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HERBALGRAM

The Journal of the American Botanical Council

Number 85 | February – April 2010



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The State of Clinical Cannabis Research in the United States

Dozens of varieties of cannabis (*Cannabis sativa*, Cannabaceae) grow on a 12-acre outdoor plot controlled by the National Center for Natural Products Research (NCNPR) at the University of Mississippi.^{1,2} This operation supplies cannabis, commonly referred to as marijuana, for all research in the United States, through a contract between NCNPR and the National Institute on Drug Abuse (NIDA), a part of the National Institutes of Health (NIH). Although NIDA puts the contract up for bid every 5 years, it has awarded this contract solely to NCNPR since 1968. NCNPR has thus been the only federally-permitted source of cannabis, which it can distribute to researchers only as directed by NIDA—a situation that both entities hesitate to call a monopoly.

“We always look very carefully at all the proposals that come in,” said Steve Gust, PhD, special assistant to the director of NIDA (oral and e-mail communications, September 2–November 15, 2009). “It just so happens that the University of Mississippi was the first one and has been very effective in maintaining their competitiveness.”

Due to NIDA’s monopoly on the production of cannabis, cannabis research is regulated unlike that of any other substance. While all human clinical research using controlled substances must receive approval from the Drug Enforcement Administration (DEA) and permission from the US Food and Drug Administration (FDA) to proceed with an Investigational New Drug (IND),^{3,4} since 1999, cannabis research proposals must additionally receive scientific merit approval from the Public Health Service (PHS).^{1,5} Research protocols for no other controlled substance require PHS review, and the policy for this process does not specifically state why the PHS review is required. According to Dr. Gust, PHS involvement is necessary because NIDA is unqualified for judging medicinal research protocols, as the agency’s focus is drug abuse.¹ Dr. Gust explained that even if a cannabis research proposal is approved by DEA and FDA, it can still be denied by PHS.

Additionally, before a cannabis researcher can receive permission from FDA for his or her IND to proceed, NIDA must first decide that it has sufficient cannabis available to support the proposed study.⁵ According to Dr. Gust, NIDA also determines availability for additional scheduled substances, but while these can be manufactured and distributed by non-governmental entities, the government allows cannabis to be distributed only through NIDA.¹

“It just so happens that NCNPR is the only legal source of marijuana, so researchers come to us,” said Dr. Gust.

NIDA maintains that its scope of authority is based on US Department of Human Health Services (HHS) policy and an international treaty called the Single Convention on Narcotics of 1961 (the Single Convention), which NIDA says requires the United States to have only one source of cannabis—an interpretation that has been disputed by others.¹ It also recognizes that the study of cannabis’ potential as a medicine is not within its mission

to “lead the nation in bringing the power of science to bear on drug abuse and addiction.”⁶

Several groups, including the Institute of Medicine (IOM) and American Medical Association (AMA), have said that more research on cannabis’ medicinal properties needs to be conducted.^{1,7} But some researchers who wish to study the plant’s potential as a medicine have become frustrated with the NIDA/PHS process, as they have had difficulty in obtaining the necessary approvals and material.¹

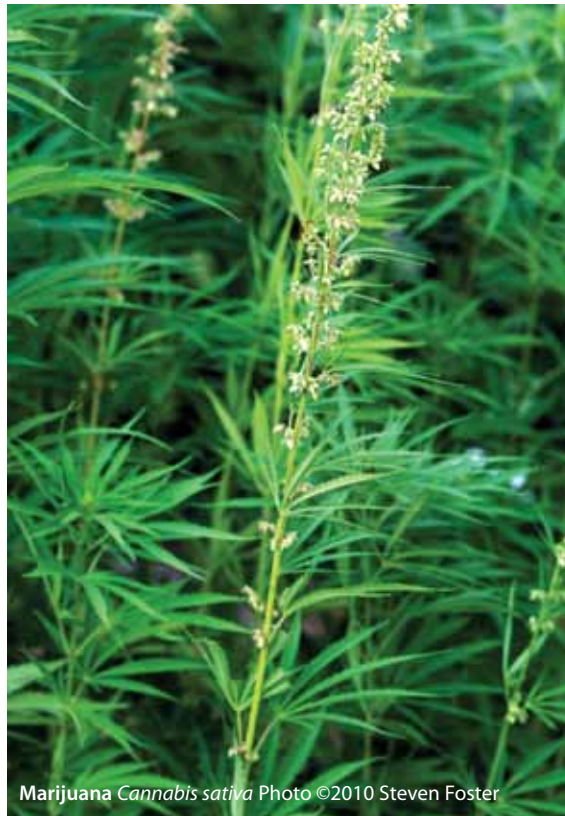
Hoping to change this situation, Lyle E. Craker, PhD, a professor of plant and soil sciences at the University of Massachusetts at Amherst, applied directly to DEA in 2001 to be a private cultivator of cannabis for medicinal research.¹ Dr. Craker chose not to

apply for the NIDA contract due to NCNPR’s 42-year history of winning it and because, if he had applied for and won the contract, he could only distribute cannabis to research approved by NIDA. His action was based on the Controlled Substances Act’s (CSA) provision that DEA shall register manufacturers of Schedule I controlled substances if it is in the public interest and in accordance with international treaties.³ When DEA had not responded after 3 years, Dr. Craker sued the administration for the lengthy delay.

Though Dr. Craker has considerable experience cultivating and studying medicinal plants, he previously had little interest in cannabis, as funding had never been offered for its study.¹ But in 2001, he was approached with an offer from Rick Doblin, PhD, founder of the Multi-disciplinary Association for Psychedelic Studies (MAPS), a nonprofit that aims to treat conditions for which conventional medicines provide limited relief by developing so-called psychedelics (agents that affect and

expand consciousness) and cannabis into prescription medicines. With support from officials at his university, Dr. Craker agreed to a partnership with MAPS to grow cannabis at his university in an indoor facility for DEA- and FDA-approved medicinal research.

“What we’re trying to do is to convince the government that [marijuana] is something we should further test in order to conclusively uphold, or refute, the preliminary evidence suggesting it has medicinal properties that are helpful to mankind,” said Dr. Craker




Marijuana *Cannabis sativa* Photo ©2010 Steven Foster

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(oral communication, October 15, 2009).

If Dr. Craker and MAPS' efforts eventually end the NIDA cultivation monopoly, the PHS/NIDA process would also end, said Dr. Doblin (oral and e-mail communications, September 11–December 7, 2009). During interviews for this article, Dr. Gust initially confirmed this: “If a research protocol had a source of marijuana other than NIDA...” and “was privately funded, then NIH, NIDA, and PHS would not be involved at all,” he said. Later, however, Dr. Gust said it is “not at all clear” if Dr. Craker/MAPS receiving a license to grow cannabis would stop PHS from having to review applications under Single Convention requirements. Dr. Craker has received support from the American Civil Liberties Union (ACLU), dozens of US Representatives, the late Senator Edward Kennedy (D-MA) and Senator John Kerry (D-MA), and numerous newspapers and associations, including medical, patient, political, and religious organizations.^{1,8}

DEA Rejection and Administrative Hearing

After Dr. Craker sued DEA for the 3-year delay, a Court of Appeals in the District of Columbia ordered the administration to respond. DEA then proposed to reject Dr. Craker's application, saying that the Single Convention requires the federal government to limit cannabis available for research to one source.¹ The Single Convention states that having only one agency is allowed if permitted by the signatory's constitution, and that “special stocks” and retail “stocks” (defined as reserves held by pharmacists or other authorized distributors and institutions or people with therapeutic or scientific function) are exempt from the scope of a monopoly.

DEA also said that granting the application would not be in the public interest because marijuana is the most heavily-abused of all Schedule I substances and smoked marijuana is not an acceptable form of delivery for any potential marijuana medication.¹ The administration further asserted that registering Dr. Craker would go against HHS policy, and that cannabis research has not been limited by the current process.

An administrative hearing took place in August 2005 in order to review DEA's rejection.¹ Administrative Law Judge Mary Ellen Bittner presided over the hearing and considered several regulating documents, which included regulations specifying that DEA is not required to limit the number of manufacturers to less than what would be needed to provide effective diversion controls or “solely because a smaller number is able to produce an adequate and uninterrupted supply.” She also heard testimony and considered documentary evidence from both parties.

Dr. Craker and MAPS had the responsibility to show why his registration would be in the public interest.¹ They asserted that the Single Convention repeatedly refers to “cultivators” in the plural sense and that the National Cannabis Agency in the United Kingdom, a signatory nation of the Single Convention, licenses multiple sites to produce, possess, or supply cannabis.

Additionally, in his testimony, Dr. Doblin explained several instances in which researchers following the NIDA/PHS process have been denied access to cannabis for medicinal research. For example, Donald Abrams, MD, a cancer and integrative medicine specialist at the University of California at San Francisco, applied to NIDA to purchase cannabis for research on potential benefits for AIDS patients in 1994. Though FDA contribution influenced

the design of the study and several institutional review boards approved it, NIDA denied the application.⁹ (NIDA later provided Dr. Abrams with marijuana and \$1 million in order to study the risks of marijuana in HIV-positive patients.)¹

Beginning in 1997, Ethan Russo, MD, a leading cannabinoid researcher, submitted 3 protocols for research on cannabis for treating migraines.¹ According to a 1999 letter from Dr. Russo to DEA, PHS denied Dr. Russo's protocol despite its being approved by FDA and Dr. Russo's institutional review board earlier that year. In the hearing, DEA said that Dr. Russo was not registered by the administration to conduct cannabis research.

MAPS and private analytical lab Chemic Labs (Canton, MA) joined in 2003 to study vaporization as an alternative to smoking cannabis.¹ During the 6-year process to gain approval of the proposed study's protocols, PHS eventually submitted review comments, which were “not what Chemic Labs considered to be well-informed but were designed to be overly critical,” said Dr. Doblin. PHS reviewers ultimately asked Chemic to conduct about \$60,000 worth of studies to prove the calibration of its instruments, which is not necessary for the pilot study, he said, adding that Chemic has since decided to stop trying to conduct the research.

“We've had to sit and watch the field of medicinal marijuana research go nowhere,” said Dr. Doblin, adding that new medical marijuana research has the potential to contradict past and present claims of the plant's negative effects. “The herb has achieved such a symbolic notion in the culture that it is obstructing the research.”

DEA argued in the hearing that cannabis research is not being limited.¹ Dr. Gust has voiced a similar opinion: “The facts are that there has been more clinical research on marijuana in the last 5 years than the previous 20, mostly conducted at California's Center for Medicinal Cannabis Research (CMCR), most with positive findings.” According to Dr. Doblin, CMCR was able to obtain NIDA cannabis because its mission does not seek to develop cannabis into a pharmaceutical. A DEA staff member testified that Dr. Doblin's pharmaceutical intentions did raise issues within the administration.¹

Although each of CMCR's proposed studies have been approved by NIDA/PHS, CMCR will soon shut down due to lost funding once its last 2 remaining studies are completed, said the center's Study Coordinator Ben Gouaux (e-mail, November 24, 2009). Additionally, all CMCR studies have been Phase I or Phase II trials, not Phase III trials, which are typically much larger and require more resources, added Gouaux. To his knowledge, Gouaux said, GW Pharmaceuticals is the only other entity currently conducting medicinal research on cannabis in its botanical form (in the United Kingdom).*

In further attempts to show why Dr. Craker's registration is necessary, Dr. Doblin testified that NIDA cannabis from NCNPR is low in THC content, requiring patients to smoke more of it, and that some of it contained seeds, stems, and sticks, and was old and harsh.¹ Dr. Russo published research in 2002 regarding the quality of NIDA cannabis provided to surviving patients in the federal government's Compassionate IND program, which FDA created in 1976 due to glaucoma patient Robert Randall's pursuit for legal marijuana for self-treatment.¹⁰ Some 15 to 34 patients eventually received Compassionate IND approval, which

*Gouaux's statement refers to research on cannabis in its whole botanical form. A reviewer of this article noted that there has been research with herbal cannabis in Canada and studies with Cannador, a cannabis extract in Europe.

allowed them to legally obtain NIDA marijuana, but in 1992 the administration of President George H.W. Bush closed the program to new members. Dr. Russo and the other researchers found that the NIDA marijuana cigarettes consisted of a “crude mixture of leaf with abundant stem and seed components,” with a green and herbal odor and “thick, acrid, and pervasive” smoke.¹⁰ According to a letter to DEA, Dr. Russo separately obtained 100 grams of NIDA marijuana in 1997, but because it was of “such poor quality,” he decided it was not representative of true medicinal cannabis and never used it.¹

Additionally, Dr. Abrams, who completed 2 clinical studies at CMCR, told DEA that the NIDA cannabis contained seeds, leaf, and some stems, making the potency inconsistent and adversely affecting his research.¹ Four patients quit one of these studies.

DEA, however, testified that it believes NIDA cannabis is of an acceptable quality.¹ While the administration said it did not speak with the Compassionate IND patients because they are not researchers, it did speak with several researchers whom NIDA supplied with cannabis for medicinal studies. The director of CMCR, Igor Grant, MD, told DEA that NIDA cannabis was mostly absent of seeds and stems, though this varied depending on the potency, and he also said the cannabis was sometimes harsh and caused coughing but that this did not affect the research. Ronald Ellis, MD, PhD, said the quality of the NIDA cannabis did not affect his research, though some patients said the smoke was harsh and made it difficult to finish the marijuana cigarette, and one quit the study due to a cough related to the marijuana’s harshness.

Dr. Gust and Mahmoud ElSohly, PhD, principal investigator of NCNPR’s marijuana program, testified that they had never received any formal complaints on the quality of the cannabis.¹ Dr. ElSohly noted that NCNPR began using a new machine in 2001 that reportedly removes the majority of stems and seeds. When reached for comment, Dr. ElSohly said that even the marijuana cigarettes produced prior to 2001 had “very, very few seeds and therefore the comments by some on that issue are grossly exaggerated” (e-mail, December 21, 2009). He also testified that NCNPR is required to first send the inventory’s oldest marijuana to researchers, unless NIDA approves the sending of newer material.

Dr. ElSohly further testified that CMCR researchers had requested cannabis of 8% tetrahydrocannabinols (THC) level. The marijuana cigarettes sent to the center turned out to have a level above 7% and below 8%, a discrepancy that, according to Dr. ElSohly, was not substantial enough to affect the research. A CMCR staff member told DEA that the center’s researchers would

prefer a more consistent strength of cannabis.

Dr. ElSohly said that NCNPR has produced cannabis for cigarettes at up to 8% THC levels, bulk cannabis with levels of 13-14%, and has the ability to produce cannabis with a level of 20% or higher on a small scale. While producing these levels of THC potencies is not technically beyond Dr. ElSohly’s capabilities, he just happens to produce low potency cannabis to distribute to researchers, said Dr. Doblin. “Theoretically [Dr. ElSohly] should be able to produce any [potency] we wanted,” he said. “But he’s only looking at THC when other cannabinoids are clearly important. NIDA’s marijuana has virtually no CBD.” In response to this, Dr. ElSohly said that higher potency cannabis (7-8% THC) delivered by NCNPR to CMCR a few years ago was not well tolerated by study subjects, and CMCR subsequently requested cannabis at 6% THC. As for cannabis containing CBD, he said, “we have not had the first request for that.” Dr. Doblin noted that the MAPS/Chemic protocol requested marijuana with THC and CBD, but because NIDA never approved it, this request was never forwarded to Dr. ElSohly.

When Dr. Craker’s DEA application was posted to the *Federal Register* in July of 2003, Dr. ElSohly was the only person to file an objection.¹ He stated that “We strongly feel that it is absolutely unnecessary to approve another manufacturer’s registration . . . Approval of the UM-Amherst would result in a duplication of existing resources without any foreseeable benefits.”

Stressing that he respects Dr. ElSohly, Dr. Craker said the problem lies in NIDA’s mission and the terms of the NCNPR-NIDA contract. He and Dr. Doblin have also stated that NCNPR and Dr. ElSohly’s non-NIDA cannabis cultivation¹ is a conflict of interest. NCNPR has an additional DEA permit to grow

cannabis for Mallinckrodt, a division of Covidien (Hazelwood, MO; formerly Tyco Healthcare), which will soon market a generic version of the synthetic THC-containing drug Marinol® (Solvay Pharmaceuticals, Brussels, Belgium).¹ Unlike Marinol, the generic version will use THC extracted from the cannabis plant (which is less expensive) by Dr. ElSohly. As NIDA can distribute NCNPR’s cannabis only for research, Dr. ElSohly’s separate permit makes him the only person in the country who can legally grow marijuana for commercial purposes.

If MAPS were ever to win approval of a marijuana prescription, it would have to purchase the material from Dr. ElSohly, who would have a monopoly on the supply and could set any price he chose, Dr. Doblin testified. Dr. ElSohly said that this would be impossible because under its DEA permit to grow cannabis for the extraction of THC, NCNPR “cannot distribute [whole] marijuana at all.” He said that Dr. Doblin would have to purchase cannabis



Illustration of **Marijuana** *Cannabis sativa* from *American Medicinal Plants: An Illustrated and Descriptive Guide to the American Plants Used as Homeopathic Remedies; Their History, Preparation, Chemistry and Physiological Effects* by Charles F. Millsbaugh (1887).

Image courtesy of Steven Foster

for his whole botanical-based medicine from some federal government agency, which would set the price. But because NIDA cannot distribute cannabis for commercial purposes, it is unclear what the source of cannabis for potential FDA-approved medicines would be.

DEA Judge Recommendation and Recent Events

In February 2007, Judge Bittner's final decision recommended that Dr. Craker be granted permission to grow and produce research-grade cannabis.¹ She reasoned that registering Dr. Craker would not violate the Single Convention, that cannabis grown by Dr. Craker would not likely be diverted, and that the existing supply of cannabis is not adequate as some DEA- and- FDA-registered researchers are prevented from obtaining the necessary material. She also said that the NIDA contract does not provide adequate competition and the HHS policy applies only to cannabis that HHS makes available and not to cannabis from a separate source. In January of 2009, as President George W. Bush was leaving office and President Barack Obama was preparing to be inaugurated, DEA Deputy Administrator Michele Leonhart, a Bush appointee, rejected Bittner's recommendations and ruled against granting Dr. Craker's request.

Because Leonhart's ruling was partly based on evidence not included in the hearing, Dr. Craker has since filed a motion to reconsider, said Dr. Doblin. In May of 2009, DEA requested that Dr. Craker submit a list of potential witnesses and documents, which he did.^{8,11} When contacted, DEA declined to comment on the ongoing case. Dr. Craker and MAPS are waiting on DEA's next step, said Dr. Doblin.

Dr. Gust said that NIDA does not have a position on Dr. Craker's application, but also said "The supply of marijuana for research is restricted by international drug treaties and not any 'monopoly'; that the [US government] is quite open to research on this issue, and in fact no clinical studies of medical marijuana have ever been disapproved by the PHS. The implication that NIDA in some way restricts or controls research in this area is patently untrue; there is plenty of marijuana available from the government for studies, and despite all the contentions, it is pretty easy to get."

"If [it] were the case [that the US government is open to medical

marijuana research], what would be the harm in licensing Craker?" asked Dr. Doblin. "The international treaty obligation argument is not valid, as determined by [Judge] Bittner." Dr. Doblin said Dr. Gust's statement that PHS has never disapproved of clinical studies using medical marijuana was also used by DEA in its rejection of Dr. Craker's application. But this is false, he said. Dr. Russo's marijuana for migraine protocol was rejected by PHS after the PHS/NIDA protocol review process was put into place, and this evidence is part of the Motion to Reconsider, he continued.

If DEA eventually denies the application, Dr. Craker will continue with the case's appeal in federal court, said Dr. Doblin. But the court cannot issue Dr. Craker the license. All it can do is direct DEA to reconsider the decision, which could in turn lead to a process of continual delays, he added. Dr. Craker and Dr. Doblin said they think that DEA is waiting for President Obama to appoint a new DEA deputy administrator and are hoping that he stays true to his campaign promise to focus on science over politics.

Conclusion

The lengthy delays in Dr. Craker's case highlight the significance of the state-level medical marijuana movement. As of December 2009, 14 states[†] and Washington, DC had approved some use of marijuana for medical reasons, and others are considering such legislation.¹² The US Department of Justice has advised federal prosecutors not to bring charges against medical marijuana patients and distributors who comply with their state's law. While more people are able to obtain marijuana for treatment under some states' laws, little research is being done to document the efficacy and safety of cannabis as a medicine.

Dr. Gust testified that both NIH and HHS accept that eventually there will be pharmaceuticals based on cannabis components, as well as purified pharmaceuticals administered by non-smoke delivery systems.¹ But medicines, such as Marinol, that are based on isolated components of cannabis ignore research demonstrating that some botanicals, e.g., cannabis, produce beneficial effects based on a synergistic activity of their constituents, said Dr. Doblin. In a 2005 interview, Lester Grinspoon, MD, associate professor emeritus of psychiatry at Harvard University and author of 2 books on medicinal marijuana, stated that the US government welcomes pharmaceuticals like Marinol and Sativex[®] because it can



Marijuana *Cannabis sativa* Photo ©2010 Steven Foster

[†]The following states having approved some use of marijuana for medical reasons: California, Alaska, Colorado, Hawaii, Maine, Maryland, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont and Washington. [Ref: Stout D., Moore S. U.S. won't prosecute in states that allow medical marijuana. *New York Times*. A1: October 20, 2009]

control them, and the situation creates an appearance of cooperation and takes attention away from the movement for botanical medicinal marijuana.¹³ (Sativex is an oromucosal spray containing cannabis extracts and manufactured by GW Pharmaceuticals, currently in late stage clinical trials in the United States for treatment of cancer pain.)

While limited, research on the medicinal effects of cannabis show some benefits, including the relief of nausea, appetite loss, depression, and pain in patients suffering from cancer, HIV, and amyotrophic lateral sclerosis (ALS, often referred to as Lou Gehrig's Disease), and the reduction of intraocular pressure, which commonly causes glaucoma patients to go blind.¹⁴ An NIH expert panel has previously said that research shows marijuana to be beneficial for cancer chemotherapy patients, and in 1999 an IOM report also concluded that some patients can benefit from marijuana.¹⁵ On November 10, 2009, AMA reversed its previous position that marijuana has no medical value, recognizing that it does have therapeutic benefits for patients with neuropathic pain, reduced muscle mass, and multiple sclerosis.⁷

The majority of modern cannabis research in the United States has taken place at CMCR, which has completed 11 studies to date, most of which found positive results.¹⁶ Dr. Abrams found vaporization of marijuana to be a safe mode of delivery and marijuana to effectively relieve chronic neuropathic pain in HIV patients. Dr. Abram's study, funded by NIDA, on the risks of cannabis in HIV patients found that cannabis did not harm the patients' immune systems or affect the viral load in their blood, nor did it negatively interact with protease inhibitor drugs, and the patients gained weight. Dr. Ellis found that cannabis provided greater pain relief than placebo in patients with HIV neuropathy. Dr. Russo's research determined that smoking cannabis led to an improved quality of life for 4 patients from the Compassionate IND program and that it also was an effective treatment for pain, muscle spasms, and intraocular pressure elevations common with glaucoma.¹⁰

Many concerns on the potential harmful effects of cannabis remain. Much of this centers on the notion that smoking marijuana can have similar effects on the lungs as does smoking cigarettes.¹⁷ Donald Tashkin, MD, an emeritus professor of medicine at the University of California Los Angeles, however, recently commented that the evidence for an association between use of cannabis and abnormalities in lung function is inconsistent. He went on to write that the current evidence suggests that smoking cannabis by itself does not lead to chronic obstructive pulmonary disease or lung cancer.¹⁸

MAPS and Dr. Craker believe that having an alternate cultivator of cannabis for research would promote the advancement of science and research.¹ More researchers would want to study the substance because the PHS/NIDA process and lengthy delays would be eliminated and the cannabis would be of a reliable quality, said Doblin.

Since his application and lawsuit have become better known, Dr. Craker said he has received much feedback from ill persons or people with ill friends and relatives who benefit from smoking cannabis. At the beginning of this process, Dr. Craker thought that DEA would be interested in licensing him.

"[I thought that] if they had friends or relatives suffering, then they would be happy to have this as a medicine," he said. "I thought the decision was easy to make." HG

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—Lindsay Stafford