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The Drug Policy Letter

number 28

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THE DRUG WAR IN BLACK AND WHITE

ONE IN THREE YOUNG BLACK MEN IN THE UNITED STATES IS UNDER CRIMINAL JUSTICE CONTROL • ONE IN 15 BLACK MALES IS INCARCERATED • 683,200 BLACK MALES ARE BEHIND BARS, COMPARED WITH 674,400 WHITE MALES • BLACKS MAKE UP 12% OF THE U.S. POPULATION, 13% OF DRUG USERS, BUT 55% OF CONVICTIONS FOR DRUG POSSESSION • IT TAKES FIVE GRAMS OF CRACK TO GET FIVE YEARS IN FEDERAL PRISON, VERSUS 500 GRAMS OF POWDER COCAINE • 94% OF 3,430 CRACK DEFENDANTS IN FEDERAL COURTS IN 1994 WERE BLACK • AIDS IS NOW THE LEADING CAUSE OF DEATH FOR BLACK MEN AGES 25 TO 44 • 73,415 BLACK AMERICANS HAD INJECTION-RELATED AIDS OR HAD DIED FROM IT BY THE END OF 1994 • IN 1994, TWICE AS MANY NEW CASES OF INJECTION-RELATED AIDS WERE DIAGNOSED AMONG BLACK AMERICANS (14,443) AS WERE DIAGNOSED AMONG WHITES (7,168) • FOR BLACK INJECTING DRUG USERS, THE RISK OF GETTING AIDS IS SEVEN TIMES THE RISK OF DYING FROM AN OVERDOSE

CASA'S HOUSE OF CARDS 

How a recent analysis of "drug-related" crime gets it all wrong.

THE NEWEST ENTRY IN THE PROPAGANDA war against drug policy reform is a 62-page white paper produced by Joseph Califano's Center on Addiction and Substance Abuse entitled, "Legalization: Panacea or Pandora's Box?" CASA's report aims to be the definitive deconstruction of arguments for legalization, but it is full of holes.

A case study of the problems with the report is the chapter on "drug-related" crime and violence. The chapter begins with an overview of the position taken by drug war critics: "Legalization advocates contend that drug-related violence is really drug-trade-related violence. They argue that what we have today is not a drug problem, but a drug prohibition problem, that anti-drug laws spawn more violence and crime than the drugs themselves" [emphasis in original]. That is a decent summary, although few, if any, reformers argue that we have no drug problem at all. How does CASA attack the reformers' position?

Tactic #1: Ignoring alcohol and more relevant research. CASA begins by citing a study of 130 "drug-related" homicides (in New York State in 1984), noting the study's finding that about 60 percent of the murders resulted "from the psychopharmacological effects of the drug" — people killing because of their intoxication — with 20 percent related to the drug trade and 3.1 percent traced to economic incentives — murdering for money to buy drugs.

But what "drugs" were involved in these homicides? To judge by how CASA presents these figures, one would reasonably assume that the study covered illicit drugs only. Not so. The study — which was done by Paul Goldstein and Henry Brownstein and published in a book called *Drugs, Crime and the Criminal Justice System* — reveals the prominent role of alcohol use in these crimes.

In reporting their results, the researchers provide summaries of eight of the psychopharmacological murders. Reading them, one quickly finds barroom brawls and people drinking heavily just before committing murder. Alcohol is mentioned in seven of the eight case summaries.

If you don't account for alcohol — a legal drug long established as a major contributor to violent behavior — then the statistics do not say much about the role of illegal drugs in homicides.

CASA wanted to portray its opponents as mistaken for suggesting that the drug trade, not drug use, plays a major role in violence. But CASA's source does not refute the position taken by anti-prohibitionists. Indeed, it does not even give a good picture of the work of Goldstein and Brownstein. Ironically, the same authors later produced one of the seminal studies *strengthening* the case against

prohibition.

That study — not cited by CASA — classified "drug-related" homicides (this time in New York City in 1988) by motives and circumstances. (See *Contemporary Drug Problems*, Winter 1989, and *The Drug Policy Letter*, March/April 1990.) The researchers found that 74 percent of "drug-related" homicides (162 out of 218) occurred as a result of the drug trade, with only 14 percent (31 homicides) traceable to psychopharmacological causes. Two out of three of these psychopharmacological murders involved alcohol use.

These results strongly indicated that the unstable black market for crack cocaine led to a rash of homicides in New York City in 1988, while the use of the drug barely registered as a cause of murder. Only five of the 218 "drug-related" homicides studied were linked to crack use, while 106 out of 162 drug-trade murders were in the crack trade.

There are two key advantages to this later Goldstein/Brownstein study over the study cited by CASA: 1) the homicides studied occurred during the late-1980s explosion of crack in New York City, and 2) the conclusions more carefully differentiate among drugs and their roles in homicide; a whole section focuses on crack cocaine. The researchers concluded, "while these events [homicides] were tragedies, they are hardly the basis for claims that crack induces violent behavior." *

Any way you slice it, CASA's choice of a source here is suspect. If CASA was aware of the later Goldstein/Brownstein study, but chose to cite the earlier study instead, this chapter is a shell game. If CASA was unaware of the later study, one must ask why the group purports to be expert in this matter. But, even granting such naivete, CASA's glossing over alcohol's major role in murders labeled simply "drug-related" is either sloppy or deceptive — or both.

Tactic #2: Presuming that drug use causes violence. Later in this chapter on crime and violence, CASA mentions "psychopharmacological violence, such as that caused by cocaine psychosis," and alleges that cocaine, crack, methamphetamine and PCP are "drugs closely associated with violent behavior." Here, CASA is establishing a link to a popular, though misguided, prejudice — the notion that the use of illegal drugs frequently makes people violent.

CASA notes only an *association* between these drugs and violence, rather than stating outright that drug use is the *cause*. But most readers will miss this distinction, since it comes amid speculation on the results of legalizing drugs, including "the threat of rising violence."

To support this fear, CASA notes that "past increases in the New York City homicide rate have been tied to increases in cocaine use." The cite is to an article in the July 6, 1994

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An Examination of Benefits
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edition of the *Journal of the American Medical Association*.

The *JAMA* article summarizes findings from a study of homicides in New York City in 1990 and 1991. However, the article does not say what CASA is implying — that users of cocaine were responsible for outbursts of violence. The study was about the demographics of murder victims, not the circumstances of the deaths or the motives of the killers.

The *JAMA* authors did comment that "it is likely that cocaine use was related to the high rates of homicide, particularly among African-Americans and Latinos." What was the association of cocaine use with homicide? The researchers could not specify. But they did speculate, offering two possibilities: that drug users provoked their killers while high, or that victims were killed as a result of the burgeoning drug trade.

In choosing to cite the *JAMA* article, CASA must have assumed that many of these murders were induced by drug use. Yet *JAMA* provides no support for that notion. CASA's inferred cocaine-crazed killer simply would not have appeared in this study's data on victims. *JAMA* is an authoritative source, but CASA misrepresented this article's contents.

Moreover, CASA failed to examine the *JAMA* article's own citations, which include seven studies of violence in the cocaine trade. One is the 1989 Goldstein/Brownstein study that pointed to prohibition as the cause of most "drug-related" murders in New York City. Why were the *JAMA* writers aware of that study and others, while CASA remained blind to the research in the field?

CASA's prejudice is evident in this conclusion: "any decreases [after legalization] in violent acts committed because of the current high cost of drugs would be more than offset by increases in psychopharmacological violence." That is an assertion that, to be credible, would require a careful comparison of data and reasonable projections. But CASA did not do that heavy lifting, and the studies cited in this chapter do not support the group's conclusion.

Tactic #3: Devising dubious comparisons, neglecting data supporting critics. One of the most potent arguments against drug prohibition is that it creates incentives for crime on a massive scale. We have already seen CASA try to confuse the relationship of drugs and prohibition to violence by ignoring a confounding factor, alcohol, and by misrepresenting studies of "drug-related" homicides. The other major category of prohibition-driven crime is the range of offenses committed by users to get money for drugs.

This category of crimes, often called "acquisitive" or "economic-compulsive" crime, consists mainly of property crimes, since drug users want cash or items they can sell. Yet each such crime carries the risk of escalation into violence. Some research suggests that one in four property crimes is committed for drug money.

CASA makes just one attempt to diminish reformers' argument that prohibition causes much of this crime. The relevant passage: "U.S. Department of Justice statistics reveal that six times as many homicides, four times as many assaults

The Center on Addiction and Substance Abuse at Columbia University describes itself as a "think/action tank" concerned with abuse of both legal and illegal drugs. CASA is led by Joseph Califano Jr., who served presidents Johnson and Carter in top domestic policy roles, and Dr. Herbert Kleber, an addiction researcher and



deputy drug czar for President Bush. Funding for CASA is mainly from private sources, though the group has project grants from federal agencies. To order the anti-legalization white paper, send \$8 to CASA at 152 W. 57th St., New York, NY 10019-3310.

and almost one and a half times as many robberies are committed under the influence of drugs as are committed in order to get money to buy drugs." The cite is to a 1991 survey of state prison inmates published by the Justice Department's Bureau of Justice Statistics (BJS).

CASA is not refuting the anti-prohibition argument, but instead is drawing attention to a comparison of dubious relevance. The right question would be: Does the high price of drugs under prohibition drive a significant amount of property crime? Boiled down, CASA's point is: Drug intoxication is a more prevalent cause of crime than the need for drug money.

The role of drug intoxication as a causal factor in crime is, again, not as clear as CASA suggests. As with the previous data on drugs and violence, CASA failed to account for alcohol in the data cited here. A closer look at the BJS survey of prison inmates reveals a familiar pattern: two out of three of the homicides and two out of three of the assaults that involved illegal drug use also involved alcohol use.

This repeated failure to acknowledge the role of alcohol in violent crimes is especially strange coming from CASA. In its other reports and programs, the group rightly takes a "big picture" view of substance abuse, consistently including the dangers and costs of alcohol and tobacco use. This white paper seems to be CASA's worst slip into the traditional blame-drugs-first posture of prohibitionists.

If drug intoxication accounts for more crimes than the need for drug money, CASA has not proved it. And CASA never tried to counter the notion that much property crime is driven by the need for drug money.

Incredibly, CASA ignored data in the same BJS report that supports this notion. On the very same page of the BJS report from which CASA pulled its data are the following facts (the first two appear in bold type):

- "Money for drugs motivated more than a quarter of the inmates sentenced for robbery, burglary or larceny."
- "Drug users were more likely to have committed crimes that could get them money."
- Percentages of offenses for which the motive was money for drugs — robbery: 27 percent; burglary: 30 percent; larceny: 31 percent; drug trafficking: 25 percent.

These figures indicate that, in this country, one in four property crimes and a quarter of major drug crimes are driven by the need for drug money. If true, these facts would bolster anti-prohibition arguments. Is it any wonder CASA failed to notice or report them? ♦

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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 marihuana (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 Marihuana 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/ Factorium/ 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	61.8	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	1.1	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 (premenopausal)

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.

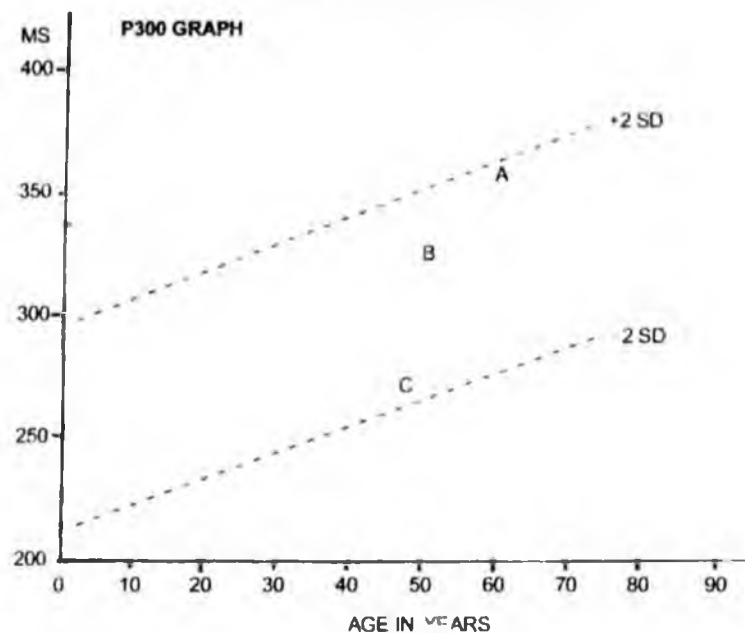
The patient had a P300 test performed with a latency of 355 milliseconds, within normal limits for a normed population in this laboratory (Figure 1).

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 and 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 pm 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 nursued. 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 Marino![®] 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 nonnal 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 (Fligiel 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 marijuana (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 employ 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 that 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®

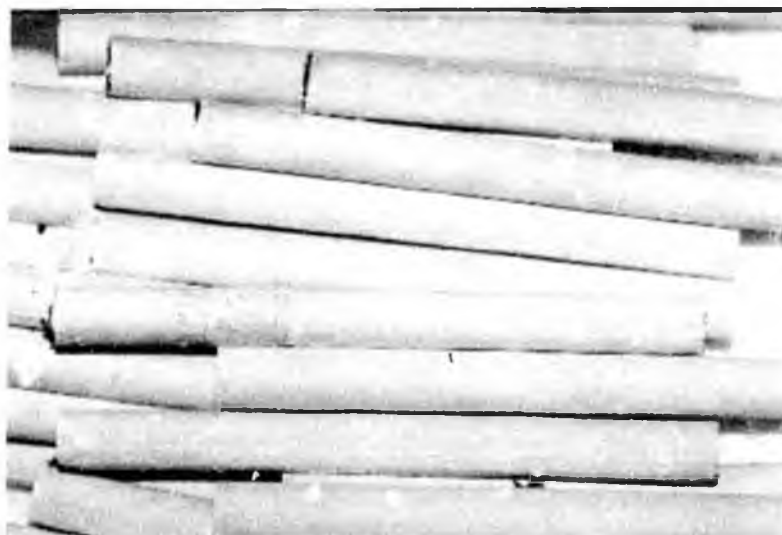
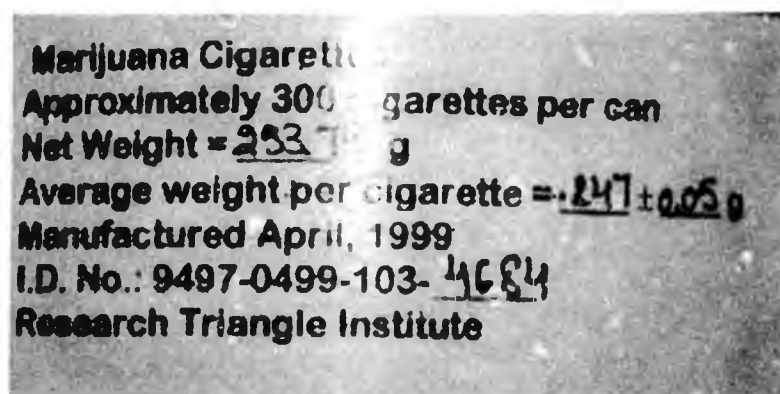


FIGURE 4. Steel Canister with Label



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

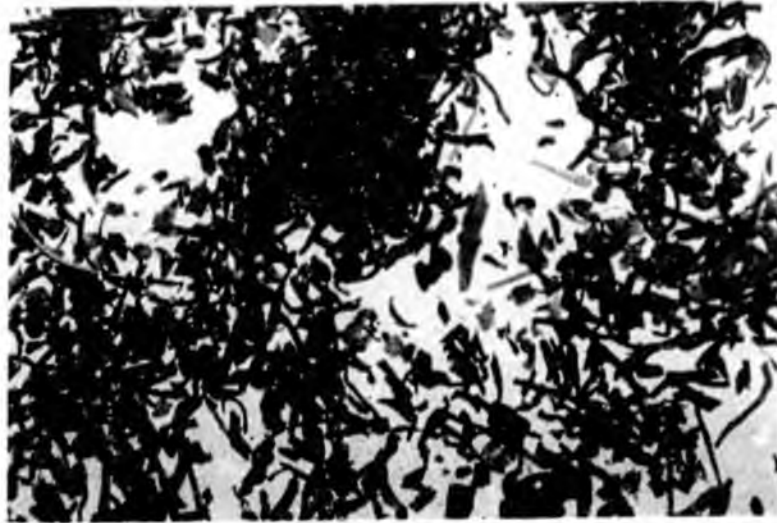


FIGURE 6. Close-Up of Debris from Three NIDA Cannabis Cigarettes



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 intraocular 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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Review

The good and the bad effects of (–) *trans*-delta-9-tetrahydrocannabinol (Δ^9 -THC) on humans

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Abstract

This review analyzes the therapeutic usefulness of Δ^9 -tetrahydrocannabinol and its potential to induce adverse reactions on humans. During the last 30 years an enormous amount of research was carried out resulting in the disclosure of the cannabinoid system in Central Nervous System, with its CB₁ and CB₂ receptors, and the agonist anandamide. Under the clinical point of view, Δ^9 -THC produces some therapeutic benefits which are beyond reasonable doubt. Thus, the effects on nausea/emesis due to cancer chemotherapy, as appetite promoter, on some painful conditions and on symptoms of multiple sclerosis are clearly demonstrated.

Δ^9 -THC is not devoid of ill effects. On the cognitive domain it impairs the human capacity to discriminate time intervals and space distances, vigilance, memory and the performance for mental work. On the psychic area Δ^9 -THC may induce unpleasant reactions such as disconnected thoughts, panic reactions, disturbing changes in perception, delusions and hallucinatory experiences. However, long term effects on the psyche and cognition are not known as there are no reports of prolonged use of Δ^9 -THC. Actually, it has been proposed by WHO that Δ^9 -THC should be rescheduled to schedule IV of the United Nations Convention on Psychotropic Drugs, as it does not constitute a substantial risk to public health and its abuse is rare if at all.

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Keywords: Δ^9 -THC; Dronabinol dependence; Abstinence; Multiple sclerosis; Nausea and vomiting; Appetite promoter**Contents**

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In an interesting review article on the history of cannabis use as a medicine—*The Forgotten Medicine*—by Aitken and Mikuriya (1980), two quotations deserve attention: “in 1890 Dr J. Russel Reynolds, Physician in Ordinary to Queen Victoria wrote: Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess;” and “quote from the Egyptian Government’s Annual Report on Narcotics, 1944: Cannabis is a thoroughly vicious drug, deserving the odium of civilized people”.

Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism and even ideology have managed to lead cannabis to ups

and downs concerning both its medicinal properties and its toxicological and dependence-inducing effects. However, several breakthroughs occurred during the last 50 years and, consequently, the situation is now settled, at least partially, in that cannabis and its main active principle Δ^9 -THC may actually be valuable medicines and the plant cannabis is not a ‘thoroughly vicious drug’.

Delta-9-tetrahydrocannabinol, or 6a, 7, 8, 10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-benzo[b,d]-pyran-1-ol, is a substance possessing several stereochemical variants. One of them is (–)-*trans*-delta-9-tetrahydrocannabinol, also called dronabinol or Δ^9 -THC.

It was isolated, identified and synthesized in the 1960s (Gaoni and Mechoulam, 1964). The identification of several other cannabinoid compounds were also achieved in

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the following years. Among them the isomer Δ^8 -THC which is, however, less potent than Δ^9 -THC (Karniol and Carlini, 1973).

Almost three decades later, cannabinoid receptors in the brain were described (for reviews see Howlett, 1995; Childers and Breivogel, 1998; Perwee, 1997, 1999) their cloning were achieved (Zinaldi-Carmona et al., 1996) and anandamide, the endogenous cannabinoid, was isolated and identified (Devane et al., 1992; Mechoulam et al., 1998a; Martin et al., 1999). Several analogs of anandamide were synthesized and structure-activity relationships were established (Mechoulam et al., 1998b).

All accomplishments concerning the chemistry of marijuana constituents and the description of an endogenous cannabinoid system were accompanied by a great deal of research on cannabinoid pharmacology and opened up opportunities to resume clinical research with these substances, mainly Δ^9 -THC.

1. Beneficial effects (therapeutic effects) of Δ^9 -THC

Much of the research carried out more recently in several countries dealt with old therapeutic folk uses of marijuana (Consoe et al., 1975; Mechoulam and Carlini, 1978; Mechoulam et al., 1984), such as the possible anti-epileptic and hypnotic properties of Δ^9 -THC and cannabidiol, the latter a non-hallucinogenic cannabis constituent (Cunha et al., 1980; Carlini and Cunha, 1981). Other therapeutic indications such as anti-emetic, as antispasmodic, as analgesic, in glaucoma, as hypnotic, in asthma, in epilepsy, as appetite stimulant, as anxiolytic, and in Tourette syndrome, deserved also pre-clinical and clinical studies (Nakano et al., 1978; Ilana et al., 1981; Musty, 1984; Sethi et al., 1986; Ashton, 1999; Ashton, 2001; Williamson and Evans, 2000; Söderpalm et al., 2001; Robson, 2001; Müller-Vahl et al., 2002).

For a few therapeutic indications Δ^9 -THC produce beneficial clinical results that are beyond reasonable doubt (for review articles see Formukong et al., 1989; Mechoulam et al., 1998a; Williamson and Evans, 2000; Robson, 2001; Grotenhermen and Russo, 2002; Iversen, 2003). In the present review article four of them will be approached, namely, the (Δ^9 -THC) effects on nausea/vomiting, on appetite, on pain and on symptoms of multiple sclerosis.

One such clinical indication refers to the anti-emetic effect in cases of chemotherapy associated nausea and emesis. The first randomized, double-blind placebo-controlled trial was that of Sallan et al. (1975) showing that Δ^9 -THC was more effective than placebo in controlling nausea/vomiting of cancer patients receiving chemotherapy. The control of emesis afforded by Δ^9 -THC far exceeds that provided by prochlorperazine (Ort et al., 1980); it abolishes totally or partially the nausea and vomiting refractory to

standard anti-emetic agents in 72% of patients (Lucas and Laszlo, 1980).

Poster et al. (1981) reviewed seven well-controlled studies on the subject; in six of them Δ^9 -THC was a superior anti-emetic compared to control agents. These authors also concluded that toxic effects were manageable and suggested that THC use represents a major advance in anti-emetic therapy. In a more recent review (Tramer et al., 2001) on the anti-emetic effect of cannabis compounds, involving 1366 cancer patients participating in 30 randomized studies, it was shown that cannabinoids act slightly better than alizapride, chlorpromazine, haloperidol, domperidone, metoclopramide, prochlorperazine and thiethylperazine in crossover trials. These patients selected cannabinoids for future chemotherapy (Tramer et al., 2001). Very successful treatment for nausea and vomiting was also reported by Musty and Rossi (2001). These authors examined the reports obtained from six American States, which conducted clinical trials on 748 cancer patients who smoked marijuana, and 345 patients who used oral Δ^9 -THC. Both treatments promoted, respectively, 70–100% and 76–88% relief from nausea and vomiting.

The beneficial effects of Δ^9 -THC on nausea/vomiting are partially counterbalanced by the adverse reactions reported by the patients such as drowsiness, apprehension and anxiety, dry mouth, etc. It is possible that such undesirable side effects may be minimized by simultaneous administration Δ^9 -THC and cannabidiol, as observed in healthy subjects (Karniol et al., 1974; Zuardi et al., 1982).

Another clinical indication that is well established refers to the appetite promoter effect of marijuana and of cannabinoids (Hollister, 1971; Mechoulam and Carlini, 1978; Mattes et al., 1994). It is a clinical fact that HIV patients are prone to severe weight loss due to anorexia (Clebowski et al., 1989); Δ^9 -THC improved appetite in these patients, and consequently brought also a betterment of their nutritional status and of other symptoms such as improving mood and decreasing nausea (Struwe et al., 1993; Beal et al., 1995, 1997). The anorexia-cachexia associated with cancer may also be counteracted by Δ^9 -THC (Eker et al., 1979; Gorter, 1991; Plasse et al., 1991). In fact, the promotion of appetite in marijuana smokers is a well-known fact (Foltin et al., 1988); therefore it is not surprising that Δ^9 -THC has been considered as an effective appetite stimulant drug in cancer patients (Regelson et al., 1976).

An interesting corollary of these findings is the recent demonstration of the potent anorectic effect in obese animals of the substance SR 141716, an antagonist of the cannabinoid receptor CB₁ (Colombo et al., 1998; Mechoulam and Fride, 2001; Cota et al., 2003; Vickers et al., 2003).

It has also been shown in rats that cannabinoid antagonists may prevent the relapse of cocaine use (De Vries et al., 2001; Piomelli, 2001) and the self-administration of methamphetamine (Vinklerová et al., 2002).

According to Girottenhermen (2002a) the effects of cannabinoids on painful conditions of several aetiologies are relatively well confirmed. In fact, several recent review articles analysed anecdotal reports and controlled clinical trials on the analgesic effect of Δ^9 -THC and other cannabinoids in painful conditions such as cancer, damaged nerves, migraine, post-operative pain, spinal cord injury, dental pain, phantom limb pain, etc. (Noyes et al., 1975; Formukong et al., 1989; Ashton, 1999; Williamson and Evans, 2000; Robson, 2001; Holdecroft, 2002; Vaughan and Christie, 2002). The very ancient use of marijuana smoking as a headache and migraine medicament, reviewed by Russo (1998, 2001), adds support to the contention that Δ^9 -THC and other cannabinoids are indeed active in alleviating pain.

In general, all the reports and trials analysed in the above mentioned reviews acknowledge that Δ^9 -THC does indeed have analgesic properties which, according to some authors, approximately matches that of codeine. However, side effects such as sedation, dizziness, ataxia, blurred vision, tachycardia, psychological disturbances as anxiety and fear near panic states, may limit its use. Nevertheless, it also should be taken into consideration that these side effects are not life threatening as those from opiates, which also produce an array of adverse reactions.

Recently, Campbell et al. (2001) reviewed 20 randomized control led trials, nine from those being analyzed; a total of 222 patients participated in five trials on cancer pain, two on postoperative pain and two on chronic non-malignant pain. They concluded that the analgesic effects of cannabinoids were as effective as 50–120 mg of codeine.

The effects of *Cannabis sativa* L. on muscle spasticity, tremors, and neuropathic pain are known since at least the 19th century; in fact, famous physicians of that time, such as W. O'Shaughnessy in India and J.R. Reynolds in England (the personal physician of Queen Victoria), were enthusiastic prescribers of Indian Hemp (Aitken and Mikuriya, 1980; Robson, 2001; C. Spoon and Bakalar, 1993). Near 150 years later, Consoe et al. (1997), through interviews with 112 multiple sclerosis (MS) patients, confirmed the striking improvement (according to the patient's reports) afforded by cannabis smoking on MS symptoms such as the relief of chronic pain, night-time spasticity, tremor, impaired balance and trigeminal neuralgia associated with the disease.

Results obtained with clinical trials employing Δ^9 -THC in MS patients are consistent with the claims of the Consoe's respondents (1997). Thus, Petro and Ellenberger (1981), Clifford (1983), Ungerleider et al. (1987), Meinel et al. (1989), Maurer et al. (1990), Brenneisen et al. (1996), reported that MS patients receiving Δ^9 -THC presented improvements in tremor, ataxia, spasticity, nocturia and in well-being; adverse reactions as dysphoria, headache, dry mouth, a 'high' sensation were also described.

On the other hand, at least two studies did not confirm these beneficial effects. In one of them (Killenstein et al., 2002) Δ^9 -THC not only was unable to reduce spasticity, but also worsened the MS patients global impression; Greenberg et al. (1994), on the other hand, found that marijuana smoking further impaired the posture and balance in MS patients.

However, any possible doubts that might exist on whether or not Δ^9 -THC is an useful medicine for MS symptoms, were removed by the results obtained in four very recent randomized, double-blind, placebo-controlled trials (Anonymous, 2002a, b). In these studies, 344 patients suffering from MS and neuropathic pain received a cannabis extract containing Δ^9 -THC and cannabidiol (CBD) as its principal components; the medicine was delivered by mean of a spray into the mouth. The four studies evaluated the effects of the Δ^9 -THC/CBD mixture on, respectively; neuropathic pain (66 patients), chronic refractory pain due to MS (70 patients), general symptoms of MS (160 patients), and pain due to brachial plexus injury (48 patients). In all the four studies a statistically significant improvement in the symptomatology and an excellent safety profile were obtained which could in part be due to the self-titration of the dose by the patients (Anonymous, 2002b). A first detailed study on this striking beneficial effect of Δ^9 -THC/CBD mixture on the multiple sclerosis symptomatology has been published very recently (Wade et al., 2003); 24 patients obtained great relief from pain; bladder control, muscle spasms and spasticity were also improved. Side effects were predictable and well tolerated.

This lack of side effects could also be due to fact that cannabidiol is able to block anxiety and other ill effects of Δ^9 -THC (Karmiol et al., 1974). In conclusion it can be said that the statement by Drs Hare and Christie (1892) more than 100 years ago ('Cannabis is very valuable for the release of pain, particularly that depending on nerve disturbances: it produces sleep, it gives great relief in paralysis and tends to quiet tremors...') was finally proved to be correct.

2. Adverse effects of Δ^9 -THC

Cannabis sativa L. was and is the most used drug by human beings for hedonistic purposes (UNODC, 2003). And even so, until the recent past, it was not considered as a potent inducer, if at all, of dependence in humans, this being due to the way dependence was defined in the past (Swift and Hall, 2002). However, with the adoption of the DSM-III and other similar criteria to define dependence, there have been recent reports stating that a certain proportion of chronic marijuana users may become dependent (Anthony et al., 1994; Budney et al., 2001; Swift et al., 2001a, b). Another point deserving attention is the very low incidence of ill effects under chronic use. For example,

Russo et al. (2002) described four patients who participated in a Compassionate Investigational New Drug (IND) Program of the American FDA, smoking standardized, heat-sterilized quality-controlled low grade marijuana cigarettes, for 11–27 years. Aside from mild changes in pulmonary function observed in two patients, no other physiological and neurological disturbances were found.

When the subject comes to Δ^9 -THC, the dependence issue becomes clearer. Due to the enormous progress in chemistry, pharmacology, toxicology and clinical pharmacology of Δ^9 -THC, leading to its clinical usefulness, the United Nations in 1991 changed the status of Δ^9 -THC, by removing it from Schedule I (use only for research purposes) and placing it in Schedule II (medical use allowed under strict control of production, trade and stocks) of the 1971 Convention on Psychotropic Drugs. Abstinence symptoms, after being exposed to rather large doses of Δ^9 -THC (80–210 mg/day) were observed in humans participating in clinical laboratory experiments (Jones et al., 1981; Haney et al., 1999). However, according to the WHO Expert Committee on Drug Dependence, abuse of Δ^9 -THC is rare (WHO, 2003); thus, from 103 countries responding a WHO questionnaire, only two indicated some abuse of Δ^9 -THC: Denmark and USA. Actually, the United States informed that only three cases of Δ^9 -THC abuse during the 1992–1994 period were reported by the American Association of Poison Control Centers. In this context it is rather interesting that anandamide has little if any capacity to induce abstinence symptoms and physical dependence in rats (Aceto et al., 1998).

Based on these facts, the WHO Expert Committee on Drug Dependence further considered that the abuse liability of Δ^9 -THC does not constitute a substantial risk to public health and proposed that Δ^9 -THC should be rescheduled to schedule IV of the United Nations 1971 Convention on Psychotropic Substances (WHO, 2003).

Δ^9 -THC does not cause prominent physical changes in users; some degree of dry mouth, blurred vision and ataxia may be reported, and objectively, an increase in heart rate occurs (Carlini et al., 1974).

Δ^9 -THC may adversely affect the psyche, cognition and the psychomotor performance of humans. Examples of acute effects on cognitive functions are: impairment and even loss of the capacity to discriminate or to produce time and distance intervals (Karniol and Carlini, 1973; Carlini et al., 1974; for review see Grotenhermen, 2002b). Thus, volunteers receiving 5–20 mg of Δ^9 or Δ^9 -THC delivered through inhalation perpetrated gross errors when producing a time interval of 60 s; this unwanted effect was present up to at least for 20 min after the cannabinoids aspiration (Karniol and Carlini, 1973). Other ill effects are a decrease of vigilance, of the ability to inhibit responses and to perform arithmetic tasks (for reviews see Leweke, 2002; Iversen, 2003).

Among the psychic effects of acute administration of Δ^9 -THC are feelings of well being, relaxation

and anxiolysis; users may also suffer unpleasant reactions, such as disconnected thoughts, panic reactions, feelings of depersonalization, disturbing changes in perception, delusions and hallucinatory experiences (for reviews see Campbell et al., 2001; Leweke, 2002).

The long-term effects of Δ^9 -THC on the psyche, cognition and brain structures of human beings are not yet, known, as there are not reports of prolonged use of Δ^9 -THC. Thus, there is no mention in the scientific literature of an 'motivational syndrome' caused by the cannabinoid; furthermore it is worth mentioning that even for chronic marijuana use there is no conclusive evidence for the occurrence of this syndrome (Hall and Solowij, 1997; Hollister, 1998; Solowij and Grenyer, 2002; Iversen, 2003).

Similarly, there are no data in scientific literature reporting neuropathological changes in the brain of Δ^9 -THC users; actually, such changes have not been convincingly demonstrated in the brain of marijuana users (for review see Iversen, 2003).

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Long-term effects of exposure to cannabis

Leslie Iversen

The long-term use of cannabis, particularly at high intake levels, is associated with several adverse psychosocial features, including lower educational achievement and, in some instances, psychiatric illness. There is little evidence, however, that long-term cannabis use causes permanent cognitive impairment, nor is there any clear cause and effect relationship to explain the psychosocial associations. There are some physical health risks, particularly the possibility of damage to the airways in cannabis smokers. Overall, by comparison with other drugs used mainly for 'recreational' purposes, cannabis could be rated to be a relatively safe drug.

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Abbreviations

THC Δ^9 -tetrahydrocannabinol

Introduction

Cannabis is the most commonly used illicit drug. In many countries, more than 50% of young people have used it at least once and it is widely perceived as relatively safe. Many people believe that there are genuine medical uses for cannabis-based medicines and it seems likely that such products will gain official approval in several Western countries. Concurrently, there is a move towards relaxation of the criminal penalties associated with the recreational use of cannabis — ranging from the downgrading of criminal penalties in the UK to the possibility of full legalization in Canada and Switzerland. In light of these changes in attitude, it is timely to consider again the adverse effects associated with long-term cannabis use over a period of years, as no drug can ever be considered completely safe.

Effects on cognition

Several studies have addressed the question of whether severe deficits in cognitive function develop in chronic

heavy users of cannabis, or in animals treated for prolonged periods with the drug. Most reports have shown that there are deficits in the performance of complex cognitive tasks in long-term cannabis users, although there is little evidence that these are qualitatively or quantitatively more severe than those seen after acute drug use [1].

More controversial is the question of whether long-term cannabis use can cause irreversible deficits in higher brain function that persist after drug use stops. Human studies are fraught with difficulties, as described in detail by Earleywine [1]. Indeed, many studies have suffered from poor design. One confounding factor in human studies is that comparisons have to be made between groups of drug users versus non-users; however, it is usually impossible to compare the baseline performance of these groups before cannabis use to see if they are properly matched. Pope *et al.* [2], for example, tested 69 early-onset heavy cannabis users (who began smoking before the age of 17) in a battery of neuropsychological tests after a two-week period of abstinence. The group performed significantly worse than late-onset users or controls, but also displayed a lower verbal IQ. When the data were adjusted for this, all differences between early-onset users and others ceased to be significant.

It is not sufficient to identify a group of cannabis users and simply to test them after stopping cannabis use. One study, for example, recruited 63 current heavy users who had smoked cannabis at least 5000 times in their lives and 72 control subjects [3]. The subjects underwent a 28-day washout from cannabis use, monitored by urine assays. At days 0, 1 and 7, the heavy users scored significantly below control subjects on a battery of neuropsychological tests, particularly in recall of word lists. However, by day 28, there were no differences between the groups in any of the test results, and no significant association between cumulative lifetime cannabis use and test scores. The fact that drug-induced effects on cognitive performance can persist for up to a week after stopping the drug (perhaps because of the persistence of Δ^9 -tetrahydrocannabinol [THC] in the body, or because of a subtle withdrawal syndrome) means that many earlier studies that did not allow a sufficiently long washout period might be invalid.

One way of assessing cognitive function is to measure IQ. Fried *et al.* [4] tested the effects of cannabis use in a group of 70 young people by subtracting each person's IQ score at nine years of age (before drug use) from their score at age 17-20 years. Current cannabis use was found to be significantly correlated in a dose-dependent manner with a decline in IQ scores. However, no such decline was seen

in subjects who had formerly been heavy cannabis users and had stopped taking the drug. The authors concluded that cannabis does not have a long-term effect on global intelligence.

This general conclusion was also supported by a review of the 40 published studies that met adequate criteria, which failed to detect any consistent evidence of persisting neuropsychological deficits in cannabis users — although some studies reported subtle impairments in the ability to learn and remember new information [5].

Cannabis and psychiatric illness

There has been a long-standing concern that cannabis use might precipitate mental illness in some users. It is clear that an acute schizophrenia-like psychosis can occur in response to a high dose of cannabis [6^{*}], but whether cannabis use can cause persistent psychiatric illness in people who had not previously shown psychotic symptoms remains contentious. A recent re-analysis of the results of a large scale study of >50 000 Swedish men (age 18–20 years) conscripted into the Swedish army between 1961 and 1970 suggested that those who had used cannabis >50 times before the age of 18 years had a 6.7-fold increased risk of developing schizophrenia in later life [7]. A review of this and four other longitudinal cohort studies also concluded that early cannabis use might be a causal factor for schizophrenia-like illness in later life [8^{**}]. However, the interpretation of such studies is fraught with many difficulties, as reviewed by Macleod *et al.* [9^{**}]. These authors highlighted that proof of a causal relationship is subject to many confounding factors. When known confounding factors were applied to the Swedish army data, for example, the odds ratio was reduced from 6.7 to 3.1 [7]. This, in turn, suggests that other residual unidentified confounding factors are also likely to exist. The published studies show that the existence of 'prodromal' symptoms of psychosis clearly increased the risk of subsequent psychiatric illness in cannabis users [8^{**}]. This factor was adequately controlled for in only one of the five published longitudinal studies [10]. In this New Zealand cohort, even when those exhibiting prodromal symptoms of psychosis were eliminated, those who started cannabis use by age 15 years (but not those who started later) showed a fourfold increase in the risk of developing schizophrenia-like illness by age 26 years. However, the number of subjects involved was small (there were 26 15-year old cannabis users, of whom three developed mental illness) so the statistical power of this study was limited. Degenhardt *et al.* [11] sought to test the hypothesis of a causal relationship between cannabis use and schizophrenia by a careful examination of the incidence of schizophrenia in Australia during the past 30 years. Although the prevalence of cannabis use had increased markedly during this period, there was no evidence of a significant increase in the incidence of schizophrenia. The question of whether

cannabis use can precipitate psychiatric illness in a vulnerable minority of previously well people remains unanswered. One could equally argue that a tendency to psychotic illness might increase the likelihood of early cannabis use [9^{**}]. It is possible that cannabis may precipitate schizophrenic illness earlier in vulnerable people who exhibit 'schizophreniform' tendencies. Such a conclusion is supported by the results of a study of 122 newly admitted schizophrenia patients in the Netherlands, which showed a strong association between cannabis use and the age of onset of the first psychotic episode in men, with users experiencing their first psychotic episode 6.9 years earlier than non-users [12].

Other studies have explored the association between cannabis use and depression. One longitudinal study in Australia reported that daily use of cannabis by teenage girls (but not boys) led to an approximately twofold increased risk for depression/anxiety in later life [13]. A review of other studies of this type suggested that heavy cannabis use may increase depressive symptoms in some users, but whether this represents a causal relationship is again unclear [14].

Psychosocial sequelae of cannabis use

Apart from the potential risk of mental illness, there has been a long standing concern that adolescent use of cannabis could lead to reduced educational achievement and reduced motivation — sometimes referred to as an 'amotivational syndrome' [1].

Cherek *et al.* [15] attempted to assess this experimentally in a study in which human participants earned money by responding on a complex lever-pressing schedule. There was a significant reduction in the number of responses, time spent and money earned when the subjects were re-tested while smoking cannabis, indicating a drug-induced reduction in motivation.

Various longitudinal studies have sought to establish the relationship between cannabis use and subsequent educational achievement. A study of 1265 New Zealand children [16] showed that cannabis use was dose-dependently related to an increased risk of leaving school without qualifications, failure to enter university and failure to obtain a university degree. A similar conclusion was reached in reviews of other published studies of this type [9^{**},17]. The review by Macleod *et al.* [9^{**}] was particularly comprehensive; the authors studied 48 published longitudinal studies on the use of cannabis, of which 16 were considered to provide the most robust evidence. Their conclusions for cannabis use were, firstly, a consistent association with reduced educational achievement; secondly, a consistent association with use of other drugs; thirdly, an inconsistent association with psychological problems of various types; and finally, an inconsistent association with antisocial or other

problematic behaviours. They concluded that "Available evidence does not support an important causal relation between cannabis use and psychosocial harm, but cannot exclude the possibility that such a relation exists".

Whatever the nature of the association, it seems clear that long-term heavy cannabis use carries a variety of negative attributes. A case control study compared 108 heavy-use long-term cannabis users, who had on average smoked 18 000 times, with 72 age-matched controls who had smoked cannabis <50 times [18^{**}]. The heavy-use cannabis smokers reported significantly lower educational attainment and lower income than did controls. When asked to rate the subjective effects of cannabis on cognition, memory, career, social life, physical and mental health and various quality-of-life measures, a large majority of heavy-use cannabis smokers reported negative effects of their drug use.

Cannabis and substance dependence

Although it was previously thought that cannabis was not a drug of addiction, it is now recognized that cannabis use can lead to substance dependence in perhaps as many as 10% of regular users, according to the internationally accepted DSMIV definition of 'substance dependence' [6^{*}]. In both animals and humans, a clear withdrawal syndrome can be identified [6^{*}]. In rodents, chronic administration of THC or synthetic cannabinoids leads to downregulation and desensitization of cannabinoid CB₁ receptors in the brain [19]. This might partly explain the tolerance that develops in both animals and humans on repeated use of the drug. In regular cannabis users, abstinence leads to a withdrawal syndrome characterized by negative mood (irritability, anxiety, misery), muscle pain, chills, sleep disturbance and decreased appetite. A placebo-controlled study showed that these symptoms were significantly reduced by oral administration of THC, suggesting that the withdrawal syndrome and underlying substance dependence were related to effects of THC on the cannabinoid CB₁ receptor, rather than to any other component of herbal cannabis [20].

Other potentially toxic effects of long-term cannabis use

Some of the most serious adverse effects of smoked cannabis are on the respiratory system. Although little progress has been made recently in quantifying such risks, warnings continue to be issued about the potential for long-term damage or even malignancy in the airways [21]. It is known that lung macrophages isolated from cannabis smokers exhibit impaired anti-bacterial activity, and one experimental study showed that this might be caused, in part, by reduced expression of inducible nitric oxide synthase and decreased production of nitric oxide [22]. A review of the evidence for immunosuppressant effects of cannabis concluded that, with the exception of the effects of cannabis smoking on broncho-alveolar immu-

nity, there is no evidence that cannabis causes any other serious immunosuppression in users [23]. The authors suggested that the effects on lung macrophages might be related to the ability of cannabis in animal studies to cause a shift from Th1 to Th2 cytokine production.

With increasing use of cannabis, there remains a concern that cannabis use during pregnancy might impair foetal development. Reviews of data from humans, however, suggest that such effects are minimal for cannabis users when compared with the well-documented adverse effects of tobacco or alcohol use [24,25^{*}]. Nevertheless, treatment of pregnant rats with high doses of THC did lead to significant reductions in expression of neural adhesion molecule 1.1 in the foetal brain — a key protein for brain development [26].

Conclusions

A review of the literature suggests that the majority of cannabis users, who use the drug occasionally rather than on a daily basis, will not suffer any lasting physical or mental harm. Conversely, as with other 'recreational' drugs, there will be some who suffer adverse consequences from their use of cannabis. Some individuals who have psychotic thought tendencies might risk precipitating psychotic illness. Those who consume large doses of the drug on a regular basis are likely to have lower educational achievement and lower income, and may suffer physical damage to the airways. They also run a significant risk of becoming dependent upon continuing use of the drug. There is little evidence, however, that these adverse effects persist after drug use stops or that any direct cause and effect relationships are involved.

In contrast, cannabis might have beneficial effects in some medical indications. There is considerable literature obtained from animal studies to suggest that cannabis has analgesic effects [27]. Until recently, however, there has been a dearth of controlled clinical studies to validate such effects in patients. This has now changed, with the publication in the past two years of a number of double-blind placebo-controlled trials showing the effectiveness of cannabinoids in relieving chronic neuropathic pain [28,29] or pain associated with multiple sclerosis [30^{**}, 31]. The largest of these trials involved 630 multiple sclerosis patients and showed significant pain relief after 15 weeks of treatment with either pure THC or cannabis extract [30]. It seems likely that medicinal cannabis will re-enter the Pharmacopoeia.

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Marijuana and Actual Driving Performance

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LIST OF ABBREVIATIONS

11-OH-THC	11-Hydroxy- Δ^9 -Tetrahydrocannabinol
ANWB	Algemene Nederlandse Wielrijders Bond (Royal Dutch Tourist Association)
BAC	Blood Alcohol Concentration
CS-C	Curve Surface in Body Sway Test with Eyes Closed
CS-O	Curve Surface in Body Sway Test with Eyes Open
CTT	Critical Tracking Test
CV-H	Coefficient of Variation (SD/M) of Headway
CV-IBI	Coefficient of Variation (SD/M) of Interbeat Interval Times
DOT	Department of Transportation
ECG	Electrocardiogram
EtOH	Ethanol
IBI	Interbeat Interval Time
MANOVA	Multivariate Analysis of Variance
NHTSA	National Highway Traffic Safety Administration
NIDA	National Institute on Drug Abuse
PWR-HR	Relative Amplitude in the Power Density Spectrum of Heart Rate between the Frequencies of .07 and .14 Hz
RT	Reaction Time
SD	Standard Deviation
SDLP	Standard Deviation of Lateral Position
SDSP	Standard Deviation of Speed
SDST	Standard Deviation of Steering Wheel Angle
SE	Standard Error (i.e. SD divided by the Square Root of the Number of Observations)
SED	Standard Error of the Mean Difference
SP	Mean Speed
THC	Δ^9 -Tetrahydrocannabinol
THC-COOH	11-Nor- Δ^9 -Tetrahydrocannabinol-9-Carboxylic Acid