin, Lawrence S. and M. Ross Johnson. 1987. Structure-activity relationships of tricyclic and nonclassical bicyclic cannabinoids. In: *Structure-Activity Relation-*

- ships of Tricyclic and Nonclassical Bicyclic Cannabinoids*. Rapaka, R.S. and A. Makriyannis (eds.). National Institute on Drug Abuse Research Monograph 79. Washington, DC: National Institute of Drug Abuse. Pg. 31-47.
- Meng, Ian D., Barton H. Manning, William J. Martin, and Howard L. Fields. 1998. An analgesia circuit activated by cannabinoids. *Nature* 395:381-383.
- Nahas, Gabriel G. 1984. *Marihuana in Science and Medicine*. New York: Raven Press.
- National Commission on Marijuana and Drug Abuse. 1972. *Marijuana: A Signal of Misunderstanding*. Washington, DC: Government Printing Office. [Reprinted as a Signet Special. New York: New American Library]
- National Organization for the Reform of Marijuana Laws (NORML) v. John E. Ingersoll [Director, Bureau of Narcotics and Dangerous Drugs], 497 F.2d 654 (1974).
- National Organization for the Reform of Marijuana Laws (NORML) v. Drug Enforcement Administration (DEA), 559 F.2d 735 (1977).
- National Organization for the Reform of Marijuana Laws (NORML) v. Drug Enforcement Administration (DEA) et al. Civil Action No. 79-1660, U.S. District Court of Appeals for the D.C. Circuit (June 4, 1982).
- Onaivi, E.S., M.R. Green, and B.R. Martin. 1990. Pharmacological characterization of cannabinoids in the elevated plus maze. *J Pharmacol Exp Ther* 253:1002-9. Cited in Felder and Glass 1998.
- Oviedo, Angelica., John Glowa and Miles Herkenham. 1993. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain Res* 616:293-302.
- Parker, L.A. and T. Gilles. 1995. THC-induced place and taste aversion in Lewis and Sprague-Dawley rats. *Behav Neurosci* 109:71-78. Cited in Felder and Glass 1998.
- Paton, W.D.M. 1979. Concluding summary. In: *Marihuana: Biological Effects: Analysis, Metabolism, Cellular Responses, Reproduction, and Brain: Proceedings of the Satellite Symposium on Marihuana, 7th International Congress of Pharmacology*. Nahas, G., W.D.M. Paton, and M.C. Braude. (eds.) New York: Pergamon Press. pg. 736.
- Paton, W.D.M.. 1976. Concluding Summary. In *Marihuana: Chemistry, Biochemistry, and Cellular Effects. (Proceedings of the Satellite Symposium on Marihuana of the 6th International Congress of Pharmacology.)* Nahas, G., W.D.M. Paton and J. Idanpaan-Heikkila (eds.). New York: Springer-Verlag. pg. 552.
- Rodriguez de Fonseca, F.R., M.R. A. Carrera, M. Navarro et al. 1997. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science* 276:2050-2054. Cited in Califano 1998.
- Russo, Ethan. 1998. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. *Pain* 76(1-2):3-6.
- Segak, Mark. 1987. Chapter 6. Cannabinoids and analgesia. In: *Cannabinoids as Therapeutic Agents*. 1986. Raphael Mechoulam (ed.) Boca Raton, FL: CRC Press. pg. 105-120.
- Smith, Forrest L., Ken Fujimori, John Lowe and Sandra P. Welch. 1998. Characterization of δ^9 tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* 60(1):183-191.

- Takahashi, R.N. and G. Singer. 1981. Cross self-administration of Δ^9 -tetrahydrocannabinol and d-amphetamine in rats. *Braz J Med Biol Res* 14:395-400. Cited in Felder and Glass 1998.
- Tanda, G., F.E. Pontieri and G. Di Chiara. 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common opioid receptor mechanism. *Science* 276: 2048-2050. Cited in Califano, 1998. Cited in Felder and Glass 1998.
- Taylor, H. Gordon. 1998. Analysis of the medical use of marijuana and its societal implications. *J Amer Pharm Assoc* 38(2):220-227.
- United States Code Congressional and Administrative News. 1970. 91st Congress—Second Session, 1970. Volume 3. St. Paul, MN: West Publishing Co. 1970.
- Whalen, Mary Kate (Drug Enforcement Administration) 1997. Letter to Simone Monasebian, 19 December.
- Young, Francis. 1988. In the matter of marijuana rescheduling petition, docket 86-22, opinion, recommended ruling, findings of fact, conclusions of law and decision of administrative law judge. September 6, 1988. Washington, DC: Drug Enforcement Administration.

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