

Montanans for Responsible Legislation

EXHIBIT 15
DATE 2/2/2011
HB 101

po box 7556
Missoula, MT
59807

responsiblemontanans@gmail.com
(406)285-1034

Over the course of recent history it has become clear that the Montana Medical Marijuana Act, passed in 2004 by over 60% of Montana's voters, has not been implemented as planned. The law's ambiguity not only creates problems for our peace officers in regards to enforcement, but its 'grey areas' have left our state's seriously ill open to the exploitations and abuses of an opportunistic few. However, the flaws inherent to title 50, chapter 46 do not run deep enough, nor are they so far without proper remedy, to warrant the re-criminalization of 30,000 Montanans; to do away with this very important concept of compassionate access; to fly directly in the face of science and public opinion; to necessitate a repeal of our Medical Cannabis Law.

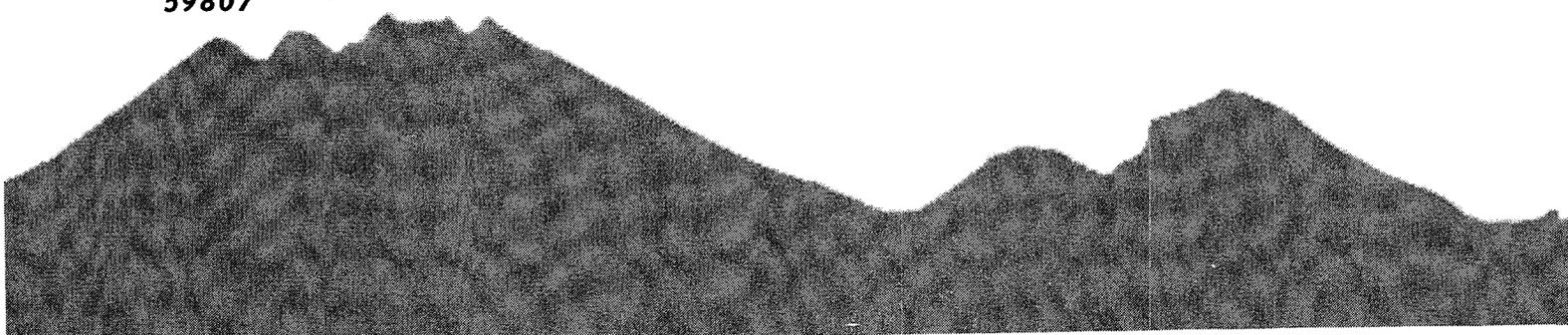
MRL represents the very people Montana voted to protect in 2004 -- the very same people crying out today for reform; just the proper kind of reform. Our constituents demand the protection from prosecution afforded under the Medical Marijuana Act - we understand that neither illness, nor its treatment, is a crime. They demand stricter standards of medical care, statute requiring continuing education for physicians in this fledgling field of cannabis science, and for the allowance of lab testing for their medicine.

I look forward to working with lawmakers throughout this session to develop a workable, regulatory model - one that honors the spirit of I-148, and one that protects the very people Montana voted to protect in 2004.

"Montanans for Responsible Legislation is a nonprofit public education group working to ensure safe access for, and the equal treatment of, both medical cannabis patient and provider. Through civil litigation, public education, and our lobbying activities with the Montana State Senate and House of Representatives these goals are achieved. We serve as an unbiased, community supported interface with the state legislature -- voicing the concerns and desires of the greater Montana Cannabis community."

Thank you,

**Doug Chyatte
Montanans for Responsible Legislation
responsiblemontanans@gmail.com
(406)285-1034
po box 7556
Missoula, MT
59807**



Montanans for Responsible Legislation

www.m4rl.net

(406)285-1034

Dear lawmakers:

I worked 22 years for the sheriff's department, and I am against HB 161.

Parents who are trying to repeal the medical marijuana act need to become aware of the following facts: Thousands of kids in the USA each year experience alcohol poisoning and many of these kids die from it. Many kids in this country have also died after abusing prescription narcotic and tranquilizer pills. Are these parents aware that meth is the number one cause of teenage suicide in Montana?

Has anyone ever died from "marijuana poisoning"? I would have to say 'No'... I never heard of such an event during my years at the Liberty County sheriff's dept. and cannot recall a single case of that happening. In the panic to save children from the real dangers of meth, alcohol and prescription narcotics, the "group for repeal" have misguidedly targeted marijuana.

I saw how alcohol consumption caused many vehicle fatalities over the years in our county. I saw meth abuse involved in many incidents of domestic and public violence. I do not recall marijuana as a factor involved in car accidents or violence issues.

There is an assault being placed upon the entire medical marijuana initiative due to the activities of Jason Christ and his traveling marijuana clinics. Is the solution to blast the entire I-148 program out of the water, along with the patients who have been helped? No. It was the citizens who voted for this natural treatment option. Common sense would tell us to simply put a stop to Jason Christ's activities and his offensive traveling marijuana clinics. If one pharmacist is caught selling prescription drugs illegally out the back door of his pharmacy, are we going to shut down all prescription drug sales in Montana? How ridiculous, we would simply prosecute the single pharmacist who broke the law. We must apply this same wisdom to herbal medicines such as marijuana.

Medical marijuana should not be denied to anyone who suffers illness and needs it. It is medicine. When it's used in the proper way and doctor-supervised, marijuana is a

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godsend to many. In our civilized society we are taught to do all we can with research and resources to help all suffering people.

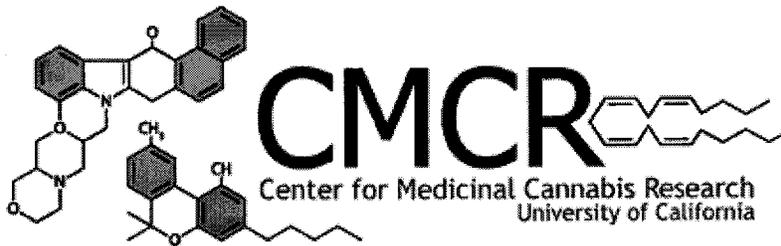
I do not believe legislators are acting in justice if they take away a medicine from any person who has been helped by it. We should continue to make the safest, most natural and most non-addicting pain medicine available to all people, and one of the most safe of those is doctor-supervised marijuana.

I am a senior citizen who has always been a republican. One of the smartest, most strategic, and compassionate moves republicans could make right now would be to keep this medical freedom available for Montanans.

Darlene Lyle

P.O. Box 62

Joplin, MT 59531



CENTER FOR MEDICINAL CANNABIS RESEARCH

*Report to the Legislature and Governor of the State of California
presenting findings pursuant to SB847 which created the CMCR and provided state funding*

Director:

Igor Grant, M.D.

University of California, San Diego

Co-Directors:

J. Hampton Atkinson, M.D.

Andrew Mattison, Ph.D.*

University of California, San Diego

Thomas J. Coates, Ph.D.

University of California, Los Angeles

**Deceased*

Objective

In 1999, the California legislature passed and Governor Gray Davis signed SB847, which commissioned the University of California to establish a scientific research program to expand the public scientific knowledge on purported therapeutic usages of marijuana.

We hereby submit this report of our scientific findings pursuant to this objective.

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"Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body."

~ *Institute of Medicine, 1999*

"The question of whether marijuana has any legitimate medical purpose should be determined by sound science and medicine."

~ *Asa Hutchinson, Former DEA Administrator, 2001*

"The scientific community, the medical community in particular, is divided on the real therapeutic effectiveness of marijuana. Some are quick to say that opening the door to medical marijuana would be a step toward outright legalization of the substance. But none of that should matter to physicians or scientists. It is not a question of defending general public policy on marijuana or even all illegal drugs. It is not a question of sending a symbolic message about "drugs". It is not a question of being afraid that young people will use marijuana if it is approved as a medicine. The question, and the only question, for physicians as professionals is whether, to what extent and in what circumstances, marijuana serves a therapeutic purpose."

~ *Canadian Senate Special Committee On Illegal Drugs. Cannabis: Summary Report, 2002.*

"Although the indications for some conditions (e.g., HIV wasting and chemotherapy-induced nausea and vomiting) have been well documented, less information is available about other potential medical uses. Additional research is needed to clarify marijuana's therapeutic properties and determine standard and optimal doses and routes of delivery."

~ *American College of Physicians, 2008*

"The Center for Medicinal Cannabis Research is currently conducting scientific studies to determine the efficacy of marijuana in treating various ailments. Until that research is concluded, however, most of what the public hears from marijuana activists is little more than a compilation of anecdotes."

~ *John Walters, Former Director of the White House Office of National Drug Control Policy, 2002*

Executive Summary

The Center for Medicinal Cannabis Research (CMCR) at the University of California was created in 2000 to conduct clinical and pre-clinical studies of cannabinoids, including smoked marijuana, to provide evidence one way or the other to answer the question “Does marijuana have therapeutic value?” To accomplish this objective, the CMCR issued calls for applications from researchers at leading California institutions, developed a close working relationship with state and federal agencies to gain regulatory approvals, established panels of nationally-recognized experts to rigorously review the merit of applications, and funded carefully designed studies that have now been published in high impact scientific journals, making significant contributions to the available literature on cannabis and the cannabinoids.

Summary of Results to Date

In total, the CMCR has approved fifteen clinical studies, including seven clinical trials, of which five have completed and two are in progress. The CMCR has also approved four pre-clinical studies, all of which have completed.

By design CMCR clinical studies focused on conditions identified by the Institute of Medicine for which cannabis might have potential therapeutic effects, based on current scientific knowledge (Institute of Medicine, 1999). To date, four CMCR-funded studies have demonstrated that cannabis has analgesic effects in pain conditions secondary to injury (e.g. spinal cord injury) or disease (e.g. HIV disease, HIV drug therapy) of the nervous system. This result is particularly important because three of these CMCR studies utilized cannabis as an add-on treatment for patients who were not receiving adequate benefit from a wide range of standard pain-relieving medications. This suggests that cannabis may provide a treatment option for those individuals who do not respond or respond inadequately to currently available therapies. The efficacy of cannabis in treatment-refractory patients also may suggest a novel mechanism of action not fully exploited by current therapies. In addition to nerve pain, CMCR has also supported a study on muscle spasticity in Multiple Sclerosis (MS). Such spasticity can be painful and disabling, and some patients do not benefit optimally from existing treatments. The results of the CMCR study suggest that cannabis reduces MS spasticity, at least in the short term, beyond the benefit available from usual medical care.

Table 1. Clinical Studies Published or Submitted for Publication

| | |
|--|--|
| Donald Abrams, M.D. UC San Francisco | Cannabis for Treatment of HIV-Related Peripheral Neuropathy |
| Donald Abrams, M.D. UC San Francisco | Vaporization as a Smokeless Cannabis Delivery System |
| Jody Corey-Bloom, M.D., Ph.D. UC San Diego | Short-Term Effects of Cannabis Therapy on Spasticity in MS |
| Ronald Ellis, M.D., Ph.D. UC San Diego | Placebo-controlled, Double Blind Trial of Medicinal Cannabis in Painful HIV Neuropathy |
| Mark Wallace, M.D. UC San Diego | Analgesic Efficacy of Smoked Cannabis |
| Barth Wilsey, M.D. UC Davis | Double Blind, Placebo Controlled Trial of Smoked Marijuana on Neuropathic Pain |

To date, six of the studies have published (or are in the process of publishing) results in respected medical journals, garnering national and international attention from other researchers, media outlets, governmental agencies, and the general public (see Table 1). These results have helped to bring together accomplished international experts on cannabis and cannabinoids and foster scientific dialog on the possible utility of cannabis as a therapeutic agent.

Adverse side effects experienced by participants included cough, nausea, dizziness, sedation and changes in cognition. However, these effects were typically mild and resolved rapidly after treatment. Currently approved analgesics are not without side effects, and the effects observed in CMCR studies tended to be no worse than would be expected with other potent analgesics. Following the conclusion of the two studies currently in progress, CMCR will have exhausted its available funding for clinical work, though the CMCR will continue to maintain a sample bank and to consult with researchers and policy-makers as needed.

The majority of CMCR studies that have been discontinued were cancer studies that experienced difficulty in recruiting participants. Many severely ill individuals were reluctant to volunteer for a rigorous research protocol where the experimental treatment addressed disease symptoms (i.e. nausea, pain) but did not affect tumor growth directly. Other factors, such as requirement that patients have stable pain scores over a period of time leading into the study, prohibition from driving for the duration of the study, and difficulty in providing cannabis for home administration may also have played a role in the lack of success in recruiting this population. A further impediment to participation in CMCR studies, particularly in cancer patients, was the inability of CMCR to continue to provide study drug beyond the study period to patients who find active treatment beneficial. Additionally, some individuals already were using cannabis to treat pain or other symptoms, and so had less incentive to participate in research.

The CMCR portfolio also included basic science studies in animals and in human cells (pre-clinical research). This research was supported because it had the potential to provide insights into therapeutic use of cannabinoids in human disease. One study provided evidence, by way of recordings of nerve cell activity and in awake animals, of analgesic effects of cannabis-like compounds on head and facial pain, suggesting that clinical trials of cannabis might be warranted in patients with headache or other facial pain. Another study reported that cannabis did not interfere with the function of blood cells involved with immunity, an important finding considering potential therapeutic use of cannabis compounds will be in persons with chronic illnesses.

Other CMCR Activities

In addition to the research, CMCR has also functioned as a catalyst for discussion and examination of the potential development of cannabis as medicine. In July, 2002, CMCR sponsored a workshop "Future Directions in Cannabinoid Therapeutics" featuring presentations by intellectual and scientific leaders in the field of cannabinoid science from around the world. CMCR hosted a second meeting in summer 2004 to address recent progress in science that would be likely to lead to clinical trials of new cannabinoid compounds. "Future Directions in Cannabinoid Therapeutics II: From the Bench to the Clinic" brought together the major stakeholders in the development of cannabinoid therapeutics in order to survey laboratory compounds that are most promising for testing in human trials and to confront potential stumbling blocks to testing and development of these compounds. A special issue of the journal *Neuropharmacology* (2005) was dedicated to publishing the research presented at this meeting.

Executive Summary (cont.)

CMCR researchers have also published two literature reviews on the neuropsychological effects of cannabis use in order to better understand the potential hazards of cannabis use in short and long-term treatment settings (Grant, et al., 2003 & Gonzalez, et. al, 2002 – see reference list).

Conclusion

As a result of the vision and foresight of the California State Legislature Medical Marijuana Research Act (SB847), the CMCR has successfully conducted the first clinical trials of smoked cannabis in the United States in more than 20 years. As a result of this program of systematic research, we now have reasonable evidence that cannabis is a promising treatment in selected pain syndromes caused by injury or diseases of the nervous system, and possibly for painful muscle spasticity due to multiple sclerosis. Obviously more research will be necessary to elucidate the mechanisms of action and the full therapeutic potential of cannabinoid compounds. Meanwhile, the knowledge and new findings from the CMCR provide a strong science-based context in which policy makers and the public can discuss the place of these compounds in medical care.

Mission Statement

“The Center for Medicinal Cannabis Research (CMCR) will conduct high quality scientific studies intended to ascertain the general medical safety and efficacy of cannabis products and examine alternative forms of cannabis administration. The Center will be seen as a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities.”

Scientific and Legislative Precursors of the CMCR

Discovery of Cannabis Receptors in the Brain

During the late 1980's and early 1990's, a series of significant scientific breakthroughs revealed an in-built system of cannabinoid receptors and cannabinoid signaling molecules in the human brain. Cannabinoid receptors are located throughout the central nervous system and peripheral tissues and are implicated in nervous system excitability, movement, analgesia, neuroprotection, and feeding behaviors, including newborn suckling.

Scientific Reports

Following this period of scientific discovery and expanded understanding of the physiological basis of cannabinoid action, there was renewed interest in potential therapeutic applications of cannabinoid chemicals. The National Institutes of Health Ad Hoc Group of Experts and the Institute of Medicine, following thorough review of the existing scientific literature, identified medical conditions warranting further research regarding the possible therapeutic effects of marijuana. Medical evidence for likely therapeutic benefit was identified in the areas of appetite stimulation, neurological and movement disorders, analgesia, and nausea and vomiting.

1997: National Institutes of Health, Workshop on the Medical Utility of Marijuana

1999: Institute of Medicine Report, "Marijuana and Medicine: Assessing the Science Base"

(Available through the CMCR website at: <http://cmcr.ucsd.edu/geninfo/marijuana.htm>)

Legislative Origins

The triggering event which led to the creation of the CMCR was the passage by the people of California in 1996 of Proposition 215, the Compassionate Use Act, which approved the medical use of marijuana (although at that time the exact role the substance should play in patient care remained ambiguous). Following that, in 1999, the Legislature of California passed Senate Bill (SB) 847, authored by then Assemblyman, later Senator John Vasconcellos, after extensive negotiations with then Attorney General Dan Lungren, providing the bipartisan legitimacy that enabled this bill to obtain the required two-thirds vote in each house of the California legislature. SB847 proposed (subject to the approval of the Board of Regents of the University of California) to create a three-year program overseeing objective, high quality medical research that would "...enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent," stressing that the project "should not be construed as encouraging or sanctioning the social or recreational use of marijuana." In August 2000, the Center for Medicinal Cannabis Research was established at the University of California to carry out this mission. In 2003, after CMCR had demonstrated its ability to carry out the proposed program of research, SB295 was approved to remove the 3-year program limitation included in the founding legislation.

1996: California voters pass the Compassionate Use Act of 1996.

1999: California State Legislature passes the Medical Marijuana Research Act of 1999 (SB847).

2000: Center for Medicinal Cannabis Research is established as a state-funded research center at the University of California to solicit, review, and support clinical and limited preclinical research

2000: CMCR issued its first call for proposals

2003: SB295 is passed, re-authorizing the CMCR to continue indefinitely

CMCR Review Process

In order to evaluate the scientific validity of the proposals submitted, the CMCR engaged senior scientists from around the nation to serve as a Scientific Review Board (SRB). Studies recommended for funding by the Scientific Review Board were then submitted for review to the Research Advisory Panel of California (RAP-C), the Office of Public Health and Science of the federal Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the National Institute on Drug Abuse (NIDA), and the Drug Enforcement Administration (DEA). Upon final approval from each of the above agencies, studies were authorized to order cannabis cigarettes from NIDA and to begin recruiting patients. This process is described in Figures 1 and 2.

Figure 1. CMCR Scientific Review

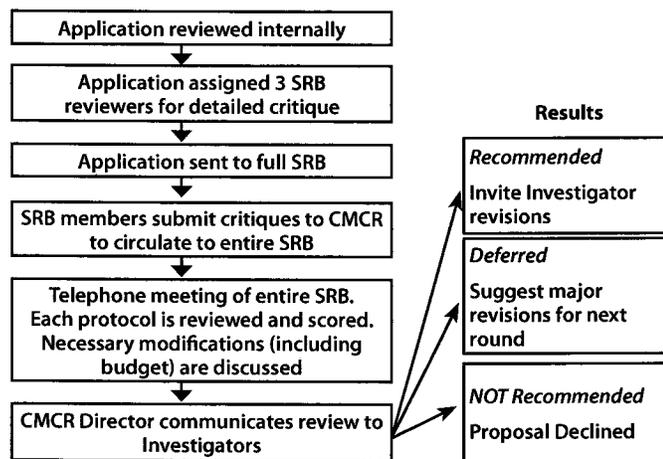
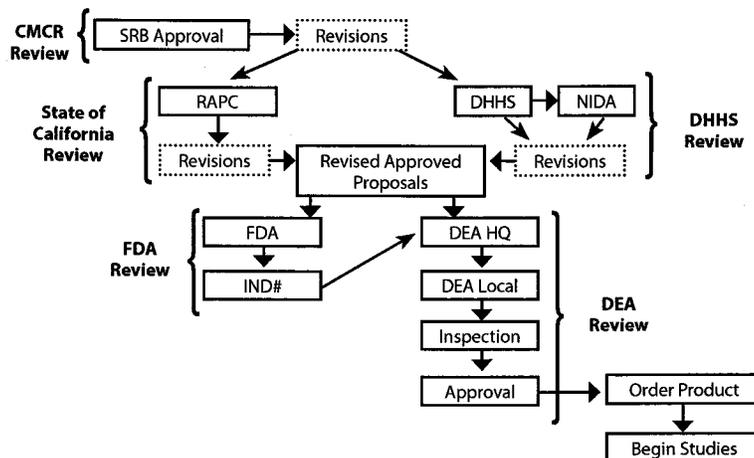


Figure 2. CMCR Regulatory Approval Process



CMCR Vision for Cannabis Therapeutics Research

CMCR envisions its role in the investigation of cannabis and cannabinoid compounds in three main research domains involving smoked cannabis, non-smoked preparations, and eventually new pharmaceutical drug candidates formulated to act directly on the endocannabinoid system.

Stage I: Smoked Cannabis

- Develop state and federal review process, and solicit proposals for initial studies.
- Conduct well-designed, rigorously controlled clinical trials of smoked cannabis. Until alternative delivery systems and new molecules are available, smoked cannabis offers the most efficient delivery of cannabinoids for clinical trials.
- Cannabis cigarettes are provided by the National Institute on Drug Abuse (NIDA).

Work Accomplished

CMCR has developed the scientific and administrative infrastructure to support application, review, selection, and implementation of studies, and has developed a rigorous process of peer review of scientific proposals by independent Scientific Review Board. CMCR has also established a relationship with state and federal agencies (RAPC, DEA, FDA, DHHS, NIDA) to facilitate regulatory approval.

The CMCR first solicited applications in fall 2000, and has funded fifteen clinical and four pre-clinical studies throughout California. The CMCR has issued five calls for proposals, most recently in summer 2006.

Stage II: Non-Smoked Preparations

- Explore the safety and effectiveness of non-smoked forms of medicinal cannabis.
- Expand trials to include alternative, non-smoked delivery of cannabis preparations.
- Alternative delivery may include vaporization, patches, suppositories, and alternative oral forms.

Work Accomplished

In the area of non-smoked routes of cannabis administration, Dr. Donald Abrams' study, "Vaporization as a 'Smokeless' Cannabis Delivery System," has been completed and the results published in the *Journal of Clinical Pharmacology & Therapeutics*. This study found that vaporization was a safe and effective mode of delivery. Two CMCR clinical trials are now in progress utilizing vaporization.

Stage III: Molecules To Target Endocannabinoid System

Stage III represents long-term goals for cannabinoid research. If the CMCR were to continue, the long-term research objectives would be to:

- Collaborate with laboratories around the world who are working on specific molecules (both natural and synthetic) to activate, modulate, or deactivate the body's in-built cannabinoid system.
- Perform Phase I, II, and III clinical trials on new molecules targeting the endocannabinoid system.

Overview of Research Program

Studies in Pain and Other Neurologic Conditions

Chronic pain—pain on a daily or almost daily basis for six months or longer—is one of the most prevalent and disabling conditions in California and in the US generally. Whereas many types of pain are caused by stimulation of specialized pain receptors on nerve endings, due to injury of tissues, neuropathic pain is produced either by direct damage to the central (brain, spinal cord) or peripheral nervous system itself, or by abnormal functioning of these systems. Infections, diabetes, physical trauma, strokes, and many other diseases can injure the nervous system, with resulting pain, which persists even though pain receptors themselves are not directly activated. It is therefore not surprising that neuropathic pain is widespread, affecting 5-10% of the US population. Only a few classes of medications are approved for use as analgesics in these conditions (opioids, anticonvulsants, antidepressants), and many patients obtain only partial relief, even when using combinations of all available therapies. Among the most difficult to treat neuropathic pain conditions are those secondary to HIV, diabetes, and to physical trauma to the nervous system. Because these neuropathic disorders are so prevalent, and treatment alternatives are so limited, the CMCR focused on these conditions.

A distinguishing scientific feature of this program of pain research, made possible only by the coordinating function of the CMCR, is the commonality of measures and methods across the research studies. This allows for the distinctive advantage of comparability of results across studies. Additionally, when possible we studied treatment of the same type of pain condition (e.g., HIV neuropathy) in more than one geographic site. Finding comparable results at two or more sites studying the same disease is scientifically important, since this suggests that the results are generally valid, rather than being due to chance or the specific characteristics of a single sample of patients, or of a particular team of researchers.

This research used the gold standard design for assessment of therapeutic effects, the randomized clinical trial. In this approach participants are assigned by chance, like flipping a coin, to an experimental treatment, in this case cannabis, or to a placebo (an inactive treatment). The placebo in all of our studies was a marijuana (cannabis) cigarette, made with cannabis from which the “active” ingredients, for example delta-9-tetrahydrocannabinol (THC), had been removed. The cigarette therefore had the appearance and the aroma of a marijuana cigarette, but without the crucial chemical ingredients hypothesized to be therapeutically active. Randomization ensures factors which might skew the results (like age, duration or intensity of pain) are equally present in both the experimental and placebo condition. Placebo is essential, since the expectation of pain relief from any treatment is a powerful analgesic itself. All of our protocols used measures of pain recommended by expert consensus as standard in the field. For studies of smoked cannabis, the researchers used a standard, timed method of inhalation; research using vaporized cannabis used similar, state-of-the-art technology. Researchers measured blood concentrations of the primary active ingredient of cannabis (THC), allowing estimates of relationships between dose, concentration, and magnitude of pain relief.

To date, the CMCR has completed four studies in the treatment of neuropathic pain. Two studies have focused on neuropathic pain resulting from HIV infection or the drugs used to treat HIV, one has focused on neuropathic pain of varying causes, and one has used an experi-

mental model of neuropathic pain tested in healthy volunteers. The results from these four studies have been convergent, with all four demonstrating a significant decrease in pain after cannabis administration. The magnitude of effect in these studies, expressed as the number of patients needed to treat to produce one positive outcome, was comparable to current therapies. Two additional studies involving neuropathic pain are underway.

Multiple sclerosis (MS) is one of the most common chronic and disabling diseases of the nervous system. Caused by loss of the insulating sheath surrounding nerve fibers, the disease usually begins in young adulthood. Although it may initially wax and wane in intensity and be of mild severity, it often steadily progresses, causing fatigue, loss of balance, muscle weakness, and muscle spasticity. Affecting up to 70% of people with the disease, muscle spasms lead to pain, inability to walk, and difficulties with self-care, causing most of the everyday life disability from this disease. There is as yet no cure for MS. Treatments for muscle spasticity are only partially effective and have side effects which are not easily tolerated, making the search for new therapies of high importance. Given this background, the CMCR identified MS spasticity as an additional target for therapeutic research. As with all CMCR studies, the research used the most rigorous scientific approach to testing therapies, a randomized clinical trial, supplemented by modern measurement of muscle spasticity, everyday function, life quality, and side effects. Results to date have found a significant improvement in both an objective measure of spasticity and pain intensity in patients whose standard therapy had provided inadequate relief.

Synopsis of CMCR Published Clinical Study Results

“The Effect of Cannabis on Neuropathic Pain in HIV-Related Peripheral Neuropathy”

Donald I. Abrams, M.D., University of California, San Francisco

The primary objective of this study was to evaluate the efficacy of smoked cannabis when used as an analgesic in persons with neuropathic pain from HIV-associated distal sensory polyneuropathy (DSPN). In a double blind, randomized, five-day clinical trial patients received either smoked cannabis or placebo cannabis cigarettes. Patients continued on any concurrent analgesic medications (e.g., gabapentin, amitriptyline, narcotics, NSAIDs) which they were prescribed prior to the trial; the dose and amount of the medications were recorded daily.

The full results of this study appear in the journal *Neurology* (Abrams, et al., 2007– see reference list). In brief, 55 patients were randomized and 50 completed the entire trial. Smoked cannabis reduced daily pain by 34% compared to 17% with placebo. The study concluded that a significantly greater proportion of patients who smoked cannabis (52%) had a greater than 30% reduction in pain intensity compared to only 24% in the placebo group. This result is clinically important, since the threshold of a 30% reduction in pain intensity is associated with meaningful improvement in quality of life in other research on pain outcomes.

Cannabis appeared to be well-tolerated and there were no safety concerns raised. By design, all patients had smoking experience with cannabis. There were more side effects in those receiving cannabis than placebo, with the most frequent being sedation, anxiety, and dizziness, but these were all rated as “mild.”

“Placebo-Controlled, Double Blind Trial of Medicinal Cannabis in Painful HIV Neuropathy”

Ronald J. Ellis, M.D., Ph.D., University of California, San Diego

The primary objective of this study also was to evaluate the efficacy of smoked cannabis when used as an analgesic in persons with HIV-associated painful neuropathy. In a double-blind, randomized, clinical trial of the short-term adjunctive treatment of neuropathic pain in HIV-associated distal sensory polyneuropathy, participants received either smoked cannabis or placebo cannabis cigarettes. A structured dose escalation-titration protocol was used to find an individualized, effective, safe, and well-tolerated dose for each subject. Participants continued on their usual analgesic medications throughout the trial, with the dose and amount of these medications being recorded daily.

The full results of this study were published in the journal *Neuropsychopharmacology* (Ellis, et al., 2008 – see reference list). In brief, 34 eligible subjects enrolled and 28 completed both cannabis and placebo treatments. Among completers, pain relief was significantly greater with cannabis than placebo. The proportion of subjects achieving at least 30% pain relief was again significantly greater with cannabis (46%) compared to placebo (18%). It was concluded that smoked cannabis was generally well-tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV-associated neuropathy. Once again these results appeared to be relevant to everyday clinical practice, because the magnitude of pain relief is associated with that which improves life quality, and also because the benefit was above and beyond that conferred by the patients’ usual analgesics.

As in the study described above, side effects were more frequent with cannabis than with placebo, with the most common being sleepiness or sedation, fatigue, and difficulty with concentration. These were “mild” for the most part and did not raise safety concerns.

“A Double-Blind, Placebo-Controlled Crossover Trial of the Antinociceptive Effects of Smoked Marijuana on Subjects with Neuropathic Pain”

Barth Wilsey, M.D., University of California, Davis

This study's objective was to examine the efficacy of two doses of smoked cannabis on pain in persons with neuropathic pain of different origins (e.g., physical trauma to nerve bundles, spinal cord injury, multiple sclerosis, diabetes). In a double-blind, randomized clinical trial participants received either low-dose, high-dose, or placebo cannabis cigarettes. As customary in CMCR trials, participants were allowed to continue their usual regimen of pain medications (e.g., codeine, morphine, and others).

The full results of this study have been published in the *Journal of Pain* (Wilsey, et al., 2008 – see reference list). Thirty-eight patients underwent a standardized procedure for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis; of these, 32 completed all three smoking sessions. The study demonstrated an analgesic response to smoking cannabis with no significant difference between the low and the high dose cigarettes. The study concluded that both low and high cannabis doses were efficacious in reducing neuropathic pain of diverse causes.

Disagreeable or unpleasant side effects were significantly more likely with high dose cigarettes compared to low dose or placebo, whereas there was no difference in these effects between low dose and placebo sessions. There was no indication of mood changes (e.g., sadness, anxiety, fearfulness).

“Analgesic Efficacy of Smoked Cannabis”

Mark Wallace, M.D., University of California, San Diego

This study used an experimental model of neuropathic pain to determine whether pain induced by the injection into the skin of capsaicin, a compound which is the “hot” ingredient in chili peppers, could be alleviated by smoked cannabis. Another aim of the study was to examine the effects of “dose” of cannabis, and the time course of pain relief. In a randomized double-blinded placebo controlled trial, volunteers smoked low, medium, and high dose cannabis (2%, 4%, 8% THC by weight) or placebo cigarettes.

The full results of this study were published in the journal *Anesthesiology* (Wallace, et al., 2007 – see reference list). Nineteen healthy volunteers were enrolled, and 15 completed all four smoking sessions. In brief, five minutes after cannabis exposure, there was no effect on capsaicin-induced pain at any dose. By 45 minutes after cannabis exposure there was a significant decrease in capsaicin-induced pain with the medium dose (4%) and a significant increase in pain with the high dose (8%). There was no significant effect seen with low dose (2%). There was a significant inverse relationship between pain perception and plasma THC. In summary, this study suggested that there may be a “therapeutic window” (or optimal dose) for smoked cannabis: low doses were not effective; medium doses decreased pain; and higher doses actually increased pain. These results suggest the mechanism(s) of cannabinoid analgesia are complex, in some ways like non-opioid pain relievers (e.g., aspirin, ibuprofen) and in others like opioids (e.g., morphine).

“Short-Term Effects of Cannabis Therapy on Spasticity in Multiple-Sclerosis”

Jody Corey-Bloom, M.D., University of California, San Diego

This objective of this study was to determine the potential for smoked cannabis to ameliorate marked muscle spasticity (chronic painful contraction of muscles), a severe and disabling symptom of multiple sclerosis. In a placebo-controlled, randomized clinical trial spasticity and global functioning was examined before and after treatment with smoked cannabis. Patients were allowed to continue their usual treatments for spasticity and pain while participating in the research.

The full results of this study are being submitted for publication. Initial results were presented at the meeting of the American College of Neuropsychopharmacology in 2007. Thirty patients with multiple sclerosis were enrolled. Compared to placebo cigarettes, cannabis was found to significantly reduce both an objective measure of spasticity, and pain intensity. This study concluded that smoked cannabis was superior to placebo in reducing spasticity and pain in patients with multiple sclerosis, and provided some benefit beyond currently prescribed treatments.

“Vaporization as a ‘Smokeless’ Cannabis Delivery System”

Donald Abrams, M.D., University of California, San Francisco

The aim of this study was to evaluate the use of a vaporization system (the Volcano; VAPORMED® Inhalatoren; Tuttlingen, Germany) as a “smokeless” delivery system for inhaled cannabis. Because of concerns regarding the practicality and palatability of using cannabis cigarettes as a standard treatment, there has been an interest in developing alternative delivery systems. Participants were randomly assigned to receive low, medium, or high dose (1.7, 3.4, or 6.8% tetrahydrocannabinol) cannabis cigarettes delivered by smoking or by the vaporization system on six study days.

The full results of this study have been published in the journal *Clinical Pharmacology & Therapeutics* (Abrams, et al., 2007 – see reference list). Eighteen healthy volunteers were recruited to participate in the research. The analysis indicated that the blood levels of vaporized cannabis are similar to those of smoked cannabis over a six hour period. However, blood concentrations of THC at 30 and 60 minutes after inhalation were significantly higher in vaporized cannabis as compared to smoked cannabis. In addition, carbon monoxide levels were significantly reduced with vaporization compared with smoked cannabis. Fourteen participants preferred vaporization, 2 preferred smoking, and 2 reported no preference. In summary, vaporization of cannabis was found to be a safe mode of delivery, and participants had a preference for vaporization over smoking as a delivery system in this trial.

Recently Completed And Ongoing Studies

“Sleep and Medicinal Cannabis”

Sean Drummond, Ph.D., University of California, San Diego

The primary objective of this study was to determine the effects of cannabis on insomnia and poor sleep quality, which are experienced by up of 90% of HIV-infected individuals. Participants in this study were individuals enrolled in the UCSD randomized trial comparing cannabis and placebo as an analgesic in painful HIV-associated neuropathy (see Dr. Ellis, above).

The results of this study suggest that cannabis administration during the day does not affect objective or subjective measures of sleep approximately 7-8 hours after the last use of cannabis.

“Impact of Repeated Cannabis Treatments on Driving Abilities”

Thomas Marcotte, Ph.D., University of California, San Diego

The principal aim of this study was to examine whether routine administration of cannabis in the medical treatment of HIV-related neuropathy and spasticity associated with multiple sclerosis results in significant impairment in driving abilities. Participants in this study were individuals enrolled in the randomized clinical trials of cannabis for painful HIV neuropathy and for spasticity in multiple sclerosis conducted at UCSD (see Dr. Ellis and Dr. Corey-Bloom, above).

The results of this study are in preparation. Subjects were tested using a computerized driving simulator commonly used to demonstrate the effects of alcohol on driving ability. The driving simulator presents different driving conditions and circumstances and was done at four points: before cannabis, and at one, three, and 18 hours after the final dose in the therapeutic trials. These data will provide insights regarding the real life impact of using cannabis as medicine.

“Efficacy of Inhaled Cannabis in Diabetic Painful Peripheral Neuropathy”

Mark Wallace, M.D., University of California, San Diego

The primary objective of this ongoing study is to evaluate the efficacy of smoked cannabis when used as an analgesic in painful neuropathy due to diabetes. In a double-blind, randomized, placebo-controlled trial, participants will inhale low, medium, or high dose vaporized cannabis or placebo. Concurrent testing with experimentally-induced pain will help identify the potential mechanisms of therapeutic effects.

This study is actively recruiting its intended sample of 20 participants. No preliminary results are available at this time.

“The Analgesic Effect of Vaporized Cannabis on Neuropathic Pain”

Barth Wilsey, M.D., University of California, Davis

The primary aim of this study is to evaluate the analgesic effects of vaporized cannabis in patients with neuropathic pain of different origins. In a randomized clinical trial the effects of placebo and of low and medium (1.7 % and 3.5%) dose cannabis on clinical pain and on experimentally induced pain will be assessed. As noted above, use of experimentally-induced pain may help identify mechanism of actions.

This study is beginning to recruit participants. No preliminary results are available at this time.

Completed Pre-Clinical Studies

In addition to testing the possible benefits of medicinal cannabis, the CMCR supported a small number of laboratory and animal studies which might lead to either developing new treatments in humans, or better understanding the mechanisms of therapeutic actions.

“Mechanisms of Cannabinoid Analgesia”

Howard Fields, M.D., Ph.D., University of California, San Francisco

The aim of this study was to determine whether cannabinoids might be a useful class of medication for migraine and other headaches or facial pain conditions.

The full results of this study were published in the journal *Pain* (Papanastassiou et al., 2003 – see reference list). A cannabis-like drug (WIN 55,212-2) given to rats under anesthesia showed reduced activity of individual nerve cells transmitting pain, whereas giving another drug which blocked cannabis receptors on these nerve endings reversed this effect. Moreover, the analgesic effect of the cannabis-like drug was evident in tests of facial pain (heat) in awake rats. This study therefore provided direct scientific evidence, at the level of both individual nerve cells and in awake animals, of analgesic effects of cannabis-like compounds on head and facial pain. Randomized clinical trials in humans might be conducted to determine if cannabis could treat facial pain or headache.

“Cannabinoids in Fear Extinction”

Mark Barad, M.D., Ph.D., University of California, Los Angeles

The aim of this study was to determine if a cannabis-like agent could suppress fear-inducing memories or images that might be the basis for some psychiatric conditions such as Post-Traumatic Stress Disorder (PTSD) and other anxiety disorders. Therapeutic effects were thought possible because earlier research suggested that specialized in-built cannabinoid receptors in the brain are necessary for suppression of normal fears.

Tests using three different synthetic cannabis-like compounds showed no significant differences in behavior between mice treated with study drugs and untreated mice trained to fear specific locations. This study suggests that acutely enhancing the brain’s internal cannabinoid system does not extinguish specific fears (of place memory) in animals.

“Effects of Cannabis Therapy on Endogenous Cannabinoids”

Daniele Piomelli, Pharm.D., Ph.D., University of California, Irvine

The aim of this study was to determine the short-and longer-term effects of THC on the natural in-built system of nervous system chemical transmitters called endocannabinoids, which help regulate movement, cognition, pain and other physiological processes. Amplification or interference with activity of this system could influence outcomes of cannabinoid treatment.

These experiments contributed preliminary data to work that was later published in the journal *Neuropsychopharmacology* (Giuffrida et al., 2004 – see reference list). A synthetic cannabis-like compound had no effects on the levels of anandamide, an endocannabinoid, in blood or in brain tissue from regions involved in memory, motivation, movement, and wakefulness. Chronic, but not acute, treatment caused a marked increase in anandamide levels in the brain hippocampus, a region crucially involved in learning and memory. This study provides evidence indicating that exposure to cannabis-like drugs can alter endocannabinoid signaling in the brain. Alterations in this important signaling system might be involved in mediating the actions of cannabis in humans.

“Effects of Medicinal Cannabis on CD4 Immunity in AIDS”

Rachel Schrier, Ph.D., University of California, San Diego

The aim of this study was to determine if cannabis might suppress the immune system in individuals with HIV. This is an important question since already fragile immunity is characteristic of AIDS and other serious illness where cannabis might be used.

Results of the study are being prepared for publication. Briefly, immune system cells (CD4+ white blood cells) obtained from 15 individuals with AIDS participating in another study were exposed to three concentrations of THC in tests of their functional “competence.” There was no evidence of acute impairment of immune function at concentrations achievable in living humans. These results parallel other research showing that short-term cannabis administration does not diminish the circulating number of this white blood cell essential for immunity.

Discontinued Studies

Five clinical studies were discontinued before completion, because they could not accrue a sufficient number of participants. The scientific and safety design of two studies, one studying the combination of cannabis and opioids (e.g., morphine) for cancer pain relief, and one on relief of muscle spasticity in multiple sclerosis, required either a nine day hospitalization or 16 weeks without driving an automobile. Understandably, chronically ill patients were reluctant to be re-hospitalized for research, or to surrender driving privileges for an extended period.

Two other cancer studies faced different “real life” obstacles to recruitment. One study on cannabis for severe nausea and vomiting due to chemotherapy could not identify a sufficient number of patients with sufficiently severe nausea. It appeared that current anti-nausea treatments are often highly effective. Alternative or adjunctive therapy may be required only by a minority of patients. Another project on cannabis for advanced cancer pain unresponsive to all other analgesics found that local hospice agencies were willing to refer potential participants. These patients, however, were often already smoking cannabis for pain control. One study of cannabis for use at home for neuropathic pain did not elicit sufficient interest, despite outreach to the community through advertisements and focus groups. Although the outcomes of these studies is disappointing, valuable lessons were learned in terms of design of future studies and selection of appropriate populations for study.

Summary And Future Directions

Results of CMCR studies support the likelihood that cannabis may represent a possible adjunctive avenue of treatment for certain difficult-to-treat conditions like neuropathic pain and spasticity. In establishing the University of California CMCR, the California Legislature enabled the creation of what is now arguably a world-class resource both for state-of-the-art clinical trials on medicinal cannabis and its derivatives, and for developing knowledge on the potential and limitations of cannabinoid therapeutics for selected indications. By facilitating high caliber clinical trials, whose results are published in leading peer-reviewed scientific journals, the CMCR is providing physicians and policy makers with solid scientific data to inform both medical research and policy decisions. As a seasoned and unique resource, the CMCR is well-positioned to inform public health and policy decision-makers.

Worldwide, the merit of new therapies is rigorously evaluated by a series of clinical trials, termed Phase I, Phase II, Phase III, and Phase IV. In Phase I, usually involving 20-50 participants, several possible doses of a drug are tested, safety is assessed, and hints of therapeutic value are revealed. Drug development then proceeds to Phase II trials (which may recruit up to several hundred individuals) to more accurately gauge the efficacy of treatment along with determining short term side effects and risks. Results from Phase II trials with smoked cannabis in neuropathic pain form the basis of the CMCR's efforts to date. In the next step, Phase III trials, involving hundreds to several thousand patients, are designed to provide definitive assessment of the efficacy of new treatment for specific conditions (usually by comparing the newer therapy to the best "standard" treatment available), while also adding to a better understanding of benefit-risk relationships. Finally Phase IV trials, conducted after a treatment is licensed or approved for general medical use, gather additional information on benefits, risks, and optimal use of the therapy. The expertise developed at CMCR is well-suited to contribute to each of these phases of cannabinoid research.

Were support for the CMCR to continue, research might focus on 1) larger placebo-controlled studies to generate definitive data on therapeutic merit (i.e., Phase III trials), 2) head-to-head comparisons with other current therapies (in Phase II or III studies), or 3) expanded studies evaluating cannabis as an adjunct to existing treatment with opioids and non-steroidal anti-inflammatory drugs (i.e. Phase II and III research determining if cannabinoids have an "opioid-sparing" effect, that is, if they might allow use of lower doses of opioids without sacrificing pain relief). Other Phase II and III studies might move from the question of efficacy to overall effectiveness, that is, evaluating 1) alternative delivery systems (e.g., vaporization) that reduce the harmful effects of smoking, 2) models of take-home treatment that more accurately mimic the way drugs are prescribed, and 3) long-term studies to assess emergent toxicities, stability of treatment effects, and possible development of tolerance to treatment over time. This research might extend into formal Phase IV trials.

Studies also might be conducted on newly-developed synthetic agents which enhance, antagonize, or otherwise modulate the cannabinoid system, comparing their efficacy to cannabis as a botanical product. In any event the "fundamental" nature of the endocannabinoid system—evident by its participation in essential functions like movement, pain, moods and other behaviors—suggests continuing clinical research on cannabis might yield important contributions to health care.

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†Contents of CMCR special issue of the journal *Neuropharmacology*

Chronic Cannabis Use
in the Compassionate Investigational
New Drug Program:
An Examination of Benefits
and Adverse Effects
of Legal Clinical Cannabis

Ethan Russo
Mary Lynn Mathre
Al Byrne
Robert Velin
Paul J. Bach
Juan Sanchez-Ramos
Kristin A. Kirlin

ABSTRACT. The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic benefits and adverse effects of prolonged use of “medical marijuana” in a cohort of seriously ill patients. Use of cannabis was approved through the Compassionate Investigational New Drug (IND) program of the Food and Drug Administration (FDA). Cannabis is obtained from the National Institute on Drug

Ethan Russo, Robert Velin, and Paul J. Bach are affiliated with Montana Neuro-behavioral Specialists, 900 North Orange Street, Missoula, MT 59802 USA (E-mail: erusso@blackfoot.net).

Mary Lynn Mathre and Al Byrne are affiliated with Patients Out of Time, 1472 Fish Pond Road, Howardsville, VA 24562 USA (E-mail: Patients@medicalcannabis.com).

Juan Sanchez-Ramos is affiliated with the Department of Neurology, University of South Florida, Tampa, USA.

Kristin A. Kirlin is affiliated with the Department of Psychology, University of Montana, Missoula, MT 59812.

Address correspondence to: Ethan Russo at the above address.

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Abuse (NIDA), and is utilized under the supervision of a study physician. The aim of this study is to examine the overall health status of 4 of the 7 surviving patients in the program. This project provides the first opportunity to scrutinize the long-term effects of cannabis on patients who have used a known dosage of a standardized, heat-sterilized quality-controlled supply of low-grade marijuana for 11 to 27 years.

Results demonstrate clinical effectiveness in these patients in treating glaucoma, chronic musculoskeletal pain, spasm and nausea, and spasticity of multiple sclerosis. All 4 patients are stable with respect to their chronic conditions, and are taking many fewer standard pharmaceuticals than previously.

Mild changes in pulmonary function were observed in 2 patients, while no functionally significant attributable sequelae were noted in any other physiological system examined in the study, which included: MRI scans of the brain, pulmonary function tests, chest X-ray, neuropsychological tests, hormone and immunological assays, electroencephalography, P300 testing, history, and neurological clinical examination.

These results would support the provision of clinical cannabis to a greater number of patients in need. We believe that cannabis can be a safe and effective medicine with various suggested improvements in the existing Compassionate IND program. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com> © 2002 by The Haworth Press, Inc. All rights reserved.]*

KEYWORDS. Cannabis, medical marijuana, hashish, investigational new drug, compassionate use, NIDA, FDA, herbal medicine, analgesia, spasticity, chronic pain, glaucoma, multiple sclerosis, epidemiology, history of medicine, drug policy

INTRODUCTION

The Missoula Chronic Clinical Cannabis Use Study was proposed to investigate the therapeutic benefits and adverse effects of prolonged use of "medical marijuana" in a cohort of seriously ill patients approved through the Compassionate Investigational New Drug (IND) program of the Food and Drug Administration (FDA) for legal use of cannabis obtained from the National Institute on Drug Abuse (NIDA), under the supervision of a study physician. The aim was to examine the overall health status of 8 surviving patients in the program. Four patients were able to take part, while three wished to remain anonymous, and one was

too ill to participate. Unfortunately, that person, Robert Randall, succumbed to his condition during the course of the study. Thus, 7 surviving patients in the USA remain in the Compassionate IND program.

Despite the obvious opportunity to generate data on the use of cannabis and its possible sequelae in these patients, neither NIDA, other branches of the National Institutes of Health, nor the FDA has published an analysis of information from this cohort. An examination of the contents of the National Library of Medicine Database (PubMed), and search engines of NIDA employing multiple combinations of key words failed to retrieve a single citation. The Missoula Chronic Cannabis Use Study thus provides a unique and important opportunity to scrutinize the long-term effects of cannabis on patients who have used a known dosage of standardized, heat-sterilized quality-controlled supply of low-grade medical marijuana for 11 to 27 years.

The results are compared to those of past chronic use studies in an effort to gain insight into the benefits and sequelae of this controversial agent in modern health care.

PREVIOUS CHRONIC CANNABIS USE STUDIES

The first systematic modern study of chronic cannabis usage was the *Indian Hemp Drugs Commission Report* at the end of the 19th century (Kaplan 1969; Indian Hemp Drugs Commission 1894). The British government chose not to outlaw cultivation and commerce of the herb after ascertaining that it had negligible adverse effects on health, even in chronic application.

Similar conclusions were obtained in the "LaGuardia Report" of 1944 (New York, NY), Mayor's committee on marijuana (Wallace, and Cunningham 1944), which was the first to employ clinical and scientific methods of analysis.

Three important systematic epidemiological studies undertaken by research teams in the 1970's exhaustively examined medical issues in chronic cannabis use, but remain obscure due to limited press runs and out-of-print status. The first of these was *Ganja in Jamaica: A Medical Anthropological Study of Chronic Marijuana Use* (Rubin and Comitas 1975). Therapeutic claims for cannabis were mentioned, but the focus of study was on "recreational use." Sixty men were included in a hospital study of various clinical parameters if they had maintained a minimum intake of 3 spliffs a day for a minimum of 10 years. Jamaican ganja "spliffs" formed of unfertilized female flowering tops (sinsemilla) tend

to be much larger than an American "joint" of 500-1000 mg. The potency of the cannabis was analyzed with measures in 30 samples ranging from 0.7-10.3% THC, with an average of 2.8%.

In 1977, a detailed study was undertaken in Greece, titled *Hashish: Studies of Long-Term Use* (Stefanis, Dornbush, and Fink 1977). Once again 60 subjects smoking for more than 10 years were selected. Hashish potency was 4-5% THC and was generally mixed with tobacco. Alcoholics were excluded.

In 1980, *Cannabis in Costa Rica: A Study of Chronic Marijuana Use* was published (Carter 1980). Forty-one subjects smoking for 10 years or more were recruited. Although 10 or more cigarettes per day were smoked, the weight of material was only 2 g with an estimated THC range of 24-70 mg per day. Thirteen samples were assayed with a range of 1.27-3.72%, and average of 2.2% THC. Claims of benefit for cough, asthma, headache, hangovers, anorexia, impotence, depression and malaise were mentioned, but once more, the focus was on social use.

The current study is the first designed to examine clinical benefits and side effects of chronic clinical cannabis usage in which known amounts of quality-controlled material has been employed.

A BRIEF HISTORY OF THE COMPASSIONATE IND

Robert Randall was diagnosed with severe glaucoma at age 24 and was expected to become totally blind long before he turned 30. He soon began a fascinating medical odyssey that has been memorialized in his "personal reflection" co-authored by his wife, Alice O'Leary, titled *Marijuana Rx: The Patients' Fight for Medicinal Pot* (Randall and O'Leary 1998), and other books (Randall 1991a; Randall 1991b). Until the day he died on June 2, 2001 at age 52 of complications of AIDS, Randall retained his vision, and remained a vocal advocate for the benefits of clinical cannabis.

His own journey commenced when he independently discovered that smoking a certain amount of cannabis eliminated the annoying visual haloes produced by his glaucoma. A subsequent arrest in August 1975 for cannabis cultivation led in turn to his dogged pursuit of the right to a legal means to supply his medicine of choice. He subsequently learned of medical support for his treatment (Hepler and Frank 1971). D. Pate has published two more recent reviews (Pate 1999; Pate 2001).

Through painstaking documentation and experimentation, Randall subsequently confirmed the inability of medical science to control his

intraocular pressure (IOP) by any legal pharmaceutical means. In contrast, smoked cannabis in large and frequent amounts was successful, where even pure THC was not. As Dr. Hepler observed in their experiments together (Randall and O'Leary 1998, p. 60), "... clearly, something other than THC or in addition to THC is helping to lower your pressures. . . . It seems that marijuana works very, very well."

After a great deal of bureaucratic wrangling, Randall obtained his first government supplied cannabis in November 1976, and the legal case against him was subsequently dismissed. The material he received from his study physician was cultivated in a 5-acre plot at the University of Mississippi, mostly from seeds of Mexican origin, and was rolled and packaged at the Research Triangle Institute in North Carolina under the supervision of the National Institute on Drug Abuse (NIDA).

Randall was encouraged to be thankful, but silent, about his treatment. Instead, he chose a different path (Randall and O'Leary 1998, p. 134), "Having won, why go mum? There were souls to save. Better to trust my fellow citizens and shout in to the darkness than rely on a devious Government dedicated to a fraudulent prohibition." He chose to make it his mission to seek approval of clinical cannabis for other patients. He developed protocols for glaucoma, multiple sclerosis, chronic pain, and AIDS that he shared with prospective medical marijuana candidates. Randall proved to be a tireless and persistent researcher, ferreting out hidden facts useful to his cause. Through the Freedom of Information Act (FOIA), he discovered in 1978 that the government's cost of cannabis cultivation and production was 90 cents per ounce (28 g), with 2/3 of this cost attributable to security measures. Thus, the actual cost of production approximated 1 cent per gram (US \$0.01/g).

Supply and quality control issues arose frequently, and Randall and other patients experienced delays in receipt of shipments or substitution of weaker strains that required doubling of smoked intake.

The AIDS epidemic and its subsequent involvement in the medical marijuana issue suddenly provided an unlimited supply of available patients for the Compassionate IND program, and Randall assisted them as well. Some succumbed before their supply was approved, or shortly thereafter. By 1991, 34 patients were enrolled in the program according to Randall (Randall and O'Leary 1998), while other sources cite the number as only 15. Facing an onslaught of new applications, the Public Health Service (PHS) in the Bush administration closed the program to new patients in March 1992. A significant number had received medical approval but were never supplied. Randall sought to ascertain who signed the ultimate termination order through the FOIA, but was never

successful in this endeavor. At the time of this writing, 7 patients survive in the program.

METHODS

The identities of 6 of 8 of the original Compassionate IND program subjects were known to Patients Out of Time and were contacted in relation to participating in a study of the clinical parameters cited as concerns with chronic cannabis usage. Four subjects agreed to participate, and 3 traveled to Missoula, MT for testing at Montana Neurobehavioral Specialists, and Saint Patrick Hospital on May 3-4, 2001. One patient was tested to the extent possible in her local area due to physical limitations on travel (Patient Demographics: Table 1). Tests included the following (Tests Performed: Table 2): MRI scans of the brain, pulmonary function tests (spirometry), chest X-ray (P-A and lateral), neuropsychological test battery, hormone and immunological assays (CD4 counts), electroencephalography (EEG), P300 testing (a computerized EEG test of memory), and neurological history and clinical examination.

Past medical records were reviewed insofar as possible and the histories were supplemented with additional information. All patients signed informed consent documents, and the St. Patrick Hospital/Community Hospital Joint Investigational Review Board (IRB) reviewed the protocol.

RESULTS AND DISCUSSION

Case Histories and Test Data on Four Compassionate IND Program Patients

In the following section case histories, clinical examinations and objective test results are presented.

Patient A

Medical History: This almost 62-year-old female was born with congenital cataracts in Cali, Colombia and spent 13 years of her life there. There was a question of possible maternal exposure to malaria or quinine. Over time the patient required a series of 11 surgeries on the right eye and 3 on the left for the cataracts and had resulting problems with

TABLE 1. Chronic Cannabis IND Patient Demographics

| Pt. | Age/Gender | Qualifying Condition | IND Approval/ Cannabis Usage | Daily Cannabis/ THC content | Current Status |
|-----|------------|---|---------------------------------|--------------------------------|---|
| A | 62/F | Glaucoma | 1988 25 years | 8 grams/ 3.80% | Disabled Operator/ Singer/ Activist/ Vision stable |
| B | 52/M | Nail-Patella Syndrome | 1989 27 years | 7 grams/ 3.75% | Disabled Laborer/ Factotum/ Ambulatory |
| C | 48/M | Multiple Congenital Cartilaginous Exostoses | 1982 26 years | 9 grams/ 2.75% | Full time Stockbroker/ Disabled Sailor/ Ambulatory |
| D | 45/F | Multiple Sclerosis | 1991 11 years | 9 grams/ 3.50% | Disabled clothier/ Visual impairment/ Ambulatory aids |

glaucoma. Her last surgery was complicated by hemorrhaging, leading to immediate and complete loss of vision OD.

By 1976, the patient's intraocular pressure was out of control with all available drugs, many of which caused significant side effects. At that time she started eating and smoking cannabis to treat the condition. She underwent extensive testing in that regard, measuring pressures to titrate the dosage of cannabis. She initially had personal issues with the concept of smoking. Without cannabis her intraocular pressures may run into the 50's, while with it, values are in the teens to 20's. In 1988, she was arrested for cultivation of 6 cannabis plants. Her ophthalmologist noted (Randall and O'Leary 1998, p. 303), "it's quite clear-cut this is the only thing that will help her." At her trial, she stated in her own defense (Randall and O'Leary 1998, p. 305), "Marijuana saved my sight. I don't think the law has the right to demand blindness from a citizen." She was acquitted on the basis of "medical necessity," but her approval for the Compassionate IND program took 6 months. She had smoked cannabis on her own from black market sources for 12 years previously.

TABLE 2. Tests Performed: Chronic Cannabis IND Study

| |
|--|
| MRI scan of the brain |
| Pulmonary function tests (Spirometry) |
| Chest X-ray, P-A & lateral (Patients A-C) |
| Neuropsychological tests |
| Wechsler Adult Intelligence Scale—3rd Edition (WAIS-III) |
| Wechsler Memory Scale—3rd Edition (WMS-III) |
| California Verbal Learning Test (CVLT) |
| Halstead-Reitan Battery |
| Trail Making Test A & B. |
| Grooved Peg Board |
| Finger Tapping and Category Subtests |
| Controlled Oral Word Association Test |
| Thurstone Word Fluency Test |
| Category Fluency Test (animal naming) |
| Wisconsin Card Sorting Test (WCST) |
| Conner's Continuous Performance Test—2nd Edition (CPT-II) |
| Beck Depression Inventory—2nd Edition (BDI-II). |
| Endocrine assays |
| FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone, progesterone |
| Immunological assays |
| CBC, CD4 count |
| Electroencephalography (EEG) (Patients A-C) |
| P300 testing (Patients A-C) |
| Neurological examination |

At present, she also uses Timoptic® (timolol, beta-blocker) eye drops daily in the morning, but has concerns about resulting bronchoconstriction.

She normally uses cannabis 3-4 grams smoked and 3-4 grams orally per day. She feels that the amount that she receives legally from NIDA is insufficient for her medical needs. At times she accepts donations from cannabis buyers' clubs. She admits that the results of these outside cannabis samples on her intraocular pressure are unclear. She has had occasion to go to Amsterdam where intraocular pressures were measured in the teens simply employing cannabis available there. She has used Marinol® on an emergency basis, such as on traveling to Canada, in doses of up to 5-10 mg qid. She reports that it lowers intraocular pressure for one day, but within 3-5 days becomes useless for that purpose.

The patient has a history of cigarette smoking as well, 1-2 packs a day. She quit in 1997, but subsequently went on a "binge" of cigarette

smoking for 13 months, finally quitting on New Year's Day 2001. She feels that past pulmonary function has been normal.

She also notes lifelong insomnia that is alleviated by eating cannabis. Without such treatment, she feels she would sleep 4 hours, whereas with it she sleeps 6-7. She also feels that the drug produces antidepressant and antianxiety effects for her. She has a history of scoliosis, but notes no symptoms from this and feels that muscle relaxant effects of cannabis have made her quite limber.

The patient had a history of delirium associated with malaria as a child. She had some hardware in her foot from a 1980 surgery after a fall from platform shoes. She had a hysterectomy for fibroids. The patient was menopausal at age 48 and has had no hormone replacement treatment. There is no known history of specific meningitis, encephalitis, head trauma, seizures, diabetes, or thyroid problems. She is on no medicine save for cannabis and timolol eye drops. There are allergies to penicillin and tetracycline. She completed the equivalent of high school, and is right handed.

Family history is largely negative, although her 2 children had some cataract involvement.

Social history revealed that the patient has worked in the past as a switchboard operator. She is currently disabled due to legal blindness from her condition. She supports herself on Social Security Disability Income (SSDI). She has been an activist with respect to clinical cannabis. The patient drinks alcohol at a rate of about a bottle of wine a week. She had past heavy use of caffeine, but now drinks decaf only. The patient walks for exercise about an hour a day.

Medical Test Results: Objective: Weight: 132 lbs. OFC (Occipito-frontal Circumference): 55.5 cm. BP: 104/62. General: Very pleasant, cooperative 62-year-old female. Head: normocephalic without bruits. ENT: noteworthy as below. Neck: supple. Carotids: full. Cor: S1, S2 without murmur. On auscultation of the chest, there seemed to be a prolonged expiratory phase, but no wheezing. Mental Status: The patient was alert and fully oriented. Fund of knowledge, right-left orientation, praxis and naming skills were normal. She was unable to read a grade 6 paragraph with large type due to visual blurring. When it was read to her, memory of the contents was within normal limits. She performed serial 3's well. She remembered 3 objects for 5 minutes. On a word list task she named 15 animals in 30 seconds (normal 10-12). Speech and affect were normal.

Cranial Nerves: I: intact to coconut scent. II: acuity had recently been measured. There was no vision OD, 20/200 OS corrected. Visual

fields OS intact to confrontation. Optokinetic nystagmus (OKNs) was present in that eye in all fields. The patient is aphakic with an irregular eccentric pupil OS and clouding OD. The disk on the left appeared normal. There was prominent horizontal nystagmus resembling a congenital pattern. External extraocular movements were normal. Remaining cranial nerves V and VII-XII appeared intact in full.

Motor: The patient had normal tone and strength with no drift. Sensation was intact to fine touch, sharp/dull, vibration, position and graphesthesia. Romberg was negative. The patient performed finger-to-nose and heel-to-shin well. Rapid alternating movements of the hands were slightly clumsy and fine finger movements slightly deliberate. Gait including toe and heel were normal with tandem gait normal, but very carefully done. Reflexes were 2-3+, symmetric with downgoing toes.

The patient underwent a battery of tests. On pulmonary function tests (Table 3), a Functional Vital Capacity (FVC) was 103% predicted. Forced Expiratory Volume in 1 second (FEV_1) was 84% of predicted and the FEV_1/FVC ratio was 0.67. This was read as showing a mild obstructive defect based on the above ratio and flow volume curve morphology. No restrictive abnormality was noted. A CBC was wholly within normal limits (Table 4). Absolute lymphocyte count was 4.0, CD4 61.6% and absolute CD4 count 2465, all within normal limits. A full endocrine battery was performed (Table 5), including FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone, and progesterone, all within normal limits for age and gender.

TABLE 3. Pulmonary Function Tests

| Patient/Parameter | A | B | C | D |
|--------------------------|--------------------------|---|------------------------------|--|
| FVC (% Predicted) | 103 | 107 | 108 | 79 |
| FEV_1 (% Predicted) | 84 | 95 | 67 | 76 |
| FEV_1/FVC | 0.67 | 0.78 | 0.51 | 0.86 |
| Interpretation | Mild obstructive Defect. | WNL. Slightly prolonged forced expiratory time. | Moderate obstructive defect. | No obstructive defect. Minor changes not excluded. |

TABLE 4. Hematological/Immunological Parameters

| Parameter/Pt. | A | B | C | D |
|--|------|--------------|------|------|
| CBC | WNL | Polycythemia | WNL | WNL |
| Lymphocytes, Absolute Count (K/ μ L) | 4.0 | 3.4 | 1.8 | 2.3 |
| CD4 percent | 61.6 | 68.7 | 49.1 | 58 |
| CD4 Absolute Count (/ μ L) | 2465 | 2324 | 911 | 1325 |

TABLE 5. Endocrine Parameters

| Parameter/Pt. | A | B | C | D |
|-------------------------|--------------------------------------|-------------------------|-------------------------|---|
| FSH (mIU/ml) | 32.8 | 5.4 | 3.0 | 12.4 |
| LH (mIU/ml) | 20.6 | 3.8 | 4.1 | 16.2 |
| Prolactin (ng/ml) | 7.2 | 7.8 | 5.1 | 4.1 |
| Estradiol (pg/ml) | 8.0 | 10.0 | 10.0 | 212 |
| Estrone (pg/ml) | 15.0 | 20.0 | 22.0 | 146 |
| Estrogen, total (pg/ml) | 23.0 | 30.0 | 32.0 | 538 |
| Testosterone (ng/dl) | 7.0 | 505.0 | 296.0 | 34 |
| Progesterone (ng/ml) | 0.61 | 0.42 | 0.68 | 2.1 |
| Interpretation | WNL for age and gender (menopausal). | WNL for age and gender. | WNL for age and gender. | WNL for age, gender and cycle (pre-menopausal). |

An EEG was performed during wakefulness and early stages of sleep (read by EBR). A normal alpha background was identifiable at 12 hertz, along with a great deal of beta activity. Occasional left frontal phase reversing sharp waves were seen with rare episodes of slight slowing in the same area.

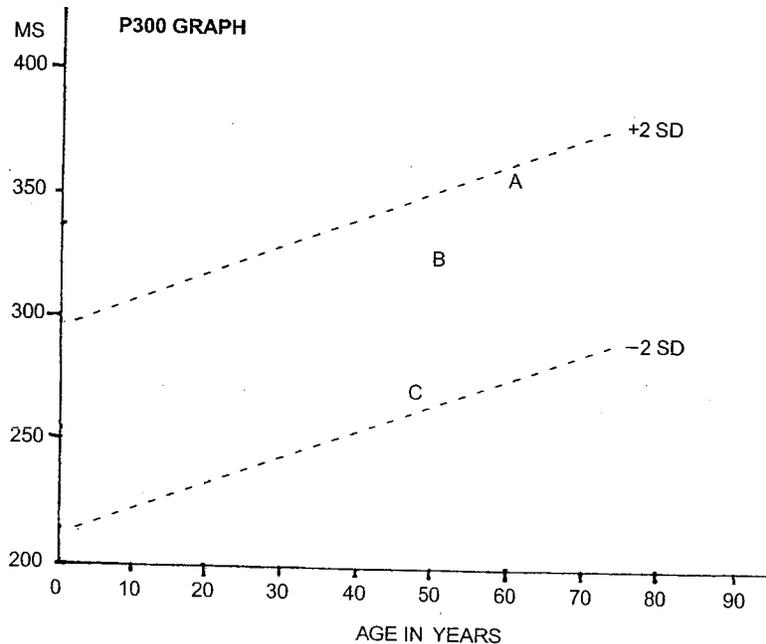
The patient had a P300 test performed with a latency of 355 milliseconds, within normal limits for a normed population in this laboratory (Figure 1).

The patient had an MRI brain study without contrast. This was read as showing a mild, symmetric, age consistent cerebral atrophy. A small focus of T2 hyperintensity and increased signal was noted on the FLAIR sequence in the mid-pons to the left of midline with no surrounding mass effect or edema. This was felt to be a nonspecific finding representing gliosis most likely from microvascular ischemic change. No corresponding signal abnormality was seen in the same area on a diffusion-weighted sequence.

A chest x-ray showed slight hyperinflation of the lung fields with no other findings.

Patient A was very pleasant and cooperative throughout the neuropsychological assessment and appeared to put forth very good effort. She did have very significant visual deficits and as a result, several instruments were dropped from the battery, including Grooved Peg Board,

FIGURE 1. P300 Latency Graph



Picture Arrangement, Symbol Search, and the Faces and Family Pictures Subtests from the Wechsler Memory Scale-3rd Edition (WMS-III). She was able to complete the Trail-Making Test A & B from the Halstead-Reitan Neuropsychological Battery, Spatial Span from the Wechsler Memory Scale-3rd Edition (WMS-III), and the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III)-Picture Completion, Digit Symbol, and Matrix Reasoning, but these were not used in interpretation secondary to the very probable interfering effects of her limited sight.

Review of the WAIS-III revealed a Verbal IQ in the upper end of the Average Range (VIQ = 108), and a Performance IQ in the Extremely Low Range, at only the 2nd percentile (PIQ = 69). This latter, however, is secondary to visual deficits as she had extremely low scores on the Digit Symbol and Picture Completion subtests. She obtained an age scaled score of 7 on Block Design; this performance was also adversely impacted by her visual defects to a mild degree.

Assessment of attention and concentration revealed that these abilities are mildly-to-moderately impaired relative to age-matched controls. She demonstrated an abnormally high number of omission errors on the Conner's Continuous Performance Test-2nd Edition (CPT-II) as well as significant variability of reaction time.

Formal assessment of learning and memory revealed that this subject's ability to acquire new verbal material on the WMS-III is within the Average Range relative to age-matched peers. Her Auditory Immediate Index score was in the average range as was her Auditory Delayed Index. She obtained index scores of 97 and 108 on these two indices, respectively. Recognition memory for auditory material was actually in the High Average range, the 75th percentile (Index Score = 110). In contrast she did much more poorly on visual measures secondary to very significant visual defects.

On the California Verbal Learning Test (CVLT), the subject generally performed within normal limits. Although initial learning trials were two standard deviations below expected limits, her ultimate acquisition at Trial 5 was one standard deviation above normative data sets. Short Delay Free Recall was perfectly normal and long delay recall was only one standard deviation below expected levels. This loss of recalled items from short delay to long delay free recall represented a loss that is approximately 1 standard deviation more than expected. Thus, she appeared to have mild difficulties with initial acquisition of very complex verbal material and also appeared to have minimal-to-mild difficulty retaining it in memory relative to age-matched peers.

Higher-level executive functions appear to be entirely normal in this patient. The Wisconsin Card Sorting Test (WCST) yielded a T-score of 63, while she obtained a T-score of 42 on the Category Test. Thus, she is still within the parameters seen in a normative data set of age and education-matched peers.

This subject's performance on the Thurstone Word Fluency Test was also entirely normal with a T-score of 51. Likewise, on the Controlled Oral Word Association Test, she obtained an overall score placing her at the 78th percentile. She produced 26 items on the Animal Naming Test over a 60-second period. This is within normal limits.

On the Beck Depression Inventory-2nd Edition, she obtained an overall score of 6, arguing against significant depressive symptoms.

In summary, Patient A appears to have mild-to-moderate difficulty with attention and concentration, and minimal-to-mild difficulty with the acquisition and storage of very complex new verbal material. General learning, however, as measured on the Wechsler Memory Scale-3rd Edition (WMS-III) appears to be within normal limits. Higher-level executive functions and verbal fluency abilities are well within normal limits.

Patient B

Medical History: This 50-year-old white male carries the diagnosis of the nail-patella syndrome, also known as hereditary osteo-onychodysplasia, a rare genetic disorder producing hypoplastic nails and kneecaps and renal insufficiency. Information was obtained from the patient, a published affidavit (Randall 1991b), and submitted medical records.

He first smoked cannabis in 1970, but did not become "high." Rather, he felt more relaxed, without his customary muscle spasms and pain. He first actually used clinical cannabis in a different manner. At the time he was mining, and he developed chemical burns in his hands. A Mexican lady gave him a tincture of cannabis flowering tops in grain alcohol to apply. This reduced his hand swelling and burning.

He has been smoking cannabis regularly for medical purposes since about 1974. During a medical crisis in 1985, he suffered a decrease in supply of available cannabis. His recollection is that all the various analgesics he received during this time were ineffective and produced of dangerous side effects including sedation and incapacity.

By 1988, he pursued regular usage of cannabis, about 1/8 of an ounce (3 1/2-4 g/d) a day when available. He initiated inquiries with the FDA

to obtain legal cannabis. Ultimately, with the assistance of Robert Randall, he received approval from the government in March 1990.

He related a history of deformities from birth including missing fingernails, loose finger joints, and small patellae. He was frequently ill as a child, and at age 10, suffered a progression from conjunctivitis to varicella, strep throat and rheumatic fever. He was hospitalized for 6 months, and required another 3 months of bed rest. Subsequently, he underwent four right knee surgeries, reconstructions and rotations, including 3 arthroscopies. He had had a right wrist graft with non-fusion. He had had right elbow surgery and had a "nicked" ulnar nerve. In the late 1960's he developed both hepatitis A and B with prolonged hospitalizations. Despite this, he pursued heavy manual labor in mining, construction, auto bodywork and aircraft repair. He lost all his teeth by age 21. In 1972 he dislocated his knee and had 3 subsequent surgeries. In 1976 he had a wrist fracture with subsequent surgery and later fusion. In 1978 he was hospitalized after a nail wound in his foot failed to heal. In 1983, he injured his back in a fall. Pain continued.

After a 1985 chiropractic session, he became acutely ill with severe back pain. He was given narcotics, and suffered renal failure. He was transferred to a university center. Lithotripsy sessions were followed by transurethral procedures in attempts to clear his nephrolithiasis. Eventually an open procedure was performed for perinephric abscess, but the flank wound failed to heal over the course of a year. Ultimately, it was determined that he was suffering a tubercular nephritis. He took triple therapy with isoniazid (INH), rifampin and pyridoxine regularly for 18 months. Eventually, a massive debridement was necessary, before the flank wound eventually healed. His prolonged convalescence forced him to close his business.

On September 3, 1987, he complained of persistent flank pain and low back discomfort increasing over the preceding 2 years treated with multiple modalities, including TENS unit. He also was using an abdominal binder. Pain radiated to the buttocks and posterior thighs. X-rays of the lumbar spine showed spondylolisthesis grade 1 in the lumbar area with no significant motion of flexion extension views.

On April 8, 1988, the patient was seen for right knee pain after a twisting injury and fall. An effusion developed. X-rays showed a micropatella consistent with nail-patella syndrome, but no evidence of fracture. He was treated conservatively. In October, 1988, chest x-ray showed a diffuse nodular infiltrate unchanged since September 1985.

By June 7, 1989, the patient was in a wheelchair, but was able to ambulate with a cane. Previous x-rays showed bilateral iliac spurs. His

chart notes included an FDA consent form in relation to the patient's use of cannabis (Figure 2). On subsequent visits, he had been approved for the Compassionate IND program, and was smoking 10 cannabis cigarettes a day.

On April 1, 1991, some cough was noted attributed to cigarettes. As a baseline, very severe pain was noted in the extremities, but this was reduced to slight to moderate on subsequent visits. By April 17, 1991, the patient was on no medicines except for cannabis. By January 18, 1993, he was said to have only slight to moderate problems with a cane for support. There were some abdominal spasms.

On the May 14, 1996 visit, he was smoking 10 cannabis cigarettes a day. He used occasional aspirin for increased pain. He had resumed smoking 1/2 to 1 pack of cigarettes a day. Examination was fairly unremarkable save for orthopedic deformities. He was able to walk on his toes and heels. The patient was given 2 more packages of 300 marijuana cigarettes.

On July 16, 1996, the patient was seen for disability examination. It was noted the patient had suffered for many years from lack of strength, mobility and range of motion, and persistent episodes of nausea and muscle spasms. The note indicated, "the marijuana helps the patient function better in the sense that he has increased flexibility, increased strength and range of motion. He has less nausea and less muscle spasm." He needed to shift into different positions at home to get comfortable and could do a sit down type job for an hour or two at most before experiencing spasms, pain and nausea. He had limited backward flexion, and limited right hand strength. He was unable to kneel. He could walk 50 feet before needing to rest, used a cane and sometimes a wheelchair for longer distances. It was felt he could not be a traveling salesman, and any prospective job would require frequent rests. Overall, he was assessed as having a significant functional impairment due to nail-patella syndrome, and was judged unemployable in the short or long term, with little rehabilitation potential.

A May 9, 1997 letter indicates, "continues to smoke about 8-10 marijuana cigarettes per day and still continues to benefit from that medication. He has less pain, less spasms, he is able to ambulate better. His nausea is improved, he is able to sleep better. He is making some slow deterioration of this disease process." It goes on to say, "I personally do feel that [Patient B] continues to benefit from marijuana and hope that we can continue providing this unfortunate man with marijuana medication."

FIGURE 2. Informed Consent Document, Patient B

FD 1571 Attachment 10(b)

PATIENT CONSENT FORM

I, _____ understand that this study will evaluate marijuana's use in the treatment of symptoms of chronic pain and muscle spasticity caused by severe spinal cord injuries. As a patient who suffers from intense pain and uncontrollable spasticity, I am interested in marijuana's potential medical uses and I volunteer to participate in this study of marijuana's effect on my symptoms.

I realize that in addition to marijuana's possible benefits in controlling pain and reducing spasticity, the drug may also cause various side effects including, but not limited to, alterations in consciousness and mood, anxiety, euphoria, drowsiness, depression, disorientation, paranoia, confusion, rapid pulse, pounding of the heart, dizziness, fainting, bloodshot eyes and dryness of the mouth. Although not validated by clinical studies, I understand some researchers believe marijuana may cause damage to the lungs and brain, changes in hormone levels, personality changes and/or reduce the body's ability to fight infection. However, I also understand marijuana, at the dosages I will receive, has been well tolerated by other patients who smoke marijuana to reduce intraocular pressures, control nausea and vomiting and ease spasticity. Due to marijuana's reported side effects I agree not to operate a car or other motor vehicle if I become intoxicated while smoking marijuana.

During this study I will be under the care of my doctor. I understand that if I experience any adverse effects while smoking marijuana I should report these effects to my physician. If I leave my doctor's care I understand my access to marijuana will be terminated unless another physician responsible for my care receives FDA approval to provide me with marijuana. I also understand that if for any reason I decide to leave this program, my doctor will notify the FDA of my decision and marijuana will be unavailable to me for this purpose.

Signed _____ Date _____, 1989

Witness _____ Date _____, 1989

Witness _____ Date _____, 1989

On May 10, 2000, a letter to FDA noted the patient continued to do well on the therapy, smoking 8-10 cigarettes per day without other medication. He continued to function well using a cane and occasionally a wheelchair when bothered by spasms and nausea.

At present, he utilizes about 7 grams a day or 1/4 ounce of NIDA material that is 3.75% THC, and was processed in April 1999. The patient cleans the cannabis to a minimal degree first, estimating a loss of about 25% of material. He indicates that he has been short on his supply 3 times in 10 years, generally for 1-2 weeks, secondary to lack of supply or paperwork problems. When this occurs he suffers more nausea and muscle spasms and is less active as a consequence. He was never allowed to try Marinol[®], and points out that he could not afford it in any event.

The patient reports continued problems with pain in the back, hips and legs, also in the upper extremities, right greater than left. When he undergoes spasms the pain rises to a 10 on a 10-point scale and is associated with projectile emesis. His baseline level of pain is 6-7/10. He notes that this pain was never helped by prescription medicines. Morphine sulfate produced a minimal decrement in pain for up to two hours, but caused inebriation. By the third day of application it would become totally ineffective. Without cannabis he feels that he would need very high doses of narcotics. He previously had dependency issues and took heroin for 2 years in the mid-1960's. Eventually he had become allergic to most pharmaceutical preparations, or had side effects of nausea. The latter continues, particularly in static positions, which without cannabis treatment he rates as a 10/10. In 1985, he was without cannabis for some 30 days and lost 57 pounds when his supply ran out at the same time that he had TB nephritis.

In relation to the spasms, these can occur anywhere in his body. He feels the medicine eliminates them or substantially reduces nocturnal manifestations. Without it he would be "running" at night.

He has no history of diabetes, thyroid problems, meningitis, encephalitis, or head trauma. He may have had seizures associated with fever. The patient has taken rare antibiotics for staph infections of the skin. He feels that he has had lots of reactions to synthetic chemicals of various types, which he considers quite serious. The patient left school at age 14 originally, but attained a GED and had some junior college experience. He is left-handed.

Family history is noteworthy for nail-patella syndrome in mother, niece, two sisters, nephew and daughter. One sister died of the disease

at age 44. He has two unaffected children. His affected daughter does not receive legal cannabis. His father died of TB and tumors at age 40.

Social History: He currently smoked cigarettes about 1/2 pack a day, but as high as a pack a day in the past. The patient drinks beer about 1 a month, with little alcohol use in 10 years. The patient last worked full-time in 1985, and part-time in 1990. He is on SSDI, but does volunteer and activist work. The patient is able to walk very little due to pain, but bikes when he can a short distance (about 4 miles every other day). The patient sleeps from 10 p.m. to 6 a.m., but this is disrupted due to pain or nausea.

Medical Test Results: Weight: 173 lbs. Height: 69 inches (BMI: 25.6). OFC: 60 cm. BP: 122/80. General: Very pleasant, cooperative 50 YOM who appears somewhat wizened. Head: normocephalic without bruits. ENT was noteworthy for edentulous state. Neck: supple. Carotids: full, without bruit. Cor: S1, S2 without murmur. The patient has a large indentation scar in the right flank. Palpation to the spine was unremarkable. Chest auscultation revealed a prolonged expiratory phase without wheezing. Abdominal examination was unremarkable. He had dysplastic nails.

Mental Status: The patient was alert and fully oriented. Fund of knowledge, right-left orientation, praxis and naming skills were normal. He read a grade 6 paragraph well with good recall. Serial 3's were well done. Signature was normal. He remembered 2 of 3 objects after 5 minutes with hesitation, failed the third with hint, but got it with choice of 3. He had a hoarse voice. He named 11 animals in 30 seconds (normal). Affect was normal. Cranial Nerves: I: intact. II: acuity was measured as 20/25 OD, 20/50 OS uncorrected. Fields and OKNs were normal. Fundi were benign. Pupils equally reactive with full EOMs and no nystagmus. Remaining cranial nerves V and VII-XII were unremarkable. On motor examination, the patient had hypotonicity, but decreased bulk. The patient lacked full elbow extension on the right. His strength was generally 4+ secondary to limitations and pain. There was no arm drift. Sensation was intact to fine touch, vibration, position and graphesthesia, but there was some slight vibratory loss in the feet. Romberg was negative. The patient performed finger-to-nose well. Heel-to-shin required partial assist of the hands. Rapid alternating movements of the hands were very slow on the right secondary to mechanical problems. Fine finger movements were normal. The patient had a stiff, bent gait, but toe gait appeared more normal. On heel gait he favored the left leg. Tandem gait was difficult due to back pain and he

wavered some. I was unable to ascertain reflexes at the biceps on the right, but responses elsewhere were 1-2+ with downgoing toes.

The patient underwent the prescribed battery of tests. Pulmonary function tests revealed an FVC of 107% of predicted, FEV₁ of 95% of predicted, and FEV₁/FVC of 0.75. This was interpreted as within normal limits, but with a slightly prolonged forced expiratory time (Table 3). A complete blood count showed some mild polycythemia, probably due to tobacco smoking. An absolute lymphocyte count was 3.4 with CD4 count 68.7% and absolute count of 2324 (Table 4). The patient had a full endocrine battery. Measurement of FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone and progesterone were wholly within normal limits for age and gender (Table 5). An EEG was performed during wakefulness and was within normal limits, but did demonstrate some low voltage fast activity in the beta range, with no focal or epileptiform activity. The patient had a P300 response with a latency of 338 milliseconds, within normal limits for the laboratory (Figure 1). An MRI of the brain without contrast was read as normal. A PA and lateral chest was read as normal.

Patient B was friendly and cooperative and appeared to put forth very good effort on neuropsychological testing. On the WAIS-III, he obtained Verbal and Performance IQ Scores in the Average Range (VIQ = 105 and PIQ = 92). In terms of overall intellectual functioning, he obtained an overall score placing him at the 50th percentile (Full Scale IQ = 100). Assessment of attention and concentration with the CPT-II revealed that these abilities tended toward mildly-to-moderately impaired relative to the normative data set. He made an abnormally high number of omission errors and also demonstrated substantial variability in his reaction time. He also became more variable as time progressed over this 14-minute measure.

On the WMS-III, he obtained Auditory Immediate and Auditory Delayed Index scores of 89 and 86, placing him in the low average range. His Auditory Recognition Delayed Index was in the average range with an index score of 90. Visual Immediate and Visual Delayed abilities were also in the low average range with index scores of 88 on both. Overall, these performances are within normal limits, albeit it in the low average range.

On the CVLT, this patient's initial acquisition of items after the first trial was one standard deviation below expected levels, and his recall after five learning trials was two standard deviations below. Short Delay Free Recall and Long Delay Free Recall were essentially at the same level. Thus, his acquisition of very complex verbal material does appear

at least mildly impaired. Interestingly, he does not lose this information from memory after a delay.

Assessment of higher level executive functions yields an overall performance on the WCST at a mildly impaired level relative to age and education matched peers, with a T-score of 38. His overall performance on the Category Test was in the borderline range with a T-score of 40. He also had difficulty following new complex sequences with a T-score of 40 on the Trails A Subtest and a T-score of 32 (mildly-to-moderately impaired) on the Trails B component.

Simple motor testing reveals that Tapping Speed was within normal limits, but he had difficulty with fine motor coordination on the Groove Pegboard Test with his dominant left hand. He obtained a T-score of 36 on this particular measure with his left hand, a T-score of 42 with his right hand.

On the Thurstone Word Fluency Test, he obtained a T-score of 54 and a T-score of 40.2 on the Controlled Oral Word Association Test. Animal naming was within normal limits with a total score of 22.

In summary, Patient B does appear to have a mild-to-moderate impairment of attention and concentration, and his ability to acquire new, complex detailed verbal material also appears to be mildly-to-moderately impaired. There is quite some variability in this regard, however, with performances on the Wechsler Memory Scale-3rd Edition (WMS-III) being generally within normal limits, and his California Verbal Learning Test (CVLT) performance falling approximately 2 standard deviations below expected levels. He had difficulty on motor tasks. His performances may have been adversely affected by peripheral pain as he complained of such during the assessment process. His overall score of 0 on the Beck Depression Inventory (BDI) argues against significant depressive symptoms.

Patient C

Medical History: This 48-year-old male carries a diagnosis of multiple congenital cartilaginous exostoses, an autosomal dominant disorder. History was obtained from the patient, a published affidavit (Randall 1991b), and submitted progress notes dating from December 5, 1996.

He recalls few medical problems until age 10, when he threw a baseball and his arm became paralyzed for a few hours. Radiographs revealed what was interpreted as an old fracture that had healed with jagged bone fragments. Multiple referrals ensued, and ultimately 250 bony tumors were found throughout his body. He was diagnosed as hav-

ing multiple congenital cartilaginous exostoses. Each was capable of growth, massive tissue disruption, pain, and malignant transformation. By age 17, he underwent multiple surgical procedures on the left leg, and right wrist. By age 12, constant pain and frequent hemorrhages severely limited his gait along with other basic functions. He required a home tutor by grade 7. By age 14, he required ongoing narcotics for analgesia, escalating to Dilaudid® (hydromorphone), and Sopor® (methaqualone, now Schedule I in USA) for sleep. He reports resultant fatigue, ennui, and disorientation as side effects.

At age 20, he developed a large bone spur on the right ankle, which recurred dramatically after one surgery. Amputation was recommended, but refused. At age 22, a fist-sized tumor was removed from the pelvis. A medical odyssey ensued, which failed to identify better therapies and he required massive doses of hydromorphone, methaqualone, and muscle relaxants.

He described himself as a conservative young man who was against drugs, but in college acquiesced to try marijuana. He enjoyed chess, but was normally able to sit for only 5-10 minutes without pain. One day, he smoked cannabis and an hour into a chess match he remained pain-free. After discussion with his doctor, he experimented by smoking it regularly for 6 months. He noted a marked enhancement of his analgesia, and a reduction on his dependence on hydromorphone (taken intravenously for some time), Demerol® (meperidine), and hypnotics. Cannabis analgesia exceeded that of any prescription drugs.

He began to investigate possible legal avenues to obtain cannabis, and met Robert Randall in 1978. By 1979, he was spending \$3000 annually on therapeutic cannabis through the black market, an unsustainable burden. A Byzantine bureaucratic process ensued over several years, with final FDA approval of his IND application in November 1982. Weekly monitoring sessions including needle electromyography (EMG) were deemed necessary to assess the effects of treatment in his protocol.

Subsequently, he described numerous instances of delayed shipments of cannabis, or exhaustion of supplies of higher potency product. Substitution of 1% THC cannabis required a doubling of dosage to 20 cannabis joints a day.

He was once arrested in Florida despite documentation, handcuffed and jailed overnight, sustaining an ankle hemorrhage in the process. Only 4 of 7 confiscated joints were ultimately returned. Beyond this, he describes cannabis as much safer than prescribed medicine, and free of

serious adverse effects except chest pain with prolonged usage of inferior product.

In 1992, Patient C had occasion to try Marinol® during a stockholders meeting in Canada due to his legal proscription from traveling with cannabis. Although he had no side effects on a dose of 10 mg, it was without any benefits, and left his muscles very tight and painful.

Detailed progress notes from the last several years were obtained and will be summarized. December 5, 1996, the patient was using 10-20 mg of baclofen and 10-15 cannabis cigarettes a day. Assessment was of multiple congenital cartilaginous exostoses with hepatitis C, and GE reflux. He was prescribed diazepam 5 mg for spasm. An EKG was read as showing normal sinus rhythm. February 28, 1996, the patient had pulmonary functions with FVC 112% of predicted, FEV₁ of 79% of predicted, read as indicating mild obstruction.

January 24, 1997, he had episodic spasm with pain affecting both arms and legs. It was noted at the time that the patient had a malunion of the right radius. He was down to 2-3 cannabis cigarettes a day, as he had received no supply from NIDA since September 1996, due to logistical problems in seeing his study physician. A transfer of providers was recommended.

September 4, 1997, he remained on baclofen 10 mg p.m., 5 mg a.m. and Prilosec® (omeprazole) for epigastric discomfort that had been going on for 7 years, and cannabis 12 cigarettes a day. September 9, 1997, the patient had a chest x-ray with no findings. September 9, 1997, the patient had laboratory tests done, including a CBC, non-reactive hepatitis A and B tests, and normal thyroid functions. Glucose was low at 24, potassium high at 5.4, SGOT 79 with other parameters negative. September 17, 1997, the patient was said to be doing well smoking 10-12 cannabis cigarettes a day with dramatic decreases in frequency and intensity of flexor spasms. He was also taking baclofen. It was noted that with strong spasms the patient would bruise his skin and sometimes even bleed. His weight was constant, appetite normal. Neurological exam was fairly unremarkable. He was asked to slowly decrease the baclofen to 2.5 mg bid.

May 13, 1998, the patient was said to be doing quite well. In the interim, a liver biopsy demonstrated minimal changes secondary to hepatitis C. Chest x-rays were said to show no changes. The prior December the patient had twisted his left knee with a lot of swelling, and an MRI revealed a minor crack in the tibial head. Pain was under good control with 12 cannabis cigarettes a day with only occasional muscle spasms. Exam was unremarkable. He was said to be doing quite well off of the

baclofen and was asked to continue 12 cigarettes of cannabis a day. May 26, 1999, the patient related no difficulty breathing. Weight was constant. There was dull pain in the ankles and some sharp shooting also in the knees. There was minor weakness in the right hand with no other deficits. The remainder of the exam was normal. The patient was felt to be doing well and advised to continue 12 cannabis cigarettes a day. October 6, 1999, the patient was seen in follow up, was on omeprazole, Vitamin C, and cannabis. The patient had some congestion and mildly productive cough. He was felt to have acute bronchitis and was given cough syrup. January 5, 2000, the patient had pulmonary functions done with an FVC 118% of predicted, FEV₁ 82% of predicted. This was felt to indicate borderline obstruction. January 13, 2000, glucose was 126, BUN 26, SGOT 71 with other parameters normal, including CBC. Hepatitis C antibody was reactive with other titers negative. Thyroid functions were normal. An SGPT was 181.

May 4, 2000, the patient was occasionally playing softball and had no complaints of shortness of breath. Again there was mild weakness of the hand with other muscles normal. It was felt that the patient was doing well without aches, pains or spasms on his cannabis.

November 21, 2000, the patient had noticed some increased discomfort following a motor vehicle accident the prior month wherein he was rear-ended and had neck pain. Subsequently, he noted persistent pain in the right thigh. An x-ray was negative. He tried physical therapy, heat and electrical stimulation. He noted more muscle tension with weather change. No neurological changes were observed.

December 28, 2000, the patient was on his omeprazole and cannabis. January 6, 2001, SGOT was 50, SGPT 94 with normal CBC and PSA. A cholesterol total was 221 with LDL 136.

At the time he was examined in Missoula, he noted constant baseline pain of 9-10 on a 10-point scale without cannabis. At rest, with cannabis this fell to a 4/10. He was smoking 9 grams a day of 2.7% THC NIDA cannabis, or 11 ounces every 25 days. At times he has had to cut back due to an inadequate supply. He would sometimes have to use street cannabis at a cost \$110 per quarter ounce (circa \$16/g) of an estimated 4-5% THC content. Interestingly, although he found the flavor was an improvement over the government supply, he noted little difference in analgesic effect except, but perhaps greater relaxation effect. Interestingly, even with extensive cannabis use there are only two times he thinks that he ever may have been "high." One time he left his coat somewhere in freezing weather, which is extremely uncharacteristic, and the other he had been without cannabis for a long time and briefly

felt euphoric while smoking. However, once he advanced to a second joint, this feeling was gone.

The patient has the most problems with the left arm where pain is a 7-8/10 when there are flare-ups despite medicine. This decreases after he takes rofecoxib (Vioxx®) for a week. He experiences pain in both knees, but usually minimal (1-2/10) with his cannabis. He may periodically pull a muscle or hemorrhage, especially in the ribs. He has occasional problems in the wrist.

The patient's sleep remains disrupted rarely attaining 6 hours total. Typically, he is up every 45 to 60 minutes with stiffness and needs to have pillows to position himself. He once got 8 hours of sleep with methaqualone (now illegal in USA), waking only twice.

He feels that his hepatitis C is asymptomatic and was probably due to a transfusion in his teens. Although he did use hydromorphone intravenously for a long period of time, he feels that he pursued a scrupulous aseptic technique. Besides surgeries noted above, he has dental caps due to bruxism, and tonsillectomy. He has had past hypertension, which he feels was work related. There is no history of diabetes, thyroid problems, meningitis, encephalitis, head trauma or seizures. He uses only omeprazole 30 mg a day regularly in addition to his cannabis. He is allergic to barbiturates. The patient had 3 semesters of college. He is primarily right-handed, somewhat ambidextrous.

Family history is negative for other known involvement, but his father was adopted. His mother has migraine.

Social History: The patient works full time as a stockbroker. He is also a very decorated disabled sailor. He plays softball once a week. He may use a stationary bike about 10 minutes at a time, but this is subject to weather effects. He does not smoke tobacco. The patient drinks about 1.75 liters of Jack Daniels whiskey every 10-14 days, which helps him sleep. He does not drink coffee.

Medical Test Results: Weight: 153 lbs. Height: 5' 4 1/2". General: Very pleasant, cooperative 48-year-old white male who is somewhat obese (BMI: 25.5). Head: normocephalic without bruits. ENT: unremarkable. Neck: supple. Carotids: full, without bruits. Cor: S1, S2 without murmur. The patient had very slight gynecomastia. He has prominent exostoses of the left shoulder, left wrist, right shoulder, and right calf. Auscultation of the chest revealed a prolonged expiratory phase without wheezing. Abdominal palpation was negative.

Mental Status: The patient was alert and fully oriented. He knew the president and had normal right-left orientation, praxis and naming skills. He read a grade 6 paragraph well with good recall. Serial 3's were

done very rapidly. He remembered 3 objects for 5 minutes. He named 15 animals in 30 seconds, which is well above the average of 10-12. Speech and affect were normal.

Cranial Nerves: I: intact. II: fields and OKNs were normal. Fundi were benign. Pupils were equally reactive with full EOMs and no nystagmus. Remaining cranial nerves V and VII-XII were unremarkable. On motor exam, the patient had some limitation due to pain, but seemed to have good strength throughout except for 4+/5 foot dorsiflexion on the right. There was no drift. Sensation was intact to fine touch, vibration, position and graphesthesia, but there was decrease in sharp/dull discrimination at the top of the right foot secondary to post-operative changes. Romberg was negative. Finger-to-nose and rapid alternating movements of the hands were normal. Heel-to-shin was incomplete on the right, better on the left. Fine finger movements were minimally decreased. On gait testing the patient slightly favored the right leg at the ankle. Toe gait looked better. Heel gait was barely possible due to pain on the right side. Tandem gait was minimally hesitant. Reflexes were 1+, symmetric with downgoing toes.

Medical Test Results: On pulmonary function tests, an FVC was 108% of predicted and FEV₁ 67% of predicted. A FEV₁/FVC was 0.51 felt to be indicative of a moderate obstructive defect based on the latter ratio and flow volume curve morphology. No restrictive abnormality was noted (Table 3).

A CBC was wholly within normal limits. An absolute lymphocyte count was 1.8 with CD4 49.1% and CD4 absolute count of 911 (Table 4). An endocrine battery, including FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone and progesterone, was wholly within normal limits for age and gender (Table 5).

An EEG was performed during wakefulness and early stages of sleep, which was within broad normal limits. There was a good bit of low voltage fast activity in the beta range. No focal nor epileptiform activity was appreciated. A P300 showed a latency of 262 milliseconds felt to be within normal limits for the lab (Figure 1).

An MRI was performed without contrast. There was felt to be no definite abnormality of an acute nature. There were some minor changes in the right parietal area suggestive of a mild degree of gliosis with associated dilated perivascular spaces of doubtful significance. There was a small area of abnormal signal in the right parotid gland overlying the right masseter muscle felt to be probably benign.

A P-A and lateral chest x-ray were performed. This was read as showing a pulmonary nodule in the left upper lobe with minimal airway

changes. One examiner (EBR) reviewed those films and felt that the lesion was actually located in a rib. As a result, the patient underwent a CT scan of the chest after returning home. This showed no evidence of mass, lymphadenopathy, or pulmonary nodules. A small amount of pleural calcification was noted. An exostosis was noted in the right anterior 3rd rib, accounting for the false-positive chest x-ray.

On neuropsychological testing, Patient C was pleasant, cooperative, and appeared to put forth very good effort. His attention was noted to be quite poor at times and many instructions had to be repeated.

On the WAIS-III, he obtained Verbal and Performance IQ Scores in the Average Range with a Verbal IQ of 103 and a Performance IQ of 104. In terms of overall intellectual functioning, he is currently performing at a level equal to or above 58 percent of the general population (Full Scale IQ = 103).

Assessment of attention and concentration with the CPT-II revealed that immediate attentional abilities were within normal limits. His ability to concentrate, however, did appear mildly impaired, as he tended to lose efficiency with the passage of time. Thus, vigilance appeared to be mildly decreased relative to a normative data set.

On the WMS-III, Patient C obtained an Auditory Immediate Index in the Average Range at the 70th percentile. His Auditory Immediate Index was 108. Auditory Delayed Index was also 108, placing him in the Average Range, and his Auditory Recognition Delayed Index was 115, placing him in the High Average Range. The Visual Immediate Index was 115 with a Visual Delayed Index of 122, performances in the High Average and Superior Ranges, respectively.

On the CVLT, this patient's initial acquisition on Trial One was two standard deviations below expected levels and his acquisition of only ten items by Trial 5 was one standard deviation below expected levels. Short Delay Free Recall was also one standard deviation below expected levels but he performed within normal limits if provided cues. His ultimate free recall after a 20-minute delay was also one standard deviation below expected levels. There was not a substantial loss of information between Long Delay and Short Delay Free Recall trials. Thus, his ability to acquire very complex and detailed new verbal material does appear minimally-to-mildly decreased relative to age matched peers, well below his ability to acquire new thematically organized verbal material, which was in the above average range. Memory, however, appears normal.

Assessment of higher level executive functions yielded a T-score of 45 on the WCST and a T-score of 44 on the Category Test from the

Halstead-Reitan Neuropsychological Battery. His ability to follow new complex sequences was entirely within normal limits as indicated by T-scores of 52 and 62 on Trail Making Test A and B, respectively.

Simple motor speed measured by Finger Tapping was within normal limits, bilaterally, as was fine motor coordination measured by the Grooved Pegboard Test.

His performance on the Thurstone Word Fluency Test yielded a T-score of 56, which is entirely within normal limits relative to age and education-matched peers. Likewise, his overall performance on the Controlled Oral Word Association Test yielded a T-score of 52.52, and Animal Naming Fluency also was within normal limits. His overall score on the Beck Depression Inventory-2nd Edition (BDI-II) was 0.

Overall, Patient C appears to have mild difficulty sustaining attention and also minimal-to-mild difficulty with the acquisition of very new, complex verbal material. Overall, however, he appears to be functioning quite well.

Patient D

Medical History: This 45-year-old female carries a diagnosis of multiple sclerosis (MS). The patient was interviewed by telephone (EBR) in lieu of the possibility of contemporaneous examination. The patient feels her first problem may have occurred at age 18 when her vision sequentially went completely black for two months with slow improvement over a subsequent four months. A possible attribution to oral contraception was hypothesized. She was subsequently evaluated at a quaternary referral center and diagnosed as having retro-bulbar neuritis. She was prescribed nicotinic acid. On re-evaluation in 1983, no active disease was noted. On May 29, 1986, best corrected vision was 20/30 OD, 20/25 OS. By May 19, 1988, values fell to 20/200 OD, and 20/70 OS. The patient was formally diagnosed as having MS April 1 of that year with associated bilateral optic neuropathy. She had had symptoms for perhaps 6 months with blurring in both eyes and leg spasms that interfered with walking. The patient had never used cannabis recreationally, and began it only because of her symptoms.

She has been followed in her local area by a psychiatrist and neurologist. Extensive, well-documented notes commencing December 20, 1989 were provided, and will be summarized. When first seen on that date the patient was married for the second time. It was noted that she had been diagnosed with MS about a year and a half previously and had been on diazepam from time-to-time. She was taking 10 mg tid to cope

with stress. She had previously tried trazodone and buspirone, had become paralyzed with her MS, and was consequently very frightened of these medicines. On examination she was felt to be quite anxious and was provisionally diagnosed as having a dysthymic disorder.

On March 20, 1990, she seemed to be suffering from more depression, although she managed to smile. She described difficulty with self-esteem and hopelessness. She had only been taking diazepam intermittently and was rather prescribed Prozac® (fluoxetine) 20 mg and Xanax® (alprazolam) 0.25 mg up to 3 times a day. She was felt to have recurrent major depression. On subsequent visits the patient had slight adjustments of medicine and was feeling better by May 2, 1990. By August 6, 1990, the patient was having greater difficulties with insomnia. She was given trazodone 50 mg at bedtime on a trial basis: August 24, 1990, the patient was only sleeping until 4 a.m., which was about 2 hours better than without medicine. This was increased to 75 mg.

The patient had heard about some studies of using cannabis in MS as a relaxing agent. She indicated that she had tried this with a good relaxation response. There was a discussion of possible effects on the lungs, and her expected diminished life expectancy because of MS. She was given a prescription for Marinol® (dronabinol, synthetic THC) 10 mg to be tried q 4 hours prn to see if this would help with relaxation and nausea. When seen September 5, 1990, she had found that the Marinol® had reduced the nausea considerably and had even helped her vision. She continued on fluoxetine.

September 27, 1990, the patient was not sleeping well, possibly due to fluoxetine, and was given a benzodiazepine. October 17, 1990, the patient was seen in follow up and was on Xanax® (alprazolam). It was noted that she had improvement with Marinol®, but the patient noted she actually had a better response to smoked cannabis. They began to look into obtaining a legal supply.

December 3, 1990, the patient reported increased depression and was increased to 40 mg a day of fluoxetine. December 5, 1990, the patient had recurrent depression even on the fluoxetine 2 a day and low dose alprazolam. Apparently, her doctor had received notification that he could no longer prescribe Marinol® "off label" unless a Schedule I permit for cannabis was being pursued. December 19, 1990, the patient reported nausea, for which some of her remaining Marinol® had helped. January 16, 1991, the patient complained of spasticity spells and episodes of nausea. She had run out of Marinol® and had no cannabis supply. She indicated she had tried other medications without success and was resistant to try others due to side effects.

February 20, 1991, the patient had purchased illicit cannabis in the interim. April 16, 1991, the patient continued on fluoxetine 20 mg bid. More jerkiness was noted with increased spasticity. She had not smoked cannabis before coming in. It was felt that she would need 6 cannabis cigarettes a day to reduce symptoms. May 10, 1991, she was taking alprazolam about every 2 weeks. She was continuing to have some spasms. She continued to try cannabis illicitly, but had not yet obtained it legally. June 14, 1991, she had lost her driver's license due to visual problems associated with MS. During this interval there were more marital issues. July 2, 1991, it was indicated the patient was legally blind and there were no possible corrective measures. Plans were in place to obtain legal cannabis for spasticity and nervous problems. It was noted that cannabis seemed to be very effective for her clinically. August 7, 1991, the patient was still without a supply and complained of her legs jerking at night, and increased difficulty walking. The patient requested Marinol[®], but this could not be prescribed. She was given baclofen 5 mg tid to try.

August 30, 1991, she received her first shipment of NIDA cannabis, seven months after approval of the Compassionate IND. The patient was advised that she should confine her use to government cannabis. She was having problems with her gait, able to walk only with a cane. There were continued vision problems. She complained of left sided weakness. The patient smoked a cannabis cigarette in front of the doctor, which led to her feeling better. It was suggested she try 3 cannabis cigarettes a day. September 3, 1991, the patient reported that the government supply of cannabis did not have the "punch" that street bought material had. Her dose was increased to 5 joints a day. It was indicated that her spasticity responded positively to the dose increase. September 11, 1991, the patient was on 5 NIDA cigarettes a day. This was helping her spasticity. She was unclear as to whether her vision was helped. September 20, 1991, it was felt that 7 cigarettes a day would be necessary. The patient reported increased muscular activity, uncontrollable at times. October 2, 1991, the patient had run out and was noticeably more spastic on examination. Her dose was increased to 10 a day. October 9, 1991, the patient was on 10 cannabis cigarettes a day of the strongest available dosage, which seemed to help her spasticity. She was walking without a cane. It was not felt that her depression was improved. November 4, 1991, she had been out of her supply for 10 days. Spasticity increased and she complained of pain in the left leg. Increased tone was noted throughout the body. December 5, 1991, apparently a supply came in of lower potency cannabis. December 19, 1991, it was felt she

had continued improvement of her spasticity with better gait. February 14, 1992, she was using 1 can of cannabis a month, equal to 300 cigarettes. The patient reported she had not been falling. March 13, 1992, she continued the cannabis at the same rate, plus 40 mg of fluoxetine and no alprazolam. The patient reported she was able to walk, swim better, and do all of her ADL's much easier than she could prior to the cannabis. There was no observable gait disturbance on exam.

April 14, 1992, it was felt that she got a lot of relief from her medicine and that it "probably offers her greater efficacy in her spasticity, also, than Valium would." May 19, 1992, the patient continued to be stable with no exacerbations of her MS and the spasticity under good control. There were concerns about periodontal disease from her dentist. It was thought she might do better with less smoking of a higher potency supply. The patient was also smoking cigarettes and was subsequently advised to avoid tobacco. By July 17, 1992 she continued to respond to cannabis. September 18, 1992, reflexes were equal and not hyperactive. November 16, 1992, there was an increase of depression slowly and insidiously. December 9, 1992, the patient had been off of her treatment for a week and was very shaky. Smoking a joint in front of her doctor caused her to become calm, less shaky and better able to walk. January 19, 1993, she got her first cans of the stronger cannabis, which the patient felt more effective after smoking one joint. March 22, 1993, she was smoking 6-7 a day. She seemed better after smoking one in the office. April 22, 1993, the patient was smoking 10 cigarettes a day. Smoking produced a decrease in spasticity as observed. There were no adverse effects that were noted in the office. May 24, 1993, the patient was tried on lorazepam. June 24, 1993, the patient was upset with financial issues and was placed on Mellaril® (thioridazine). July 22, 1993, when she was examined, no tremor or spasticity was noted. Again cannabis was smoked with no adverse effects noted. August 30, 1993, the patient requested a decrease in her fluoxetine. She felt that spasticity and depression were both helped by the cannabis. September 29, 1993, the patient reported that on a lower fluoxetine dose she was getting tearful. Reflexes were not hyperactive. November 2, 1993, the patient had some paresthesias on the left side, but was maintaining good motor control. December 28, 1993, she was tried on bupropion. January 4, 1994, problems had been noted on bupropion and it was not as effective. She was tried on sertraline. She reported that the cannabis helped her to not think about her MS. She was having fewer spasticity problems.

February 4, 1994, when the patient smoked cannabis in the office, she seemed to be a little more talkative and relax significantly with less

spasticity and no adverse effects. February 28, 1994, again significant relief from spasticity was noted upon smoking. March 30, 1994, the patient had some numbness and tingling in the limbs. The patient reported the new material was stronger and had a better effect. May 9, 1994, some increase in emotional lability was noted. The patient was taken off of sertraline and put on Effexor® (venlafaxine). May 25, 1994, she was unable to tolerate the latter and was started back on fluoxetine. August 29, 1994, she continued on fluoxetine and cannabis. Smoking a joint calmed her and limited tremor. September 28, 1994, it was indicated in relation to cannabis "it seems to have a positive effect on her mental status overall." October 31, 1994, the patient was felt to be without signs of depression. She actually lowered her dose on a higher potency material. February 1, 1995, the patient was on diazepam again. February 14, 1995, she was increasingly shaky and tearful. March 29, 1995, she was hardly able to walk due to an exacerbation. May 2, 1995, she still needed support. At the same time the patient was having marital difficulties. August 4, 1995, the patient reported she could see much better with the cannabis. By September 6, 1995, she was walking quite well and was no longer on diazepam, merely the fluoxetine and cannabis. October 4, 1995, she continued to walk well with no problems.

January 17, 1996, an MRI revealed multiple bilateral periventricular and diffuse white matter changes in the cerebrum and cerebellum, but seemingly fewer than on a April 4, 1995 study.

April 19, 1996, the patient had been out of cannabis for a week and was experiencing more spasticity and ambulation difficulties. She was more depressed. May 17, 1996, the patient had been tried on a stimulant. July 10, 1996, the patient reported that cannabis was the only thing that had helped her with her symptoms over the course of her illness.

By September 25, 1996, the patient had been without medicine for a month and had to buy it on the street. She had lost weight and her condition had reportedly decompensated to some degree. The patient reported a 10-pound weight loss. November 13, 1996, the patient was having difficulty sleeping, but did not wish to take trazodone. November 27, 1996, the patient had fallen and had a brief loss of consciousness. December 5, 1996, she had had an episode of spasticity that was the worse she had ever had, starting in the neck and going down her back. January 8, 1997, cannabis came in after a summer drought since September 25. An emergency supply was requested. January 22, 1997, the patient remained concerned about lack of cannabis supply. February 5, 1997, she continued with this concern. February 19, 1997, there was discussion of difficulty the patient had experienced with the authorities in an airport.

April 2, 1997, it was felt the patient continued to get a great deal of relief from smoking 10 joints a day without any adverse effects. July 2, 1997, the patient was observed to become more loquacious and interactive after dosing.

January 29, 1998, the patient was not complaining of spasticity, seeming to have considerable relief with cannabis. Her fluoxetine was lowered to 20 mg a day. March 24, 1998, it was felt that she had a very slow progression of her MS helped by her consumption of cannabis. September 22, 1998, the patient said that the medicine took away her fear of the disease and when she would get a pain she would be able to smoke and take it away.

October 27, 1998, she apparently had been out of her supply for 6 weeks, but had gotten by smoking only 4 cigarettes a day instead of the usual 10. January 24, 1998, the patient was doing relatively well and was walking with a cane. December 22, 1998, she was having increasing problems. January 26, 1999, the patient indicated that medicine helped her maintain her weight. March 24, 1999, it was observed, "I think her spasticity is being helped with the cannabis." April 23, 1999, she continued to get good relief with 10 cigarettes a day. June 24, 1999, the patient reported some increasing difficulty with walking in the heat and hot weather. July 20, 1999, she was said to have no tremor or spasticity. September 1, 1999, she was having some exacerbation and difficulty walking and limping because her right leg was not working as well. October 20, 1999, the patient reported the only bad side effect would be when she smoked too much she would tend to go to sleep. She discussed alternative treatments for multiple sclerosis with her doctor and they agreed not to pursue them. November 19, 1999, the patient was walking on a wide base felt to be the result of a mild exacerbation. November 24, 1999 neurological examination confirmed greater ataxia. Methylphenidate was prescribed.

December 1, 1999, an MRI of the brain was said to reveal multiple focal white matter changes in bilateral cerebral areas especially in the basal ganglia and in the cerebellar peduncle, compatible with MS.

January 12, 2000, the patient was tried on Ritalin® (methylphenidate). She was switched to Remeron® (mirtazapine) from fluoxetine. February 22, 2000, the patient reported that her eyes were improved. March 9, 2000, visual acuity was 20/200 OD and 20/80 OS. April 6, 2000, it was felt that she had no declines in function from cannabis use.

June 27, 2000, her cannabis had been late coming in and she had cut from 10 to 6 or 7 cigarettes a day, feeling that that had hurt her physically and that she was not walking as well. January 31, 2001, the patient

was a little bit down and labile, but by February 28, 2001, she was not depressed or hyper. April 11, 2001, she was having some trouble walking due to a flare of symptoms, which had been present for a month, but she noted no changes in vision.

When the patient was interviewed by EBR (June 2001), she reported that her vision was currently clear with cannabis. She was able to ambulate without aids, but has to stop after a block or less due to weakness. She swims a few days a week. She feels that there is no nystagmus in her vision and no diplopia. She characterizes her MS as mildly progressive.

The patient indicated that she received the cannabis legally in 1991 and continues to smoke 10 cigarettes a day. She currently receives material of 3.5% THC content that was processed April 1999. Her study physician requests the highest potency material available, which has recently varied between 2.9-3.7% THC. When she uses outside cannabis of higher potency, she feels that she gets twice the relaxation. There is no chronic cough or other difficulties. The patient feels that Marinol® at 10 mg was too strong. She used it for 6 months before the cannabis. Customarily she splits each of her supplied cigarettes in two, and manicures it slightly. When she is not on cannabis she has had no withdrawal symptoms, but has had increase in movement problems.

The patient has had a tubal ligation. She continues to menstruate on a regular monthly basis. Her main problems have been depression and some degree of anxiety. I asked about other diagnoses and she replied that she had "10 personalities and they are all feeling fine!" She denied history of diabetes, thyroid problems, meningitis, encephalitis, head trauma or seizures. The patient remains on fluoxetine 40 mg a day. She is allergic to penicillin. The patient had 1 year of college. She is right handed.

Family history is noteworthy for father having narcolepsy and a sister who is bipolar.

Social History: She had one child by choice. The patient is a retired clothier, and is unable to work at this time. She is currently smoking 1/2 pack of cigarettes a day, previously 1 pack a day, and has smoked since age 20. The patient does not drink at all, has not for 5 years, nor has she ever had a problem with alcohol. She does not drink coffee. She customarily sleeps 8 hours.

Medical Test Results: The patient is 5 feet tall and 97 pounds (BMI: 19). On pulmonary function tests, an FVC was 79% of predicted, and FEV₁ 76% of predicted. The FEV₁/FVC was 86 (Table 3). There was felt to be no obstruction based on this ratio or analysis of the F/V curve

morphology. Early small airway disease and borderline restrictive disease (e.g., due to MS) were not excluded.

A CBC was wholly within normal limits. An absolute lymphocyte count was 2.3 with CD4 of 58% and CD4 absolute count of 1325 (Table 4). An endocrine battery was performed, with values of FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone and progesterone, all within normal limits for age and gender (pre-menopausal female) (Table 5).

Neuropsychological tests were performed in her home on June 17, 2001. Some confusion was noted throughout the evaluation and significant fatigue over the course of the day was also apparent. She did not have significant difficulty with instructions, however, and effort and cooperation were sufficient to obtain what is believed to be valid data. As a result of significant visual deficits, many visually based tests were omitted and interpretations from those requiring significant visual input were provided in a very cautious manner. For example, this patient required a magnifying glass in order to accomplish the Picture Completion and Trails subtests that very likely had a significant negative impact on her overall performance.

On the WAIS-III, the patient obtained a Verbal IQ of 93. A Performance IQ was not calculated secondary to significant visual deficits that interfered with assessment in this realm. On the WMS-III, the patient performed, on verbal measures, in the Low Average Range. Immediate auditory memory was at the 18th percentile, with an auditory delayed index in the Average Range. Her ability to acquire non-thematically-organized verbal material was in the mildly impaired range relative to age-matched peers, but her retention was actually very good. Also, she did very well on a test measuring her ability to acquire verbal paired associates with a learning slope actually in the above average range, and excellent retention. Her ability to acquire more detailed and non-thematically-organized verbal information was moderately-to-severely impaired relative to age-matched peers. Overall performances on the CVLT ranged from two to five standard deviations below expected levels. Numerous intrusions during both free and cued recall were noted at levels above and beyond what is generally seen in the normative population. She made eight false-positive errors on recognition testing, which are also an abnormally high number of errors.

Concentration was noted to be markedly impaired in this patient, following the mildly-to-moderately impaired range overall. Assessment of Executive Functions reveals that abstract concept formation and logical analysis abilities were significantly reduced, falling in the moderately impaired range overall. The patient was also noted to be quite perse-

verative, having difficulty shifting cognitive strategies. In slight contrast, flexibility of thought as measured by the Similarities Subtest from the WAIS-III, was within normal limits. Verbal Fluency was within normal limits relative to age and education-matched peers.

In summary, this patient appears to have decrements in concentration, low average learning, and memory efficiency for new thematic material and verbal paired associates. Her ability to acquire more detailed and non-thematically-organized verbal information is at least moderately impaired. Memory functions, however, appear to be normal in the sense that once she acquires information, she seems to hold it quite effectively. Higher level executive functions are reduced at a moderate level despite a very remarkable psychiatric history. Responses to the BDI-II were well within normal limits.

Patient D thus demonstrates numerous neurocognitive impairments. The general pattern is not particularly uncommon in the context of multiple sclerosis and significant psychiatric dysfunction. This profile, when combined with the others from the data set do not provide any consistent pattern that one could reasonably ascribe to the therapeutic use of cannabis.

Review of Neuropsychological and Cognitive Data

The scientific study of the effects of chronic cannabis on cognition has remained problematical since such concerns were first raised. Despite intensive effort in this regard, little in the way of "hard findings" or consistent results has emerged. A complete review of alleged problems is beyond the scope of this article, but a few citations are meritorious.

In the Jamaican studies (Rubin and Comitas 1975), 19 neuropsychological tests were administered to chronic cannabis users and controls with no major significant differences between groups. In fact, ganja smokers scored the highest on Wechsler Adult Intelligence Scale (WAIS) Digit Span performance ($p < 0.05$). The authors concluded (p. 119), "in a wide variety of human abilities, there is no evidence that long-term use of cannabis is related to chronic impairment."

In Greece (Kokkevi and Dornbush 1977), no differences were noted between hashish users and age and socio-economically matched controls in total or Performance IQ (PIQ) scores on the WAIS. Controls performed better on three subtests: Comprehension ($p < 0.01$), Similarities ($p < 0.005$), and Digit Symbol Substitution ($p < 0.05$). Control Verbal IQ (VIQ) surpassed that of users ($p < 0.05$). However, these results must be viewed in light of the fact that normal population studies in

Greece revealed PIQ:VIQ differences of 7 points. Thus, the authors concluded (p. 46), "These observations do not provide evidence of deterioration of mental abilities in the hashish users."

In Costa Rica, an extensive battery of neuropsychological measures showed no pathological changes (Carter 1980). It was observed (p. 188), "we failed to uncover significant differences between user and nonuser groups—even in those subjects who had consumed cannabis for over eighteen years."

Subsequently follow-up studies were performed on some of this cohort, and certain significant differences were claimed, including learning of word lists and selective and divided attention tasks (Fletcher et al. 1996). However, a detailed critical analysis of those results in *Marijuana Myths, Marijuana Facts* (Zimmer and Morgan 1997) seems to deflate any such claim.

Lyketsos et al. (1999) studied effects of cannabis on cognition in 1318 adults over a period of 12 years. No differences were noted in the degree of decline between heavy, light, and non-users of cannabis on the Mini-Mental State Examination (MMSE). Critics have indicated that the latter represents too crude a tool to measure the issue properly.

In a series of studies in the 1990's summarized in a book, *Cannabis and Cognitive Functioning* (Solowij 1998), Nadia Solowij studied subjects employing cannabis at least twice a week on average for a period of 3 years. After a review of data, the author stated (p. 227), "the weight of the evidence suggests that the long-term use of cannabis does not result in any severe or grossly debilitating impairment of cognitive function." She did note more subtle difficulties in attention parameters including distraction, loose associations and intrusion errors in memory tasks. In a recent review of cognitive effects of cannabis (Solowij and Grenyer 2001), it was observed (p. 275), "the long term risks for most users are not severe and their effects are relatively subtle. . . ."

Results from the current study seem to indicate similar findings. As part of a Comprehensive Neuropsychological Evaluation, all subjects were administered a battery of instruments including the WAIS-III, the WMS-III, the CVLT, the Trail Making Test A and B, Grooved Peg Board, Finger Tapping, and Category Test, the Controlled Oral Word Association Test, the Thurstone Word Fluency Test, a Category Fluency Test (Animal Naming), the WCST, the CPT-II, and the Beck Depression Inventory—2nd Edition (BDI-II).

Comparing Patients A-D, it appears that all four do have at least mild difficulty with attention and concentration, and verbal acquisition of varying complex new verbal material (as measured on the CVLT),

which is at least minimally impaired. Importantly, however, higher-level executive functions generally appear to be within normal limits in two of the subjects.

Difficulties in attention and concentration as well as new complex verbal learning may be directly related, and must be understood in the context of not only these subjects' chronic cannabis use, but also their underlying chronic diseases and clinical syndromes, with attendant fatigue and preoccupation. Interestingly, depressive symptoms are not currently noted at a clinical level in any of the subjects despite their chronic medical conditions or long-term cannabis use. None displayed evidence of social withdrawal or apathy characteristic of the alleged "amotivational syndrome." Rather, all were animated, engaging in conversation and demonstrating an active involvement with their ongoing care and the current research.

Overall, once more, no significant attributable neuropsychological sequelae are noted due to chronic cannabis usage.

Review of Neuroimaging

In 1971, it was reported that "consistent cannabis smoking" of 3-11 years in ten patients produced evidence for cerebral atrophy employing air encephalography (Campbell et al. 1971), an excruciatingly painful and long abandoned technique. Subsequent study by Kuehnle et al. (1977) employing CT scans on 19 men with long durations of heavy cannabis usage failed to show any changes in the ventricles or sub-arachnoid spaces. They criticized the prior study for lacking controls on antecedent head trauma or other causes of neurological damage. In the same issue of the *Journal of the American Medical Association*, Co et al. (1977) studied an additional 12 heavy cannabis smokers who displayed no CT abnormalities.

In 1983, an additional 12 subjects who smoked more than 1 g of cannabis daily for 10 years were studied by CT scans of the brain, and only one with concomitant history of alcoholism showed any abnormalities compared to controls (Hannerz and Hindmarsh 1983).

Most recently, Block et al. (2000) employed automated imaging analysis with MRI to examine 18 young heavy users of cannabis. No abnormalities were ascertained. The authors stated (p. 495), "frequent marijuana use does not produce clinically apparent MRI abnormalities or detectable global or regional changes in brain tissue volumes of gray or white matter, or both combined." It was recently noted (Solowij and Grenyer 2001, p. 270), "There is no evidence from human studies of

any structural brain damage following prolonged exposure to cannabinoids.”

Despite this additional documentation, the claim of brain damage and cerebral atrophy remains a popular myth in prohibitionist rhetoric.

Current MRI studies on Patients A-C with a General Electric Sigma LX MR 1.5 Tesla magnet system reveal no clear abnormalities. Patient A had age-compatible atrophy, and Patient C had minor tissue changes of a non-specific nature, commonly seen in middle-aged populations. Patient D has previously demonstrated MRI brain lesions consistent with MS, with possible improvement observed during the period of clinical cannabis usage.

Review of Neurophysiology Tests

In discussing the issue of cannabis and cerebral effects, Homer Reed observed (Reed 1975, pp. 122-123), “The association between many of the EEG measures used to indicate CNS changes and the clinical condition of the patient is approximately zero.” That notwithstanding, various researchers have advanced numerous claims of pertinent EEG changes due to cannabis. Cohen (1976) noted differences in computerized EEG measures of delta band power and theta band phase angle (lead/lag) relationship. No mention was made of the alleged significance of these tests, or of the results of standard EEG.

All the Jamaican subjects had EEG examinations (Rubin and Comitas 1975). As previously noted in other studies, 9 of 30 cannabis smokers had significant low voltage fast activity in the beta range. Although this finding may indicate sedative effects of medication, it is often ascribed to a normal variant. Three of the 30 were said to have unequivocal focal abnormalities, but 4 of 30 controls had similar findings, and another had diffuse abnormalities. Overall, no significant differences were noted between ganja smokers and controls.

Similarly, in Greece (Panayiotopoulos et al. 1977), 8.8% of 46 hashish smokers had abnormal EEGs, while 15% of 40 normal controls were so characterized. The authors stated (p. 62), “We failed to find either an abnormality or an particular EEG change in the resting EEG records of chronic hashish users. . . .”

Current results, performed on a 21-channel Nicolet Voyageur digital EEG system and read by EBR, confirm the presence of low voltage fast activity in Patients A-C, and intermittent sharp waves and rare subtle slowing in the left frontal area in Patient A. Age appropriate atrophy was seen in the same patient on MRI, but she has no history of seizures

or CNS insults. There are no corresponding abnormalities on neurological examination. Similar abnormalities are identified on EEGs of 6% of patients, whereas there is only a 0.5% prevalence of seizure disorders in the general population. In essence, no EEG pathology of an attributable nature seems apparent in the study group on the basis of cannabis usage.

With respect to P300 responses, a type of electrophysiological event related potential, even greater caution is necessary. This parameter is offered as an electrophysiological measure of memory, inasmuch as prolongation of its latency occurs with age. The test was popular in the 1980's as an objective test for dementia. Amplitude differences have also been noted in different clinical conditions, but were termed (Spehlmann 1985, p. 370), "of uncertain diagnostic importance because of the great normal variability of the P300 amplitude." Overall, these issues and significant incidence of false positives and false negatives have largely relegated use of this technique to the sidelines as a clinical tool.

Solowij (1998) studied the P300 in chronic cannabis users vs. controls, and noted results felt to be indicative of (p. 150), "inefficient processing of information and impaired selective attention." These consisted of reduced processing negativity to relevant attended stimuli, inappropriately large processing negativity to a source of complex irrelevant stimuli, and reduced P300 amplitude to attended target stimuli to that of controls.

In contrast, Patrick et al. (1995) examined the P300 in psychologically normal chronic cannabis users and controlled the data for age. Results showed no amplitude differences.

More recent studies have shown significant reductions in P300 amplitude in schizophrenia (Martin-Loeches et al. 2001), but also in cigarette smokers (Anokhin et al. 2000), with notable effects according to motivational instructions (Carrillo-de-la-Pena and Cadaveira 2000), and even diurnal variations (Higuchi et al. 2000).

Our study employed a Nicolet Viking 3P 4-channel system with a P300 oddball paradigm. Patients A-C displayed P300 latencies that were well within norms for age-matched controls (Figure 1).

Review of Pulmonary Issues

Pulmonary concerns remain paramount in relation to chronic cannabis smoking. Excellent recent reviews are available (Zimmer and Morgan 1997; Tashkin 2001; Tashkin 2001). In brief, cannabis smoking produces an increase in cough and bronchitis symptoms, but to a lesser degree than in tobacco smokers (Sherrill et al. 1991). Daily cannabis

smokers seek medical care for smoking-associated health concerns at a slightly higher rate than non-smokers (Polen et al. 1993). In a large epidemiological study, cannabis use was associated with little statistical association on total mortality in women, and non-AIDS mortality in men (Sidney et al. 1997).

One of the primary associated risks of tobacco smoking is the development of emphysema and lesser declines in bronchial function over time. A careful longitudinal study of chronic smokers has demonstrated a longitudinal decline in the FEV₁ in tobacco smokers, but not heavy cannabis smokers (Tashkin et al. 1997).

Some association of cannabis smoking has been observed to head and neck cancers (Zhang et al. 1999), and pre-cancerous cytological changes have been noted in the lungs in bronchoscopy studies (Fligel et al. 1988), but to date, no cases of pulmonary carcinoma have been noted in cannabis-only smokers.

In examining the data from chronic cannabis use studies, in Jamaica, a slight downward trend not attaining statistical significance was noted on forced vital capacity (FVC) values (Rubin and Comitas 1975). A similar downward trend was observed on FEV₁ without statistical significance. No differences between cannabis smokers, occasional smokers and non-smokers were observed on FEV₁/FVC ratios. Results of all tests may have been affected by concomitant tobacco usage.

The Greek studies did not closely examine pulmonary function, and although an increase in bronchitis symptoms was noted in hashish smokers over abstainers, the former group also smoked more tobacco. Differences were not statistically significant in any event (Boulougouris, Antypas, and Panayiotopoulos 1977).

In the Costa Rican studies, no spirometry measures were significantly different between cannabis users and non-users. However, statistical trends were, in fact, positive with respect to cannabis usage. Cannabis smokers displayed larger indices of small-airway patency. The authors suggested that in concomitant smoking of tobacco, cannabis seemed to counteract the expected effects of tobacco on small airways. The author stated (Carter 1980, p. 171), "at least it cannot be said of the users that they have suffered an additive of [sic-"or"] synergistic decrement in pulmonary function over that attributable to tobacco alone."

In our Patients A-C, no ultimate chest radiographic changes of significance were noted, despite a false-positive reading of pulmonary nodule in Patient C. It is of particular note that he has had a previous bronchoscopy procedure with no reported cytological changes.

Observed pulmonary function values in this cohort reveal no clear trends except a slight downward trend in FEV₁ and FEV₁/FVC ratios, and perhaps an increase in FVC (Patients A-C) (Table 3). Concomitant tobacco smoking (Patients A, B, and D) complicates analysis. It is particularly interesting that Patient B, a current concomitant smoker of tobacco displayed the best spirometry values, while those in Patient C, a never-smoker of tobacco were the worst. His underlying connective tissue disease may have played an active role in this finding. His use of the lowest grade cannabis and highest amount per day are the more likely explanation.

Significant questions remain as to the role of low-grade NIDA cannabis as a contributor to the above findings, which will subsequently be discussed.

Review of Hematological Studies

No effects on complete blood counts or hemoglobin were observed in the LaGuardia Commission report (New York, NY). Mayor's committee on marihuana (Wallace and Cunningham 1944). In the Jamaican studies, slight increases were observed in hematocrit and hemoglobin readings in cannabis smokers over controls, but results were affected by concomitant tobacco use (Rubin and Comitas 1975). No hematological data was obtained from the Greek studies.

In Costa Rica, a downward trend was observed in hematocrit readings of cannabis smokers, but this was not statistically noteworthy (Carter 1980).

In our studies (Table 4), Patient B, a concomitant tobacco smoker, displayed a mild degree of polycythemia and slightly elevated WBC. No other hematological changes of any type were evident in the other three patients.

Review of Immunological Parameters

Immune system damage remains an area of contention with respect to cannabis usage (Zimmer and Morgan 1997), but one in which there is considerably more heat than light. A closer examination of the available literature may allay concern.

In the chronic use studies in Jamaica, no decrement was observed in cannabis smokers vs. controls in either lymphocyte or neutrophils counts (Rubin and Comitas 1975). Neither were significant changes noted in the data in Costa Rica (Carter 1980).

In the 94-Day Cannabis Study, initial acute low values were observed in T cell counts, but these returned to normal over the course of the testing (Cohen 1976).

A closer examination of the pertinent literature raises concerns on theoretical levels to a greater degree than practical ones. Excellent reviews are available (Klein, Friedman, and Specter 1998; Hollister 1992; Cabral 2001; Cabral 2001).

Early reports of inhibition of cell mediated immunity in cannabis smokers (Nahas et al. 1974) were refuted by later studies in which no impairment of lymphocytic response to phytohemagglutinin in hashish smokers was observed (Kaklamani et al. 1978).

A seminal review of the topic was undertaken by Hollister (1992), who stated (p. 159), "evidence of altered immune functions is derived mainly from in vitro tests or ex vivo experiments, which employed doses of cannabinoids far in excess of those that prevail during social use of marijuana." More recently, Klein, Friedman and Specter (1998) have similarly noted (p. 102), "Although cannabinoids modulate immune cell function, it is also clear that these cells are relatively resistant to the drugs in than many effects appear to be relatively small and totally reversible, occur at concentration higher than needed to induce psychoactivity ($> 10 \mu\text{M}$ or $> 5 \text{ mg/kg}$), and occur following treatment with nonpsychoactive cannabinoid analogues." They added (p. 102), "The public health risk of smoking marijuana in terms of increased susceptibility to infections, especially opportunistic infections, is still unclear." Finally, despite concerns raised by THC effects on immunity in animals and *in vitro*, Cabral and Dove Pettit (1998) admitted (p. 116), "Definitive data which directly link marijuana use to increased susceptibility to infection in humans currently is unavailable."

A particular public health concern surrounds cannabis effects on HIV/AIDS. Four studies among others may reduce related concern. Kaslow et al. (1989) demonstrated no evidence that cannabis accelerated immunodeficiency parameters in HIV-positive patients. Di Franco et al. (1996) ascertained no acceleration of HIV to full-blown AIDS in cannabis smokers. Whitfield, Bechtel and Starich (1997) observed no deleterious effects of cannabis usage in HIV/AIDS patients, even those with the lowest CD4 counts. Finally, Abrams et al. (2000) studied the effects of cannabis smoking on HIV positive patients on protease inhibitor drugs in a prospective randomized, partially blinded placebo-controlled trial. No adverse effects on CD4 counts were observed secondary to cannabis.

In our studies of four subjects (Table 4), Patient B had an elevated WBC count, probably attributable to the stress of phlebotomy, but without accompanying disorders of cell count differential. All patients had CD4 counts well within normal limits.

Review of Endocrine Function

Topical reviews of this topic are contained in two recent publications (Murphy 2001; Zimmer and Morgan 1997). As with other physiological systems, much data is based on animal studies, and early claims of deleterious effects on acute endocrine function are not necessarily supported by subsequent investigations or chronic use studies.

One long held claim is the production of gynecomastia in males associated with cannabis use. A case study of 3 cannabis smokers with this malady was reported by Harmon and Aliapoulios (1972). A more thorough investigation a few years later failed to show any differences in cannabis use in affected males between users and controls (Cates and Pope 1977).

Similarly, Kolodny et al. (1974) reported decreased testosterone levels in chronic marijuana smokers, while no differences in testosterone or luteinizing hormone (LH) levels were identified in a 3-week trial of smokers vs. non-smokers (Mendelson et al. 1978).

LH levels in menopausal women showed no significant changes after cannabis usage (Mendelson et al. 1985), but the next year, a similar group noted a 30% suppression of LH in women by smoking a single cannabis cigarette during the luteal phase (Mendelson et al. 1986).

Subsequently, a more in-depth study of both sexes was undertaken to assess multiple hormone effects comparing subjects with different levels of cannabis usage vs. controls (Block, Farinpour, and Schlechte 1991). No significant effects were noted on testosterone, LH, FSH, prolactin or cortisol in young women and men.

Jamaican chronic use studies were confined to examinations of thyroxine and steroid excretion with no significant findings observed due to cannabis use (Rubin and Comitas 1975).

In the 94-Day Cannabis Study, acute drops in testosterone and LH levels were noted after smoking a cannabis cigarette (Cohen 1976). Subsequent drops in testosterone levels were noted after the 5th week of daily usage. LH levels fell after the 4th week and FSH after the 8th week to unspecified degrees.

In Costa Rica, no differences were noted in male testosterone levels between abstainers and cannabis smokers stratified according to amount

of use (Carter 1980). Similarly, fertility was unimpaired, with both groups having identical numbers of progeny. The author stated (p. 172), "These findings cast serious doubt on cause-and-effect relationship between marijuana smoking and plasma testosterone level in long-term use."

Zimmer and Morgan (1997) summarized their observations by stating (p. 92), "There is no scientific evidence that marijuana delays adolescent sexual development, has a feminizing effect on males, or a masculinizing effect on females."

The latter statement would seem to be borne out by our findings. While one male subject had a minor degree of gynecomastia associated with obesity, none of the Patients A-D displayed any abnormal values in any endocrine measure (Table 5).

Patient A has two children, Patient B has three, and Patient D had one by choice.

Problems in the Compassionate IND Program

All four patients described varying degrees of logistical difficulties in obtaining their medicine. All have to travel or make special arrangements with their study physician, who is the arbiter of the potency of received material. All described incidents of inadequate supply or provision of inferior quality cannabis. All have had to supplement their supplies of cannabis from illegal black market sources at times.

All have experienced inconveniences or security concerns when traveling. One, Patient C, was arrested, detained, and had some of his medicine permanently confiscated without replacement.

Patients A-C decried the lack of an official identity card that might be readily recognized and accepted by law enforcement and security personnel. Rather, all used combinations of letters and other documents to convey their legal status to interested authorities, often to the accompaniment of much doubt and suspicion. All describe significant worry and anxiety about their medicine supplies, and whether official promises of continuation of the program will be honored.

A paramount issue affecting the Compassionate IND patients revolves around cannabis quality. It has been well established that recreational cannabis smokers prefer higher potency materials (Herning, Hooker, and Jones 1986; Chait and Burke 1994; Kelly et al. 1997). The same pertains for most clinical cannabis patients.

Chait and Pierri (1989) published a detailed analysis of NIDA marijuana cigarettes that is worthy of review in this context. NIDA mari-

juana is grown outside, one crop per biennium, harvested from a 5-acre facility at the University of Mississippi. Average yield of "manicured material" is 270 g per plant or 270 g per square foot (letter from NIDA, Steven Gust to Chris Conrad, August 18, 1999). Material is shipped to the Research Triangle Institute in North Carolina where it is chopped and rolled on modified tobacco cigarette machines, then stored partially dehydrated and frozen. Cigarettes average 800-900 g in weight. Material requires rehydration before usage, which the IND patients usually achieve by storage overnight in a refrigerated plastic bag with leaves of lettuce.

As of 1999 (letter, Steven Gust to EBR, June 7, 1999), NIDA had available cannabis cigarettes of 1.8%, 2.8%, 3.0%, and 3.4% THC, and bulk cannabis of up to 5% THC content. Other cannabinoid components were not quantitated. It was further stated that the strongest material was not provided to patients in their cigarette shipments because it was too sticky and would interfere with the rolling machine's functioning (Personal Communication to EBR, Steven Gust, December 1999).

Static burn rates of NIDA cannabis cigarettes were inversely related to potency (Chait and Pierri 1989), while the number of puffs that could be drawn from each cigarette averaged 8.8. While total particulate matter increased with potency, arguably less smoked material is necessary for medicinal effect. Of more concern, carbon monoxide levels were highest in the lower potency material; that is, CO was inversely proportional to THC content. Finally, test subjects in their study of NIDA cannabis reported (pp. 66-67), "that the marijuana is inferior in sensory qualities (taste, harshness) than the marijuana that they smoke outside the laboratory. Some have stated that it was the worst marijuana they had ever sampled, or that it tasted 'chemically treated.'"

All the study patients criticize the paper employed to roll the cannabis cigarettes as harsh, and tasting poorly. NIDA cannabis cigarettes resemble Pall Mall® brand tobacco cigarettes without the logo (Figure 3).

All study patients clean their cannabis and re-roll the material to varying degrees, although at least one former IND patient, now deceased, used the NIDA cigarettes unaltered.

NIDA cannabis is shipped to patients in labeled metal canisters containing 300 cigarettes (Figure 4), and material is frequently two or more years old upon receipt. Even under optimal storage conditions, a certain degree of oxidation of cannabinoids can be expected (Grotenhermen 2001). Most consumers prefer a supply of cured cannabis that is as fresh as possible.

FIGURE 3. NIDA Joints/Pall-Mall®

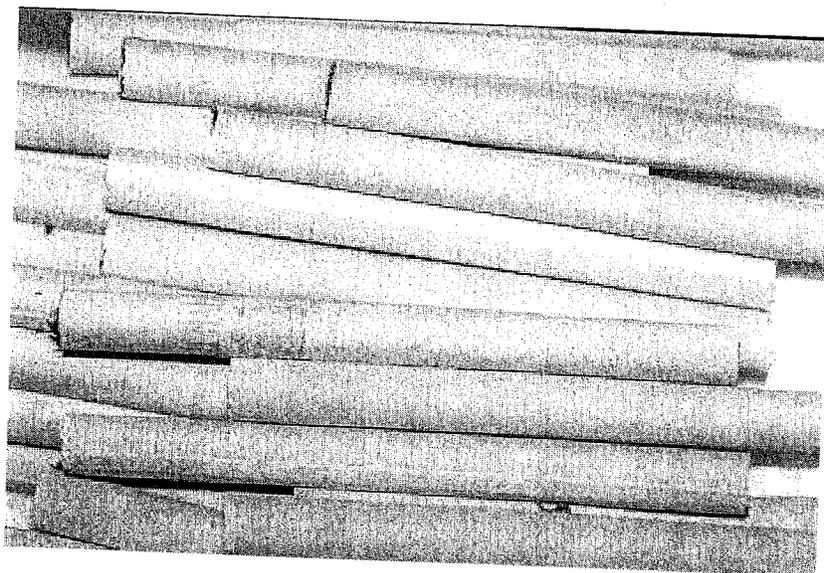
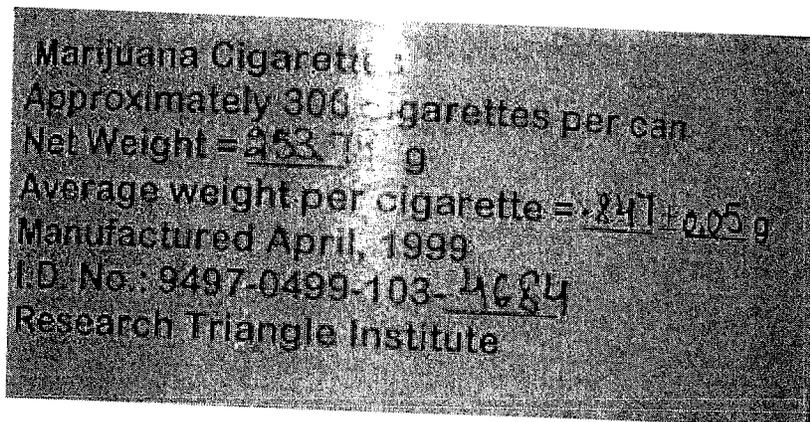


FIGURE 4. Steel Canister with Label



A close inspection of the contents of NIDA-supplied cannabis cigarettes reveals them to be a crude mixture of leaf with abundant stem and seed components (Figures 5-6). The odor is green and herbal in character. The resultant smoke is thick, acrid, and pervasive.

In contrast, a typical sinsemilla "bud" is seedless, covered with visi-

FIGURE 5. Loose NIDA Cannabis as Provided to Compassionate IND Patients



FIGURE 6. Close-Up of Debris from Three NIDA Cannabis Cigarettes



ble glandular trichomes (see journal cover), and emits a strong lemony or piney terpenoid scent. The smoke is also less disturbing from a sensory standpoint to most observers.

Whittle, Guy, and Robson (2001) describe in detail the markedly contrasting steps undertaken in a government approved clinical cannabis program in the United Kingdom. Their material is organically grown in soil with no chemical treatment under controlled indoor conditions. All male plants are eliminated, and only unfertilized female flowering tops are harvested for further processing. This material is assayed for cannabinoid and terpenoid content, with controlled ratios through genetic selection of seed strains before extraction. THC yields obtained are routinely 15-20% (Personal Communication, GW Pharmaceuticals, 2000).

Harm reduction techniques in relation to clinical cannabis consumption are well advanced (Russo 2001; Grotenhermen 2001a, 2001b). Particular attention is merited toward vaporization techniques that provide cannabinoid and terpenoid component administration to prospective clinical cannabis patients without pyrolysis (Gieringer 1996a; Gieringer 1996b; Gieringer 2001). Sublingual administration of cannabis extracts is another most promising technique of clinical cannabis administration (Whittle, Guy, and Robson 2001).

Three of the four study subjects have employed Marinol®, and found it inadequate or a poor substitute for cannabis in symptomatic relief of their clinical syndromes.

CONCLUSIONS AND RECOMMENDATIONS

1. Cannabis smoking, even of a crude, low-grade product, provides effective symptomatic relief of pain, muscle spasms, and intra-ocular pressure elevations in selected patients failing other modes of treatment.
2. These clinical cannabis patients are able to reduce or eliminate other prescription medicines and their accompanying side effects.
3. Clinical cannabis provides an improved quality of life in these patients.
4. The side effect profile of NIDA cannabis in chronic usage suggests some mild pulmonary risk.
5. No malignant deterioration has been observed.
6. No consistent or attributable neuropsychological or neurological deterioration has been observed.
7. No endocrine, hematological or immunological sequelae have been observed.

8. Improvements in a clinical cannabis program would include a ready and consistent supply of sterilized, potent, organically grown unfertilized female flowering top material, thoroughly cleaned of extraneous inert fibrous matter.
9. It is the authors' opinion that the Compassionate IND program should be reopened and extended to other patients in need of clinical cannabis.
10. Failing that, local, state and federal laws might be amended to provide regulated and monitored clinical cannabis to suitable candidates.

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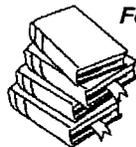
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