

SB

74

FRANK H. MURKOWSKI
GOVERNOR

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January 20, 2005

The Honorable Ben Stevens
President of the Senate
Alaska State Legislature
State Capitol, Room 111
Juneau, AK 99801-1182

Dear President Stevens:

Under the authority of art. III, sec. 18, of the Alaska Constitution, I am transmitting a bill relating to marijuana. I believe it is time for the Alaska Legislature to take a stand and debunk the myth that marijuana is a harmless recreational drug.

It is very troubling to me that our young people have access to the drug and are using it. In recent years, Alaska had the highest rate in the nation of persons over the age of 12 trying marijuana for the first time. Approximately two-thirds of these new smokers were children ages 12 - 17. This same age group of children made up over half of the state's 363 treatment admissions in 2003 for marijuana abuse. Many more go untreated each year.

The problem is particularly great for Alaska Natives. In 2003, the self-reported rate of current use for Alaska Native students in the ninth grade (age 15) was 36.96 percent, nearly three times the rate for non-Native Alaska students. For tenth graders, the rate of current use by Alaska Native students was 41.77 percent. Alaska Natives also made up approximately 35 percent of the statewide treatment admissions for marijuana abuse in 2003. The numbers of our youths trying marijuana for the first time and entering treatment foretells a dim future if nothing is done.

Although marijuana smoke contains hundreds of substances, some of them carcinogenic, the principal psychoactive ingredient is delta-9 tetrahydrocannabinol (commonly known as THC). In the 1960's and 70's, marijuana was primarily used by college students and "hippies," and the average THC content was less than one percent. But today, the average THC content in marijuana is six times that level, at 6.4 percent. Drug dealers in Alaska have turned indoor marijuana growing into a science and marijuana grown here has been found with a THC content in excess of 20 percent. Our young people thus have access to, and are using, marijuana that is a potent hallucinogenic.

In 1975, the Alaska Supreme Court studied marijuana and concluded, in *Ravin v. State*, that the scientific evidence on its effects did not justify making it a

COMMITTEE COPY

crime for adults to possess small amounts in private. More recently, the Alaska Supreme Court has shown an unwillingness to reconsider the latest scientific evidence on the harmful effects of marijuana. A rational evaluation of marijuana's harmful effects must occur, and the Legislature should do that -- not the courts. This bill would provide a forum for the Legislature to hear expert testimony on the effects of marijuana and to make findings that the courts can rely on in cases where marijuana is an issue.

In addition to educating the Legislature, courts, and the public about the harmful effects of marijuana, this bill would deter possession and use of marijuana by increasing criminal penalties for certain types of possession. It also would provide a fair and efficient process for determining the usable weight of live marijuana plants in criminal prosecutions.

Current law makes it a class B felony to give or sell marijuana, and schedule IVA and VA controlled substances, to someone age 18 or younger, but only if the dealer is at least three years older. Right now, if a 19-year-old gives a small amount of marijuana to a 17-year-old, it is the lowest level misdemeanor offense. When the law classifies such conduct as such a low-level offense, it provides no deterrence for young adults.

Marijuana is particularly harmful for young users, and it should be a serious crime to give or sell marijuana to someone under age 21, no matter how old the "dealer" may be. Expanding the current class B felony penalty for providing marijuana, and schedule IVA and VA controlled substances, to someone under age 21, regardless of the age difference between the user and the dealer, would allow the Superior Court to punish adults who supply our youths.

The bill also would make it a class C felony (the lowest felony level) to possess four ounces or more of marijuana, compared to current law, which reserves this felony level only for those who possess a whole pound or more. Four ounces of high-THC marijuana has a street value of up to \$2,000. Given the increase in the value and potency of marijuana, it is appropriate to apply higher penalties to possession of this amount.

The bill also would adjust misdemeanor penalties related to marijuana. The bill would make it a class A misdemeanor to possess one ounce or more of marijuana, as compared with current law, which allows misdemeanor penalties even for those who possess from a half-pound to up to one pound of marijuana. The bill would reserve the lowest misdemeanor penalties (class B misdemeanor), for possession of less than one ounce of marijuana, which is still a significant amount, both in dosage and cost.

The Honorable Ben Stevens

January 20, 2005

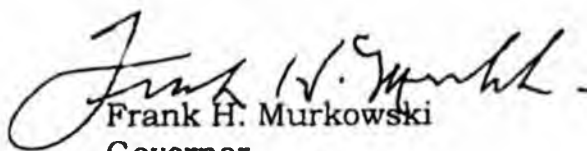
Page 3

The bill also tackles marijuana and driving, which even the Supreme Court in *Ravin* recognized as a potentially serious problem back in 1975. Unlike alcohol, there is no effective way for law enforcement officers to quickly and easily test the amount of marijuana in a person's blood, breath, or urine. Thus, the best way to deter using marijuana and driving is to prohibit it in motor vehicles. This bill would make it a class A misdemeanor for the driver of a motor vehicle to possess any amount while driving or operating a motor vehicle. This is the same level of offense as driving under the influence, although this bill does not require mandatory penalties as required for driving under the influence (DUI) offenses. The bill also would make it a class B misdemeanor if a passenger in a motor vehicle possesses any marijuana, or if the driver allows a passenger to do so.

Finally, the bill would provide a fair and efficient process for determining the usable weight of live marijuana plants. Under current statutory law, to determine the weight of marijuana from a growing plant, the law enforcement officers must harvest, dry, and process the marijuana just like a marijuana grower would. This is required for two reasons. First, the plants cannot be allowed to remain damp, or a mold will form that not only destroys the evidence, but is also dangerous to the officers handling the plants. Second, this processing is statutorily required because the plant can only be weighed after it has been "reduced to its commonly used form." (AS 11.71.080.) The obvious problem with this statute is that it forces the law enforcement officers to operate large marijuana drying and processing facilities at great expense and effort. The plants must be spread out and dried, and then the law enforcement officers must begin the laborious task of separating the less usable stalks from the leaves, buds, and flowers. Even then, there are often arguments in court about whether the law enforcement officers correctly processed the plants, or whether they left in too many stalks. This bill solves the problem by allowing the law enforcement officers to weigh the unprocessed harvested plants, and declares that one-sixth of that weight is used for determining what level of crime is involved. The one-sixth ratio was determined by experimentation of the Alaska State Troopers, and represents an average of several test batches of live marijuana plants that were dried and processed to their "commonly used form."

I urge your prompt and favorable action on this measure.

Sincerely yours,


Frank H. Murkowski
Governor

Enclosure

STATE OF ALASKA

DEPARTMENT OF LAW

OFFICE OF THE ATTORNEY GENERAL

Frank H. Murkowski, Governor

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March 1, 2005

Sectional Analysis of SB 74 (Marijuana)

(Prepared by the Department of Law, March 1, 2005)

SB 74 would enlarge the class of persons to whom delivery of certain controlled substances constitutes a crime; add new types of misconduct involving certain controlled substances that constitute a crime; lower the possession threshold amounts for certain degrees of misconduct involving a controlled substance; make the possession of any amount of marijuana a crime; and change the formula for calculating the aggregate weight of marijuana plants.

Sec. 1: Section 1 sets out the purpose of the bill.

Sec. 2: Section 2 sets out the bill's findings.

Sec. 3: Section 3 makes it a crime under the statute to deliver certain controlled substances to someone under the age of 21. Under the current law, delivery to someone who is under 19 and at least three years younger constitutes a crime.

Sec. 4: Section 4 lowers the minimum amount of certain controlled substances a person must possess to constitute a crime under the statute from one pound to four ounces.

Sec. 5: Section 5 lowers the minimum amount of certain controlled substances a person must possess to constitute a crime under the statute from one pound or more to one ounce or more. It also criminalizes under the statute the act of possessing certain controlled substances while driving or operating a motor vehicle, aircraft, or motorized watercraft.

Sec. 6: Section 6 lowers the minimum amount of certain controlled substances a person must possess to constitute a crime under the statute from less than one-half pound to less than one ounce.

Section 6 also adds the following types of conduct to the list of conduct that is criminalized under the statute:

- manufacture, delivery, or possession with intent to manufacture or deliver less than one ounce of certain controlled substances;

- possession of certain controlled substances while a passenger in a motor vehicle, aircraft, or motorized watercraft;
- being the driver or operator of a motor vehicle, aircraft, or motorized watercraft and knowingly permitting a passenger to possess certain controlled substances.

Sec. 7: Section 7 changes the calculation of the aggregate weight of a marijuana plant to be a percentage of the measured weight of a plant after its roots have been removed.

Sec. 8: Section 8 sets out an immediate effective date.

FISCAL NOTE

STATE OF ALASKA
2005 LEGISLATIVE SESSION

Fiscal Note Number: 1
 Bill Version: SB 74
 (S) Publish Date: 1/21/05

Revision Date/Time (Note if correction): _____ Dept. Affected: Public Safety
 Title An Act relating to marijuana use and possession; RDU Alaska State Troopers
marijuana and misconduct controlled substance Component AST Detachments
 Sponsor Rules Committee
 Requester Governor Component No. 2325

Expenditures/Revenues (Thousands of Dollars)

Note: Amounts do not include inflation unless otherwise noted below.

OPERATING EXPENDITURES	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Personal Services						
Travel						
Contractual						
Supplies						
Equipment						
Land & Structures						
Grants & Claims						
Miscellaneous						
TOTAL OPERATING	0.0	0.0	0.0	0.0	0.0	0.0

CAPITAL EXPENDITURES						

CHANGE IN REVENUES ()						

FUND SOURCE (Thousands of Dollars)

1002 Federal Receipts						
1003 GF Match						
1004 GF						
1005 GF/Program Receipts						
1037 GF/Mental Health						
Other (Specify Type—Do not abbreviate)						
TOTAL	0.0	0.0	0.0	0.0	0.0	0.0

Estimate of any current year (FY2005) cost: 0.0

Mark this box (X) if funding for this bill is included in the Governor's FY 2006 budget proposal: ☐

POSITIONS

Full-time						
Part-time						
Temporary						

ANALYSIS: (Attach a separate page if necessary)

Passage of this Act will have no fiscal impact on the Department of Public Safety. The potential increase in the number of arrests for violations can be handled by available staff. Provisions of this Act will help deter marijuana use and possession overall. The Act also addresses the issue of driving under the influence of marijuana which is a serious problem. Contrary to some contention on the subject, marijuana is not a harmless recreational drug.

Prepared by: Lieutenant Todd Sharp
 Division: Alaska State Troopers
 Approved by: Commissioner William Tandeske
 Agency: Department of Public Safety

Phone 907-269-4532
 Date/Time 1/20/05 2:20 PM
 Date 1/20/2005

FISCAL NOTE

STATE OF ALASKA
2005 LEGISLATIVE SESSION

Fiscal Note Number: 2
 Bill Version: SB 74
 (S) Publish Date: 1/21/05

Revision Date/Time (Note if correction): _____ Dept. Affected: Administration
 Title An Act relating to marijuana RDU Legal and Advocacy Services
use and possession... Component Public Defender Agency
 Sponsor Rules Committee
 Requester Governor Component No. 1631

Expenditures/Revenues (Thousands of Dollars)

Note: Amounts do not include inflation unless otherwise noted below.

OPERATING EXPENDITURES	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Personal Services	115.5	115.5	115.5	115.5	115.5	115.5
Travel	4.8	4.8	4.8	4.8	4.8	4.8
Contractual	35.9	35.9	35.9	35.9	35.9	35.9
Supplies	2.7	2.7	2.7	2.7	2.7	2.7
Equipment	6.7	0.7	0.7	0.7	0.7	0.7
Land & Structures						
Grants & Claims						
Miscellaneous						
TOTAL OPERATING	165.6	159.6	159.6	159.6	159.6	159.6

CAPITAL EXPENDITURES						

CHANGE IN REVENUES ()						

FUND SOURCE (Thousands of Dollars)

1002 Federal Receipts						
1003 GF Match						
1004 GF	165.6	159.6	159.6	159.6	159.6	159.6
1005 GF/Program Receipts						
1037 GF/Mental Health						
Other (Specify Type--Do not abbreviate)						
TOTAL	165.6	159.6	159.6	159.6	159.6	159.6

Estimate of any current year (FY2005) cost: 0.0
 Mark this box (X) if funding for this bill is included in the Governor's FY 2006 budget proposal: ☐

POSITIONS

Full-time	1	1	1	1	1	1
Part-time						
Temporary						

ANALYSIS: (Attach a separate page if necessary)

This proposed bill significantly increases the penalties for possession, use, and delivery of marijuana. It raises from a B misdemeanor to a B felony in many cases the delivery of marijuana, in any amount to someone under 21. Possession of 4 ounces or more of marijuana is raised to a C felony from a misdemeanor. It also adjusts the misdemeanor penalties related to marijuana and creates new misdemeanors for possessing marijuana while driving, permitting a passenger to possess it, or being a passenger in possession. This bill would have an impact on Agency operations. We handle 500 misdemeanor drug cases, primarily involving marijuana. At least half of these would become felonies. Felonies take more work than misdemeanors. Also more misdemeanors would be prosecuted for less amounts and vehicle related offenses. This will increase by 50% the current number of misdemeanor cases handled by the Agency. The Agency will need one full time attorney to meet this increased case and work load. The position would be in Kenai, since their numbers are increasing in this area, and almost match Anchorage.

Prepared by: Linda K. Wilson, Deputy Director Phone (907)334-4416
 Division Public Defender Agency Date/Time 1/19/05 10:32 AM
 Approved by: Micheal Tibbles, Deputy Commissioner Date 1/19/2005
 Agency Department of Administration

FISCAL NOTE

STATE OF ALASKA
2005 LEGISLATIVE SESSION

Fiscal Note Number: 3
 Bill Version: SB 74
 (S) Publish Date: 1/21/05

Revision Date/Time (Note if correction): _____ Dept. Affected: LAW
 Title "An Act making findings relating to marijuana
use and possession; relating to marijuana and misconduct.." RDU CRIMINAL
 Component CDCO
 Sponsor _____
 Requester Governor Component No. _____

Expenditures/Revenues (Thousands of Dollars)

Note: Amounts do not include inflation unless otherwise noted below.

OPERATING EXPENDITURES	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Personal Services						
Travel						
Contractual						
Supplies						
Equipment						
Land & Structures						
Grants & Claims						
Miscellaneous						
TOTAL OPERATING	0.0	0.0	0.0	0.0	0.0	0.0

CAPITAL EXPENDITURES						

CHANGE IN REVENUES ()						

FUND SOURCE (Thousands of Dollars)

1002 Federal Receipts						
1003 GF Match						
1004 GF						
1005 GF/Program Receipts						
1037 GF/Mental Health						
Other (Specify Type--Do not abbreviate)						
TOTAL	0.0	0.0	0.0	0.0	0.0	0.0

Estimate of any current year (FY2005) cost: 0.0

Mark this box (X) if funding for this bill is included in the Governor's FY 2006 budget proposal: ☐

POSITIONS

Full-time						
Part-time						
Temporary						

ANALYSIS: (Attach a separate page if necessary)

This bill creates a new statutory section making findings regarding the mental and physical health risks, illegality and dangers of marijuana use. The bill makes changes to AS 11.71.030, .040, .050, and .060 concerning the crime of misconduct involving a controlled substance by adding additional offenses and significantly decreasing the amount of marijuana in possession that would constitute a violation. All of the conduct prohibited in this bill is already a crime in Alaska, although recent decisions by the appellate courts have made it difficult to investigate and prosecute some of these offenses. We do not expect the policies of police agencies to change significantly in response to this bill, and therefore we do not expect a workload increase above and beyond what was experienced before the courts made prosecution more difficult. Anticipated fiscal impact is zero.

Prepared by: Kathryn Daughetee, Director Phone 465-3673
 Division: Administrative Services Division Date/Time 1/14/05 11:19 AM
 Approved by: Kathryn Daughetee for Gregg D. Renkes, Attorney General Date 1/14/2005
 Agency: Department of Law

FISCAL NOTE

STATE OF ALASKA
2005 LEGISLATIVE SESSION

Fiscal Note Number: 4
 Bill Version: SB 74
 (S) Publish Date: 1/21/05
 Dept. Affected: Health & Social Services
 RDU Juvenile Justice
 Component Probation Services

Revision Date/Time (Note if correction):

Title RELATING TO MARIJUANA USE AND POSSESSION

Sponsor (RLS) BY REQUEST OF THE GOVERNOR

Requester GOVERNOR

Component No. 2134

Expenditures/Revenues

(Thousands of Dollars)

Note: Amounts do not include inflation unless otherwise noted below.

OPERATING EXPENDITURES	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Personal Services						
Travel						
Contractual						
Supplies						
Equipment						
Land & Structures						
Grants & Claims						
Miscellaneous						
TOTAL OPERATING	0.0	0.0	0.0	0.0	0.0	0.0

CAPITAL EXPENDITURES						

CHANGE IN REVENUES (0)						

FUND SOURCE

(Thousands of Dollars)

1002 Federal Receipts						
1003 GF Match						
1004 GF						
1037 GF/Mental Health						
Other(Specify Type-do not abbreviate)						
Other(Specify Type-do not abbreviate)						
TOTAL	0.0	0.0	0.0	0.0	0.0	0.0

Estimate of any current year (FY2005) cost:

Mark this box (X) if funding for this bill is included in the Governor's FY 2006 budget proposal: ☐

POSITIONS

Full-time						
Part-time						
Temporary						

ANALYSIS: (Attach a separate page if necessary)

This bill is not anticipated to have a significant impact on Division of Juvenile Justice staff workloads and therefore no fiscal impact.

Prepared by: Patty Ware
 Division: Juvenile Justice
 Approved by: Joel S. Gilbertson, Commissioner
 Agency: Department of Health and Social Services

Phone 465-2112
 Date/Time 01/20/2005
 Date 01/20/2005

STATE OF ALASKA

DEPARTMENT OF LAW

OFFICE OF THE ATTORNEY GENERAL

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March 4, 2005

VIA HAND DELIVERY

The Honorable Sen. Fred Dyson
Chair, Senate Health, Education, and Social
Services Committee
State Capitol, Room 121
Juneau, AK 99801-1182

The Honorable Sen. Ralph Seekins
Chair, Senate Judiciary Committee
State Capitol, Room 125
Juneau, AK 99801-1182

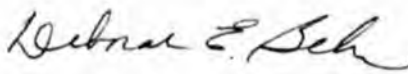
Re: Scheduling SB 74(Marijuana)

Dear Chairmen:

The Department of Law respectfully requests that SB 74 (Marijuana) be scheduled for a joint hearing at your earliest convenience. A sectional analysis, copy of the bill, and fiscal notes are attached.

Sincerely,

SCOTT J. NORDSTRAND
ACTING ATTORNEY GENERAL

By: 
David Marquez
Deputy Attorney General

Cc: w/attachments
Leg.office
Dave Marquez

Gayle Keller

From: Barks [barks@acsalaska.net]
Sent: Monday, March 28, 2005 1:51 PM
To: Sen. Ben Stevens; Sen. Bert Stedman; Sen. Bettye Davis; Sen. Con Bunde; Sen. Donny Olson; Sen. Fred Dyson; Sen. Gary Stevens; Sen. Gary Wilken; Sen. Gene Therriault; Sen. Gretchen Guess; Sen. Hollis French; Sen. John Cowdery; Sen. Johnny Ellis; Sen. Kim Elton; Sen. Lyda Green; Sen. Lyman Hoffman; Sen. Tom Wagoner
Subject: Some information on Marijuana , please read in the ENTIRETY

Some information on Marijuana , please read in the ENTIRETY

Some information about Marijuana , please read before you vote , on the 4 ozs of marijuana issue .

I ask how much alcohol is consumed during an average legislative session by everyone that is involved in the session " including the governor mansion ? [I hear that one security guard down there was fired for even mentioning the amount of booze that our good legislative branch , including help , friends and lobbyist consumed during a legislative session .]

[Referring to included test]

If the same " like test " were applied to people that consumed alcohol in the same degree that the marijuana was consumed in these test , what would the results be ?

Not everyone that smokes a little marijuana goes off the deep end , also not everyone that drinks a little alcohol goes off the deep end ,

At the present time up to 4 ozs of marijuana is legal , if kept in the home . Also cases and cases of alcohol can be legally kept in the home .

So if keeping up to 4 ozs of marijuana is going to be made illegal , then keeping or using alcohol should be made illegal " . Keep the playing field level . Don't be hypocrites

If you vote to change law on marijuana then you should consider voting to make alcohol illegal .

As far as marijuana affecting children in the home , it probably pales , compared to alcohol .

But how would this state get along without the tax on alcohol sales , but that is a different subject , for a different time .

I neither use , or allow in my home , alcohol or marijuana , but I dislike hypocrites , " Like some of those on the hill "

Ora Whittle
barks@acsalaska.net
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P.O. Box 10260
Fairbanks , Alaska 99710

Original page:

<http://my.webmd.com/content/Article/100/105717.htm>

Marijuana's Effects Linger in the Brain Blood Flow to Brain Altered Weeks After Smoking Pot By Jennifer Warner

WebMD Medical News Reviewed By Brunilda Nazario, MD
on Monday, February 07, 2005

Feb. 7, 2005 - The effects of marijuana in the brain may linger long after the last joint goes out.

A new study shows that blood flow to the brain in people who smoked marijuana remained altered up to a month after they last smoked pot.

Researchers say the findings may help explain the problems with memory and thinking found in previous studies of chronic marijuana users.

Marijuana's Effects on the Brain

In the study, which appears in the Feb. 8 issue of Neurology, researchers studied the blood flow in brain arteries of 54 marijuana users and 18 nonusers.

The marijuana users volunteered to participate in an inpatient program and abstained from marijuana use for a month.

Blood flow in the brain was analyzed at the beginning of the study and at the end of the month for the marijuana users.

Researchers found blood flow was significantly higher in marijuana users than in nonusers, both at the beginning and at the end of the study.

However, the marijuana users also had higher scores on the pulsatility index (PI), which is a measure of resistance to blood flow.

Researchers say the level of resistance to blood flow among light and moderate marijuana users improved over the course of the abstinence month. But there was no improvement among heavy marijuana users.

This resistance is thought to be caused by the narrowing of blood vessels that happens when the body's own ability to regulate the circulatory system becomes impaired.

"The marijuana users had PI values that were somewhat higher than those of people with chronic high blood pressure and diabetes," says researcher Ronald Herning, PhD, of the National Institute on Drug Abuse in Baltimore, Md., in a news release. "However, their values were lower than those of people with dementia. This suggests that marijuana use leads to abnormalities in the small blood vessels in the brain, because similar PI values have been seen in other diseases that affect the small blood vessels."

Light marijuana users smoked two to 15 joints per week, moderate users smoked 17 to 70 joints per week, and heavy users smoked 78 to 350 joints per week.

SOURCES: Herning, R. Neurology, Feb. 8, 2005; vol 64: pp 488-493. News release, American Academy of Neurology.

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Original page:

<http://my.webmd.com/content/Article/70/80972.htm>

This article is from the WebMD

Medical News Archive

Heavy Marijuana Use Doesn't Damage Brain Analysis of Studies Finds

Little Effect From Long-Term Use

By Sid Kirchheimer

WebMD Medical News Reviewed By Michael Smith, MD

on Tuesday, July 01, 2003

July 1, 2003 -- Long-term and even daily marijuana use doesn't appear to cause permanent brain damage, adding to evidence that it can be a safe and effective treatment for a wide range of diseases, say researchers.

The researchers found only a "very small" impairment in memory and learning among long-term marijuana users. Otherwise, scores on thinking tests were similar to those who don't smoke marijuana, according to a new analysis of 15 previous studies.

In those studies, some 700 regular marijuana users were compared with 484 non-users on various aspects of brain function -- including reaction time, language and motor skills, reasoning ability, memory, and the ability to learn new information.

Surprising Finding

"We were somewhat surprised by our finding, especially since there's been a controversy for some years on whether long-term cannabis use causes brain damage," says lead researcher and psychiatrist Igor Grant, MD.

"I suppose we expected to see some differences in people who were heavy users, but in fact the differences were very minimal."

The marijuana users in those 15 studies -- which lasted between three months to more than 13 years -- had smoked marijuana several times a week or month or daily. Still, researchers say impairments were less than what is typically found from using alcohol or other drugs.

"All study participants were adults," says Grant, professor of psychiatry and director of the Center for Medicinal Cannabis Research Center at the University of California, San Diego School of Medicine.

"However, there might be a different set of circumstances to a 12-year-old whose nervous system is still developing."

10 States OK Marijuana Use

Grant's analysis, published in the July issue of the Journal of the International Neuropsychological Society, comes as many states consider laws allowing marijuana to be used to treat certain medical conditions. Earlier this year, Maryland became the 10th state to allow marijuana use to relieve pain and other symptoms of AIDS, multiple sclerosis, cancer, glaucoma, and other conditions -- joining Alaska, Arizona, California, Colorado, Hawaii, Maine, Nevada, Oregon, and Washington.

Medicinal marijuana is available by prescription in the Netherlands and a new marijuana drug is expected to be released in Great Britain later this year. In the U.S. and elsewhere, Marinol, a drug that is a synthetic form of marijuana and contains its active ingredient, THC, is available by prescription to treat loss of appetite associated with weight loss in AIDS patients.

Grant says he did the analysis to help determine long-term toxicity from long-term and frequent marijuana use. His center is currently conducting 11 studies to determine its safety and efficacy in treating several diseases.

"This finding enables us to see a marginal level of safety, if those studies prove that cannabis can be effective," Grant tells WebMD. "If we barely find this effect in long-term heavy users, then we are unlikely to see deleterious side effects in individuals who receive cannabis for a short time in a medical setting, which would be safer than what is practiced by street users."

Grant's findings come as no surprise to Tod Mikuriya, MD, former director of non-classified marijuana research for the National Institute of Mental Health Center for Narcotics and Drug Abuse Studies and author of The Marijuana Medical Handbook: A Guide to Therapeutic Use. He is currently president of the California Cannabis Medical Group, which has treated some 20,000 patients with medicinal marijuana and Marinol.

'Highly Effective Medicine'

"I just re-published a paper of the first survey for marijuana toxicity done in 1863 by the British government in India that was the most exhaustive medical study of its time in regards to possible difficulties and toxicity of cannabis. And it reached the same conclusion as Grant," Mikuriya tells WebMD.

"This is merely confirming what was known over 100 years ago, as well as what was learned by various government findings doing similar research -- marijuana is not toxic, but it is a highly effective medicine."

In fact, marijuana was available as a medicinal treatment in the U.S. until the 1930s.

Lester Grinspoon, MD, a retired Harvard Medical School psychiatrist who studied medicinal marijuana use since the 1960s and wrote two books on the topic, says that while Grant's finding provides more evidence on its safety, "it's nothing that those of us who have been studying this haven't known for a very long time.

"Marijuana is a remarkably safe and non-toxic drug that can effectively treat about 30 different conditions," he tells WebMD. "I predict it will become the aspirin of the 21st century, as more people recognize this."

SOURCES: The Journal of the International Neuropsychological Society, July 2003. Igor Grant, MD, professor of psychiatry, University of California, San Diego School of Medicine; director, UCSD Center for Medicinal Cannabis Research Center. Tod Mikuriya, MD, president, the California Cannabis Research Medical Group, Oakland; former director of non-classified marijuana research, the National Institute of Mental Health Center for Narcotics and Drug Abuse Studies. Lester Grinspoon, MD, professor emeritus of psychiatry, Harvard Medical School, Boston; author, Marijuana: The Forbidden Medicine and Marijuana Reconsidered.

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Original page:

http://my.webmd.com/content/Article/24/2950_883.htm

This article is from the WebMD

Medical News Archive

Long-Term Pot Smokers Risk Brain Damage

By Jeanie Lerche Davis

WebMD Medical News Reviewed By Michael Smith, MD

March 5, 2002 -- Call it what you want -- pot, marijuana, wacky tobacky. But there's strong evidence that long-term, heavy smoking of cannabis can cause serious memory and attention impairments.

A study published in the March 6 issue of The Journal of the American Medical Association is the first to look at long-term, entrenched cannabis users who were seeking treatment for their habit -- largely because they were having trouble functioning in everyday life. Previous research looking at this issue has shown altered brain function and thinking among cannabis users -- even in the unintoxicated state.

This study -- the first to look at marijuana's long-lasting effects -- compares brain function in people who smoked marijuana long-term (an average of 24 years) with short-term users (10 years average) and people who did not use the drug.

It confirms what many have suspected: "that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use," researcher Nadia Solowij, PhD, writes in the study. Solowij is a psychologist in the National Drug and Alcohol Research Centre at the University of South Wales, Sydney, and the University of Wollongong, Australia.

Solowij's study focused on 102 people who used cannabis nearly every day, 65 of whom were in a marijuana treatment program. After giving them a series of nine tests, researchers found that long-term users performed "significantly less well" than short-term users and nonusers.

Cannabis users made more errors on the tests and were significantly less able to recall newly learned words. They also had more difficulty performing increasingly complex tasks. Both long-term and short-term users performed poorly in estimating time intervals.

Overall, long-term users had widespread memory difficulties with learning, retention, and retrieval skills, according to Solowij. Shorter-term cannabis users are not impaired to an extent that would interfere with memory and thinking abilities in daily life, she writes.

These results do not indicate a severe memory problem but could nevertheless mean an impairment in memory and thinking that could impact functioning in daily life, she says. The impairments develop gradually and probably become evident on tests after one or two decades of use.

Her research suggests that people using other substances -- in addition to marijuana -- would have greater impairments. However, "the risk to most medical cannabis users is likely to be small, as long as they are not maintained at high doses for many years," she writes.



Alaska State Legislature

RECEIVED
MAR 31 2005

Please enter into the record my testimony to the

SENATE HEALTH Education & Social Services

Committee name

Committee on

SB 74

, dated 3-24-05

Bill/Subject

First I would like to state that I am in no way an advocate for the use of marijuana. I am sincerely concerned with the health and social wellbeing of our people as am I with our constitutional rights.

As I understand Senate Bill # 74 the desire is to create a "Legislative Record", based on evidence and testimony to that which is so harmful to the public that it warrants repealing, to some degree, our constitutional right to privacy.

I could not be more strongly opposed to this action, based on the criteria set forth. If you examine what causes harm to our society, our health and contributes to criminal behavior, then compare marijuana to alcohol and tobacco the statistical evidence is staggering.

Over the past thirty years, deaths contributed to tobacco and alcohol when compared to marijuana exceeds ten million to one, not to mention health costs to survivors and their quality of life. When considering criminal behavior attributed to alcohol, such as domestic violence, and automobile deaths and injuries the statistical evidence is much the same, its overwhelming. Marijuana does not even appear on the same map.

So if you open this door to "Legislative Record" you should be prepared to hear the indisputable evidence of that which is exceedingly more harmful. Perhaps a better solution would be to place alcohol and tobacco under the same laws governing marijuana. It would surely limit the public's exposure to harm in a variety of ways, and you would not be sending the pot user to "Criminal College", while allowing the drunken drivers three chances to kill someone.

James V. Julian

Signed:

Testifier

Representing (Optional)

PO Box 520128

Address

892-6201

Phone number

Shafer Commission, 1972

(National Commission on Marihuana and Drug Abuse),
Commissioned by President Richard M. Nixon

- Commission members included 4 MD's, 2 PhD's, 1 theologian, and 5 elected officials
- 26 staff professionals, including additional MD's and PhD's, assisted the commission
- 49 support staff, analysts, and researchers were involved
- More than 1 year was spent in its investigations and preparation of its report

**National Research Council
of the National Academy of Science, 1982
“An Analysis of Marijuana Policy”**

- 4 years of effort
- Included a review of the 1972 National Commission on Marijuana and Drug Abuse report
- Conclusion: “On balance, we believe that a policy of partial prohibition is clearly preferable to a policy of complete prohibition.”

Institute of Medicine, 1999

“Marijuana and Medicine: Assessing the Science Base”

- Division of Neuroscience and Behavioral Health, IOM
- Took testimony from hundreds of doctors, scientists, treatment professionals, and many others
- Worked from 1997 to 1999
- Conclusions included:
 - “Compared to most other drugs...dependence among marijuana users is relatively rare.”**
 - “There is no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use”**
 - “It does not appear to be a gateway drug”**
 - “Earlier studies purporting to show structural changes in the brains of heavy marijuana users have not been replicated with more sophisticated techniques.”**

Report of the National Commission on Ganja, Jamaica, 2001

- “nine months of consultation and reflection,
- “visits to every parish and hearings amounting to 3776 pages of transcriptions”
- “The Commission is persuaded that the criminalisation of thousands of people for simple possession for consumption does more harm to the society than could be done by the use of ganja itself.”

Advisory Council on the Misuse of Drugs, Great Britain, 2002

“The Classification of Cannabis under the Misuse of Drugs Act 1971”

- “...based on a detailed scrutiny of the relevant scientific literature, including four reviews commissioned by the Department of Health in 1998, as well as an update commissioned by the Home Office and completed in November 2001”
- “The Council ... recommends the reclassification of all cannabis preparations to Class C [least harmful].”

House of Commons Home Affairs Committee, 2002

“The government’s drugs policy: Is it working?”

- “We have taken oral evidence from 45 witnesses over a total of 11 evidence sessions.”
- “...more than 200 people and organisations...provided written submissions...”
- “We support, therefore, the Home Secretary's proposal to reclassify cannabis from Class B to Class C.”

Report of the Canadian Senate Special Committee on Illegal Drugs, 2002

“Cannabis: Position for Canadian Public Policy”

- “product of a team effort over a period of 2 years”
- The Parliamentary Research Branch synthesized and analyzed literature on legal studies and socio-criminological studies. In all, the Committee received 23 reports.
- Heard testimony from expert sociologists and lawyers, psychologists and physicians, police officers and criminologists
- The Committee held more than 40 days of public hearings...more than 100 persons from all backgrounds.

Even the most recent commission reports echo the findings of many earlier commissions, including the LaGuardia Commission in 1944, and going back to the British Indian Hemp Drugs Commission in 1894.

The independent reports have been astonishingly consistent for well over a century:

“...continued criminalization of cannabis remains unjustified based on scientific data on the danger it poses.”

--Final Report of the Canadian Senate Special Committee, 2002

FISCAL NOTE

STATE OF ALASKA
2005 LEGISLATIVE SESSION

Fiscal Note Number: _____
 Bill Version: SB 74
 () Publish Date: _____

Revision Date/Time (Note if correction): _____ Dept. Affected: _____
 Title Crimes Involving Marijuana/Other Drugs BRU Alaska Court System
 Component Trial Courts
 Sponsor Senate Rules
 Requester Governor Component No. 768

Expenditures/Revenues (Thousands of Dollars)

Note: Amounts do not include inflation unless otherwise noted below.

OPERATING EXPENDITURES	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Personal Services						
Travel						
Contractual						
Supplies						
Equipment						
Land & Structures						
Grants & Claims						
Miscellaneous						
TOTAL OPERATING	*	*	*	*	*	*

CAPITAL EXPENDITURES						

CHANGE IN REVENUES ()						

FUND SOURCE (Thousands of Dollars)

1002 Federal Receipts						
1003 GF Match						
1004 GF						
1005 GF/Program Receipts						
1037 GF/Mental Health						
Other (Specify Type--Do not abbreviate)						
TOTAL	*	*	*	*	*	*

Estimate of any current year (FY2005) cost: 0.0

Mark this box (X) if funding for this bill is included in the Governor's FY 2006 budget proposal: ☐

POSITIONS

Full-time						
Part-time						
Temporary						

ANALYSIS: (Attach a separate page if necessary)

Senate Bill 74 decreases from one pound to four ounces the amount of marijuana sufficient to constitute a felony offense for possession under AS 11.71.040. Under current law, possession of less than one pound of marijuana is a misdemeanor. Additionally, the bill creates new offenses related to marijuana possession in a vehicle and raises the penalties for certain delivery offenses. An increase in the number of felony filings impacts the court system because felony cases must go to a grand jury, the felony trial rate is much higher than the misdemeanor trial rate and, because those convicted of felony crimes are subject to supervised probation by the Department of Corrections, the court will see more petitions to revoke probation. Although these changes will impact the court system, the extent of that impact is too speculative to support a fiscal note at this time. However, if that impact proves to be significant the court system may return to the legislature with a request for additional funding.

Prepared by: Douglas Wooliver, Administrative Attorney Phone 463-4750
 Division Alaska Court System Date/Time 3/30/05 9:51 AM
 Approved by: Doug Wooliver for Stephanie Cole, Administrative Director Date 3/30/2005
 Agency Alaska Court System

SENATE COMMITTEE REPORT

First Committee of Referral

DATE: 1/21/05

FURTHER: Judiciary
Finance

Date of 5-Day Notice: _____
(in accordance with Uniform Rule 23)

DATE TURNED
IN TO OFFICE: 4.1.05

Health, Education and Social Services Committee considered

SENATE BILL NO. 74

SB 74 CRIMES INVOLVING MARIJUANA

"An Act making findings relating to marijuana use and possession; relating to marijuana and misconduct involving a controlled substance; and providing an effective date."

and recommends:

- ☐ be replaced with _____ CS _____ ()
- ☐ adopt previous _____ CS _____ ()
- ☐ attached amendment(s)
- ☐ adopt Letter of Intent by _____ Committee
- ☐ further referral to _____ Committee

Senate Bill:

- ☐ Same Title
☐ New Title

House Bill:

- ☐ Same Title
☐ Technical Title
Change
☐ New Title w/
SCR # _____

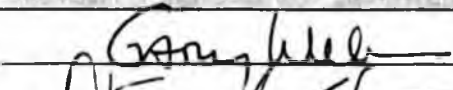
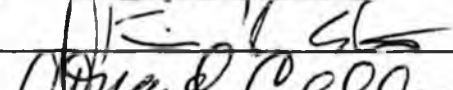
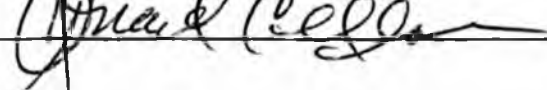
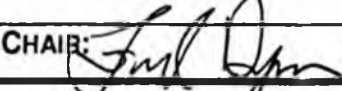
NEW FISCAL NOTE(S):

Department	Date	Fiscal	Indet.	Zero	FN#
ACS	3/30		X		

PREVIOUS FISCAL NOTE(S):

Department	Date	Fiscal	Indet.	Zero	FN#
DPS				X	1
ADM		X			2
LAW	1/14			X	3
HSS	1/20			X	4

☐ APPROPRIATION - no fiscal note

SIGNATURES AND RECOMMENDATIONS:	DO PASS	DO NOT PASS	NO REC	AMEND
	☒			
		☒		
			☒	
CHAIR: 	☒			

STATE OF ALASKA, SENATE BILL No 74 -"An Act making findings relating to the use and possession..."

EXPERT WITNESS STATEMENT:

PROFESSOR LESLIE LARS IVERSEN, PhD, FRS, University of Oxford, England

Professor Leslie Iversen, PhD, FRS Brief Curriculum Vitae:

*Visiting Professor of Pharmacology, University of Oxford 1999-
Director of the Wolfson Centre for Research on Age Related diseases at Kings
College London (1999-2004).
Director of the Neuroscience Research Centre for Merck & Co Inc in the UK (1983-
1995)
Director of the Medical Research Council Neurochemical Pharmacology Unit in
Cambridge, England (1970-1983)*

*Well known for his research on how drugs interact with chemical messengers in the
nervous system and has published more than 300 scientific papers on this topic.
Fellow of the Royal Society of London, and Foreign Associate Member of the US
National Academy of Sciences.*

*Acted as Scientific Advisor to the UK House of Lords Select Committee on Science &
Technology review of Cannabis (1998-2000)
Author of "The Science of Marijuana" Oxford University Press, 2000
Member of the UK Government "Advisory Council on the Misuse of Drugs"
Member of the UK Royal College of Physicians Working Party on medicinal cannabis
2004-2005.*

Statement:

As a scientist with expert knowledge of the medical and scientific literature on cannabis (marijuana) I feel that the statements in Senate Bill No 74 give an inaccurate picture of the scientific data about marijuana. I wish to make the following comments:

Increased potency of modern marijuana:

It is frequently stated that modern-day marijuana is 10-20-times more potent than that available in the 1960's or 1970's. But the available evidence does not support this conclusion. Scientists at the University of Mississippi Potency Monitoring project in the USA have been measuring the THC content of marijuana seizures since the 1970's. They have reported an increase of approximately 3-fold in the potency of herbal marijuana in the past 3 decades, and this is still by far the most widely used product. The European Monitoring Centre for Drugs and Drug Addiction published an overview of cannabis potency in Europe in July 2004, and reached similar

conclusions in Europe. Some samples originating from Cannabis plants grown under optimal conditions indoors may contain as much as 15-20% THC but these remain relatively rare and account for only a minority of marijuana use.

Addictive nature of marijuana:

It is recognized that some frequent heavy users of marijuana can become psychologically dependent on the drug, but few scientists would rate this in the same category of addictiveness as heroin, cocaine or amphetamines. Unlike heroin addiction, dependence on marijuana affects a minority of regular users (approximately 10%) and most dependent marijuana users are able to quit. I would rate marijuana as more similar to alcohol than to heroin in addictive potential.

Association of marijuana use with domestic violence:

This is an unusual allegation; in most instances intoxication with marijuana is not associated with violent aggressive behavior – although this may occur in rare examples. The abuse of alcohol is far more likely to be a cause of public and domestic violence.

Marijuana contains more than 400 different chemicals:

All plant derived foods or drugs contain complex mixtures of chemicals. Tomato juice, for example, contains more than 400 different chemicals – but this does not make it harmful. The leaves and flowers of the Cannabis plant (marijuana) contain more than 70 complex organic chemicals known as cannabinoids. But of these only one –delta-9-tetrahydrocannabinol (THC) - is capable of activating the cannabinoid receptor in human brain. The other cannabinoids have no known pharmacological activities and are generally regarded as harmless.

Marijuana impairs higher brain functions:

Marijuana temporarily impairs memory and other aspects of cognitive brain function, but this is no different from any other intoxicant drug – for example, alcohol. There is no evidence that marijuana use leads to significant long term damage to the brain.

Marijuana smoke is carcinogenic:

Marijuana smoke contains a similar mixture chemicals to that found in tobacco smoke, including some known carcinogens. Although a single marijuana joint delivers more tar to the lungs than a tobacco cigarette it is very difficult to see how someone smoking several marijuana joints a week could be thought to equate to a cigarette smoker consuming a full pack each day. The arithmetic simply does not add up. Furthermore, although there is a hypothetical risk of lung cancer from marijuana smoke, there is no evidence for such a relationship in fact.

Summary and Conclusions:

Marijuana contains an intoxicant drug (THC) that has modest dependence liability; the smoke can irritate the lungs and there is a potential risk, as yet unproven, of lung cancer. Nevertheless, I conclude that the medical risks associated the marijuana use do not equate to those of "harder" drugs such as heroin, cocaine or amphetamines. In my view marijuana is a relatively safe drug, and its use does less medical/social harm than alcohol or tobacco.

References:

Iversen, L (2000) "The Science of Marijuana", *Oxford University Press*, New York

Iversen L (2003) Cannabis and the Brain, *Brain*, 126: 1252-1260 .

Iversen L (2004) Long term effects of exposure to cannabis. *Current Opinion in Pharmacology*, 5: 69-72

Leslie Iversen
Oxford
March 18th, 2005

390,000 Americans die from tobacco each year, 108,000 from prescription drugs and 80,000 from alcohol. If you or Frank Murkowski or President Bush or the Partnership for a Drug Free America really believe making felons of substance users is the way to go, why haven't you gone after substances in relation to the damage they do and the number of people they kill?

I'll tell you why. a) prohibition doesn't work and never has
b) prohibition tramples people's rights
c) the drug corporations wouldn't allow you to

This wet noodle legislation against cannabis isn't about public health at all, it's about market share. It's with us because the corporations who make drugs, alcohol and tobacco stand to lose hundreds of millions dollars if cannabis were legalized and they know it. This is why they got together to form and fund the

✎
"Partnership for a Drug Free America."

Anheuser-Bush
Joseph Segrams and Sons
Coors Brewing Co
Hiram Walker
Stroh Brewing
Brown and Williamson
RJ Reynolds
Phillip Morris
Johnson and Johnson
DuPont
Proctor & Gamble
Bristol Myer Squibb
Hoffman-LaRouche
Sterling Drug Company etc.

This is the crew that provided the rich financial soil for the Partnership that was a player in the criminalization of cannabis in Alaska in 1990. And they got tax write offs for doing it. In addition to funding the Partnership they spend millions on both political parties each year in PAC money, soft money, bundled money and executive family donations. For Alaskans, watching these bloated drug pushers squeeze into our state politics is like watching a rhinoceros squeeze into panty hose. They are so out of touch they think no one can see. They have bought influence at the highest levels of government.

George Bush senior was on the board of directors of pharmaceutical giant Eli Lilly from 1977-1979. The Bush family has stock holdings in Eli Lilly and when we listen to GW Bush's Homeland Security Advisor, Sidney Taurel, we are listening to the CEO of Eli Lilly. So when David Murray of the White House's Office on National Drug Control Policy testifies to the Alaska Legislature that marijuana is "a dirty, dirty drug" you must take that testimony with a large grain of salt. "Drug control" is exactly what his handlers are after. If you go to "opensecrets.org" and look at the money that made Frank Murkowski the man he is today you will find that the corporate drug pushers have been very generous with Frank.

Alaska is especially worrisome to the drug companies because even after all the money they've spent here, our state has the highest percentage of pro-cannabis voters. Pot got more votes more than the governor did and they want to keep the heat turned up.

*

(11)

I urge you to take the long view. Cannabis will be legalized eventually for textiles, paper and petroleum substitutes. If you really want to do something for public health I have three suggestions:

First: Detox your political parties from corporate PAC money. If a billionaire puts an arm around your organizations' shoulder and tries to slip you a little something, "Just say, No."

Second: You have to walk the walk yourselves. To have people who drink and smoke in this building claiming to take the high road on health is ridiculous.

Third and last: If you are going to mandate something, do what works, mandate healthy alternatives to drugs.

- a) mandate ½ hour of physical exercise per day for every kid in every school in Alaska. AND FUND IT!
- b) mandate fixing the roofs of the gymnasiums and fund exercise equipment and gym teachers.
- c) mandate healthy lunch programs like we had when we were kids.
- d) mandate funding for recreational opportunities like swimming pools running tracks, hiking trails, ski programs, somatics and tai chi.

That's real health care. Mandate that and Alaskans 50 years from now will look back on this legislature and say, "Those people made us a better state."

S. Nelson 3/30/05
p. 1 of 3

Senator Fred Dyson
Chair Person, Senate HESS Committee
State Capitol
Room 121
Juneau, Alaska, 99801

Senator Fred Dyson;

I am enclosing in this package, accompanying this letter, and the 16 items listed below, as a follow-up to your invitation to submit materials for consideration in the hearings regarding Senate Bill 74 and the (questionable) recriminalization of all amounts of marijuana in Alaska, in contradiction to the Ravin Decision of 1975..

Materials listed are typically described in their entries as to whether they are in the form of an entire book, an excerpt from a larger document, or merely an abstract from a professional journal.

The items are further listed in alphabetical order, according to title, with the exceptions of items # 15 and 16, and are listed with the source of the item (if applicable) the date of publication or copyright, the pertinent page numbers (if applicable), and the names of the author(s).

The items are to be added to the formal record of and for the Senate Health Education and Social Services hearings for SB 74, for the purposes of creating a more complete discussion of credible professional materials.

The materials consist of:

- 1.) 'Cannabis 1988. Old Drug, New Dangers. The Potency Question' Tod H. Mikuriya, M.D. & Michael R. Aldrich, PH.D. Journal of Psychoactive Drugs, Vol. 20(1), January-March 1988.
- 2.) 'Cannabis Use and Cognitive Decline in Persons Under 65 Years of Age' Constantine G. Lyketsos, Elizabeth Garrett, Kung-Yee Liang, and James C. Anthony, Johns-Hopkins hospital. Baltimore Maryland. American Journal of Epidemiology 1999; 149: 794-800
- 3.) 'CASA's House of Cards; How a Recent Analysis of Drug-Related Crime Gets it All Wrong' David Fratello. The Drug Policy Letter. #28, Winter 1996. Copies of pps.22-23.
- 4.) 'Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis' Ethan Russo, et al. Journal of Cannabis Therapeutics, Vol. 2(1) 2002 pps. 3-57.
- 5.) 'The Good and the Bad Effects of (-) trans-delta-9-tetrahydrocannabinol (delta-9 THC) on Humans' E.A. Carlini. Dept of Psychobiology, Federal University of Sao Paulo, Paulista School of Medicine, Brazil. Toxicon 44 (2004) pps. 461-467

D. Nelson
3/30/05
p. 2 of 3

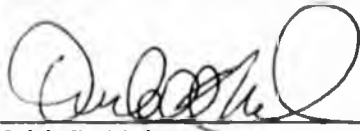
- 6.) 'Long-Term Effects of Exposure to Cannabis' Leslie Iverson. Current Opinion in Pharmacology 2005, 5:69-72
- 7.) 'Marijuana and Actual Driving Performance' US Dept. of Transportation. DOT HS 808 078 Final Report. November 1993. Complete document @ 133 pps.
- 8.) 'Marijuana and Depression' by R.F. Green & C. Ritter. Dept. of Sociology, Ohio State University-Columbus. Abstract only. Journal of Health and Social Behavior, 2000 March; 41 (1): 40-49
- 9.) 'Marijuana and Medicine: Assessing the Science Base' Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr. Editors. Institute of Medicine, National Institute of Health. March 17, 1999. Report from NIH/IOM consisting of 14 pages, and stating that there is no evidence of a causal relationship between cannabis use and other illicit drug use.
- 10.) 'Marijuana Has Moderate Effect On Driving' The Drug Policy Letter, #24, Fall, 1994. copies of pps 29 & 35
- 11.) 'Marijuana Myths, Marijuana Facts' Lynn Zimmer, Ph.D. and John P. Morgan, M.D. (Complete book) Approximately 243 pps.
- 12.) 'The Merck Manual' Seventeenth Edition, Centennial Edition, copyright 1999. Copies of pps. 1579, and 1590-1591 relating to cannabis/marijuana.
- 13.) 'Psychoactive Substance Use and the Risk of Motor Vehicle Accidents' K.L.L. Movig, et al. Accident Analysis and Prevention 36, (2004) copies of pps. 631-636.
- 14.) 'Relation of Pre-Employment Drug Testing Result to Employment Status: A One-Year Follow-Up' David Charles Parish, M.D., MPH. Dept. of Internal Medicine. Mercer University School of Medicine. Journal of General Internal Medicine, Vol. 4 (January/February) 1989. copies of pps. 44-47.
- 15.) The Economic Implications of Marijuana Legalization in Alaska. Prepared for Alaskans for Rights and Revenues, by Scott W. Bates, Principal Investigator, Boreal Economic Analysis and Research, Fairbanks, Alaska, Fall 2004. Document includes insight into more accurate costs of cannabis prohibition preceding the court's reaffirmation of the Ravin Decision of 1975, and with fewer felonies than would ultimately be prosecuted under SB 74's increased penalties, meaning that the costs of enforcement and corrections will rise above those costs recognized in the study, by at least 200%..

D. Nelson
3/30/05
p. 3 of 3

16.) Web address to the Canadian Parliament's Senate Committee Report on Illicit Drugs (Cannabis) Fall of 2002, by Senator Pierre Claude Nolin, recommending legalized taxed and regulated sales of cannabis for those aged 16 and older, and with the report being completed after nearly two years of expert witness testimony and documentation, reviewed by experts in their fields, working in conjunction with the previously referenced Parliamentary Senate Committee;

http://www.parl.gc.ca/common/Committee_SenHome.asp?Language=E&Parl=37&Ses=1&comm_id=85

I am submitting the previously listed 16 items to Alaska State Senator Fred Dyson, Senate Health, Education, and Social Services Committee Chair, via express mail, on March 30th, 2005, in consideration of the pending hearing for SB 74 scheduled for April 1st, 2005 at 1:30 P.M., with the intention, and for the purpose, that these documents be placed as evidence into the official record of the hearings regarding SB 74, concerning the (legally questionable) recriminalization of cannabis in Alaska in the homes of adults over the age of 19, and that Senate HESS Committee members and others be provided with access to these documents.



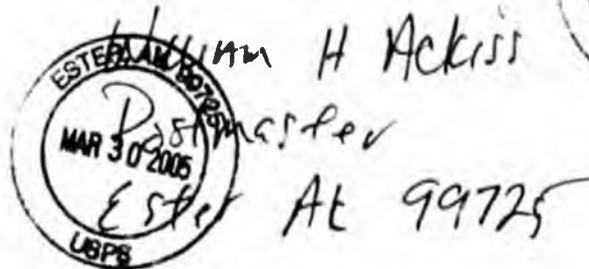
Dirk R. Nelson

March 30th 2005

Date

Sworn before me this 30th day of March, 2005..

On the 30 of MARCH 2005, MR. DIRK NELSON, known to me, signed above document. ~~WITNESSED~~ ~~WITNESSED~~



Cannabis 1988

Old Drug, New Dangers

The Potency Question

TOD H. MIKURIYA, M.D.* & MICHAEL R. ALDRICH, PH.D.**

The story of the new, allegedly stronger and more dangerous marijuana was rebirthed in January 1986 by the late Sidney Cohen, M.D., Professor of Psychiatry at UCLA: "... material ten or more times potent than the product smoked ten years ago is being used, and the intoxicated state is more intense and lasts longer." In addition, Cohen (1986) asserted that "the amount of THC [tetrahydrocannabinol] in confiscated street samples averaged 4.1 percent THC during 1984. The sinsemilla varieties were about 7 percent with some samples reaching 14 percent. . . all marijuana research to date has been done on 1 or 2 percent THC material and we may be underestimating present day smoking practices."

The average potency of marijuana samples seized by the Drug Enforcement Administration (DEA) increased from 0.5 percent THC in 1974 to 3.5 percent in 1985-1986, with sinsemilla (seedless marijuana) at 6.5 to 12 percent, announced Dr. Richard Hawks of NIDA later that year (Kerr 1986: 1). "Parents who experimented in their youth are not aware that the potency is much higher," added Donald M. Delzer, Chairman of the National Federation of Parents for Drug Free Youth (Kerr 1986: 18).

"Now perceived as a hard drug, marijuana has increased 1,400 percent in potency since 1970," proclaimed the flyer of a national conference on marijuana (Henry Ohlhoff Outpatient Programs 1986). Drug abuse treatment professionals soon elaborated on the outcry. Tennant (1986) asserted that the drug of the 1970's contained one to three percent THC, while that of the 1980's contained

five to 15 percent. Furthermore, the brain registers the difference exponentially, so the difference between one percent and 10 percent THC was not nine percent, but more like 900 percent (Garcia 1986: 3). Smith (1987) stated that Cohen "taught us that marijuana was a lot more dangerous than we originally thought, particularly with the use of more potent preparations by young people." Inaba (1987) added that "this new, stronger marijuana has a more disruptive effect on brain chemistry and body physiology than we had imagined previously," and mentioned heretofore undescribed side effects among athletes: "Baseball players who get benched a lot admit to smoking marijuana. It impairs their ability to follow the ball."

In a column for drug abuse counselors, Meyers (1987) advised "supportive therapy" for the effects of the "new" marijuana, which were described as "depersonalization, disorientation, derealization, changes in perception, and alterations in body image . . . acute brain syndromes with temporary clouding of mental processes . . . a change of time sense—where minutes seem like hours—slowed thinking, and feared perception of brain damage." Schick Shadel Health Services drug abuse treatment clinics (Unsigned 1987) now advertise that "marijuana has increased THC content from one percent THC in 1975 to six to fourteen percent THC in 1985 due to hybridization techniques. . . . For those who have become addicted to marijuana, whether it was years ago, or recently, treatment is necessary—even more critical today."

Despite the respectability of these authorities, none of these alarming claims are new, and neither is the potency issue. There are several claims intertwined: (1) that the marijuana available today is much stronger than that available previously, particularly since the early 1970's; (2) that

*Psychiatrist and Substance Abuse Therapist, 41 Tunnel Road, Berkeley, California 94705.

**Curator, Fitz Hugh Ludlow Memorial Library, San Francisco, California.

the effects of this so-called new marijuana are different from effects known earlier; and (3) that all previous marijuana research has been done with weak material and is therefore irrelevant. Before leaping on the bandwagon, one should examine the validity of these assertions.

HISTORICAL PERSPECTIVE

Extremely potent marijuana has been described for 150 years by Western scientists and (with the possible exception of the bearball syndrome) so have the effects of the *new marijuana*. There has been a great deal of research on high-potency cannabis in many countries.

In the paper that introduced cannabis to Western medicine, O'Shaughnessy (1839) discussed the widespread social and medical uses of *ganja* (sinsemilla) in India and noted symptoms of "delirium which the incautious use of the Hemp preparations often occasions, especially among young men first commencing the practice." Cannabis tinctures soon appeared in Europe and America (Robertson 1847; Savory 1843) and Fitz Hugh Ludlow (1857) described florid psychedelic trips after their oral ingestion, including all the symptoms mentioned by Meyers (1987). The Ohio State Medical Society (McMeens 1860) reviewed some 15 years of clinical experience with the drug and acknowledged the intense but physiologically benign mental effects caused by high doses or idiosyncratic sensitivity.

Wood (1869) reported the subjective effects of a tincture made from North American marijuana, experiencing a distortion in time sense, convulsions and memory loss, but no adverse aftereffects. He reported considerable success with it in the treatment of severe neuralgia. However, 15 years later Wood and Smith (1884) commented on the variable potency of cannabis and outlined appropriate treatment for overdoses in medical practice.

Early investigators (McMeens 1860; Bell 1857) attributed this variability to "defective pharmaceutical processes" employed in foreign countries, and recommended that extracts prepared at home would be preferable. However, extreme variations in locally manufactured preparations were soon recognized in the Dispensary of the United States (Wood & Bache 1868: 379-382). A practical bioassay technique was gradually perfected starting from the systematic observations of Hare (1887), followed by Evans (1894) and Marshall (1898), to compensate for batch-to-batch potency variations.

Pragmatically, the solution to the overdose/potency problem in both the United States (Wood & Bache 1868: 382) and England was to titrate the dose. In London, a patient who signed a letter to the editors of *Lancet*, W.W. (1890) reported a typical case: W.W. had inadvertently been given an overdose of cannabis for treatment of neuralgia by his doctor and had suffered perceptual distortion,

agitation, mood swings, and fear of death. Sir J. Russell Reynolds, M.D., F.R.S., physician to Queen Victoria's household, responded with a recommendation based on 30 years of experience with the drug (Reynolds 1890), stating "that Indian hemp, when pure and administered carefully, is one of the most valuable medicines we possess. . . . a minimum dose should be given to begin with, and . . . the dose should be very gradually and cautiously increased."

During the nineteenth century, social and scientific research on marijuana, as well as tinctures, were conducted with much stronger material than is available on the illicit market today. For example, the Indian Hemp Drugs Commission of 1893-1894 investigated the social, religious and medical uses of *biang* (marijuana), *ganja* (sinsemilla) and *charas* (hashish). The potencies of varieties from different parts of the subcontinent were evaluated by government chemists and botanists (Evans 1894; Hooper 1894), using the "acknowledged superiority" of Bengal *ganja* as the standard. The Commission found that the moderate use of even highly potent marijuana caused no significant physical, mental or moral damage (Kaplan 1969; Mikuriya 1968).

In the 1890's, at the peak of medical interest in the drug, British chemists (Wood, Spivey & Easterfield 1899) isolated an impure active principle, cannabinol, using a "red oil" distilled from Indian cannabis as a starting point, which was considered to be the active ingredient until the 1930's (Work, Bergel & Todd 1939; Cann 1931). In 1909, Marshall demonstrated that oxidation during storage was the primary cause of the drug's variable potency. With this advance the pharmaceutical industry shifted its attention to the production of standard extracts that could be used to assay medicinal compounds (Colson 1920). Because it had long been known that *ganja* and *charas* produced the most reliable extracts (Wallich 1883; Robertson 1847), in practical terms this meant the European and American producers had to learn how to grow *ganja*.

Sinsemilla cultivation by the Indian technique of culling male plants from the fields before female plants could set seeds—the very process to which recent researchers attribute the potency of the *new marijuana*—was exhaustively described by the British government in India (Kaplan 1969: 59-84; Prain 1893; Kerr 1877). In an effort to promote Bengali *ganja*, the British Raj imposed an export duty on inferior Bombay *ganja* at the turn of the century, and pharmacognosists in Europe and the U.S. began learning sinsemilla cultivation (Mair 1900).

Holmes (1900) discussed the potencies of Calcutta and Bombay *ganja* and recommended that the former be used for pharmaceutical preparations, either by home cultivation of *ganja* according to the Bengal methods he outlined (Holmes 1902a) or by extracting it immediately in Bengal and shipping it in tightly closed containers (Holmes 1902b). Comparing the potency of cannabis from Uganda,



Cannabis indica (3/4 Nat.).

Figure 1. *Cannabis indica* (3/4 Nat.) "Calcutta ganja, which is the very choicest."—Hare, Caspari and Rusby *National Standard Dispensatory* (1909: 374).

France and India, Holmes (1905) urged that only Indian sinsemilla preparations be admitted to the *British Pharmacopoeia*.

Likewise, Whineray (1909) and Hooper (1908) described ganja cultivation and manufacture, pointing out that cannabis grown in North America by the Indian methods could be as fully potent as Indian hemp. The *National Standard Dispensatory* of 1909, which included medicines from the pharmacopoeias of the U.S., Britain and Germany, gave the details of sinsemilla cultivation and featured a drawing of a perfect Calcutta ganja flower top (see Figure 1) as an example to be emulated by Western cultivators (Hare, Caspari & Rusby 1909: 374).

In the U.S., Hamilton and his colleagues (Hamilton 1918; Hamilton 1915; Hamilton, Lescossier & Perkins 1913; Houghton & Hamilton 1908) demonstrated that if care was exercised in cultivating and processing the plant for extraction, American-grown ganja and its extracts were as reliable as those from India and would not deteriorate significantly if stored properly. Information on cultivation of extremely potent seedless marijuana was thus widely disseminated to Western pharmaceutical producers during the first two decades of the twentieth century.

The U.S. government ignored these sinsemilla cultivation techniques at the first federal marijuana farm established in 1904 on the Potomac Flats (where the Pentagon now sits) in Washington, D.C. (Silver 1979: 262-263), and as a result the 10-foot marijuana plants grown there and elsewhere in America proved to be much less potent than good samples of Indian hemp (Eckler & Miller 1912). However, private pharmaceutical firms were more successful. The Eli Lilly and Parke-Davis companies ran a cooperative venture at Parkedale (Parke-Davis's farm near Rochester, Michigan) from 1913 until 1938 to develop cannabis extracts for medical use, at first from *Cannabis indica*, but later standardized on a highly potent strain they

developed that they called *Cannabis Americana* (Wheeler 1968). Pharmaceutical companies were marketing cannabis extracts that were uniformly effective at 10 mg dose levels (Parke-Davis & Company 1930: 82) 11 years before its official removal from medicinal availability.

In 1941, cannabis was removed from the *United States Pharmacopoeia (USP)* at the behest of the Federal Bureau of Narcotics, which suddenly claimed that marijuana had no medical uses (Mikuriya 1973: xx). Yet even the removal of cannabis from the *USP* did not end scientific and social research on highly potent forms of cannabis, ranging from the red-dirt marijuana of the Midwest to the red oil of the laboratories. Adams, Pease and Clark (1940) described improved procedures for preparing purified red oil from Minnesota wild hemp, and comparison of the potencies of Minnesota marijuana and red oil was of significant interest to Loewe, pharmacological director of the LaGuardia Committee (Mayor's Committee on Marihuana 1944: 186ff). Red oil concentrates were used along with marijuana in the LaGuardia Committee's experiments on prisoners, under Loewe's personal direction (Mayor's Committee on Marihuana 1944: 32); for a subjective account see Mezzrow and Wolfe (1946: 317ff). In the 1940's, Adams and Loewe in the U.S. and Todd in England isolated other cannabinoids, including THC, which Adams (1940) postulated as the active principle.

Such isolates were the mainstay of marijuana research during the 1940's and 1950's. A potent marijuana oil created as a truth drug for interrogation purposes by the Office of Strategic Services during World War II (Lee & Shlain 1985: 3-5) was the forerunner of later clandestine experiments conducted by the CIA and the Department of Defense at the Edgewood Arsenal in Maryland from the 1950's to the 1970's (Mikuriya 1973: xxii). Experiments with the designer drug synhexyl, a potent analog of Δ^9 -THC, were conducted from the 1940's (Adams et al. 1941)

TABLE I
COMPARATIVE RANGE OF PERCENT THC IN CALIFORNIA CANNABIS SAMPLES, 1973-1974*

Origin	No.	Range of Δ^9 -THC (%)	Remarks
Marijuana	76	0.1 - 9.5	Available in California
Mexican	5	1.1 - 3.3	0.2% - 4.3% cannabidiol
Acapulco Gold	3	2.7 - 4.2	Distinct cannabichromene
Colombian	11	0.9 - 6.9	0.0% - 6.9% cannabidiol
Panama Red	2	4.0 - 5.7	One sample 1971
Thai Sticks	9	2.4 - 9.5	Imported sinsemilla
Big Sur	2	2.7 - 2.9	Domestic sinsemilla
Maui Wowie	5	5.4 - 6.9	Domestic sinsemilla
Unidentified	41	0.1 - 7.8	Many U.S. grown
Hashish	21	0.4 - 14.2	Available in California
Lebanese	2	1.9 - 3.7	4.9% - 10.6% cannabidiol
Moroccan Kif	2	5.2	2.4% - 2.9% cannabidiol
Afghani Primo	4	1.7 - 5.9	4.2% - 7.8% cannabidiol
Kashmiri	3	6.6 - 14.2	2.4% - 4.9% cannabidiol
Pakistani	2	0.4 - 2.3	1.4% - 1.8% cannabidiol
Nepalese	3	3.4 - 11.5	One sample 1971
Unidentified	5	0.8 - 5.9	1.1% - 14.2% cannabidiol
Hash Oils	42	0.2 - 50.0	Available in California
Nepalese	3	3.4 - 10.2	
Unidentified	39	0.2 - 50.0	

*Samples submitted to PharmChem Laboratories (August 1973-August 1974), with one Panama Red sample and one Nepalese hashish sample (1971). Chromatographs examined by Aldrich (1974).

until the mid-1970's (Lemberger 1976; Pars & Razdan 1976), but were abandoned before its potential was fully explored.

In the 1960's, the identification of pure Δ^9 -THC as the active principle in cannabis (Gaoni & Mechoulam 1964) made it possible to assay the relative potencies of cannabinoids directly in human subjects (Isbell et al. 1967). Although Weil, Zinberg and Nelsen (1968) demonstrated the safety of human marijuana research, much of the U.S. research of the 1970's was conducted with low-potency marijuana because the government would not approve human research with high-potency strains. Indeed, in one early study (Jones & Stone 1970), a THC concentrate was removed from Mexican marijuana and then redistributed back into the bulk marijuana to return its potency to 0.9 percent THC. Outside the U.S., these strictures did not apply: The fact that cannabidiol interferes with the effects of Δ^9 -THC was discovered in Brazil, using both purified cannabinoids on humans (Karniol et al. 1974).

The 1960's and 1970's saw a worldwide flowering of

cannabis research, including its social, psychological, chemical, botanical and legal aspects as well as covering an enormous range of potencies and dosages. Major botanical work involved potency questions: observing phenotypes at the University of Mississippi (Fettermann et al. 1971) and in Canada (Small 1979); establishing a lectotype for *Cannabis sativa* L. (Stearn 1974); distinguishing *C. sativa* from *C. indica* and *C. ruderalis* (Schultes et al. 1974); and cultivation techniques for increased THC production (Clarke 1981; Frank & Rosenthal 1978).

Thus the claim by Cohen (1986) that "all marijuana research to date has been done on 1 or 2 percent THC material" is not accurate for the 1970's or for any other decade going back to 1839. It ignores much of the laboratory research in the U.S. that was summarized by Cohen himself (Cohen & Stillman 1976), Hollister (1986) and the National Academy of Sciences (1982), and all of the social research on high-potency marijuana in Jamaica (Rubin & Comitas 1975; Bowman & Pihl 1973), Costa Rica (Carter & Doughty 1976), Greece (Fink et al. 1976) and Africa

(DuToit 1980). It is difficult to think of any country in which the claim is true.

RECENT ESTIMATES OF POTENCY

Since the advent of quantitative analysis technology, there has been sporadic reportage of the percentage of Δ^9 -THC and other cannabinoids in natural and semisynthetic cannabis products. Notwithstanding the psychophysical effects of other cannabinoids, the amount of THC present in a marijuana sample is believed to determine the drug's potency (National Commission on Marihuana and Drug Abuse 1972: 50), and potency is usually expressed in percent THC by weight. The results of quantitative analyses performed on street samples of marijuana have been published since the late 1960's. These results are generally higher than the alleged 0.5 percent THC content of marijuana cited for the early 1970's.

Lerner and Zeffert (1968) described the development of quantitative analysis for the determination of THC content, and noted much variation among samples of marijuana, hashish, and red oil (still being used experimentally in the 1960's). The THC content of confiscated Mexican marijuana was 0.8 to 1.4 percent, hashish averaged eight percent and red oil 31 percent in 1968.

Quantitative analyses of street samples of marijuana and hashish conducted by Canadian laboratories in 1971 for the Commission of Inquiry into the Non-Medical Use of Drugs (1972: 28-29) showed a range of 0.02 to 3.46 percent THC (median=0.93%) for marijuana, with hashish ranging from 1.0 to 14.3 percent THC (median=4.82%). Samples seized in police raids were less potent: marijuana was 0.05 to 1.65 percent THC (median=0.21%), while hashish was 0.0 to 8.6 percent THC (median=1.3%). The reported difference between confiscated police seizures and street samples submitted to laboratories for analysis may be due to the voluntary samples being submitted precisely because of their extraordinary potency, or that storage conditions in police evidence lockers are hardly optimal for potency stability.

This has a bearing on the potency question because the low potency cited by both Cohen (1986) and Hawks (see Kerr 1986) referred to samples confiscated by the DEA. It has been known since the early days of its isolation (Wollner et al. 1942) that THC oxidizes to cannabinol rapidly in samples stored at room temperature (24°C). Lerner (1963) reported that the concentration of THC in marijuana decreased at a rate of three to five percent under normal room conditions, and Razdan (1970) reported a rate of 10 percent per month. The influence of temperature, light and age on potency was addressed by Starks (1977: 13-15). The low-baseline percentage of THC reported for the early 1970's may be due to this deterioration in confis-

cated, stored samples. In any case, the low baseline makes the difference in the THC content of later-reported samples appear much greater than it may have been in actuality, assuming that the marijuana smoked by consumers was fresher than stored police seizures.

For a short while in the early 1970's, PharmChem Laboratories in Palo Alto, California, tested and reported the percent of the THC content in anonymously submitted marijuana samples. For 1973, PharmChem reported an average THC content of 1.62 percent in marijuana, compared with hashish at 4.6 percent and hash oil (a refined extract of hashish) at 13.5 percent (Ratcliffe 1974).

In 1974, the DEA published guidelines that no longer allowed laboratories to provide quantitative results directly to the sample donors. This, in effect, restricted public access to analysis information to whatever government officials wished to reveal. However, nonspecific summaries of THC percentage ranges were allowed to be published (Unsigned 1974).

The results of an independent examination of gas-liquid chromatographs of street samples of marijuana from California that were submitted to PharmChem during 1973 and 1974 are shown in Table I. Seeded varieties ranged in THC from an average of 2.2 percent (Mexican) to 4.9 percent (Panama Red), while sinsemilla averaged 2.8 percent for Big Sur "Holy Weed" to above six percent for Thai Sticks and Hawaiian "Mawi Wowie." This would appear to be a much more representative sample of the types of marijuana available in California in 1973-1974 than the half-percent grade cited by Cohen (1986) and Hawks (see Kerr 1986), or the one to three percent grade cited by Tennant (1986).

A retrospective summary of street-drug analysis trends from 1969 through 1975 published by PharmChem (Terry 1977) confirms the fact that quite potent forms of cannabis were available on the illicit U.S. market by 1975: "Early quantitative work showed a range of 1.0-2.5 percent THC for average marijuana. In 1975, the range was 1.0-2.5 percent; samples in the range of 5.0-10.0 percent were not uncommon, and some contained as much as 14.0 percent THC. . . . Hash oil (concentrated from hash, usually amber or red in color) and grass oil (from marijuana, dark green or black in color) . . . vary greatly in potency, some samples [containing] up to 40 percent THC." Abundant information on the comparative potencies of cannabis grown in the U.S. and other countries in the mid-1970's was summarized by Starks (1977: 41-87).

In the spring of another election year, 1980, Cohen and DuPont launched a similar campaign, stating that confiscated marijuana in 1975 contained only 0.4 percent THC, while in 1979 the average was four percent, a tenfold increase (Brody 1980: C1). This data conflicts directly with that published by PharmChem for 1975 street samples

TABLE II
CONCENTRATIONS OF Δ^9 -THC IN DIFFERENT VARIATIONS OF MARIJUANA*

Type	Percent Δ^9 -THC by Weight	Normalized Averages (%) ^a
Nepal ^a	2.81	
Mexico ^a	1.68	1.00
Pakistan ^a	1.30	
Colombia ^a		3.00 - 3.50
India ^a		
Grown above 2,000 meters	0.46	
Grown below 2,000 meters	1.39	
Jamaica (ganja) ^b	2.80 (mean)	
United States ^a	0.35	
Sinsemilla ^a		
Fiber	0.21	
Intermediate	3.58	
Drug	6.28	3.00 - 11.00
Hashish		
United Nations standard ^c	2.22 (7.40) ^a	1.90
NIDA ^a		
Cigarette 1	0.84	
Cigarette 2	1.86 (2.8) ^a	
Crude marijuana extract ^a	20.00	
Illicit hashish oil ^a	10.00 - 30.00 (up to 60) ^a	20.00
Research harvests ^a	0.90 - 2.80	

*National Academy of Sciences (1982: 16); ^aJones (1980); ^bBraenden (1972); ^cTurner (1974); ^dTurner (1980); ^eTurner (1981); ^fTurner et al. (1979); ^gRosenkrantz (1981); ^hMarshman, Popham & Yawney (1976).

(Perry 1977) and that shown in Table I. Perhaps one should be thankful that, according to these estimates, marijuana potency *dropped* from four percent THC in 1979 to 3.5 percent THC in 1986 (Kerr 1986).

The most recent comparison of cannabis potencies was compiled from published sources from 1972 through 1981 by the National Academy of Sciences (1982: 16), and is summarized in Table II. It again demonstrates the great range of products available legally (i.e., NIDA samples) and illegally during that decade, and may in fact underestimate some potencies. For example, the 2.8 percent THC content cited for Jamaican *ganja* (Marshman, Popham & Yawney 1976) is slightly lower than the mean 2.96 percent THC material studied by Rubin and Comitas in 1970 through 1972 (Unsigned 1973), and significantly lower than the four to eight percent THC Jamaican *ganja* cited by

the National Commission on Marihuana and Drug Abuse (1972: 50).

The government "research harvests" in Table II (Rosenkrantz 1981) are considerably less potent than the sinsemilla samples that averaged three to 11 percent THC (Turner 1981, 1980). Perhaps this is because cultivators at the government marijuana farm at the University of Mississippi, like their predecessors in 1904, never learned proper sinsemilla cultivation (Turner et al. 1979), while illicit cultivators in California and Hawaii were making it standard for the industry (Frank & Rosenthal 1978: 258-259). If so, this alone could explain the wide discrepancies between the potency of marijuana reported by government sources and that actually being grown in the U.S. during the 1970's and 1980's.

SELF-ADJUSTMENT OF DOSE

An important consideration in regard to the potency issue is autotitration, the adjustment of dose by the individual user to obtain optimal effects and avoid unpleasant ones. As noted above, cautious titration of dose was standard practice when cannabis preparations were used in medicine. Smoking marijuana, customary in present social use of the drug, requires knowledge of when to stop in order to avoid symptoms of overdose. The smoked route gives rapid feedback to the user with regard to levels of effect because the drug goes directly to the brain from the lungs, unimpeded by the gut or the liver.

Researchers for the Mayor's Committee on Marijuana (1944: 13) were among the first to notice that experienced marijuana smokers in the "tea-pads" of Harlem routinely practiced autotitration. The confirmed user, they noted, "appears to be quite conscious of the quantity he requires to reach the effect called 'high.' Once the desired effect is obtained he cannot be persuaded to consume more. He knows when he has had enough . . . and is ever-conscious of preventing himself from becoming 'too high.'" Similarly the Commission of Inquiry into the Non-Medical Use of Drugs (1972: 48) observed that "great variations in potency are usually accommodated by the experienced user through a 'titration' of dose (intake is reduced or stopped when the smoker reaches the preferred level of intoxication)." For U.S. users, the National Commission on Marijuana and Drug Abuse (1972: 166) commented: ". . . whatever the potency of the drug used, individuals tend to smoke only the amount necessary to achieve the desired effect."

SUMMARY AND CONCLUSIONS

Observation of the real world of social marijuana use, where autotitration is the norm, renders the scare tactics of the *new marijuana* proponents not only inaccurate but irrelevant. There is much published evidence about the availability of highly potent varieties of cannabis from the nineteenth century through the present day. The effects attributed to the *new marijuana* are the same ones debated

for centuries in many different cultures. The assertion that "all marijuana research to date has been done on 1 or 2 percent THC material" (Cohen 1968) ignores several thousand years of human experience with the drug. The old medical cannabis extracts were stronger than most of the forms now available, though the potency of illicit hash oils by the mid-1970's was approaching the level of medicinal preparations available before their removal from the USP.

While it may be true that sinsemilla is more widely available than 10 or 15 years ago, its potency has not changed significantly from the 2.4 to 9.5 percent THC materials available in 1973-1974 (see Table I), or the five to 14 percent sinsemilla of 1975 (Perry 1977). The range of potencies available then (marijuana at 0.1% to 7.8% THC, averaging 2.0% to 5.0% THC by 1975) was approximately the same as that reported now. With such a range, the evidence simply cannot support the argument by Cohen (1986) that marijuana is "ten or more times more potent than the product smoked ten years ago." And to say that marijuana potency has increased 1,400 percent since any date in history is patent nonsense.

It is not legitimate to imply that *average* low potencies represent the *full range* of potencies available in reality. Neither is it valid to cite the *low end of the range* then as a baseline to compare with the *high end of the range* now. The claimed baseline for THC content in the early 1970's would appear to be too low, probably because confiscated, stored police samples were utilized; and this low baseline makes the claimed difference in potency appear to be greater than it has been in reality.

In sum, the *new marijuana* is not new and neither is the hyperbole surrounding this issue. The implications of the new disinformation campaign are serious. Many people, particularly the experienced users of the 1960's and their children, will once again shrug off the warnings of drug experts and not heed more reasonable admonishments about more dangerous drugs. This is not only abusive to those who look to science, the medical profession, and government for intelligent leadership, but will sully the reputations of drug educators who wittingly cry wolf, and will inevitably diminish the credibility of drug abuse treatment professionals who pass on such flawed reports.

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Cannabis Use and Cognitive Decline in Persons under 65 Years of Age. Constantine G. Lyketsos, Elizabeth Garrett, Kung-Yee Liang, and James C. Anthony (Osler 320, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21207-5371)

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The purpose of this study was to investigate possible adverse effects of cannabis use on cognitive decline after 12 years in persons under age 65 years. This was a follow-up study of a probability sample of the adult household residents of East Baltimore. The analyses included 1,318 participants in the Baltimore, Maryland, portion of the Epidemiologic Catchment Area study who completed the Mini-Mental State (MMSE) examination during three study waves in 1981, 1982, and 1993-1996. Individual MMSE score differences between waves 2 and 3 were calculated for each study participant. After 12 years, study participants' scores declined a mean of 1.20 points on the MMSE (standard deviation 1.90), with 66% having scores that declined by at least one point. Significant numbers of scores declined by three points or more (15% of participants in the 18-29 age group). There were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis. There were also no male-female differences in cognitive decline in relation to cannabis use. The authors conclude that over long time periods, in persons under age 65 years, cognitive decline occurs in all age groups. This decline is closely associated with aging and educational level but does not appear to be associated with cannabis use.



ORIGINAL CONTRIBUTIONS

Cannabis Use and Cognitive Decline in Persons under 65 Years of Age

Constantine G. Lyketsos,^{1,3} Elizabeth Garrett,⁴ Kung-Yee Liang,⁴ and James C. Anthony^{2,3}

The purpose of this study was to investigate possible adverse effects of cannabis use on cognitive decline after 12 years in persons under age 65 years. This was a follow-up study of a probability sample of the adult household residents of East Baltimore. The analyses included 1,318 participants in the Baltimore, Maryland, portion of the Epidemiologic Catchment Area study who completed the Mini-Mental State Examination (MMSE) during three study waves in 1981, 1982, and 1993–1996. Individual MMSE score differences between waves 2 and 3 were calculated for each study participant. After 12 years, study participants' scores declined a mean of 1.20 points on the MMSE (standard deviation 1.90), with 66% having scores that declined by at least one point. Significant numbers of scores declined by three points or more (15% of participants in the 18–29 age group). There were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis. There were also no male-female differences in cognitive decline in relation to cannabis use. The authors conclude that over long time periods, in persons under age 65 years, cognitive decline occurs in all age groups. This decline is closely associated with aging and educational level but does not appear to be associated with cannabis use. *Am J Epidemiol* 1999;149:794–800.

aging; cannabis; cognition; dementia

Cognitive capacity has multiple determinants, including genetic makeup, nutritional status, health status, formal education, and age-related developmental processes. This capacity generally reaches its peak in early adulthood and then declines later in life (1). Cognitive decline is a significant public health problem, given its association with impaired functioning and increased mortality (1) and its close link to dementia (2–4). Dementia is defined as the occurrence of measurable, global cognitive decline sufficient to impair functioning (5). The prevalence and incidence of dementia, now one of the most common and serious diseases of the elderly, is rapidly increasing as the world population ages (6, 7).

Epidemiologic studies of dementia and of cognitive decline have typically investigated individuals over the age of 60 years. The expected prevalence of dementia in

these age groups is 2 percent or higher (6, 7), and prevalence might be as high as 48 percent in those over age 85 (6, 7). In late life, dementing processes hamper the study of cognitive decline as a phenomenon distinct from dementia. Additionally, recent research suggests (8) and scientific consensus concurs (9) that dementia is best understood as the result of cumulative effects on the brain from diseases (e.g., Alzheimer's disease or cerebrovascular disease) and other exposures (e.g., alcohol or tobacco use), all occurring against background, possibly lifelong, declines in cognition associated with aging itself. However, epidemiologic knowledge regarding cognitive decline in persons younger than age 65 is very limited. Indeed, we could find only one published epidemiologic study of cognitive decline in younger persons: the Seattle Longitudinal Study (10).

The Seattle Longitudinal Study followed a series of community-based cohorts of individuals enrolled in a health maintenance organization. Sample sizes for individual cohorts were between 500 and 997. Participants were assessed according to a large number of tests of intelligence and cognitive capacity. The main findings were that individual cognitive abilities do not change much before age 60, with the exception of verbal fluency. Because of attrition, the Seattle Longitudinal Study did not have sufficient sample sizes to detect small cognitive declines in younger age groups. Furthermore, very few individual participants were followed for spans of more than 5 years.

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Abbreviation: MMSE, Mini-Mental State Examination.

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The major correlate of cognitive decline is increasing age (10–14). Higher educational level (14) and higher functioning (13) are associated with less cognitive decline. Being female or encountering stressful life events is not associated with cognitive decline (11, 13). Risk factors for dementia include age, prior cognitive impairment, stroke, high blood pressure, heart disease, diabetes mellitus, alcohol consumption, and depression (15–28). The use of nicotine via smoking has also been associated with a lower risk for dementia, although this finding is controversial (29). Being female has not been associated with the incidence of dementia (15, 17). Two recent studies (30, 31) have reported that lesser educational attainment is a risk factor for dementia. However, this finding has not been supported universally (17, 32, 33).

The relation between cognitive functioning or cognitive decline and use of cannabis (marijuana) has received limited attention in epidemiologic studies. Two cognitive effects of cannabis must be distinguished: acute effects, those associated with intoxication, and residual effects, which persist after the drug has left the central nervous system (34). The latter effects might be short term or long term. Cross-sectional studies, either experimentally administering cannabis or comparing users with nonusers, support the existence of short term residual effects of cannabis use on attention, ability to perform psychomotor tasks, and short term memory (34, 35). These effects are more severe in women (36) and in heavy users of cannabis as compared with light users (37).

To our knowledge, no study with published results has investigated the long term effects of cannabis use on cognition in an epidemiologic sample. According to Pope et al. (34), study designs best suited to addressing this issue are naturalistic comparisons, in large epidemiologic samples, of heavy users, light users, and nonusers of cannabis. These studies must also account for the concurrent use of alcohol and other drugs, both illicit and legal (e.g., nicotine). In addition, such studies must adjust for other factors known to influence cognition over time, such as age and education, and must investigate possible interactions between the cognitive effects of cannabis use and gender (being female).

We recently reported findings from a 13-year follow-up of 1,488 persons of all ages who had participated in the Baltimore, Maryland, portion of the Epidemiologic Catchment Area study (38). The Mini-Mental State Examination (MMSE) (39), a widely used quantitative measure of cognition, was administered to participants during wave 1 (1981) and during two follow-up waves in 1982 and 1993–1996. The design of the study allowed us to examine cognitive decline between

waves 2 and 3 in a large epidemiologic sample. We found that cognitive decline occurred in all age groups. Age, education, and minority status were all significantly associated with greater cognitive decline.

In this follow-up paper, we focus our investigation on persons under age 65 years. To our knowledge, this is the first population study that has investigated cognitive decline in this age group, in which the prevalence of dementia is very low. This permits better study of cognitive decline as a phenomenon distinct from dementia, as well as its associated risk factors. We had two goals: 1) to further delineate the epidemiology of age-specific cognitive decline in persons under 65 and 2) to investigate any long term association between cognitive decline and use of cannabis using a design similar to the one proposed by Pope et al. (34).

MATERIALS AND METHODS

Baltimore Epidemiologic Catchment Area follow-up

The Epidemiologic Catchment Area program has been described in detail elsewhere (40, 41). The Baltimore arm of this five-site study first entered the field in 1981, when the first wave of in-person assessments was completed. A second wave of assessment (including wave 2 administration of the MMSE) was conducted 1 year later, in 1982. The Baltimore Epidemiologic Catchment Area target population consisted of the adult household residents of eastern Baltimore City, an area with 175,211 inhabitants. During wave 1, 4,238 individuals were designated for interview by probability sampling methods, and 3,481 (82 percent) completed interviews. Of these persons, 2,695 completed interviews during wave 2.

In 1993, all 3,481 initial participants were targeted for tracing and interviewing. A total of 848 participants were found to have died; the remaining 2,633 were presumed to be alive, but 415 of them could not be successfully traced. Of the 2,218 persons located, 298 refused to participate, and 1,920 completed interviews. Of these, 1,488 had completed the MMSE during all three waves, approximately 11.5 years after wave 2. All study participants signed informed consent statements approved by the Institutional Review Board of the Johns Hopkins University School of Hygiene and Public Health.

Participants

In these analyses, we included only those participants who were under age 65 at wave 1 and who completed the MMSE during all three study waves ($n = 1,318$).

Measurement of cognitive decline. For each participant, an MMSE score difference was calculated by subtracting the wave 3 (1993–1996) MMSE score from the wave 2 (1982) MMSE score. The mean time interval between the points at which these MMSEs were administered was 11.6 years (standard error 0.01 years). The median interval was 11.5 years, the 25th percentile was 11.3 years, and the 75th percentile was 11.9 years. Change in MMSE score between waves 2 and 3 was the primary dependent variable in the analyses.

Classification of participants according to use of cannabis. Participants were separated into five groups based on their self-reported drug use during all three waves of the study. Group 1 (nonusers) were those who reported in all three waves that they had never used cannabis in any form ($n = 806$ (61 percent)). Group 2 (light users) were participants who had used cannabis but had never used it daily or more often for over 2 weeks ($n = 235$ (18 percent)). Group 3 were light users who reported use of any illicit substance in any study wave ($n = 131$ (10 percent)). Group 4 (heavy users) reported during at least one study wave that they had used cannabis daily or more often for over 2 weeks ($n = 137$ (10 percent)). Group 5 were heavy users of cannabis who reported use of other illicit drugs as well ($n = 8$ (1 percent)). Information on cannabis use was missing for one participant.

Classification of participants according to use of alcohol or tobacco. On the basis of the highest alcohol intake reported for the past month during any of the three study waves, participants were placed into three groups: never drinkers ($n = 67$ (5 percent)), light-to-moderate drinkers ($n = 778$ (59 percent)), and heavy drinkers, defined as those who had had more than four drinks on any one day during the past month ($n = 473$ (36 percent)). With respect to smoking, three groups were defined on the basis of self-report during any of the three waves: never smokers ($n = 347$ (26 percent)); occasional smokers ($n = 573$ (44 percent)); heavy smokers, defined as those who smoked 20–39 cigarettes per day (or the equivalent in cigars or pipefuls of tobacco) ($n = 310$ (24 percent)); and very heavy smokers, those who smoked two or more packs of cigarettes per day (or the equivalent) ($n = 85$ (6 percent)). Information on smoking was missing for three participants.

Other variables associated with cognitive decline used as covariates. Information on other variables associated with cognitive decline was recorded at wave 1. Gender was indicated as male or female. Age was grouped as follows: 18–30, 31–40, 41–50, 51–60, and 61–64 years. Minority status was indicated as

African-American or Hispanic versus other ethnicity (non-Hispanic white). Five educational subgroups were developed: 0–8 years, 9–11 years, 12 years or General Equivalency Diploma, 13–15 years, and ≥ 16 years, in conformance with common educational landmarks (grade school, some high school, completed high school or the equivalent, some college, and completed college). It is possible that some study participants, especially those in younger age groups at wave 1, completed their education after wave 1 and were thus misclassified.

Analyses

Mean MMSE score changes between waves 2 and 3 (with 95 percent confidence intervals) are reported in the tables for the entire cohort and for subgroups by age. The proportions of individuals who evidenced any increase, no change, a one-point decline, a two-point decline, a three-point decline, or a four-point or greater decline are also reported by age group. Mean change in MMSE score (with its 95 percent confidence interval) by level of cannabis use was estimated for men and women separately. The relation between level of cannabis use and MMSE score change between waves 2 and 3 was examined in a series of linear regression models with MMSE score change as the dependent variable and cannabis use as the independent variable, with or without inclusion of the other covariates. For both univariate and multiple regression models, the association of cannabis use with change in MMSE score is reported in the form of regression coefficients (with 95 percent confidence intervals). Subgroups were entered into regression models individually as "dummy" variables to allow direct comparisons of regression coefficients using one of the subgroups as the reference category.

To validate the findings from the linear regression models, we also constructed a series of proportional odds logit models (42) relating diseases or substance use to MMSE score change. These were bivariate or multivariate "analogs" to the linear models. The dependent variable was "change in MMSE score," grouped as follows: any increase, no change, a one-point decline, a two-point decline, a three-point decline, or a four-point or greater decline. Findings from these models were similar to those obtained from the linear models. For simplicity, we report only findings from the linear models.

RESULTS

Table 1 provides a description of the study cohort at wave 1 with regard to sociodemographic variables. It also shows mean MMSE scores at each study wave.

TABLE 1. Sociodemographic characteristics of the Baltimore Epidemiologic Catchment Area study cohort at wave 1 (n = 1,318) and mean MMSE* scores at waves 1-3

Variable	No.	%
Age (years)		
18-30	545	41
31-40	319	24
41-50	179	14
51-60	185	14
61-64	90	7
Gender		
Male	488	37
Female	830	63
Race		
Minority (African-American or Hispanic)	490	37
Nonminority (other)	828	63
Education (years)		
0-8	161	12
9-11	280	21
12/GED*	541	41
13-15	211	16
≥16	125	10
Mean MMSE score		
Wave 1 (1981)	28.65 (1.90)†	
Wave 2 (1982)	28.65 (1.81)	
Wave 3 (1993-1996)	27.46 (2.23)	

* MMSE, Mini-Mental State Examination; GED, General Equivalency Diploma.

† Numbers in parentheses, standard deviation.

Cognitive decline between waves 2 and 3

Table 2 shows the mean change in MMSE score between waves 2 and 3 for every age group. It also shows the proportions of participants in each age group with specific changes in MMSE score, as described above. Persons in all age groups had mean

declines greater than zero, with two thirds declining in score by at least one point. The mean decline and the proportion of persons with declining scores increased steadily with age, as expected. It is noteworthy that in every age group there was a notable proportion of participants whose score declined three points or more—a change of a magnitude that merits clinical attention (43, 44). These estimated declines must be considered in the context of MMSE measurement error, the MMSE ceiling effect, and normal variation in MMSE scores over time (see Discussion).

Association between cannabis use and score decline

Table 3 displays estimated mean changes in MMSE score according to level of cannabis use for men and women separately. Women who were nonusers of cannabis had scores that declined more than those of men who were nonusers. However, within male-female groups, there were no evident differences in score decline by cannabis use for either men or women.

Table 4 displays results from the linear regression models with MMSE change between waves 2 and 3 used as the dependent variable. The numbers shown in the table are regression coefficients estimating the relative change in MMSE score for a given group of cannabis users relative to nonusers. Model 1 included only cannabis use as the covariate. Model 2 included cannabis use and use of alcohol and tobacco. Model 3 included cannabis use plus age, gender, education, minority status, alcohol use, and tobacco use. Model 4 included cannabis use plus all of the variables from models 2 and 3. Both light and heavy users of cannabis evidenced *less* cognitive decline than nonusers, although this finding was not statistically significant at

TABLE 2. Mean change in Mini-Mental State Examination (MMSE) score from wave 2 (1982) to wave 3 (1993-1996) and proportions of participants evidencing specific MMSE score changes, by age group, Baltimore Epidemiologic Catchment Area study follow-up

Age group (years)	Change in MMSE score		Score change group											
			Any score increase		No change in score		Decline of 1 point		Decline of 2 points		Decline of 3 points		Decline of ≥4 points	
	Mean change	95% CI*	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
18-30 (n = 545)	-0.98	-0.83 to -1.13	73	13	122	22	179	33	93	17	47	9	31	6
31-40 (n = 319)	-1.08	-0.89 to -1.27	43	13	59	19	107	34	60	19	29	9	21	7
41-50 (n = 179)	-1.25	-0.92 to -1.58	35	20	30	17	39	22	37	21	17	10	21	12
51-60 (n = 185)	-1.52	-1.20 to -1.84	29	16	23	16	48	26	27	15	21	11	31	17
61-64 (n = 90)	-2.12	-1.52 to -2.72	13	14	10	11	18	20	20	22	7	8	22	24
All ages (n = 1,318)	-1.20	-1.10 to -1.30	193	15	250	19	391	30	237	18	121	9	126	10

* CI, confidence interval.

TABLE 3. Mean change in Mini-Mental State Examination (MMSE) score between wave 2 (1982) and wave 3 (1993-1996) in men and women, by level of cannabis use, Baltimore Epidemiologic Catchment Area study follow-up

Gender and level of cannabis use	No.	Mean score change in MMSE	95% CI*
Men			
Nonusers	251	-1.00	-0.73 to -1.27
Light users	104	-1.03	-0.67 to -1.39
Light users plus use of drugs	48	-1.06	-0.57 to -1.55
Heavy users	82	-0.84	-0.46 to -1.22
Heavy users plus use of drugs	3	-0.33	+5.93 to -6.59
Women			
Nonusers	555	-1.46	-1.29 to -1.63
Light users	131	-1.04	-0.71 to -1.37
Light users plus use of drugs	83	-1.07	-0.77 to -1.37
Heavy users	55	-1.15	-0.47 to -1.83
Heavy users plus use of drugs	5	-0.60	+3.09 to -4.29

* CI, confidence interval.

the conventional level of $p < 0.05$ (model 1). After adjustment for the other variables in models 2-4, there was no association between cannabis use and cognitive decline.

DISCUSSION

Cognitive decline is an age-related phenomenon that affects persons of all ages, including those under age 30 years. It becomes more pronounced with increasing age and is most evident in persons over age 59. A significant

proportion (>15 percent) of persons in all population age groups evidence declines that approach clinical significance. We offer two interpretations of this finding. One is that cognitive decline might be an inevitable phenomenon of aging, perhaps modified by genetic makeup, education, nutrition, disease, and environmental exposure. Another is that the declines are the result of slowly progressive neurodegenerative diseases (such as Alzheimer's disease) which might be lifelong in evolution but do not lead to clinical symptoms until much later in life (8). While these two lines of reasoning are not mutually exclusive, the relation between age and cognitive decline across all age groups reported here lends greater support to the former.

To our knowledge, this was the first long term prospective study in the United States that had a community sample large enough to investigate the relation between cannabis use and cognitive decline in persons under age 65 years. Other studies have found short term residual effects of cannabis use on memory and cognition (34, 35) that are more severe among women (36) and heavy users (37). However, our data suggest that over the long term cannabis use is not associated with greater declines in cognition among men, women, or heavy users. The study design we used included several of the features proposed by Pope et al. (34) as critical to addressing the long term effects of cannabis on cognition: naturalistic follow-up, a large sample size, a population basis, comparison of light cannabis use with heavy use, and the construction of models accounting for the effects of gender and use of illicit drugs, alcohol, and tobacco. Therefore, these results would seem to provide strong evidence of the absence of a long term residual effect of cannabis use on cognition.

TABLE 4. Regression coefficients (β) indicating relative differences in Mini-Mental State Examination (MMSE) score change between wave 2 (1982) and wave 3 (1993-1996), by level of cannabis use, in four regression models, Baltimore Epidemiologic Catchment Area study follow-up†

Level of cannabis use	Model 1 (cannabis use)		Model 2 (cannabis use plus use of alcohol and tobacco)		Model 3 (cannabis use plus age, gender, minority status, and education)		Model 4 (cannabis use plus age, gender, minority status, education, and use of alcohol and tobacco)	
	β	SE‡	β	SE	β	SE	β	SE
Nonusers§								
Light users	0.28*	0.15	0.22	0.15	-0.001	0.16	-0.02	0.17
Light users plus use of drugs	0.25	0.19	0.17	0.19	-0.07	0.19	-0.10	0.19
Heavy users	0.35*	0.18	0.27	0.19	0.08	0.20	0.05	0.20
Heavy users plus use of drugs	0.81	0.71	0.66	0.71	0.79	0.70	0.69	0.70

* $p < 0.10$.

† Positive numbers indicate MMSE score increases relative to the reference group; negative numbers indicate relative decreases in MMSE score.

‡ SE, standard error.

§ Reference group.

Notable limitations of this study include loss to follow-up and mortality. Cognitive functioning at baseline was a predictor of both mortality and loss to follow-up in the Epidemiologic Catchment Area study (40). Additionally, it is possible that some cannabis users in the study may have used cannabis on the day the MMSE was administered. Given the acute effects on cannabis on cognition (34), this would have tended to reduce their MMSE score on that day. This may have adversely affected accurate measurement of MMSE score changes over time.

Given that a lower level of cognitive functioning was associated with greater cognitive decline, these estimates of decline may be underestimates. The assessment of cannabis use was based on self-reports and was not confirmed with biologic measures or controlled in an experimental setting. This may have led to underestimation of cannabis use in persons with poor memory.

Another important limitation of the study is that the MMSE is not a very sensitive measure of cognitive decline, even though it specifically tests memory and attention. Thus, small or subtle effects of cannabis use on cognition or psychomotor speed may have been missed. The MMSE is not intended for the purpose for which it was used in this study, and it contains some items that assess neurologic function as well as cognition. Additionally, MMSE item analysis was not performed in this study. Given the MMSE's ease of use and widespread application, it was the most practical instrument available for brief assessment of cognitive functioning at the time the multisite Epidemiologic Catchment Area study was planned in the late 1970s. Also, given its limited sensitivity, declines noted on the MMSE are probably underestimates of true declines.

Other limitations of the MMSE include the fact that small errors, such as forgetting the present day's date, may be due to measurement error and not to true decline. Measurement error on the MMSE might be caused by a variety of factors, including the ambient environment in which the test is taken, the respondent's mood or emotional state, the respondent's adequacy of sleep the night before, the time of day at which the test is given, and other factors. However, such errors ought to be random and not systematic (equally distributed between study waves), so the effect on mean estimates should "average out" across the population and across waves of assessment.

MMSE scores in this study exhibited a ceiling effect, given that most participants scored in the 27–30 range during wave 1. However, the ceiling effect was limited to a minority of participants, those who scored 30 points at baseline, since most declines were small.

Finally, the small but tangible beneficial "practice effect" of repeated testing on MMSE score would tend to lead to higher, not lower, MMSE scores at follow-up.

We conclude that cognitive decline occurs across all age groups, with a significant proportion of persons of all ages showing declines near clinically significant levels after 12 years. Such decline is not associated with cannabis use in either men or women. A better understanding of predictors of cognitive decline in persons under age 65 years might lead to interventions designed to slow or arrest such decline. This in turn might reduce the incidence of dementia at older ages.

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The Drug Policy Letter

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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 its 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

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? ♦

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

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

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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/ Factotum/ Ambulatory
C	48/M	Multiple Congenital Cartilaginous Exostoses	1982 26 years	9 grams/ 2.75%	Full time Stockbroker/ Disabled Sailor/ Ambulatory
D	45/F	Multiple Sclerosis	1991 11 years	9 grams/ 3.50%	Disabled clothier/ Visual impairment/ Ambulatory aids

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

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

TABLE 2. Tests Performed, Chronic Cannabis IND Study

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

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

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

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

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

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

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

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

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

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

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

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

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

The patient underwent a battery of tests. On pulmonary function tests (Table 3), a Functional Vital Capacity (FVC) was 103% predicted. Forced Expiratory Volume in 1 second (FEV₁) was 84% of predicted and the FEV₁/FVC ratio was 0.67. This was read as showing a mild obstructive defect based on the above ratio and flow volume curve morphology. No restrictive abnormality was noted. A CBC was wholly within normal limits (Table 4). Absolute lymphocyte count was 4.0, CD4 61.6% and absolute CD4 count 2465, all within normal limits. A full endocrine battery was performed (Table 5), including FSH, LH, prolactin, estradiol, estrone, estrogen, testosterone, and progesterone, all within normal limits for age and gender.

TABLE 3. Pulmonary Function Tests

Patient/Parameter	A	B	C	D
FVC (% Predicted)	103	107	108	79
FEV ₁ (% Predicted)	84	95	67	76
FEV ₁ /FVC	0.67	0.78	0.51	0.86
Interpretation	Mild obstructive Defect.	WNL. Slightly prolonged forced expiratory time	Moderate obstructive defect.	No obstructive defect. Minor changes not excluded.

TABLE 4. Hematological/Immunological Parameters

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

TABLE 5. Endocrine Parameters

Parameter/Pt.	A	B	C	D
FSH (mIU/ml)	32.8	5.4	3.0	12.4
LH (mIU/ml)	20.6	3.8	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 (pre-menopausal)

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

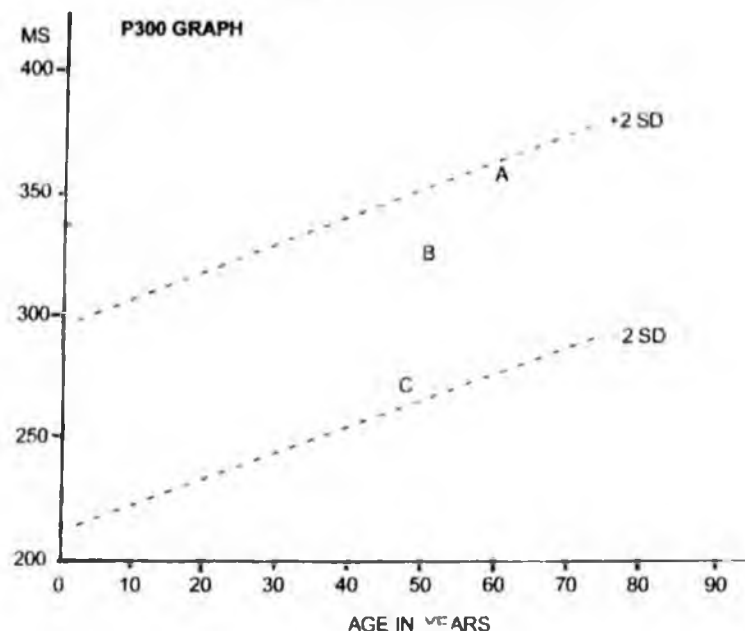
The patient had a P300 test performed with a latency of 355 milliseconds, within normal limits for a normed population in this laboratory (Figure 1).

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

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

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

FIGURE 1. P300 Latency Graph



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

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

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

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

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

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

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

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

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

Patient B

Medical History: This 50-year-old white male carries the diagnosis of the nail-patella syndrome, also known as hereditary osteo-onychodysplasia, a rare genetic disorder producing hypoplastic nails and knee-caps 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 leg 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 prn to see if this would help with relaxation and nausea. When seen September 5, 1990, she had found that the Marinol® had reduced the nausea considerably and had even helped her vision. She continued on fluoxetine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The patient indicated that she received the cannabis legally in 1991 and continues to smoke 10 cigarettes a day. She currently receives material of 3.5% THC content that was processed April 1999. Her study physician requests the highest potency material available, which has recently varied between 2.9-3.7% THC. When she uses outside cannabis of higher potency, she feels that she gets twice the relaxation. There is no chronic cough or other difficulties. The patient feels that 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 FEV_1 and FEV_1/FVC ratios, and perhaps an increase in FVC (Patients A-C) (Table 3). Concomitant tobacco smoking (Patients A, B, and D) complicates analysis. It is particularly interesting that Patient B, a current concomitant smoker of tobacco displayed the best spirometry values, while those in Patient C, a never-smoker of tobacco were the worst. His underlying connective tissue disease may have played an active role in this finding. His use of the lowest grade cannabis and highest amount per day are the more likely explanation.

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

Review of Hematological Studies

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

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

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

Review of Immunological Parameters

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

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

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

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

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

A seminal review of the topic was undertaken by Hollister (1992), who stated (p. 159), "evidence of altered immune functions is derived mainly from in vitro tests or ex vivo experiments, which employed doses of cannabinoids far in excess of those that prevail during social use of marijuana." More recently, Klein, Friedman and Specter (1998) have similarly noted (p. 102), "Although cannabinoids modulate immune cell function, it is also clear that these cells are relatively resistant to the drugs in 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 Aliapoulos (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 marihuana 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®

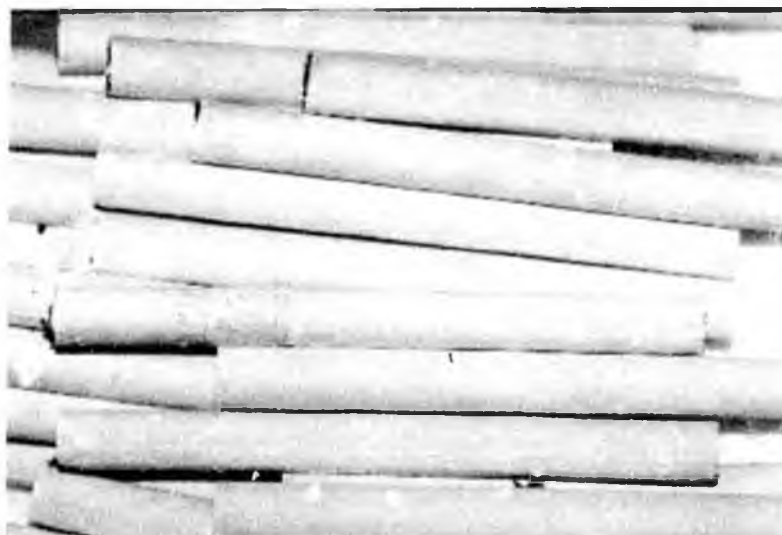
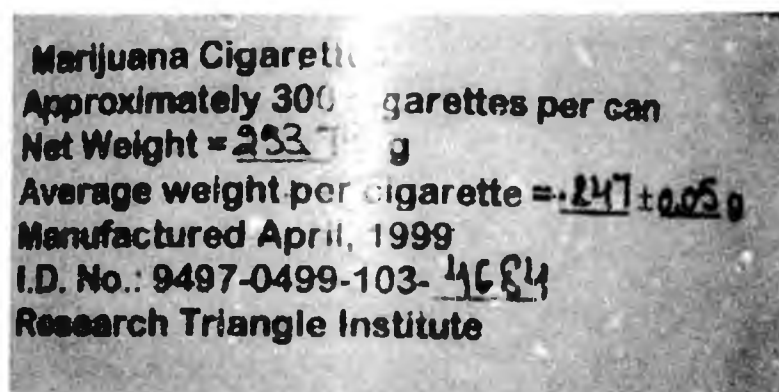


FIGURE 4. Steel Canister with Label



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

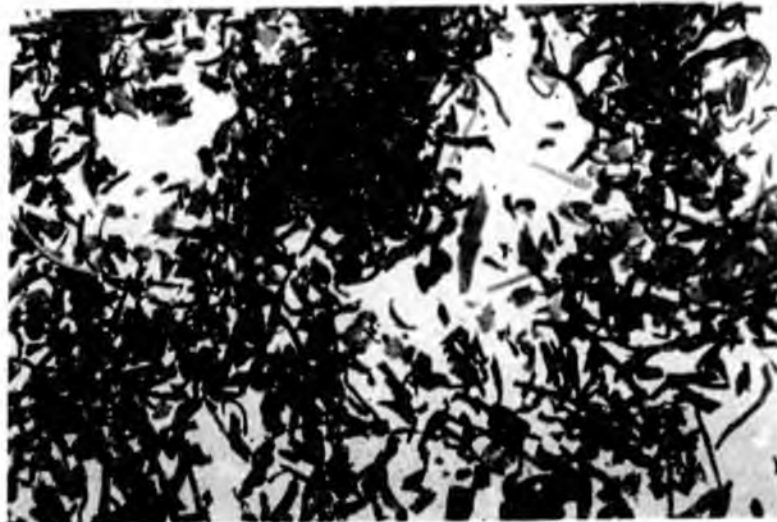


FIGURE 6. Close-Up of Debris from Three NIDA Cannabis Cigarettes



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 analyses 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

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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 more Δ^9 -THC which is, however, less potent than Δ^8 -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 (Finnaldi-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 (Consove 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; Ilaria et al., 1981; Musty, 1984; Sethi et al., 1986; Ashton, 1992; 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 (Ciebowski 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 (Ekeri et al., 1979; Ginter, 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 Gintzenhermen (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 marihuana 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 (Atken and Mikuriya, 1980; Robson, 2001; C. Ispoon and Bakalar, 1993). Near 150 years later, Consroe 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 Consroe's respondents (1997). Thus, Petro and Ellenberger (1981); Clifford (1983); Ungerleider et al. (1987); Menick 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 marihuana 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 marihuana 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^8 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 Leeweke, 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; Leeweke, 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 or 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 DSM-IV 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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Final Report

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

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EXECUTIVE SUMMARY

This report concerns the effects of marijuana smoking on actual driving performance. It presents the results of one pilot and three actual driving studies which were conducted between april 1990 and march 1992. The program was funded by the U.S. National Highway Traffic Safety Administration (NHTSA), with the exception of the alcohol part of the city driving study which was sponsored by the Dutch Road Safety Directorate of the Dutch Ministry of Transport and Public Works. The project was conducted by the Institute for Drugs, Safety and Behavior of the University of Limburg, Maastricht, The Netherlands. The major objectives of the program were to determine the dose-response relationship between Δ^9 -tetrahydrocannabinol (THC), marijuana's main constituent, and objectively and subjectively measured aspects of real-world driving; and, to determine whether it is possible to correlate driving performance impairment with plasma concentrations of the drug or a metabolite. A variety of driving tests were employed, including: maintenance of a constant speed and lateral position during uninterrupted highway travel, following a leading car with varying speed on a highway, and city driving. The purpose of applying different tests was to determine whether similar changes in performance under the influence of THC occur in all, thereby indicating a general drug effect on driving ability.

Chapter One provides background information about the drug, its pharmacological properties, the prevalence of its use, and a review of marijuana smoking and traffic safety. THC's effects on the ability of drivers to operate safely in traffic situations have traditionally been determined in two ways: from epidemiological surveys of users' involvement in traffic accidents and from empirical studies to measure the drug's influence on skills related to driving, or driving itself. Epidemiology shows that people drive after marijuana use and that drivers involved in accidents often show the drug's presence. The results are, however, inconclusive because of the high proportion of cases which also involve alcohol use and the lack of proper control groups. Therefore, the extent marijuana contributes to traffic accident causality remains obscure. Results from driving simulator and closed-course tests show that THC in single inhaled doses up to about 250 $\mu\text{g/kg}$ has relatively minor effects on driving performance, certainly less than blood alcohol concentrations (BACs) in the range of 0.08-0.10 g%.

Chapter Two describes the studies of the program and certain procedures that were common to all. These were subject recruiting, compliance with ethical and legal standards, screening for the presence of other illicit drugs and alcohol, blood sampling procedures and quantitative analyses. Subjects in all studies were recreational users of cannabis, i.e. smoking marijuana or hashish more than once a month but not daily. They were all healthy, between 21 and 40 years of age, had normal weight and binocular acuity, and were licensed to drive an automobile. Subjects were accompanied in every driving test by an licensed driving instructor, experienced in supervising subjects who operated under the influence of medicinal drugs in previous studies. Redundant control system in the test vehicle was available for controlling the car if emergency situations should arise. Marijuana and placebo marijuana cigarettes were supplied by the U.S. National Institute on Drug Abuse (NIDA).

Chapter Three presents the results of the pilot study. It was conducted in a hospital under strict medical supervision to identify THC doses that recreational marijuana users were likely to consume before driving. Twenty-four subjects, twelve males and twelve females, participated.

They were allowed to smoke part or all of the THC content in three cigarettes until achieving the desired psychological effect. Cigarettes were smoked through a plastic holder in a manner determined by the subjects. The only requirement was to smoke continuously for a period not exceeding 15 minutes. When subjects voluntarily stopped smoking, cigarettes were carefully extinguished and retained for subsequent gravimetric estimation of THC consumed. Six subjects consumed one cigarette, thirteen smoked two and four smoked three. The average amount of THC consumed was 20.8 mg, after adjustment for body weight, 308 $\mu\text{g/kg}$. There was no significant difference between males and females with respect to the weight adjusted preferred dose. It was decided that the maximum dose for subsequent driving studies would be 300 $\mu\text{g/kg}$. This is considerably higher than doses that have usually been administered to subjects in experimental studies (typically, 100-200 $\mu\text{g/kg}$ THC).

The study provided the opportunity for obtaining valuable information about THC's pharmacokinetics and its pharmacodynamic effects after marijuana smoking. Blood samples were repeatedly taken for measuring plasma concentrations of THC and its major inactive metabolite, THC-COOH. The subjects repeatedly performed certain simple laboratory tests, estimated their levels of intoxication and indicated their willingness to drive under several specified conditions of urgency. Heart rate was measured at these times. The secondary purpose of the pilot study was that of specifying relationships between [THC] and [THC-COOH] with changes in the other physiological, performance or subjective variables. Other results from the pilot study showed that perceived "high" and heart rate are very sensitive measures of marijuana intoxication which confirms prior findings. Impairments in laboratory tests performance were found at the time of peak subjective feelings but generally, objective impairment dissipated more rapidly than the feelings themselves.

The first driving study, described in *Chapter Four*, was conducted on a highway closed to other traffic. One objective of the study was to determine whether it would be safe to repeat the study on a normal highway in the presence of other traffic. The second objective was to define the dose-effect relationship between inhaled THC dose and driving performance. The same twelve men and twelve women who participated in the pilot study served again as the subjects. They were treated on separate occasions with THC doses of 0, 100, 200, 300 $\mu\text{g/kg}$. Treatments were administered double-blind and in a counterbalanced order. On each occasion, subjects performed a road tracking test beginning 40 minutes after initiation of smoking and repeated one hour later. The test, developed and standardized by O'Hanlon *et al.* (1982, 1986), involved maintaining a constant speed at 90 km/h (56 mph) and a steady lateral position between the delineated boundaries of the traffic lane. Subjects drove 22 km (13.6 mi) on a primary highway and were accompanied by a licensed driving instructor. The latter was charged with responsibility for ensuring safety at all times and was able to intervene, if necessary, using redundant vehicular controls. The primary dependent variable was the standard deviation of lateral position (SDLP), which has been shown to be both highly reliable and very sensitive to the influence of sedative drugs and alcohol. Other dependent variables were mean speed, and standard deviation of speed and steering wheel angle. Blood samples were taken prior to each driving test; and, performance in critical tracking and hand steadiness tests, heart rate, and blood pressure were measured after its termination. Questionnaires were repeatedly administered to estimate the "high" and other subjective feelings.

All subjects were willing and able to finish the driving tests without great difficulty. The study demonstrated that marijuana impairs driving performance as measured by an increase in SDLP; all three THC doses significantly affected SDLP relative to placebo. The driving

performance decrement after smoking marijuana persisted almost undiminished for two hours after smoking while drug plasma concentrations, perceived "high" and heart rate elevation had decreased. Marijuana's effects on SDLP were compared to those of alcohol obtained in a very similar study by Louwerens *et al.* (1985, 1987). It appeared that THC's effects on SDLP were equivalent to those associated with BACs in the range of 0.03-0.07 g%. Other driving performance measures were not significantly affected by THC. Intersubject correlations between plasma concentrations of the drug and driving performance after every dose were essentially nil. Thus, driving impairment cannot be predicted by prevailing plasma concentrations of THC or THC-COOH. Driving impairment was also not related to performance in the laboratory tests. Both the observed degree of driving impairment, and what subjects said and did, indicated that normal safeguards would be sufficient for ensuring safety in further testing. Hence, the final conclusion was to repeat this study on a normal highway in the presence of other traffic.

The second driving study, described in *Chapter Five*, was conducted to come a step closer to driving reality than its predecessor. Driving tests were now conducted on a highway in the presence of other traffic. The major objective of this study was to confirm the relationship between inhaled THC dose and lateral position variability in the context of a standard road tracking test. A secondary objective was to measure performance in another actual driving test, i.e. car following. The third objective was to continue efforts to correlate plasma concentrations of THC and THC-COOH with driving performance impairment as measured in both tests.

A new group of sixteen subjects, equally comprised of men and women, participated in this study. A conservative approach was chosen in designing the present study in order to satisfy the strictest safety requirements. That is, the study was conducted according to an ascending dose series design where both active drug and placebo conditions were administered, double-blind, at each of three THC dose levels. THC doses were the same as those used in the previous study, namely 100, 200, and 300 µg/kg. Cigarettes appeared identical at each level of treatment conditions and were smoked through a plastic holder in a fashion determined by the subject within a time limit of 10 minutes. If any subject would have reacted in an unacceptable manner to a lower dose, he/she would not have been permitted to receive a higher dose.

Two subjects at a time commenced smoking. Thirty minutes after onset of smoking the subjects performed a battery of laboratory tests (tracking, hand steadiness and body sway), yielded a blood sample, and rated their "high" and other subjective feelings. They were then transported to a primary highway where the driving tests were performed. Two instrumented vehicles were employed. The subjects performed the car following test on a 16 km (9.9 mi) segment of the highway for about twelve minutes. After conclusion of the car following test, both subjects then commenced the road tracking test in separate instrumented vehicles. The highway was the same as for the car following test. Subjects drove 64 km (40 mi) without stopping in about 50 minutes. At the conclusion of this test, both subjects participated again in the car following test. Subjects were then transported back to the laboratory where they rated subjective feelings, yielded a blood sample, and repeated the test battery. The subjects' heart rate was registered continuously during both driving tests.

The road tracking test was the same as in the previous study except for its duration and the presence of other traffic. Subjects were instructed to maintain a constant speed of 95 km/h (59 mph) and a steady lateral position between lane boundaries in the right traffic lane. They were allowed to deviate from this only if it would become necessary to pass a slower vehicle in the same lane. Data from the standard test were analyzed to yield the same performance measures as in the previous study; i.e. SDLP, mean and standard deviation of speed, and

standard deviation of steering wheel angle. The car following test measures drivers' ability to perceive changes in a preceding vehicle's speed and to react in a manner maintaining a constant headway. It began as the preceding and the following vehicle, respectively driven by one of the driving instructors and the subject, operated in tandem on the slower traffic lane while travelling at a speed of 100 km/h (62 mph). The subject was instructed to maintain a 50 m (164 ft) headway however the preceding vehicle's speed might vary. After driving in this manner for about one minute, the operator of the preceding vehicle released the accelerator pedal allowing its speed to fall to 80 km/h (50 mph). Immediately thereafter, the operator of the preceding vehicle accelerated to 100 km/h (62 mph). The duration of one deceleration and acceleration maneuver was approximately 50 seconds and six to eight, depending upon traffic density, were executed during one test. The subject's average reaction time to the movements of the leading vehicle, mean headway and coefficient of variation of headway during maneuvers were taken as the dependent variables from this.

All subjects were able to complete the series without suffering any untoward reaction while driving. Road tracking performance in the standard test was impaired in a dose-related manner by THC and confirmed the results obtained in the previous closed highway study. The 100 $\mu\text{g/kg}$ dose produced a slight elevation in mean SDLP, albeit nearly significant. The 200 $\mu\text{g/kg}$ dose produced a significant elevation, of dubious practical relevance. The 300 $\mu\text{g/kg}$ dose produced a highly significant elevation which may be viewed as practically relevant but unexceptional in comparison with similarly measured effects of many medicinal drugs. Following marijuana smoking subjects drove with an average speed that was only slightly lower than after placebo and very close to the prescribed level.

In the car following test, subjects maintained a headway of 45-50 m (148-164 ft) while driving in the successive placebo conditions. They lengthened mean headway by 8, 6 and 2 m (26.2, 19.7 and 6.6 ft) in the corresponding THC conditions after 100, 200 and 300 $\mu\text{g/kg}$, respectively. The initially large drug-placebo difference and its subsequent decline is a surprising result. Our explanation for this observation is that the subjects' caution was greatest the first time they undertook the test under the influence of THC and progressively less thereafter. Reaction time to changes in the preceding vehicle's speed increased following THC treatment, relative to placebo. The administered THC dose was inversely related to the change in reaction time, as it was to headway. However, increased reaction times were partly due to longer headway. Statistical adjustment for this confounding resulted in smaller and non-significant increases in reaction time following marijuana treatment, the greatest impairment (0.32 s) being observed in the first test following the lowest THC dose. Headway variability followed a similar pattern as mean headway and reaction time; the greatest impairment was found following the lowest dose.

An important practical objective of this study was to determine whether degrees of driving impairment can be accurately predicted from either measured concentrations of THC in plasma or performance measured in potential roadside "sobriety" tests of tracking ability or hand and posture stability. The results, like many reported before, indicate that none of these measures accurately predicts changes in actual driving performance under the influence of THC.

The program then proceeded into the third driving study, presented in *Chapter Six*, which involved tests conducted in high-density urban traffic. There were logical and safety reasons for restricting the THC dose to 100 $\mu\text{g/kg}$. It was given to a group of regular cannabis users, along with placebo. For comparative purposes another group of regular alcohol users were treated with a modest dose of their preferred recreational drug, and again placebo, before undertaking the

same city driving test. Two groups of sixteen new subjects apiece, equally comprised of men and women, participated. Subjects in the alcohol group were regular users of alcohol but not marijuana. Both groups were treated on separate occasions with active drug and placebo. Active marijuana was administered to deliver 100 $\mu\text{g/kg}$ THC. The driving test commenced 30 minutes after smoking. The alcohol dose was chosen to yield a BAC approaching 0.05 g% when the driving test commenced 45 minutes after onset of drinking. Active drug and placebo conditions were administered double-blind and in a counterbalanced order in each group.

Driving tests were conducted in daylight over a constant 17.5 km (10.9 mi) route within the city limits of Maastricht. Subjects drove their placebo and active drug rides through heavy, medium and low density traffic on the same day of the week, and at the same time of day. Two scoring methods were employed in the present study. The first, "molar" approach, required the driving instructor acting as the safety controller during the tests to retrospectively rate the driver's performance using a standard scale. The second, a more "molecular" approach, involved the employment of a specially trained observer who applied simple and strict criteria for recording when the driver made or failed to make each in a series of observable responses at predetermined points along a chosen route. Immediately prior to and following the driving tests subjects performed hand steadiness and time perception tests, yielded a blood sample, and were administered the same subjective questionnaires used in the previous studies.

The study showed that a modest dose of alcohol (BAC=0.04 g%) produced a significant impairment in city driving as measured by the molar approach, relative to placebo. More specifically, alcohol impaired vehicle handling and traffic maneuvers. Marijuana, administered in a dose of 100 $\mu\text{g/kg}$ THC, on the other hand, did not significantly change mean driving performance as measured by this approach. Neither alcohol nor marijuana significantly affected driving performance measures obtained by the molecular approach indicating that it may be relatively insensitive to drug-induced changes.

Driving quality as rated by the subjects contrasted with observer ratings. Alcohol impaired driving performance according to the driving instructor but subjects did not perceive it; marijuana did not impair driving performance but the subjects themselves perceived their driving performance as such. Both groups reported about the same amount of effort in accomplishing the driving test following placebo. Yet only subjects in the marijuana group reported significantly higher levels of invested effort following the active drug. Thus, there was evidence that subjects in the marijuana group were not only aware of their intoxicated condition but were also attempting to compensate for it. These seem to be important findings. They support both the common belief that drivers become overconfident after drinking alcohol and investigators' suspicions that they become more cautious and self-critical after consuming low THC doses by smoking marijuana.

The laboratory performance tests also discriminated between the drugs' effects. Hand steadiness was impaired following THC and improved following alcohol, relative to placebo. The difference between the drugs' effects was significant, both before and after the driving test. Impairment after THC was about as much as that produced by the same dose in the previous study, indicating equivalent sensitivities of the present and previous groups. Production of time intervals was not affected by alcohol, but THC significantly shortened interval production, relative to placebo.

Drug plasma concentrations were neither related to absolute driving performance scores nor to the changes that occurred from placebo to drug conditions. With respect to THC, these results

confirm the findings in previous studies. They are somewhat surprising for alcohol but may be due to the restricted range of ethanol concentrations in the plasma of different subjects.

Chapter Seven concludes the report with a general discussion of the results of the program and ends with a list of conclusions and recommendations. It starts with a discussion of the THC dose which marijuana users actually prefer for achieving their desired "high". Several questions are raised and discussed, such as: how do people regulate their THC consumption, what role plays familiarization with the drug, and what would the preferred dose have been if marijuana of much higher potency were smoked. The discussion then continues with a description of the differences between the driving tests in terms of the type of information processing each requires, automatic vs controlled, and the relevance of each to traffic safety.

Attention is further focussed on the effects of THC on driving performance. The results of the studies corroborate those of previous driving simulator and closed-course tests by indicating that THC in single inhaled doses up to 300 $\mu\text{g/kg}$ has significant, yet not dramatic, dose-related impairing effects on driving performance. Standard deviation of lateral position in the road tracking test was the most sensitive measure for revealing THC's adverse effects. This is because road tracking is primarily controlled by an automatic information processing system which operates outside of conscious control. The process is relatively impervious to environmental changes but highly vulnerable to internal factors that retard the flow of information through the system. THC and many other drugs are among these factors. When they interfere with the process that restricts SDLP, there is little the afflicted individual can do by way of compensation to restore the situation. Car following and, to a greater extent, city driving performance depend more on controlled information processing and are therefore more accessible for compensatory mechanisms that reduce the decrements or abolish them entirely.

It appears that performance is more affected by THC in laboratory than actual driving tests. Several reasons that may account for the apparent discrepancy are discussed. First, laboratory tests are experimentally controlled by drastic simplification which may affect a subject's motivation to perform the test by making it appear "unreal". Secondly, the restriction of response options in laboratory performance tests leave fewer possibilities for compensation. In real life, drivers always apply numerous skills in parallel and series. Should one become deficient, they are often able to compensate in a number of ways to achieve a satisfactory level of proficiency. Finally, after learning to drive, subjects possess such skills in abundance and one can only demonstrate how they vary with drug effects in the real task or a very close approximation thereof. Profound drug impairment constituting an obvious traffic safety hazard could as easily be demonstrated in a laboratory performance test as anywhere else. But THC is not a profoundly impairing drug. It does affect automatic information processing, even after low doses, but not to any great extent after high doses. It apparently affects controlled information processing in a variety of laboratory tests, but not to the extent which is beyond the individual's ability to control when he is motivated and permitted to do so in real driving.

Marijuana's effects on driving performance were compared to those of many other drugs. It was concluded that THC's effects after doses up to 300 $\mu\text{g/kg}$ never exceed alcohol's at BACs of 0.08 g%; and, were in no way unusual compared to many medicinal drugs. Yet THC's effects differ qualitatively from many other drugs, especially alcohol. Evidence from the present and previous studies strongly suggests that alcohol encourages risky driving whereas THC encourages greater caution, at least in experiments. Another way THC seems to differ qualitatively from many other drugs is that the former's users seem better able to compensate for its adverse effects while driving under the influence. Still one can easily imagine situations

where the influence of marijuana smoking might have an exceedingly dangerous effect; i.e., emergency situations which put high demands on the driver's information processing capacity, prolonged monotonous driving, and after THC has been taken with other drugs, especially alcohol.

Finally, the relation between driving impairment following marijuana smoking and plasma concentrations of THC and THC-COOH is discussed. It appears not possible to conclude anything about a driver's impairment on the basis of his/her plasma concentrations of THC and THC-COOH determined in a single sample.

CHAPTER 1 - MARIJUANA AND DRIVING: A REVIEW

Marijuana's effects on the ability of drivers to operate safely in traffic situations have traditionally been determined in two ways: from epidemiological surveys of users' involvement in traffic accidents and from empirical studies to measure the drug's influence on skills related to driving and driving itself. A review of results obtained from both approaches, partly relying upon previously published reviews, is provided. Its purpose is providing the reader a broader context in which the present report should be viewed. First, however, the drug and its pharmacological properties, and the prevalence of its use, will be discussed.

THE DRUG AND ITS PHARMACOLOGICAL PROPERTIES

Marijuana is the common name for any part of the hemp plant, cannabis sativa, or extracts which possess characteristic psychoactive properties in man. The plant contains more than 400 compounds. More than 60, the cannabinoids, are specific to that plant. The majority of the cannabinoid products are pharmacologically inactive. The major active product and that primarily responsible for the physiological and psychological effects of marijuana smoking is Δ^9 -tetrahydrocannabinol (THC).

Besides being used as an intoxicant to produce a psychological "high" or euphoria, marijuana has been used as a sedative and analgesic (Maykut, 1985) but also, in Eastern countries, for relieving fatigue and stimulating appetite (Murray, 1985). It reliably produces both tachycardia and marked conjunctivitis. The mechanisms by which THC produces these physiological effects or the psychological effects sought by its users are still poorly understood (Jaffe, 1990). As a therapeutic agent, marijuana has been successfully applied in some cases of glaucoma (Relman, 1982) and anorexia nervosa (Zinberg, 1979). The most promising potential clinical use of marijuana is in the treatment of nausea and vomiting caused by cancer chemotherapy (Relman, 1982; Vinciguerra *et al.*, 1988; Randall, 1990). Synthetically formulated THC was approved in 1985 by the U.S. Food and Drug Administration (FDA) for use in the treatment of emesis, and is now marketed under the trade name Marinol (Unimed, Somerville, NJ). Patients suffering from AIDS may also benefit from marijuana because of its antiemetic and appetite stimulating effects. Yet there are also reports of adverse health effects of marijuana smoking on fetal growth, sperm cell motility, female reproductive hormone function, immunological system, cardiopulmonary system and central nervous system (Jaffe, 1990; Mendelson, 1987; Maykut, 1985).

The THC content in marijuana cigarettes varies in the United States from about 0.5% to 11% (Jaffe, 1990). In The Netherlands, seized hemp material usually contains about 10% THC, though it may range from 5 to 15% and, in exceptional cases, to 25% (Dutch Forensic Laboratory, personal communication). The inhaled dose in marijuana smoke varies also widely, depending upon the smoking technique and the amount altered by pyrolysis. In general it is thought that no more than about 25% of the available THC enters the circulation when marijuana is smoked in the usual manner (Davis *et al.*, 1984; Ohlsson *et al.*, 1980; Agurell and Leander,

1971), though if it were possible to continuously inhale smoke from an entire cigarette, up to 70% would become available (Agurell and Hollister, 1986).

The metabolism of THC is exceedingly complex and more than 80 metabolites are known to be formed in man. After marijuana smoking or THC injection, the first metabolite, 11-hydroxy-THC (11-OH-THC) is formed in the lungs and liver. Its peak concentration in relation to the parent compound's is about 1:10-20 (Wall *et al.*, 1983). After oral THC the ratio is about 1:1-2. Because this metabolite's psychological activity is equipotent to the parent's, it contributes to the total marijuana effect, particularly when the drug is ingested. 11-OH-THC is converted by the liver into a number of inactive metabolites. The primary pathway leads to the formulation of 11-nor-THC-9-carboxylic acid (THC-COOH), the most abundant inactive metabolite in plasma, and in urine where it is partially conjugated.

Plasma concentrations of THC peak during the smoking process and decline in sequential exponential phases; a redistribution (α) phase wherein the drug passes rapidly out of the plasma and into fatty tissues including the brain, followed by a much more prolonged elimination (β) phase wherein it is metabolized and excreted in urine and feces. The α -phase half life ($t_{1/2\alpha}$) is only about 30 minutes, whereas that of the β -phase ($t_{1/2\beta}$) varies between 18 and 36 hours depending upon the individual (Wall *et al.*, 1983; Chiang and Barnett, 1984; Agurell *et al.*, 1986).

The peak plasma concentration of 11-OH-THC is achieved within 15-30 minutes and from there declines according to essentially the same pharmacokinetic profile as its parent. The rise in THC-COOH's plasma concentration is relatively slow, reaching an ill defined peak in different individuals within 1-2 hours. Its elimination follows a monoexponential profile with various individuals showing $t_{1/2}$'s from less than 24 to more than 72 hours. It is interesting to note that the inactive metabolite's mean plasma concentration exceeds that of THC from about the first hour onward.

Though peak concentrations of THC are achieved during smoking, the maximum psychological effect (the "high") occurs 15-30 minutes after its cessation, suggesting that brain concentrations increase as plasma concentrations decrease. Both peak concentrations and maximum "high" are roughly proportional to the inhaled THC dose, but correlations between these parameters measured simultaneously at times 3-240 min after the cessation of smoking are, albeit significant, not especially strong. For example, Ohlsson *et al.* (1980) found the overall correlation for repeated measurements obtained from 11 experienced smokers to be $r=0.53$. After four hours the psychological "high" had vanished and plasma THC levels were very low. Great interindividual variation exists in plasma levels of THC after smoking and this variation cannot be attributed to the regularity of marijuana use (Lindgren *et al.*, 1981; Agurell and Hollister, 1986).

Available evidence leads to the conclusion that it is usually impossible to predict the psychological effects of THC from its determination in a single plasma sample. But this is not the same as saying that no biological index of marijuana intoxication will ever be found. One possible candidate is THC's inactive metabolite THC-COOH. The relationship between this metabolite's plasma concentration and the perceived "high" after marijuana smoking has never been defined, although both parameters were measured in the study by Perez-Reyes *et al.* (1982). Peak and time integrated THC-COOH concentrations were proportional to the administered THC doses. Interestingly, the occurrence of the peak THC-COOH concentration coincided in time with the subjects' report of maximum "high". The authors failed, however, to measure, or at least report, the correlation between plasma THC-COOH concentration and

subjective feelings because of the metabolite's pharmacological inactivity. Yet this coincidence might signify a useful epiphenomenal correlation. This possibility was repeatedly explored in this program.

PREVALENCE OF MARIJUANA USE

Marijuana usage prevalence peaked in the late 1970s and has been declining ever since. Still, marijuana is by far the most commonly used illicit drug in the United States (Jessor *et al.*, 1986; Johnston *et al.*, 1992). The most recent data about marijuana usage prevalence are available from the 17th National Survey of American High School Seniors, and the 12th National Survey of American College Students (Johnston *et al.*, 1992). Life time prevalence among high school seniors declined from 60% in 1980 to 37% in 1991; and, among college students, from 65% in 1980 to 46% in 1991. Thirty-day prevalence declined in both groups from 34% in 1980 to 14% in 1991. About 9% of high school seniors and 7% of college students admitted daily use of marijuana in 1980. Only 2% of both groups did in 1991.

A 1988/1989 survey of cannabis use among Dutch students, 10-20 years old, provided different results (Plomp *et al.*, 1990). Considering only those in an age bracket comparable to American high school seniors and recent graduates (17-20 yrs; N=1806), the lifetime use prevalence of cannabis was 21% and 13% among males and females, respectively. Those who smoked at least once during the last month comprised 5.8% and 3.0% of the respective samples. Compared to results obtained from a similar survey executed in 1984 (Van der Wal, 1985) the lifetime and current prevalence of use have risen in The Netherlands by factors of 1.7 and 1.5, respectively.

In short, relatively more young Americans formerly used and still use cannabis than their Dutch counterparts, but the disparities between lifetime and current use prevalences are narrowing due to opposite trends in the two countries.

It is perhaps important to note in this context that possession of cannabis is prohibited by law in The Netherlands, as in the United States. The seriousness of the offense is, however, determined by the amount found in the Dutch user's possession and prosecution is unlikely to occur when that is less than 30 g (1 oz).

MARIJUANA AND TRAFFIC SAFETY

Epidemiological Research

Simpson (1986) has reviewed recent epidemiological evidence regarding marijuana's role in traffic accident causality. His first concern was to determine the frequency of driving after marijuana use in order to identify the proportion of the total driving population who may be considered "at risk" of causing an accident for that reason. His information was derived from two sources: questionnaire surveys of adolescents (16-19 years), who were licensed to drive, and roadside surveys of recent usage among passing motorists.

He mentioned the reasonably consistent results of four questionnaire surveys conducted in the United States or Canada between 1979 and 1982. About one in six teenage drivers admitted driving while smoking or shortly afterward, and about 10% said they had done so between one and five times during the preceding month. Taken at face value, these results indicate that most

users do not drive during or shortly after marijuana smoking which implies they do perceive risks associated with marijuana use and driving. Unfortunately it is not easy to generalize these results to older drivers in North America, nor to Europeans who are generally not licensed to drive until older than 18 years of age.

Only two surveys of recent marijuana use among drivers stopped at roadside check points have apparently been reported. These were widely separated in place and time. The first was completed in Canada in 1974 (Smith *et al.*, 1975), the second in Italy in 1982 (Ferrara and Rozza, 1985). Moreover, the former relied upon the drivers' admission of use and the latter upon detection of cannabinoids in urine samples. Nonetheless, the indications of recent marijuana use given by the two sets of results were not grossly different; 4% by the first and 1.2% by the second.

The incidence of drivers whose recent use of marijuana resulted in their injury or death in motor vehicle accidents can only be estimated from the detection of THC in plasma samples obtained shortly after the occurrence of the event. Hemolyzed blood samples obtained from dead victims provide unreliable estimates and analyses of urine samples to determine metabolite concentrations yield no indication of whether the drug was active at the time of the accident.

Terhune (1982) tested 497 injured drivers for the presence of a wide range of drugs during treatment at the Rochester General Hospital in New York. THC in blood was detected in 9.5% of the drivers, but more than half of them also tested positively for alcohol. Chesher and Starmer (1983) found THC in 6.7% of 104 injured drivers in New South Wales, Australia, but again about half of them showed alcohol as well. Daldrup *et al.* (1987) examined 597 blood samples from injured drivers in the region around the German city Düsseldorf for the presence of alcohol. Blood samples having alcohol concentrations (BAC) below 0.13 g% were additionally analyzed for the presence of cannabinoids; twenty-five of the 220 blood samples (10%) were positive. More recently, Soderstrom *et al.* (1988) determined prior marijuana and alcohol use in 1023 patients who were injured as the result of vehicular and nonvehicular accidents and treated in the Shock Trauma Center in Baltimore, Maryland. THC was found in blood by radioimmunoassay in 34.7% of the patients, alcohol in 33.5%. Among automobile drivers, the numbers were 31.7% and 34.6%, respectively. Again, in about 50% of the marijuana positive cases alcohol was also found. It is not clear why these results contrast with those of previous studies. The most plausible explanation is that residents of the Baltimore area tend, in general, to use THC more often than those in the other regions surveyed.

Canadian and American surveys of fatally injured drivers have generally found the incidence of those showing THC in plasma to be between 3% and 11% and in all cases the coincidence of this drug and alcohol was above 70% (Cimbura *et al.*, 1980, 1982, 1990; Donelson *et al.*, 1985; Owens, 1981; Mason and McBay, 1984). Disparate results were obtained by Williams *et al.* (1985) who found THC in plasma from 37% of 440 dead drivers in California (80% in combination with alcohol). The reason for this disparity could be due to the greater prevalence of marijuana use in California but it was more probably related to these investigators' selection criteria: they only included male drivers younger than 35 years of age in their sample. Simpson estimated that if female and older male fatalities had been included in this survey, the overall percentage showing THC would have been about 20%. This figure is still double the estimates from other studies, which reinforces suspicions about the prevalence of marijuana use in California. However neither this nor any other survey allowed for the local and contemporary comparison of the fatally injured percentage of drivers showing THC plasma levels with that of the driving population in general.

If it is true that the population at risk from driving after marijuana smoking is 4%, or less, then the higher percentages of drivers injured or killed in traffic accidents while showing plasma THC concentrations seem to be an over-representation. However, there are obvious reasons to doubt whether valid estimates of the population at risk in urban North America can be derived from data that are more than 14 years old or were obtained at two locations in Northern Italy. Even if the population at risk is as small as estimated, the surveys of THC incidence in injured or killed drivers have not provided evidence for a causal role of the drug per se in accidents. Alcohol was present in the vast majority of victims showing plasma concentrations of THC. The fact that the two drugs in combination possess a greater risk potential than either alone, is most likely. But the independent contribution of THC to traffic accident causality, particularly in concentrations which are likely to be found in most users who drive, is still questionable.

One major problem in epidemiological research on the relationship between marijuana and traffic accidents is the lack of sound control groups as have been used in studies of alcohol involvement in accidents (e.g. Borkenstein *et al.*, 1964). In those studies BACs derived from breath samples of drivers involved in accidents were compared with those of randomly selected drivers passing the accident site in the same direction at the same time of day and day of week. As Moskowitz (1985) noted, these kind of studies rely on two assumptions that do not hold well for investigations on marijuana. The first is that nearly all drivers will cooperate, which holds for alcohol studies in which typically 97% are willing to supply a breath sample, but does not hold for marijuana studies in which only 50-75% are willing to cooperate due to the necessity of sampling blood rather than breath. A second assumption is that drug concentrations found are well correlated with performance impairment, which holds for alcohol but seems not to for marijuana.

One way to circumvent this problem is the use of a culpability index, which reflects the percentage of drivers with detectable drug levels and deemed culpable compared to drug free drivers from the same sample who were also responsible for causing an accident. Warren *et al.* (1981) reanalyzed the data from Cimbura *et al.* (1980) and reported that 52% of the drug free fatally injured drivers were deemed culpable compared to 90% of those with evidence of marijuana use resulting in a culpability index of 1.7, a level also found for alcohol. Results of two other studies (Terhune, 1982; Donelson *et al.*, 1985) are consistent with these findings, whereas Mason and McBay (1984) found no evidence of marijuana as a risk factor. In contrast to these studies, Williams *et al.* (1985) found that drivers in whom only marijuana was detected were less likely to be culpable (53% vs 71%). In contrast, dead drivers showing only alcohol were judged responsible in 92% of all cases. Those showing both THC and alcohol were slightly more often responsible for causing the accident than those in whom only alcohol was found. It should be noted, however, that the frequencies of injured drivers showing THC alone are commonly very low and prohibit any definite conclusion.

In summary, epidemiological literature shows that people do drive after marijuana use and that drivers involved in accidents often show the drug's presence, but results are inconclusive especially because of the high proportion of cases that also involve alcohol use. Therefore, the extent marijuana contributes to traffic accident causality remains obscure.

Marijuana's Effects upon Driving Simulator Performance

Early studies by Crancer *et al.* (1969), Rafaelsen *et al.* (1973), Ellingstad *et al.* (1973) and Moskowitz *et al.* (1976) utilized the filmed ride approach where subjects had little or no control

over the presented imagery. Dott (1972) used a different approach for measuring subjects' decisions to pass a preceding car, or not, in the presence of an opposing vehicle portrayed as models on a continuous belt. Doses of inhaled THC varied from about 3 to 22.5 mg (43-321 $\mu\text{g/kg}$ for 70 kg, or 154 lb, persons). Smiley (1986) reviewed these early studies to conclude that THC had (1) not affected vehicle control, (2) increased decision latency before starting, stopping or overtaking, (3) reduced the willingness to accept a risk during passing maneuvers, and (4) impaired speedometer monitoring. Except in the case of one individual who, after inhaling 12 mg THC, repeatedly drove through stop lights during a filmed ride, no particular sign of dangerous driving behavior was observed.

Smiley *et al.* (1981) conducted the first study using an interactive simulator with accurate visual imagery, though not moving base dynamics. The simulated tasks contained in a 45-minute scenario included curve following, reacting to wind gusts, car following, route selection from signs, avoiding an obstacle which appeared in front of the simulated vehicle and passing. A visual choice reaction time was also superimposed on driving. Three groups of marijuana users smoked cigarettes containing 0, 100 and 200 $\mu\text{g/kg}$ THC on two occasions per dose, once with and once without alcohol. The quantity of alcohol consumed varied between groups to reach intended blood concentrations of 0.00, 0.05 and 0.08 g%, respectively. To ensure high motivation, good driving was rewarded and blatant errors, such as crashes, were penalized financially. The test began 15 minutes after the cessation of smoking. Both THC doses increased lateral position variability and the highest dose increased speed variability during curve following. Both increased headway variability, and the highest, lateral position variability during car following. Both doses caused the subjects to miss more signs indicating the need to follow another route. The high dose caused the subjects to hit the roadway obstacle more often than placebo, and also, to react slower to the subsidiary task. Yet both THC doses caused the subjects to drive in a more conservative manner. They maintained a longer headway while car following, refused more opportunities to pass, and when they did, began this maneuver at a greater distance from the approaching vehicle. Alcohol's effects in this study were generally less than THC's. Chesher (1986) was puzzled by this, calling the alcohol effect "surprisingly small" and its interactive effect with THC, "unclear". Certainly it is so that BACs of 0.08 g% and below have been enough to substantially degrade drivers' control of vehicular lateral position in real driving tests (Louwerens *et al.*, 1987; Ramaekers *et al.*, 1992a).

Stein *et al.* (1983) conducted two studies of alcohol and marijuana effects using a driving simulator and a 15-minute test scenario that were very similar to those employed by Smiley *et al.* (1981). The former administered the two drugs in complete crossover designs. THC doses of 0, 50 and 100 $\mu\text{g/kg}$ THC were combined with BACs of 0.00 and 0.10 g% in the first study. The same BACs were combined with 100 and 200 $\mu\text{g/kg}$ in the second. This time alcohol had the expected adverse effect on practically every performance parameter, THC had little effect in the first study and little in the second in spite of the higher dose. The latter did cause the subjects to operate at generally lower speeds, however. The combination of drugs produced widely different individual reactions. After the highest THC dose, the combination produced more adverse reactions than alcohol alone.

Marijuana's Effects upon Actual Driving Performance

A number of studies on marijuana's effects upon actual car driving have been reported since 1974. All studies but one were carried out on courses closed to other traffic. Klonoff (1974)

conducted the exceptional study wherein 64 subjects drove on a closed course and 38 also participated in a city driving test. In his first study subjects were assigned to one of three groups that were treated with (1) placebo, (2) 4.9 mg THC, and (3) 8.4 mg THC. They undertook eight tests: a slalom, two tunnel tests, a funnel test, a backing up, turning in a corner, a risk judgment test and an emergency braking test. Except for the latter two, the performance measure was number of cones hit. Subjects performed 20 trials in four blocks of five. Treatments were administered between the third and fourth block and each subject's performance was related to his/her performance predicted by means of regression analysis over the first three blocks. Performance after placebo was as predicted, but after marijuana, significantly worse, though not much. The low dose impaired performance in two tests (tunnel and corner) and the high dose in five (slalom, both tunnel tests, funnel and risk judgment).

Subjects in the city driving test were divided among four groups who were treated with placebo and marijuana, on separate occasions a week apart. The respective groups' treatments were (1) placebo followed by 4.9 mg THC, (2) the same in reverse order, (3) placebo followed by 8.4 mg THC, and (4) the same in reverse order. After smoking a placebo or marijuana cigarette, the subjects drove for 45 minutes over a 16.8 mi (27.0 km) route on city streets while aspects of their performance were rated by a professional examiner using an abbreviated version of the British Columbia Department of Motor Vehicles' standard driver's licensing test. All subjects were allowed to complete the test which indicates that their performance never became dangerously unsafe under the drug's influence. Nonetheless, the examiner rated the subjects' performance as significantly worse on scales of judgement and concentration following the highest but not the lowest dose. The majority showed some impairment, but 32% after the low dose and 16% after the high dose performed significantly better than they had following placebo suggesting qualitative differences between the drug's effects in different subjects.

Hansteen *et al.* (1976) tested sixteen subjects in four conditions, (1) placebo alcohol + placebo marijuana, (2) placebo alcohol + marijuana (THC dose of 21 μ g/kg), (3) placebo alcohol + marijuana (THC dose of 88 μ g/kg), and (4) alcohol (BAC 0.07 g%) + placebo marijuana. Subjects were instructed to drive through a 1.1 mi (0.7 km) course delineated by traffic cones as quickly as possible but without exceeding 30 mph (19 km/h). Performance was measured shortly after smoking and three hours later. Number of cones hit, "rough handling" (superfluous and/or awkward movements as observed by an accompanying investigator), and driving time were scored. More cones were hit and more time was taken to complete each lap after consuming the higher THC dose, but no increase in rough handling was observed. Alcohol, on the other hand, adversely affected both performance measures and diminished the time taken to complete each lap. The authors concluded that the drug effects on performance were not dramatic since no major differences were found between conditions with respect to observer ratings.

Casswell (1979) was the first who included a subsidiary task to simulate the demands for monitoring the environment. Thirteen males were tested in three treatment sessions receiving alcohol and marijuana treatments twice in each session and drove for 35 minutes after each treatment. Treatments included (1a) alcohol (0.10 g% BAC) + placebo marijuana, (1b) placebo alcohol + marijuana (6.25 mg THC), (2a) double placebo, (2b) placebo alcohol + marijuana (6.25 mg THC), (3a) alcohol (0.05 g% BAC) + marijuana (3.12 mg THC), and (3b) alcohol (0.05 g% BAC) + marijuana (3.12 mg THC). Subjects' tasks included overtaking, driving on straight sections, through a hairpin bend, and through narrow gaps, while responding to road signals, traffic signals, and auditory signals in the subsidiary task. Alcohol alone and in

combination with marijuana produced more coarse steering corrections, higher speed and increased lateral position variability. Marijuana alone was associated with lower driving speed and prolonged reaction times in the subsidiary task. Reaction times were also prolonged by the combination of marijuana and alcohol. The authors said that drivers under the influence of marijuana appeared to compensate for what they felt were the adverse effects of the drug by maintaining control effort, and decreasing speed to reduce the required rate of information processing. Alcohol, in contrast, appeared to produce more risky behavior.

Attwood *et al.* (1981) also employed normal driving tasks on a closed course. Eight males participated in a within-subjects design, receiving (1) double placebo, (2) alcohol (0.08 g% BAC) + placebo marijuana, (3) placebo alcohol + marijuana (150 μ g/kg THC), and (4) alcohol (0.04 g% BAC) + marijuana (75 μ g/kg THC). The driving tasks were performed on an airfield runway and included: maintenance of a constant lateral position and velocity, maintenance of a constant headway while following a lead car that varied in speed, bringing the car to a smooth stop at a traffic signal, and deciding whether or not to overtake a preceding vehicle in the presence of an approaching car. The latter maneuver was, however, not actually undertaken. Various measures, as speed, lateral position, acceleration and headway, were taken but the number of significant comparisons were no more than expected by chance. All measures were then subjected to a discriminant analysis that separated overall treatment effects. Overall driving performances after all drug treatments were significantly worse than following placebo when tested in this multivariate analysis. Smiley (1986) suspected that the lack of univariate effects was attributable to the low number of subjects and the lack of a subsidiary task.

Peck *et al.* (1986) assigned 84 subjects in equal proportions to four treatment conditions: (1) double placebo, (2) alcohol (0.08 g% BAC) + marijuana placebo, (3) marijuana (19 mg THC) + alcohol placebo, and (4) both drugs combined. If these subjects could have inhaled all of the drug available in the cigarette, one weighing 70 kg (154 lb; population average) would have received a dose of about 270 μ g/kg. Because of the remaining butt, the actual THC dose probably never exceeded 250 μ g/kg. The subjects were tested four times in complete replications of a driving test battery beginning shortly after drug administration and continuing at hourly intervals thereafter. Ratings of the subjects' driving proficiency were obtained from driving licence examiners who rode with the subjects or observed them from static positions at points along the course; and, by California Highway Patrol officers who followed the subjects' vehicle in a police car. A computerized system within the subjects' vehicle recorded their use of controls, speed and lateral position relative to course delineation. A risk acceptance test was included to measure the subjects' willingness and ability to drive through gaps wider and narrower than the vehicle. Other tasks involved stopping in response to signals, making a forced lane change and driving through pylons in a chicane. Finally, a standard police field sobriety examination and two standard laboratory tests (tracking and time estimation) were administered to the subjects outside of the vehicle. Several hundred measures of performance were obtained. No dramatic performance failures were reported as an effect of either drug or their combination. In general, the number of significant drug effects on particular measures were about what one might expect given the total number of statistical tests.

The investigators resorted, like Attwood *et al.*, to multivariate statistical analysis of their data. Twelve performance measures were combined in discriminant analysis, which significantly separated the effects of each drug or their combination from placebo's. The THC effect was significant over all four replications of the tests, being greatest in the first trial. Alcohol's effect was greatest in the second trial and slightly greater than THC in every one. The combination

of THC and alcohol produced significantly more impairment than did either drug alone in the first and third trials. Field sobriety checks by the police and ratings of the subjects' driving proficiency by experts failed to show any effect of THC, though these did reveal the effects of that drug in combination with alcohol. Practically the only indication of a serious effect of THC was provided by the officers following the subject's vehicle in a police car. They reported that they would have stopped the subject for suspicion of being intoxicated on 32% of all THC trials (alcohol 50%, both drugs 60%). But they also said they would have stopped 15% of the placebo treated subjects. This either indicates that the subjects were exceptionally poor drivers, or were made to appear so under conditions of the test, or that the officers were responding to cues that they ordinarily would have ignored in real driving conditions.

Smiley *et al.* (1987) tested the effects of marijuana (0, 100 and 200 $\mu\text{g/kg}$ THC) in combination with alcohol (0.00 and 0.05 g% BAC) and alcohol alone (0.08 g% BAC) on driving in a closed-course study. Treatments were administered to groups of nine males over a three hour period in a party-like atmosphere in the evening. Subjects drove shortly after smoking as well as in the following morning. Driving tasks included maintenance of a constant lateral position at 80 km/h (50 mph), curve following, car following, route navigation, obstacle avoidance, and emergency decision making. Additionally, subjects had to perform a subsidiary task requiring visual monitoring. The high THC dose resulted in increased headway and headway variability. Alcohol alone at the 0.05 g% BAC level produced increased speed. Number of subsidiary task detections decreased at 0.05 g% BAC but increased at 0.08 g% BAC. Smiley's (1986) conclusion from her own and previous studies was as follows:

"...., marijuana does appear to impair driving behaviour. However, this impairment is mediated in that subjects under marijuana treatment appear to perceive that they are indeed impaired. Where they can compensate, they do, for example, by not overtaking, by slowing down and by focusing their attention when they know a response will be required. Unfortunately, such compensation is not possible where events are unexpected or where continuous attention is required. Effects on driving behaviour are present shortly after smoking but do not continue for extended periods." (p. 133).

General Conclusion

The foremost impression one gains from reviewing the literature is that no clear relationship has ever been demonstrated between marijuana smoking and either seriously impaired driving performance or the risk of accident involvement. The epidemiological evidence, as limited as it is, shows that the combination of THC and alcohol is over-represented in injured and dead drivers and more so in those who actually caused the accidents to occur. Yet there is little if any evidence to indicate that drivers who have used marijuana alone are any more likely to cause serious accidents than drug free drivers. To a large extent, the results from driving simulator and closed-course tests corroborate the epidemiological findings by indicating that THC in single inhaled doses up to 250 $\mu\text{g/kg}$ has relatively minor effects on driving performance, certainly less than BACs in the range 0.08-0.10 g%.

CHAPTER 2 - GENERAL METHODS

Before presenting the designs and results of the individual studies in separate chapters, it seems appropriate to describe the studies of the program and certain procedures that were common to all. These were subject recruiting, compliance with ethical and legal standards, screening for the presence of other illicit drugs and alcohol, and blood sampling procedures and quantitative analyses.

DESCRIPTION OF A 4-STUDY PROGRAM

The present relationship between drivers' use of marijuana and other substances containing the psychoactive drug (THC) and their involvement in traffic accidents is exceedingly obscure. For a variety of practical reasons, epidemiological research has failed to define that relationship in a manner approximating the demonstration of alcohol's effects on traffic safety (Terhune, 1986). The classical approach of first showing that a drug is actually causing traffic accidents before determining how has simply failed for THC.

Yet abundant experimental evidence exists to show that some doses of THC can impair skills deemed important for safe driving. Unfortunately, most of it is of dubious relevance to the actual driving situation: nearly all of the studies on THC's behavioral effects were accomplished using laboratory tests that are not directly related to actual car driving. If previous experience is any guide, little of crucial importance will emerge from experimental research until it is conducted in a more "real world".

Closed-course driving studies have shown that marijuana can impair driving performance but it is unknown to what extent these effects translate into driving performance in the real world. Only one study has been conducted in real world (city driving; Klonoff, 1974). This study demonstrated that subjects perform less competently when under the influence of marijuana, but the scoring method was questioned by others as regards its relationship to safe driving performance.

Bearing these limitations of previous studies in mind a program was set up to determine the dose-response relationship between marijuana and objectively and subjectively measured aspects of real world driving; and, to determine whether it is possible to correlate driving performance impairment with plasma concentrations of the drug or a metabolite. These goals are the same as those of many unsuccessful investigations in the past. Yet none before has gone so far in seeking to achieve them in the environment where the "drugs and driving" problem actually exists. In the present studies, a variety of driving tasks were employed, including: maintenance of a constant speed and lateral position during uninterrupted highway travel, following a leading car with varying speed on a highway, and city driving. The purpose of applying different tests was to determine whether similar changes in performance under the influence of THC occurs in all thereby indicating a general drug effect on driving safety.

The program consisted of one minor and three major studies; a series of separate but interdependent experiments that successively approached driving reality. This approach was necessary to ensure subject safety throughout the program. The program started with a pilot

study (Chapter 3), conducted in a hospital under strict medical supervision, to identify THC doses that recreational marijuana users were likely to consume before driving.

The first driving study (Chapter 4) was executed on a closed section of a public highway. The major goal was to determine the dose-response and dose-response-time relationship between marijuana (three different THC doses, and placebo) and road tracking precision as measured by the "weaving" motion of the subject's vehicle during uninterrupted highway travel. Results of this are compared to those from a previous study undertaken by the investigators to measure the effects of different blood alcohol concentrations on driving performance in essentially the same test situation (Louwerens *et al.*, 1987). A practical purpose was to determine whether the drug's effects as measured in a standard driving test were of a magnitude that would safely allow application of the same test and others on public roads in traffic.

Upon completion of this study with the demonstration that THC's effects could be safely controlled, a second driving study (Chapter 5) was conducted to come a step closer to driving reality than its predecessor. The methods applied were, with the addition of a car following test, the same as those used in the first driving study. However, driving tests were now conducted on a highway in the presence of other traffic. The greatest discretion was employed in designing this study to reach limited objectives. We choose a conservative approach which closely follows that used to determine the tolerability of medicinal drugs in human pharmacological research. It is to test THC's effects on actual driving performance in an ascending dose series. The ultimate goal was to define the THC dose (or plasma concentration) limit which separates low and high risk driving performance impairment by approaching it from the bottom up.

Yet normal driving is far more complex and varied than simply to maintain a safe lateral position and headway during uninterrupted travel on a highway. A THC dose having no effect on these parameters might still impair driving performance in more complex urban driving situations. For this reason the program then proceeded into the third and final driving study (Chapter 6) which involved tests conducted in high density urban traffic. The highest dose which had no significant effect on highway driving in the previous study was given to subjects who would now operate in an urban driving test. This provided an opportunity to measure a far broader range of driving performance. If no effect were again observed, the generality of the dose-effect relationship would be strengthened. But if a new kind of impairment were observed, the conclusion would have to be that the dose effect relationship can not be validly used to define the effects of THC on driving performance, in general. The nature of the new impairment would provide insight into the kinds of traffic safety problems that may be first to appear as a consequence of the drug's effects. A second group also participated in this study and undertook the same driving test, but then after drinking alcohol (reaching an average BAC of 0.04 g%), and a placebo. This was done for two reasons; first, the alcohol condition served as a control whether the employed tools to assess driving performance were sensitive; and, secondly, it made a comparison possible between low doses of alcohol and THC.

SUBJECTS

The ideal subjects would be male and female marijuana users whose consumption of the drug represents that of the majority in that particular population. Van der Wal's (1985) data for the oldest group (17-18 years) in his sample of present Dutch cannabis users indicate that about 56%

of the males and females have a usage frequency of more than once per month and less than daily. This usage frequency was considered as the first selection criterion.

The second criterion was that the users should also be experienced drivers in possession of a driver's licence. Subjects must have driven at least 5,000 km (3,108 mi) per year over the previous three years. This criterion was, however, not always met because of the difficulties in recruiting subjects.

As the third criterion the users should have indicated on a questionnaire that they had driven within one hour after smoking cannabis at least once within the preceding year. These users not only possess the requisite driving experience under the influence of marijuana, they also constitute the "drivers at risk". In addition, the application of this criterion avoided the ethical dilemma of requiring subjects to accept a risk which they would otherwise avoid.

As a fourth criterion, the subjects should agree to refrain from their normal marijuana use for at least five days prior to their participation in any test.

Other inclusion criteria were as follows: age 21-40 years; normal (corrected or uncorrected) binocular acuity (i.e. 20/25 Snellen acuity, or better); body weight within the 85th - 115th percentile range according to the 1983 table from the Metropolitan Life Insurance Company; and, Dutch nationality. The latter criterion was a condition set by the Dutch Ministry of Health which has no authority to permit the use of an illicit drug by foreign nationals.

Exclusion criteria included the following:

1. No history of treatment for drug or alcohol abuse or addiction and no reasonable possibility of dependence occurring as the result of participation in the investigation.
2. No record of arrests or conviction for drug trafficking.
3. No history of psychiatric or organic brain disorders.
4. No overt signs of cardiovascular, respiratory, renal, hepatic, metabolic or neuromuscular disorders and no history of serious disorders of this type.
5. No current use of any psychoactive medication (tranquilizers, antidepressants etc.)
6. For females, no pregnancy or any reasonable probability that pregnancy might occur during participation in the investigation.

Some subjects volunteered spontaneously after reading about the planned study in newspapers. Other volunteers for the first two studies were primarily obtained from among the local population of marijuana users by means of advertisements. Both the second and the third driving study required new samples of subjects. In these cases it was more difficult to recruit subjects since advertisements could not be placed where they might attract the attention of news media. The desire to avoid attention was fostered by a need to ensure subjects' anonymity and avoid the media's interference with data collection involving driving in traffic on public highways and city streets. Subjects were therefore recruited in the last two studies mainly by contacts obtained from subjects from the preceding ones. Admittedly this procedure is not the best to acquire independent samples but was necessary for practical reasons.

Volunteers were screened in two stages; first from their responses to a combined cannabis use, driving experience and medical history questionnaire; and secondly, on the basis of an interview and physical examination. Furthermore law enforcement authorities were contacted, with the volunteers' consent, to verify that they had no previous arrests or convictions for drug trafficking.

Subjects were instructed to sleep normally on the nights before test days. Alcohol consumption was prohibited for 24 hours before tests, and consumption of beverages containing

caffeine, for 2 hours beforehand. Those who smoked tobacco were advised that this would also be prohibited for one hour before testing until its completion.

COMPLIANCE WITH ETHICAL AND LEGAL STANDARDS

All studies described in this report complied with the code of ethics on human experimentation established by the *Declaration of Helsinki* (1964) as amended in Tokyo (1975), Venice (1983), and Hong Kong (1989). This implies that the volunteer subjects were fully informed of all procedures, possible adverse reactions to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without penalty or censure. All subjects gave their informed consent, in writing. Their anonymity was and will be maintained in all communications from the project. The investigators provided for continuous medical supervision and emergency medical treatment during the studies. Approvals for individual studies were separately obtained from the University's Medical Ethics Committee.

Before the program started an Independent Advisory Committee was formed whose function was to ensure that the program proceeded in accordance with all medical and legal standards. This committee comprised the Assistant District Attorney, the Municipal Traffic Attorney for the City of Maastricht, a member of the University's Medical Ethical Committee, and the Dutch Regional Inspector for Public Health (Drugs). A permit for obtaining, storing and administering marijuana was obtained from the Dutch Drug Enforcement Administration.

Subjects were accompanied on every driving test by a licensed driving instructor experienced in supervising subjects who operated under the influence of medicinal drugs in previous studies. The instructor's sole task was that of monitoring ride safety. Redundant control system in the test vehicle was available for controlling the car if emergency situations should arise. However, the primary guarantor of the subject's safety was the subject himself/herself. The subject, like any licensed Dutch driver, had the legal responsibility to stop driving when feeling "under the influence" to the point where he/she could no longer be sure of his/her ability for safely controlling the vehicle. Subjects in this investigation were reminded of their responsibility and urged not to undertake any test, or to stop driving during a test in progress, if they felt incapable of driving safely. Subjects were always transported to and from their appointments and were strictly instructed not to operate their own vehicles for a period of 12 hours after having received the experimental treatment.

SCREENING FOR THE PRESENCE OF OTHER ILLICIT DRUGS AND ALCOHOL

Though it seemed unlikely that subjects would regularly resort to using other illicit drugs or alcohol prior to controlled marijuana smoking and testing, the possibility could not be definitely excluded without testing the subjects for the presence of these drugs. Therefore they were informed beforehand of the intention to obtain urine and breath samples which would be analyzed for the presence of prohibited agents.

Each subject was required to submit a urine sample immediately upon arrival at the test site. Samples were later assayed qualitatively for the following drugs (or metabolites): cannabinoids, benzodiazepines, opiates, cocaine, amphetamines and barbiturates. In addition a breath sample was analyzed on the spot for the presence of alcohol using a Lion S-D3 Breath-Alcohol

Analyzer. The urine and breath sample screening procedures were employed in all studies in the program.

Drugs other than cannabinoids were found in urine of four subjects. In the pilot study, the urine of two subjects was positive for benzodiazepines; and, of one subject for barbiturates. Analyses of six urine samples obtained from these subjects during the successive driving study failed to show the presence of these drugs. Since all urine samples from both the pilot and first driving study were analyzed after completion of the latter, the failure to detect the drugs in samples obtained during the driving study indicates that they did not abuse these drugs. Upon questioning, all three subjects denied that they had taken these drugs. Since no urine or plasma was left from these subjects, it was, however, not possible to check whether the results were false positives. Data obtained from these subjects in the pilot study were not excluded from the statistical analyses. One subject's urine, obtained prior to smoking in the 200 µg/kg condition in the first driving study, was positive for cocaine. Upon questioning, the subject replied that some friends had surreptitiously administered him cannabis cake and cocaine the day before. Assuming that the drugs' effects had dissipated the next day, these subject's data were also not excluded from statistical analyses.

BLOOD SAMPLING AND QUANTITATIVE ANALYSES

Blood samples were taken by venepuncture. Two 10 ml aliquots were obtained in every case. These were heparinized and centrifuged within 30 minutes. Plasma was placed in frozen (-20°C) storage prior to analysis. The quantitative chemical analysis of THC and THC-COOH in plasma was performed by gas chromatography/mass spectrometry (GC/MS) using deuterated cannabinoids as internal standards (Möller *et al.*, 1992). Of the many analytic techniques available at present, GC/MS is the reference method of choice (Cook, 1986). Applying this method, the detection limits for THC and THC-COOH were about 0.3 and 3.0 ng/ml, respectively. THC and THC-COOH concentrations in plasma will further be abbreviated to [THC] and [THC-COOH].

If the urine analysis (above) was positive for cannabinoids, plasma taken before smoking was also analyzed to quantitatively determine [THC] and [THC-COOH]. Subjects with detectable THC in pre-smoking plasma are shown in Table 2.1. In the pilot and first driving study, THC was detected in each pre-smoking plasma sample from two subjects and in one sample from another subject, namely prior to smoking in the 200 µg/kg condition. In the second driving study, THC was detected in one sample from one male and in five out of six samples from another male. In the city driving study, THC was not detected in any pre-smoking sample.

It seems obvious that those subjects, who had detectable [THC] before smoking, did not comply with the instruction to abstain from cannabis consumption for at least five days prior to the trial. They all had long histories (at least 7 years) of cannabis experience and were frequent (at least twice a week) users. Gieringer (1988) reports that THC may persist in the blood of chronic smokers at levels up to 4.0 ng/ml after 48 hours. It therefore remains an open question when their latest consumption was or whether they were impaired upon arrival at the laboratory.

The same pattern of pre- to post-smoking values as shown in Table 2.1 was observed in the other subjects, i.e. [THC] and [THC-COOH] increased considerably after smoking the administered marijuana cigarettes and not following placebo. Therefore, these subjects' data were not excluded from the statistical analyses.

Table 2.1 Pre-smoking and post-smoking [THC] in subjects with detectable THC in pre-smoking plasma samples.

Study	Subject no.	Condition	[THC] before Smoking (µg/ml)	[THC] after Smoking ¹ (ng/ml) ²
Pilot study	1513	*	3.0	35.5
	1525	*	1.2	13.3
1 st driving study	1507	200 µg/kg	1.9	39.3
	1513	placebo	2.0	1.8
		100 µg/kg	2.4	9.2
		200 µg/kg	2.7	34.7
		300 µg/kg	4.2	26.8
		placebo	1.1	1.1
	1525	100 µg/kg	1.5	19.5
		200 µg/kg	1.1	6.9
		300 µg/kg	2.7	13.9
		1 st placebo	0.5	0.6
2 nd driving study	1536	100 µg/kg	0.6	10.7
		2 nd placebo	0.7	0.6
		3 rd placebo	1.2	1.3
		300 µg/kg	1.3	30.9
		1 st placebo	0.6	0.5
	1537	1 st placebo	0.6	0.5

* only one condition (smoking until the desired effect was achieved).

² sampling time was 40, 30 and 35 minutes after initiation of smoking in the pilot, first and second driving study, respectively.

Fifty percent of the pre-smoking plasma samples obtained from subjects in the pilot and first driving study, whose urine tests were negative for cannabinoids, were also analyzed. These analyses were performed to examine whether any false negative urine analyses had occurred. Results showed that none of these samples contained detectable [THC] or [THC-COOH]. From these results it was inferred that in subsequent studies pre-smoking blood samples need only be taken if the urine test for cannabinoids were positive.

CHAPTER 3 - PILOT STUDY TO SELECT THC DOSES

INTRODUCTION

Doses used in all previous studies of inhaled THC have been selected without consulting the subjects beforehand to determine whether these realistically approximated doses they commonly use. In the opinion of several experts (Moskowitz, 1985; Chesher, 1986; Peck *et al.*, 1986) this has resulted in the selection of maximum doses for experimental purposes that are considerably less than those used for recreational pursuits. One could arbitrarily select higher doses but with the risk of erring in the opposite direction. A dose of, say 300 µg/kg, might be higher than any taken at one time by street users or, at any rate, higher than one they might take and then drive. If we were to select unrealistically high doses these could result in bizarre and potentially dangerous reactions in even the most controlled driving test. To avoid arbitrarily selecting the wrong maximum dose, it seemed necessary to consult the subjects in the context of a "clinical" pilot study.

The pilot study's major purpose was therefore to establish the maximum dose for subsequent driving studies. Yet it provided several opportunities for obtaining valuable information about THC's pharmacokinetics and its pharmacodynamic effects after marijuana smoking. Blood samples were repeatedly taken for measuring [THC] and [THC-COOH]. The subjects repeatedly performed certain simple laboratory tests, estimated their levels of intoxication and indicated their willingness to drive under several specified conditions of urgency. In addition, heart rate was measured at these times. The secondary purpose was that of specifying relationships between [THC] and [THC-COOH] with changes in the other physiological, performance or subjective variables.

METHODS

Subjects

Twenty-four healthy volunteers, 12 males and 12 females, volunteered to participate in this study. They were screened as described in Chapter 2. Groups of six were treated and tested per night. Sessions were conducted in the evening between 19.00 and 24.00 hours and subjects smoked and were tested at staggered intervals of 10 minutes. GC/MS analysis of plasma obtained from one male revealed trivial amounts of values THC in the first and second samples after smoking but none thereafter, and no THC-COOH in any sample. It was concluded that this subject had not inhaled smoke so his data were excluded from further analyses. Characteristics of the remaining 23 subjects are given in Table 3.1. T-tests for independent samples showed that males were more experienced smokers than females ($p < .044$). Males' driving experience was nearly significantly greater than females' ($p < .056$ & $.089$ for number of years and km (mi), respectively).

Table 3.1 Mean $\pm$ SD (range) of subjects' characteristics.

	Males (N=11)	Females (N=12)
Age (yrs)	27.0 $\pm$ 4.6 (22-38)	24.6 $\pm$ 2.9 (21-31)
Weight (kg)	69.8 $\pm$ 10.3 (56.5-87.0)	66.6 $\pm$ 9.1 (52.0-79.0)
Weight (lb)	154 $\pm$ 23 (125-192)	147 $\pm$ 20 (115-174)
Smoking Experience (yrs)	9.2 $\pm$ 5.8 (1-23)	5.0 $\pm$ 3.3 (2-14)
# Joints/Month	5.9 $\pm$ 3.7 (1-14)	5.8 $\pm$ 5.4 (1-20)
Driving Experience (yrs)	8.5 $\pm$ 5.7 (3-23)	4.8 $\pm$ 2.7 (1-12)
Driving Experience (km x 1000)	121 $\pm$ 118 (15-360)	54 $\pm$ 54 (5-175)
Driving Experience (mi x 1000)	75 $\pm$ 73 (9-224)	34 $\pm$ 34 (3-109)
# of Subjects Having Driven within 1 Hour following Cannabis Consumption:		
less than 5 times	1	9
5 times or more	10	3

Smoking Procedures

Marijuana cigarettes were supplied by the U.S. National Institute on Drug Abuse (NIDA). The cigarettes had an average weight of 767 mg and contained 2.57% or about 20 mg THC. Cigarettes were humidified by placing them at room temperature overnight in a desiccator containing a small quantity of saturated sodium chloride solution. This procedure raised the moisture content of the cigarettes from 10% to 15%, on the average. The subjects were allowed to smoke part or all of the THC content in three cigarettes until achieving the desired psychological effect. Cigarettes were smoked through a plastic holder, in a fashion determined by the subject. The only requirement was to smoke continuously for a period not exceeding 15 minutes. When subjects voluntarily stopped smoking, cigarettes were carefully extinguished and retained for subsequent gravimetric estimation of THC consumed (2.57% of the difference between the weight of the original cigarette and the remaining unsmoked portion). This method of estimating THC amounts consumed is based upon the assumption that THC is equally distributed over the entire cigarette. Perez-Reyes *et al.* (1982) analyzed THC concentrations in the unsmoked portions of marijuana cigarettes of three different potencies and indeed found that they were identical to those in the unlit cigarette.

Measurements

A test battery which lasted 20 minutes took place before smoking and was repeatedly administered at 30, 90, 150 and 210 minutes after initiation of smoking. The battery consisted of:

1. **The Critical Tracking Test (CTT).** This test, described in detail by Jex *et al.* (1966), was implemented on a IBM-compatible MS-DOS computer and measures the subject's ability to control a displayed error signal in a 1st-order compensatory tracking task. Error appears as horizontal deviation of a cursor from midpoint on a horizontal, linear scale. Compensatory joy-stick movements null the error by returning the cursor to the midpoint. The frequency

of cursor deviations, and therefore its velocity, increase as a stochastic, linear function of time. The frequency at which the subject loses control is called the critical frequency (λ_c , expressed in rad/s). Theoretically, λ_c is the reciprocal of the operating delay lag in human closed-loop manual control. The test included 5 trials of which the lowest and highest score were removed; the average of the remaining scores was taken as the final test score. Total test time duration was approximately 5 minutes.

2. Questionnaires. Subjects were required to rate their feeling of "high" as a percentage of the maximum ever experienced, and to indicate certain feelings of present cognitive and emotional state using the 16-item visual-analog scale developed and standardized for drug research by Bond and Lader (1974). Scores on the latter scales were grouped to form three cluster scores for measuring the corresponding factors: alertness, contentedness and calmness which will be expressed as percentage of the maximum. In addition, the subjects' willingness to operate a motor vehicle was assessed by asking them to declare whether they would attempt to drive for a set distance if the reasons were: *A.* unimportant though gratifying, such as for transporting a friend to another party; *B.* important but avoidable, such as for transporting a mildly sick friend home when he would otherwise have to call a taxi; and *C.* urgent, such as transporting a severely sick infant to the hospital. These ratings were made by subjects immediately after termination of smoking and after conclusion of the CTT. All questionnaires are enclosed in Appendix A.
3. Heart Rate. Heart rate was measured by counting the number of beats per minute immediately after completion of the questionnaires.
4. Hand Steadiness Test. Thereafter, hand steadiness was measured from the number of side contacts occurring as the subject attempted to hold a 1 mm (0.04 in) stylus for 15 seconds within each of five circular holes with successively diminishing diameters (3.90, 3.05, 2.70, 2.20 and 1.85 mm, respectively; or, 0.15, 0.12, 0.11, 0.09 and 0.07 in). Subjects were allowed to rest their hand on the table. The test score was defined as the total number of contacts of the stylus with any side. Since the distribution of subjects' scores were skewed, a square root transformation was applied to normalize data. The test lasted about 3 minutes.
5. Blood Sampling. A blood sample was taken by means of a venepuncture ten minutes after the beginning of the test battery. The sample (2 aliquots containing 10 ml blood apiece) was heparinized and centrifuged, and plasma was placed in frozen (-20°C) storage prior to analysis for THC and its major metabolite THC-COOH. Blood samples were taken before and at 40, 100, 160 and 220 minutes after initiation smoking.

Subjects were familiarized with the questionnaires and practiced the CTT and hand steadiness test on three separate occasions during the weeks prior to the test night until they reached a steady performance level.

Data Analysis

Parametric data were analyzed as follows. All data including baseline values entered a repeated measures multivariate analysis of variance (MANOVA) with *Sex* as a between-groups and *Time* as a within-subjects factor and the criterion for significance set at .05. If a significant *Time* effect was found, a repeated measures univariate analysis of variance (ANOVA) was performed to separately compare each post-smoking measurement with baseline. *Sex* was not a factor in these ANOVA's unless MANOVA had revealed a significant *Sex by Time* interaction. Individual

comparisons with baseline were not possible for perceived "high" ratings and plasma levels of the drug since baseline values were zero in most cases. Instead, if MANOVA revealed a significant *Time* effect, the data were further analyzed in an ANOVA trends analysis to determine the significance of linear, quadratic and cubic components. In the figures, the mean of the variable is depicted by a point and its standard error (SE) by the height of the vertical line above the point.

The subjects' expressions of willingness to drive were made on the basis of a dichotomous decision and could not for that reason be analyzed in the same manner as other variables. These data were therefore analyzed using Cochran's Q-statistic to determine if the proportion of subjects willing to drive changed over time. If they did significantly, separate changes from baseline were tested by McNemar's sign-test.

Criterion for statistical significance in individual comparisons was adjusted by means of the "Sequential Bonferroni" correction (Overall and Rhoades, 1987) to retain a constant type I error probability of .05 across the entire set of comparisons. This means that for the largest of four differences tested at once, p had to be less than $.05/4 = .013$ to be judged significant. For the second, it had to be $< .05/3 = .017$; for the third, $< .05/2 = .025$; and for the smallest difference, $p < .05$.

Significant Sex effects were generally absent. Results pertaining to differences between the sexes are therefore only reported for the exceptional cases where the differences were significant.

Two types of correlations were calculated to determine the linear relationship between two variables; i.e., the inter-subject and intra-subject correlation. The first is the most commonly used; it is obtained from pairs of variables measured in a group of subjects. In this study, for example, the correlation between [THC] and λ_c , the tracking performance score, was calculated for all subjects at each sampling time separately. This resulted in four correlations (one at $t=40, 100, 160$ and 220 min) obtained from 23 subjects ($N=23$). These correlations were tested for significant departures from zero by t-test.

The intra-subject correlation, on the other hand, is the correlation between pairs of variables within one subject. In the present study, for example, the correlation between [THC] and λ_c was also calculated for each subject, across all sampling times, separately. This resulted in 23 correlations (one from each subject) obtained from four repeated measurements ($N=4$; baseline values were excluded). These were transformed into Fisher's z-scores and then averaged across subjects yielding z_{av} , which was tested for significant deviation from zero by t-test, and transformed back to r .

Interpretations of these two types of correlation are not the same. If, in the present study, a perfect inter-subject correlation ($r = \pm 1.0$) between [THC] and λ_c existed, it would mean that one can perfectly predict λ_c of a particular subject from the knowledge of his/her [THC]. Usually, however, inter-subject correlations are much lower; and, the closer to zero, the more unreliable the predictions become.

A high average intra-subject correlation means that, on the average, scores on two variables are closely related within a subject, but not necessarily between subjects. Thus, a highly negative average intra-subject correlation between [THC] and λ_c (lower scores indicating poorer performance) would mean that, within a subject, higher plasma levels of THC are associated with poorer tracking performance. Yet this does not imply that, if two subjects are compared, the one with the higher plasma levels performs worse. That would only be the case if both the average intrasubject and the intersubject correlations were strongly negative.

RESULTS

Consumed THC

Six subjects consumed one cigarette, thirteen smoked two and four smoked three. Total THC amounts consumed are given in Table 3.2. Statistical analyses failed to reveal a significant difference between the sexes. It should be noted that these amounts of THC represent both the amount inhaled and the portion that was lost through pyrolysis and side-stream smoke during the smoking process.

Table 3.2 Mean, median and range of amounts of THC consumed, both in absolute values and relative to bodyweight (BW).

	THC consumed (mg)			THC consumed per kg BW ($\mu\text{g/kg}$)		
	mean	median	range	mean	median	range
Males (N=11)	22.3	18.6	14.7-35.2	324	292	203-524
Females (N=12)	19.4	18.9	11.3-28.2	293	292	194-440
All (N=23)	20.8	18.8	11.3-35.2	308	292	194-524

Plasma Concentrations of the Drug

Mean, median and range of [THC] and [THC-COOH] at each sampling time are shown in Tables 3.3 and 3.4. Maximum [THC] was found in the first sample after smoking at $t=40$ minutes. Males had somewhat higher [THC] and much higher [THC-COOH] values than females; the difference between both sexes was however rather constant over time, except for [THC] at $t=40$ where the difference was quite profound. These observations were confirmed by MANOVA that showed a significant Sex effect for both [THC] and [THC-COOH] ($F_{1,21}=4.3$ & 9.79; $p<.05$ & .005, respectively), but no significant Time by Sex interaction. Since consumed THC amount did not differ between both sexes, the conclusion must either be that males were more efficient smokers than females, or that they absorbed the active ingredient differently.

There was a significant Time effect for both [THC] and [THC-COOH] ($F_{3,19}=14.79$ & 11.70, respectively; $p<.001$ in both cases). Univariate trend analysis revealed that both linear, quadratic as well as cubic functions fitted the trend in [THC] over time significantly ($F_{1,21}=44.56$, 38.95 & 29.23; $p<.001$, .001 & .001; $p_c=.017$, .025 & .05, respectively) due to a rapid decline of [THC] in plasma after the first sample. THC-COOH changes over time were only significantly fitted by a linear trend ($F_{1,21}=26.92$ $p<.001$; $p_c=.017$).

The relation between consumed THC, relative to body weight, and [THC] was examined by calculation of inter-subject correlations (intra-subject correlations could not be determined from the data because each subject smoked only one dose of THC). These analyses showed moderate inter-subject correlations between both parameters at each sampling time, namely 0.42 ($p<.05$), 0.34 (ns), 0.42 ($p<.05$) and 0.45 ($p<.05$). Yet inspection revealed that the apparent strength of these correlations was almost totally attributable to two males who had consumed the greatest amounts of THC (486 and 524 $\mu\text{g/kg}$) and had also very high plasma levels of THC (45.9 and 35.5 ng/ml, respectively). When log values of [THC] and consumed THC were used, to

normalize the distributions, the correlations were small and not significant. There were no differences between males and females with respect to these correlations.

Table 3.3 Mean, median and range of [THC] in ng/ml.

		<i>t</i> =40	<i>t</i> =100	<i>t</i> =160	<i>t</i> =220
Males (N=11)	mean	17.7	5.8	2.8	1.7
	median	13.3	4.5	2.3	1.3
	range	6.7-45.9	2.5-15.2	1.2-6.8	0.7-5.1
Females (N=12)	mean	9.9	3.0	1.4	0.7
	median	7.0	2.7	1.0	0.6
	range	3.3-19.3	0.3-6.8	0.5-3.2	0.0-1.8
All (N=23)	mean	13.6	4.3	2.1	1.2
	median	9.9	3.5	1.4	0.8
	range	3.3-45.9	0.3-15.2	0.5-6.8	0.0-5.1

Table 3.4 Mean, median and range of [THC-COOH] in ng/ml.

		<i>t</i> =40	<i>t</i> =100	<i>t</i> =160	<i>t</i> =220
Males (N=11)	mean	33.9	28.1	25.3	20.8
	median	25.6	19.6	18.3	13.5
	range	12.9-96.4	12.8-72.4	9.5-63.5	8.0-67.0
Females (N=12)	mean	12.4	9.5	8.3	5.6
	median	9.6	8.2	7.5	5.5
	range	3.3-39.9	0.5-26.8	3.0-15.8	0.0-13.0
All (N=23)	mean	22.7	18.4	16.4	12.8
	median	17.3	13.9	13.6	10.1
	range	3.3-96.4	0.5-72.4	3.0-63.5	0.0-67.0

These results indicate that the between-subject variability in [THC] is not related to the between-subject variability in the consumed amount of THC; in other words, information about [THC] and the time of blood sampling after smoking, of a particular individual, does not reveal how much that subject smoked, nor vice versa.

Perceived "high"

Mean subjective ratings of "high" are shown in Figure 3.1. The subjects consistently reported their peak subjective reaction as being about 70% of the greatest ever experienced. This was achieved shortly after smoking. Their subjective feelings declined, again in a highly consistent

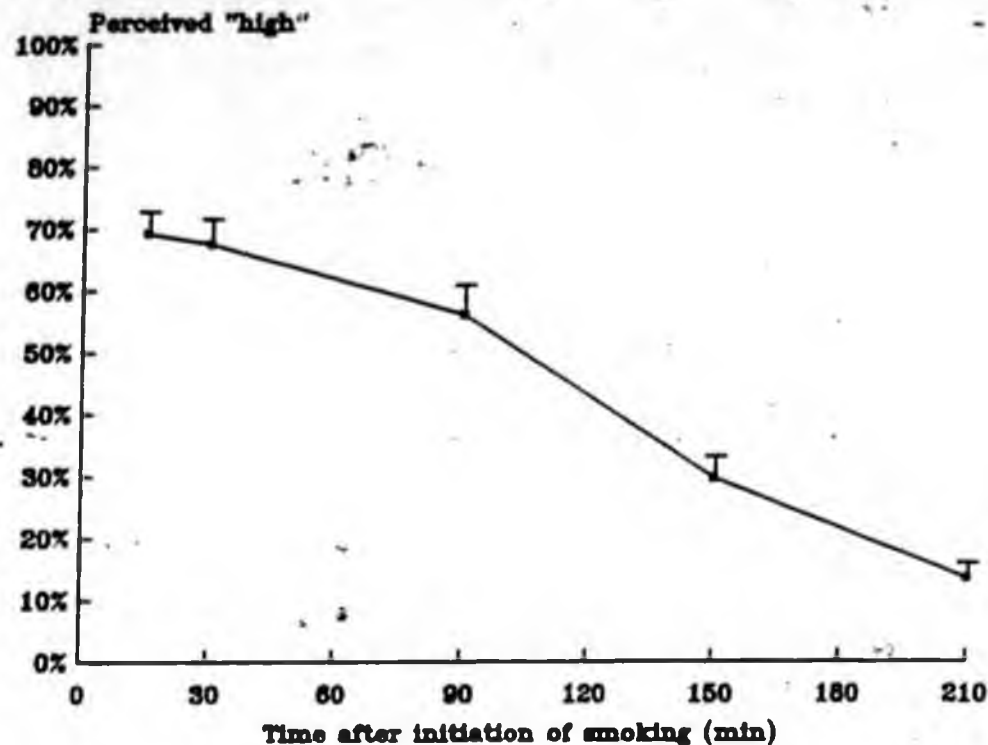


Figure 3.1 Mean (+SE) perceived "high" by Time.

manner between subjects, until arriving at a level less than 15% of the greatest ever experienced, at a time 3¼ hours after smoking.

MANOVA revealed a significant *Time* effect ($F_{4,18}=49.18$; $p<.001$). Trend analysis confirmed the impression from the data that the downward trend is best fitted by a linear function ($F_{1,21}=201.92$; $p<.001$).

Willingness to Drive

Figure 3.2 displays percentages of the subjects that declared to be willing to drive under different circumstances of a gradually more compelling nature (A. unimportant though gratifying; B. important but avoidable; and, C. urgent). Only about 20% of the subjects declared their willingness to drive for relatively unimportant reasons (A and B), but approximately 80% declared that they would do so for an urgent reason (C), while experiencing the peak subjective reaction. Willingness to drive gradually rose to about 70% for unimportant reasons, and 100% for an urgent reason, by the end of the test session.

Cochran's test revealed that time-related changes in willingness to drive were statistically significant in all three circumstances ($Q_{df=5}=46.62, 44.62$ & 15.17 ; $p<.001, .001$ & $.01$ for situations A, B & C, respectively). McNemar's test showed that the percentage of subjects willing to drive under circumstance A was significantly different from baseline until the end of the test session ($p<.001, .001, .001, .002$ & $.02$; $p_c=.01, .013, .017, .025$ & $.05$), while under circumstance B changes were only significant until 2½ hours after smoking ($p<.001, .001$ &

.004; $p_c = .01, .013 \text{ \& } .017$). McNemar's test failed to detect any significant change after smoking relative to baseline for circumstance C.

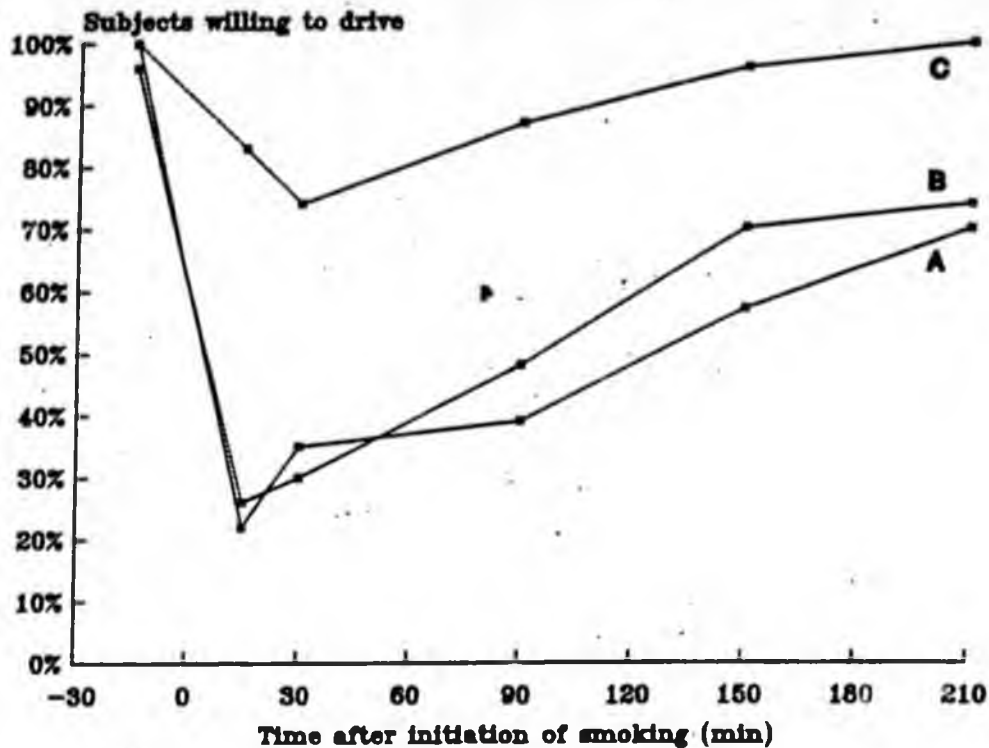


Figure 3.2 Percentage of subjects willing to drive under circumstances A, B & C (see text) by Time.

Perceived Alertness, Contentedness and Calmness

Figure 3.3 shows subjects' ratings of perceived alertness, contentedness and calmness. Scores on these factors changed significantly over time ($F_{5,17} = 8.19, 5.79 \text{ \& } 7.02$; $p < .001, .003 \text{ \& } .001$, respectively). Subjects felt significantly less alert relative to baseline until about 1½ hours after smoking ($F_{1,22} = 34.67, 20.03 \text{ \& } 16.97$; all $p < .001$; $p_c = .01, .013 \text{ \& } .017$). Separate sequential comparisons of subjective feelings of contentedness provided the same results ($F_{1,22} = 27.24, 19.98 \text{ \& } 9.99$; $p < .001, .001 \text{ \& } .004$; $p_c = .01, .013 \text{ \& } .017$). Feelings of calmness followed a different profile over time. Separate sequential comparisons showed that no significant change occurred during the first few hours after smoking, but at the end of the session subjects felt calmer than they had at baseline ($F_{1,22} = 12.25$; $p < .002$; $p_c = .01$).

Critical Tracking Test

The average frequency at which the subjects lost control (λ_c) was 4.40 rad/s before smoking and fell to 4.15 rad/s in the first test after smoking and gradually rose to baseline level in later tests. MANOVA however failed to show a significant Time effect.

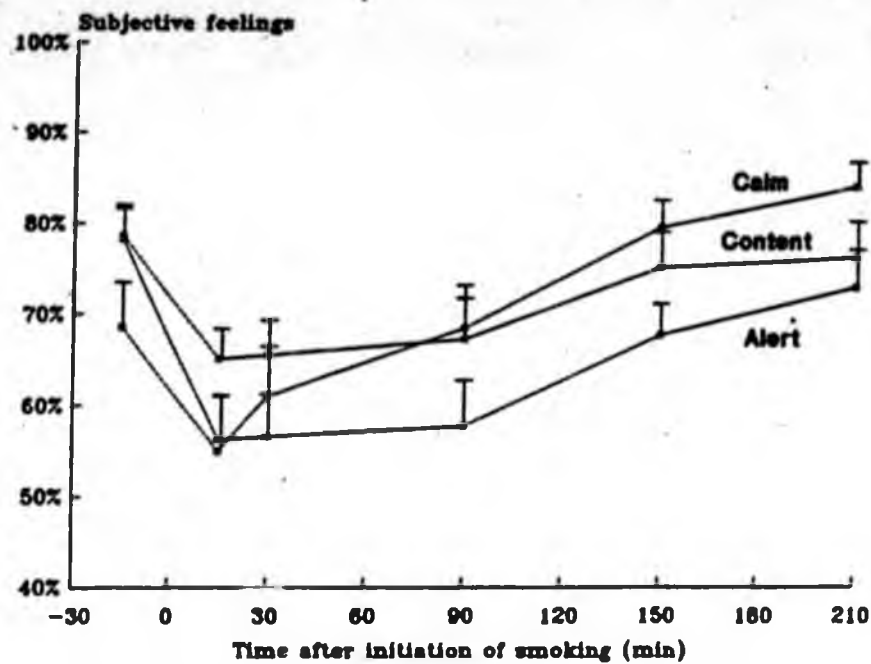


Figure 3.3 Mean (+SE) perceived alertness, contentedness and calmness by Time.

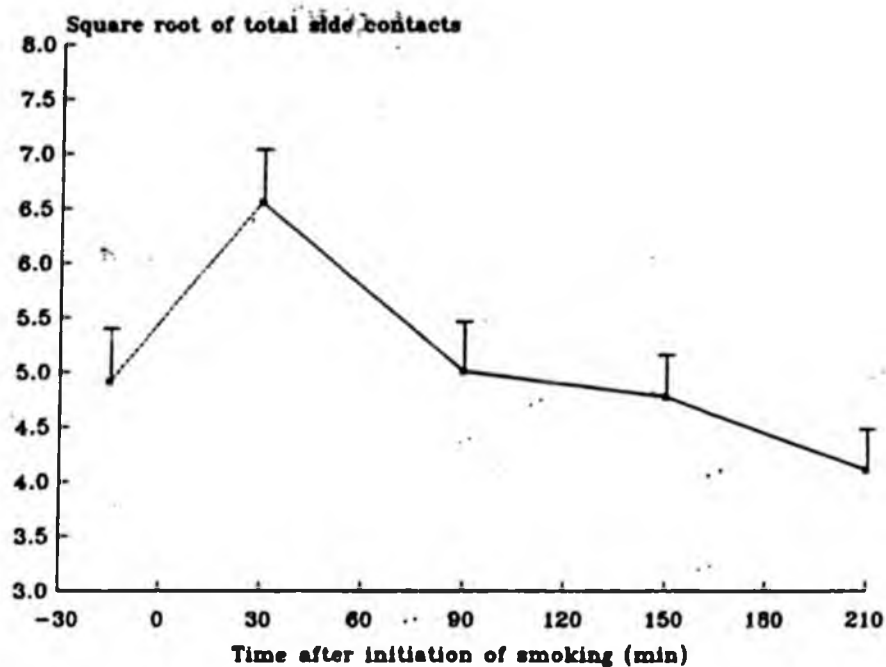


Figure 3.4 Mean (+SE) square root of total number of side contacts in the hand steadiness test by Time.

Hand Steadiness Test

Figure 3.4 demonstrates that subjects' hand steadiness diminished after smoking marijuana, but this effect dissipated rapidly after the first test. On the average, the subjects' hand steadiness was even superior at a time two hours after smoking to what it had been initially.

MANOVA revealed a significant *Time* effect ($F_{4,18}=6.38$; $p<.002$). Yet separate comparisons showed that hand steadiness was only significantly different from baseline in the first test after smoking ($F_{1,22}=16.89$; $p<.001$; $p_c=.013$).

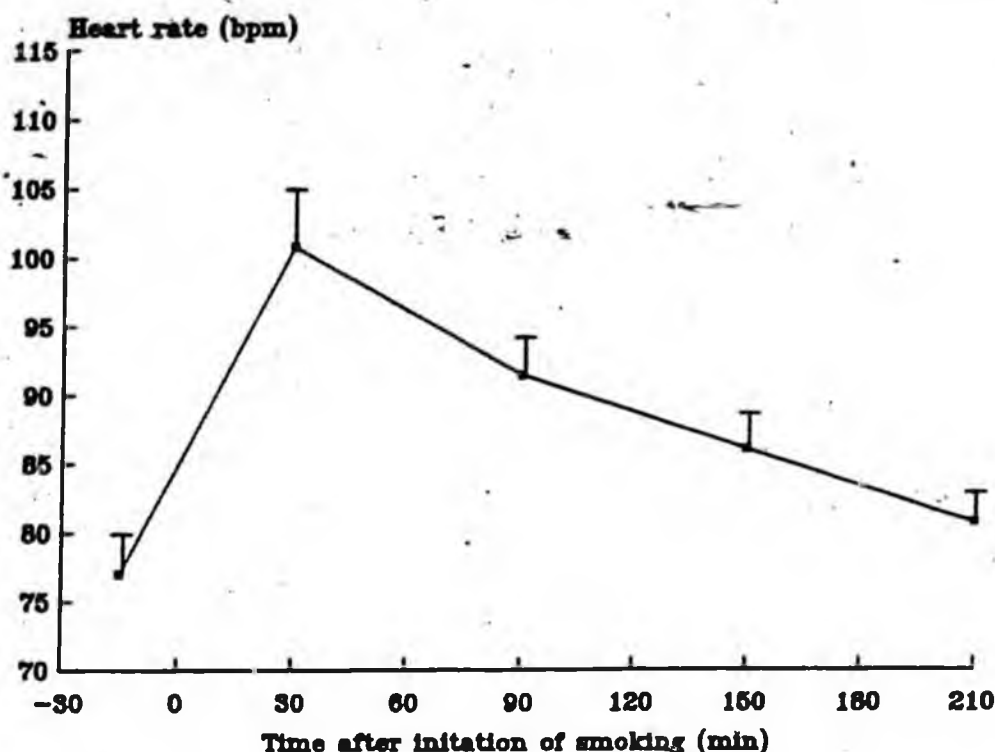


Figure 3.5 Mean (+SE) heart rate by Time.

Heart Rate

The subjects' average heart rate, presented in Figure 3.5, varied between 75 and 100 beats per minute (bpm) in close accordance with their subjective feelings. Thirty minutes after smoking, the increase in heart rate varied from 2 to 77 bpm, with a mean elevation of 24 bpm. Heart rate diminished over successive measurements approaching baseline values after 3¼ hours. MANOVA revealed a significant *Time* effect ($F_{4,18}=10.43$; $p<.001$) and separate ANOVA comparisons showed that these elevations were significantly different from baseline at each but the last measurement ($F_{1,22}=35.64, 21.90, 12.67$ & 2.37 ; $p<.001, .001, .002$ & $.14$; $p_c=.013, .017, .025$ & $.05$, respectively).

Intra-Subject Relations between Variables

Table 3.5 shows the average intra-subject correlations between [THC], $\log_{10}$ [THC], and [THC-COOH] with each of the other variables. The log transformation was again applied to

achieve a more linear and homeostatic relationship between THC values and the other variables. The constant of 1 was added to the raw [THC] values for avoiding negative log transformations. It can be concluded from this table that, within subjects, higher plasma levels of the drug were associated with, and probably produced, increased heart rate, increased feelings of perceived "high", diminished hand steadiness, and diminished feelings of calmness, contentedness and alertness. The correlation with critical tracking performance was not significant, confirming the insensitivity of the test. The log transformation of [THC] did not change the size of the correlations dramatically.

Table 3.5 Average intra-subject correlations (* $p < .05$ ** $p < .01$; 2-tailed).

	[THC]	$\text{Log}_{10}([\text{THC}] + 1)$	[THC-COOH]
Heart Rate	.79**	.82**	.68**
Perceived "high"	.88**	.95**	.87**
λ_c	-.20	-.22	-.27
Side Contacts	.48*	.45*	.39
Calmness	-.51*	-.38	.02
Contentedness	-.57**	-.59**	-.46*
Alertness	-.64**	-.72**	-.66**

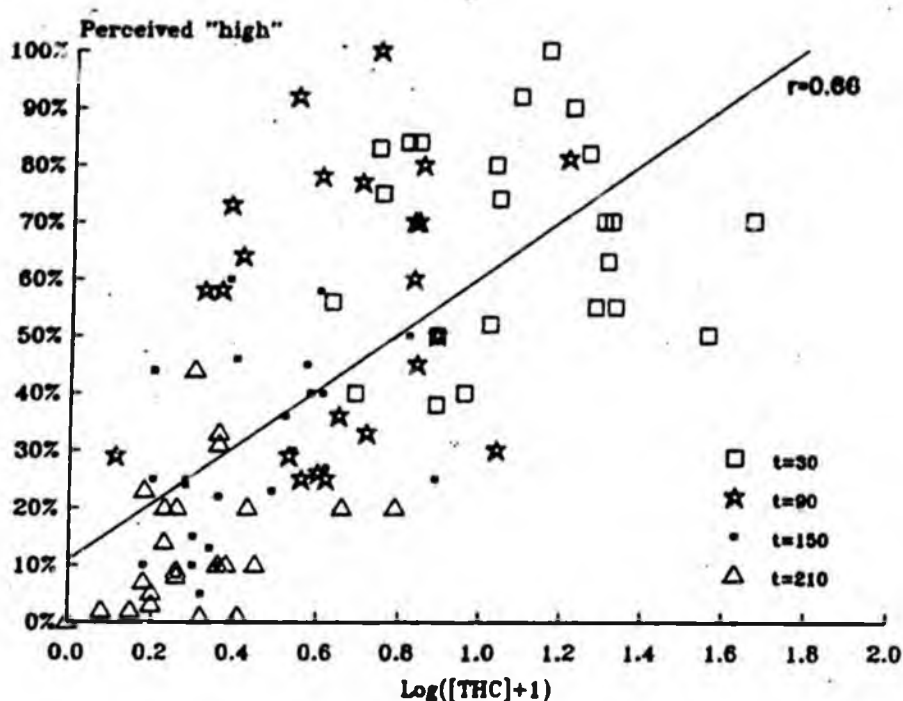


Figure 3.6 Scatter diagram of $\log([\text{THC}] + 1)$ in plasma and perceived "high". Regression line comprising all data is inserted.

Inter-Subject Relations between Variables

Inter-subject correlations between plasma concentrations of the drug and measures of subjective feelings, heart rate and performance were typically low ($r < .50$) at each sampling time. The correlations between $\log [\text{THC}] + 1$ and perceived "high", for example, were $r = 0.07$ (ns), 0.19 (ns), 0.43 ($p < .05$) and 0.35 (ns), at $t = 40, 100, 160$ and 220 minutes after initiation of smoking, respectively. These low correlations are probably due to "restriction of range", i.e. the variability in both measures is relatively small at each sampling time. If all available data ($N = 92$, 4 measurements of 23 subjects) were included in the correlational computation the highest correlation found was that between $\log [\text{THC}] + 1$ and perceived "high" ($r = 0.66$; Figure 3.6). In fact, this correlation is a combination of intra-subject and inter-subject correlations, and should therefore only be regarded as an indication of what the correlation might have been if all these data had been independent observations.

DISCUSSION

The pilot study's major purpose was to determine the amount of THC recreational users of cannabis smoke to reach a comfortable "high" and to establish from these results the maximum dose for subsequent driving studies. Median and mean amount of THC consumed were 308 and 292 $\mu\text{g/kg}$ respectively. From these results it was decided that the maximum dose for subsequent driving studies would be 300 $\mu\text{g/kg}$. This is considerably higher than doses that have usually been administered to subjects in experimental studies (typical, 100-200 $\mu\text{g/kg}$ THC). This could mean either that previous studies' THC doses were lower than those usually consumed by current users, or that the present study's subjects were less efficient smokers and, consequently, smoked more to achieve the same effect. Yet one important point should be raised. Imposed smoking procedures differ considerably between studies on marijuana's effects and can be divided at first glance in two types, self-paced in which subjects may smoke in their customary fashion and machine-paced procedures in which subjects smoke in a prescribed manner with regards to duration of inhalation of smoke and air, holding inhalation, etc. The former method is more realistic while the latter is more controlled. This study applied the former because of the disadvantage of the latter that it might induce unrealistic reactions in some subjects.

One way to contemplate this study's results is to compare the mean $[\text{THC}]$ with those found in other studies in which similar procedures were applied with respect to smoking (ad lib fashion) and plasma analysis (GC/MS using a deuterated internal standard) as we did. To the authors' knowledge only one such study has been reported, namely by Ohlsson *et al.* (1980). Marijuana cigarettes containing 19 mg THC were administered to eleven male subjects who were instructed to smoke in their own fashion such as to obtain the maximum desired "high". Subsequent gravimetric estimation showed that a mean of 13.0 mg THC was consumed. $[\text{THC}]$ values ranged between 5.4 and 18.0 (mean 12.4) ng/ml 30 minutes after termination of smoking. Only the males of the present study should be included in the comparison with Ohlsson's study, because of the significant difference found between $[\text{THC}]$ values of both sexes in the current study. Eleven males in the present study smoked 22.3 mg THC, on average, and their plasma concentrations ranged between 6.7 and 45.9 (mean 17.7) ng/ml 40 minutes after initiation of smoking. Thus, our subjects smoked 70% more THC than Ohlsson's subjects did, resulting in a 43% higher THC level in plasma, as measured 30 minutes after smoking. The average $[\text{THC}]$ found in the present study was therefore in the expected direction. This observation may lead

to the tentative conclusion that the preferred THC dose to reach a desired "high" in the present study was not due to inefficient smoking but to the fact that current marijuana (or hashish) users do smoke higher THC doses than previously administered in scientific studies.

Other results from the present study showed that perceived "high" and heart rate are very sensitive (psychological and physiological) measures of marijuana intoxication which confirms prior research. Impairments in laboratory tests performance were measured at the time of peak subjective feelings but generally, objective impairment dissipated more rapidly than the feelings themselves. All objective signs of impaired functions were gone within 1.5 hours after smoking. The explanation may be that practice and habituation effects, or both, occurred during the session concealing marijuana's impairment, or, that procedural errors have been made in administering these tests. No definitive answer can be provided and no conclusions can be drawn from this study with respect to marijuana's effects upon performance because of the lack of a control group. The study was simply not designed to estimate these effects, only to indicate whether either of these measures should be considered for inclusion in later studies. If any measure appeared to be systematically related to the inferred changes in THC's pharmacological activity over time, this measure might assume a high degree of practical importance. Correlational analyses, however, showed no strong relationships between [THC] or [THC-COOH] and performance in any test.

An important issue relating to traffic safety is whether subjects would drive a car while under the influence of marijuana. Although all subjects had admitted driving a car while intoxicated at least once before, a majority (about 65%) of the subjects was not willing to drive a car for relatively unimportant reasons shortly after smoking when experiencing the drug's peak subjective reaction. However, most said they would drive for a very urgent reason. On one hand, this means that the majority of the subjects are aware of a potential marijuana related driving impairment; on the other, a sizable minority (35%) would not refrain from driving a car for unimportant reasons when they are experiencing a "high". These subjects in particular are a source of concern with respect to traffic safety, if marijuana smoking indeed impairs driving performance. Two questions that arise from these contemplations were addressed by the succeeding driving studies; namely, 1. does marijuana adversely affect driving performance, and 2. is willingness to drive after marijuana smoking related to driving impairment?

CHAPTER 4 - MARIJUANA AND DRIVING ON A RESTRICTED HIGHWAY

INTRODUCTION

As mentioned in Chapter 1, THC's effects on actual driving performance have been assessed in a relatively small number of studies and only once in the presence of other traffic. The effects of doses up to about 250 $\mu\text{g/kg}$ were modest, if present at all. These findings provided some assurance that it would be safe for subjects to undertake carefully supervised driving tests on normal roads and in traffic, even after treatment with the somewhat higher average dose (i.e. 300 $\mu\text{g/kg}$) that was preferred by regular marijuana users in the pilot study. Nonetheless normal prudence demanded a demonstration of the test's safety in an environment resembling reality but where neither the subjects nor other road users would be endangered if the optimistic forecast proved false. One objective of the present study was to provide that demonstration using a standard test on a highway closed to other traffic.

The second objective was to define the dose-effect relationship between inhaled THC dose and that parameter of vehicular control which is measured in the standard test; i.e. standard deviation of lateral position (SDLP), an index of "weaving" amplitude the subject allows while attempting to maintain a constant speed and steady lateral position between traffic lane boundaries during uninterrupted highway driving. Alcohol's effects on SDLP were previously measured by Louwerens *et al.* (1985, 1987) in practically the same manner as THC's in this study. The earlier results showing a nearly perfect ($r=0.99$) exponential relationship between mean blood alcohol concentration (0-0.12 g%) and mean SDLP for 24 "social drinkers", serve admirably for evaluating THC's effects in the present case.

Other objectives were to measure changes in SDLP from tests after placebo to those following separate THC doses of 100, 200 and 300 $\mu\text{g/kg}$; and, to relate these objective measures of driving impairment to subjective impressions of driving quality and expressed willingness to drive in the same states of intoxication under normal circumstances.

METHODS

Subjects

The same twelve men and twelve women who participated in the pilot study served again as the subjects. Plasma from the pilot study was still not analyzed at the time data collection commenced. The male that apparently did not inhale marijuana smoke was therefore not dropped from the study. As before, his plasma samples showed neither THC nor THC-COOH. Data from this subject had to be again excluded from further analyses. Characteristics of the remaining 23 subjects are shown in the previous chapter (Table 3.1).

Design, Doses and Administration

Marijuana and placebo cigarettes were obtained from the same source as before. The subjects were treated on separate occasions with THC doses of 0, 100, 200, 300 $\mu\text{g/kg}$. Placebo

cigarettes were prepared by ethanol extraction of THC from the plant stock. Marijuana cigarettes were prepared from batches containing 1.75% THC for the two lowest, and 2.57% THC for the highest dose. Cigarettes were cut to different lengths to provide the doses appropriate for the individuals' body weights. It was necessary to provide the five largest subjects with two cigarettes at a time since one would not contain the total dose. Cigarettes were smoked through a plastic holder in a fashion determined by the subject but with the constraint that smoking had to be finished within ten minutes. After cessation of smoking, cigarettes were retained for subsequent gravimetric estimation of THC consumed. These analyses revealed that the average ($\pm$ SD) amount of consumed THC in the three marijuana conditions was 6.8 ($\pm$ 0.9), 13.6 ($\pm$ 1.9) and 20.4 ($\pm$ 2.8) mg, which equals 94 ($\pm$ 4), 186 ($\pm$ 13) and 282 ($\pm$ 18) μ g/kg, respectively, or about 6% less than target doses. Order of treatments were counterbalanced. They were administered subject- and observer-blind (i.e. the investigator who prepared the treatments was not involved in their administration or with data collection).

Testing Procedures

Eight subjects were tested per night and all 24 within a week. Subjects were tested at the same times and on the same days of the week for four consecutive weeks. Breath and urine tests were executed upon the subjects' arrival to check for the presence of alcohol and illicit drugs. If cannabinoids were found in the urine, a blood sample was taken for later verification of the presence of THC. Two subjects commenced smoking at a time at $t=0$ (Table 4.1). Driving tests were performed twice, beginning at $t=40$ and 100 minutes and lasting 15-20 minutes. Blood samples were taken before the driving tests. The subjects' pulse was taken and their performance measured in two laboratory tests that began after the driving tests. Subjective assessments were made immediately after smoking, and before and after the driving tests. Before the start of the experiment, subjects were individually trained to operate the vehicle under generally the same conditions as the tests later occurred.

Table 4.1 Schedule of activities on test-days.

Relative Time (min)	Activity
0-10	Smoking
30-35	Blood Sampling
40-60	Standard Driving Test
70-80	Tracking and Hand Steadiness Tests Heart rate and Blood Pressure
90-95	Blood Sampling
100-120	Standard Driving Test
130-140	Tracking and Hand Steadiness Tests Heart rate and Blood Pressure

Driving Test

The driving test, developed and standardized by O'Hanlon *et al.* (1982, 1986) and applied in more than 40 open- and closed-road studies by three Dutch Institutes during the last decade,

measures the ability to control an instrumented vehicle's speed and lateral position. Subjects were instructed to maintain speed at 90 km/h (56 mph), or less if they felt incapable of driving safely at that speed, and a steady lateral position between the delineated boundaries of the traffic lane.

Driving was performed over a 11 km (6.8 mi) section of a primary highway (A76) that connects the Dutch cities of Geleen and Heerlen. Two lanes in the same direction were closed to normal traffic between the hours of 19.00 and 24.00 on three consecutive week-nights over four consecutive weeks of testing. Driving began at one end of the section, involved turning at the other and ended with a return to the origin. A licensed driving instructor accompanied each subject. He was charged with responsibility for ensuring safety at all times and was able to intervene, if necessary, using redundant vehicular controls.

Two Volvo station wagons containing essentially the same instrumentation were employed in the study. The first of a pair of subjects who received treatments together departed from the origin driving one vehicle and was followed by the second driving the other after 2½ minutes. The first subject waited for the arrival of the second at the turning point before returning to the origin. The purpose was to avoid having the subjects, travelling in opposite directions, meet en route. The major instrumentation comprised devices for acquiring continuous analog signals representing steering wheel angle, vehicle speed and lateral position relative to the midline stripe delineation, and a computer system for recording those signals continuously at a 4 Hz sampling rate.

The primary dependent variable was the standard deviation of lateral position (SDLP), which has been shown to be both highly reliable (typical test-retest correlation of 0.7-0.9) and very sensitive to the influence of sedative drugs and alcohol. Other dependent variables were mean speed (SP) and standard deviation of speed (SDSP) and steering wheel angle (SDST).

Questionnaires

The same subjective questionnaires used in the pilot study were administered to the subjects immediately after cessation of smoking ($t=10$) and again at the beginning of each driving test ($t=40$ & 100). At the end of each driving test ($t=60$ & 120), the subjects were required to retrospectively rate their effort made while performing the test (Zijlstra and Van Doorn, 1985; Meyman and Zijlstra, 1986) and subjective driving quality on respective visual-analog scales. Scores on these scales will be expressed as percentage of total scale and percentage of "normal" driving quality, respectively. Questionnaires are enclosed in Appendix A.

Laboratory Tests

Two of the tests employed in the pilot study were also applied here, namely the critical tracking and hand steadiness tests. Exactly the same procedures were employed in their administration as described in the previous chapter.

Physiological Assessments

Heart rate, systolic and diastolic blood pressure were measured by means of a digital blood pressure monitor prior to the hand steadiness test.

Blood Sampling

Blood samples were taken by venepuncture. The samples (2 aliquots containing 10 ml each) were heparinized and centrifuged. The plasma fractions were placed in frozen (-20°C) storage prior to analysis for [THC] and [THC-COOH].

Data Analysis

All data measured on ratio or interval scales were taken in a mixed between-groups, within-subjects MANOVA analysis. Sex was the between-groups factor. Dose (4 levels) and Time after dosing (2 or 3 levels) were factors tested within-subjects. If a significant ($p < .05$) Dose effect was found, repeated measures ANOVAs were conducted for testing differences between measures obtained after placebo and each THC dose, separately. Data in these cases were collapsed across Sex and Time unless the MANOVA analysis had revealed a significant interaction between either factor and Dose. In the figures, the mean of the variable is depicted by the height of the bar and its standard error (SE) by the height of the vertical line above the bar.

Separate dose effects were tested using the "Sequential Bonferroni" procedure for adjusting the α -probability criterion (p_c) in accordance with the number of separate comparisons in a given set (Overall and Rhoades, 1987). This means that for the largest of three differences tested at once, p had to be less than $.05/3 = .017$ to be judged significant. For the second, it had to be $< .05/2 = .025$; and for the smallest difference, $p < .05$. The adjustment had the effect of holding the probability of making a type I error at $p \leq .05$ over the entire set of comparisons.

The subjects' expressions of willingness to drive were made on the basis of a dichotomous decision and could not for that reason be analyzed in the same manner as other variables. These data were therefore analyzed using Cochran's Q-statistic test for assessing differences between dosing conditions at each time of testing, separately.

Significant Sex effects were generally absent. Results pertaining to differences between the sexes are therefore only reported for the exceptional cases where the differences were significant.

Inter-subject and intra-subject correlations were computed and tested as described in the previous chapter.

RESULTS

Plasma Concentrations of the Drug

Though consumed dose differed little between subjects, [THC] and [THC-COOH] varied enormously. Thirty minutes after smoking 300 $\mu\text{g/kg}$, for example, [THC] ranged between 1.6 and 59.6 ng/ml. Table 4.2 shows mean, median and range of [THC] and [THC-COOH] by Dose and Time. Placebo values were not used in the statistical analyses since these were zero in most cases.

As shown by Table 4.2 plasma concentrations of the drug were clearly related to the administered dose and time of blood sampling. MANOVA confirmed this observation yielding a significant Dose ($F_{2,20} = 14.65$ & 16.59 for [THC] and [THC-COOH], respectively; both $p < .001$) and Time ($F_{1,21} = 50.76$ & 21.16 ; both $p < .001$) effect. There was a significant Dose by Time interaction for [THC] ($F_{2,20} = 10.07$; $p < .001$) and not [THC-COOH]. Though not shown

in the table, males had significantly higher [THC-COOH] values, 9 ng/ml on average, than females ($F_{1,21}=4.49$; $p<.05$); average [THC] values were virtually the same for both sexes.

Table 4.2 Mean, median and range of [THC] and [THC-COOH] in ng/ml (N=23).

		100 $\mu\text{g/kg}$		200 $\mu\text{g/kg}$		300 $\mu\text{g/kg}$	
		$t=30$	$t=90$	$t=30$	$t=90$	$t=30$	$t=90$
[THC]	mean	9.5	3.5	15.9	4.8	20.7	6.2
	median	9.0	3.2	12.0	4.3	19.1	5.6
	range	0.0-21.3	0.0-11.0	1.7-39.3	0.0-11.8	1.6-59.6	0.8-15.4
[THC-COOH]	mean	10.9	9.4	14.2	12.1	17.5	15.2
	median	7.2	4.7	13.4	9.6	13.8	11.4
	range	0.0-61.9	0.0-55.5	2.2-73.9	2.0-65.2	2.6-64.4	2.6-55.4

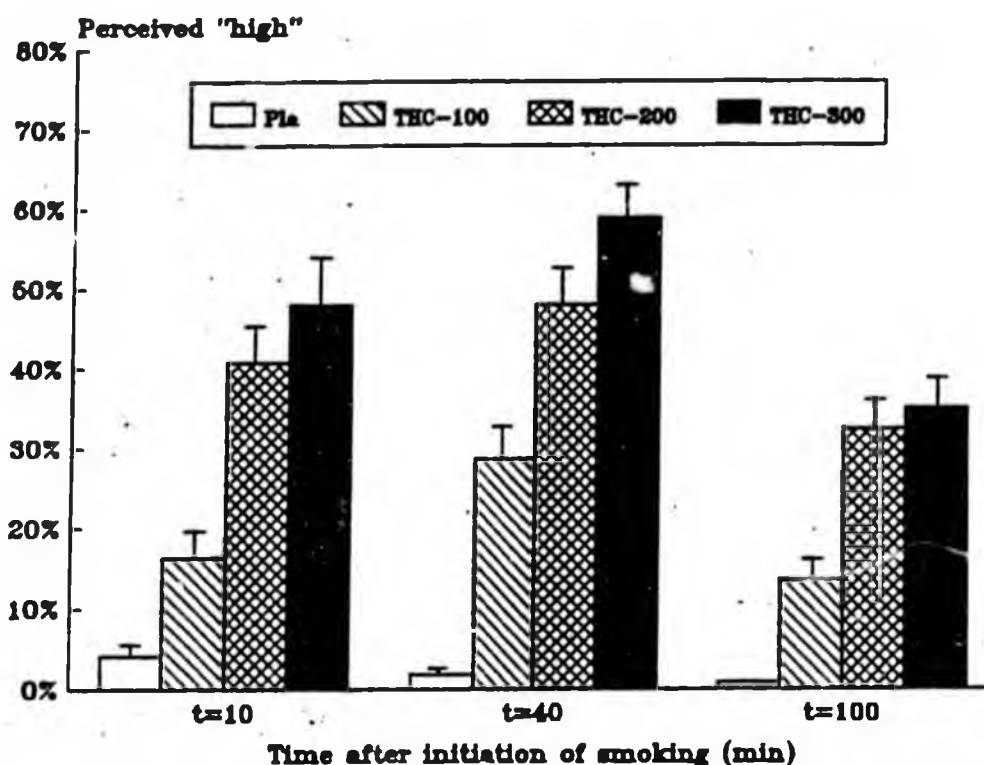


Figure 4.1 Mean (+SE) perceived "high" by Dose and Time.

Perceived "high"

Average subjective feelings of intoxication ("high") were dose-related and highest just before the first driving test (Figure 4.1). Relative to maximum personal experience, peak levels of intoxication were about 30%, 50% and 60% after 100, 200 and 300 $\mu\text{g/kg}$ doses, respectively.

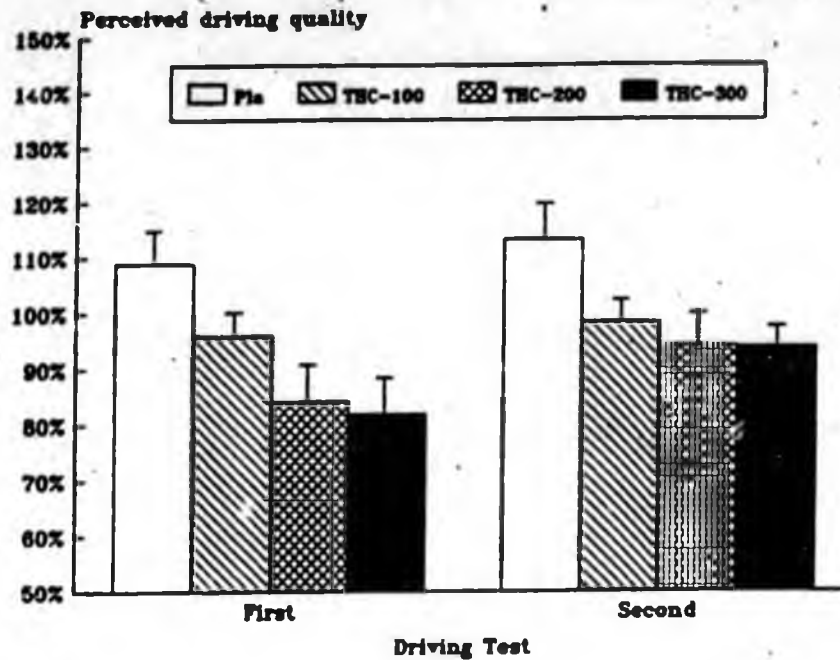


Figure 4.3 Mean (+SE) perceived driving quality, expressed as percentage of "normal", by *Dose* and *Time*.

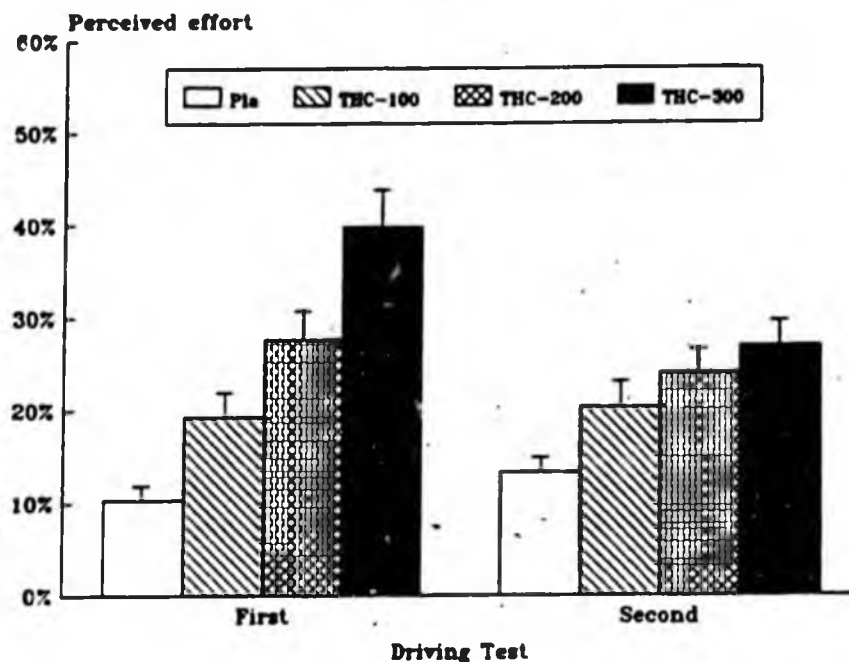


Figure 4.4 Mean (+SE) perceived effort to accomplish the test, expressed as percentage of maximum of scale, by *Dose* and *Time*.

$\mu\text{g/kg}$, respectively; $p < .012$, $.001$ & $.001$; $p_c = .05$, $.025$ & $.017$) than in the placebo condition. The *Dose by Time* interaction was significant after the two higher doses ($F_{1,22} = 8.45$ & 24.95 for the 200 and 300 $\mu\text{g/kg}$, respectively; $p < .008$ & $.001$; $p_c = .025$ & $.017$); i.e. the effort requirement diminished over the interval separating smoking and driving in these conditions...

Willingness to Drive

Table 4.3 presents the percentage of subjects willing to drive under specified conditions of different urgencies (A. unimportant though gratifying; B. important but avoidable; and, C. urgent).

Table 4.3 Percentage of subjects willing to drive under circumstances A, B & C (see text) by *Dose* and *Time*. Rightmost columns display Cochran Q-statistic (df=3) with p values.

		0 $\mu\text{g/kg}$	100 $\mu\text{g/kg}$	200 $\mu\text{g/kg}$	300 $\mu\text{g/kg}$	Cochran's Q	$p <$
A	$t=10$	96	87	48	48	23.54	.001
	$t=40$	96	65	48	43	23.22	.001
	$t=100$	96	83	65	61	16.40	.001
B	$t=10$	91	83	65	57	12.00	.008
	$t=40$	91	70	48	61	15.14	.002
	$t=100$	91	87	74	57	17.22	.001
C	$t=10$	100	96	91	74	13.11	.005
	$t=40$	100	96	87	74	11.45	.01
	$t=100$	100	96	96	87	6.33	NS

Subjects' responses were similar to those in the pilot study. The lower the administered THC dose and the more urgent the reason for driving, the more subjects declared that they would be willing to drive. According to the subjects' declarations, 40-60% would have driven for unimportant reasons shortly after the two highest doses. However, more than 75% would have driven for an urgent reason. Nearly all would have driven 1½ hours after smoking for an urgent reason when objectively measured driving performance was still impaired. Differences between treatments were significant in all cases, except one: the percentages of subjects who said they would have driven for an urgent reason 100 minutes after initiation of smoking were not different between treatment conditions.

Perceived Alertness, Contentedness and Calmness

Subjective feelings of alertness, contentedness and calmness were all affected by *Dose* ($F_{3,19} = 11.18$, 4.86 & 5.14 , respectively; $p < .001$, $.011$ & $.009$). After marijuana smoking, subjects felt less alert, content and calm. Significant *Time* effects were found for alertness and calmness ($F_{2,20} = 7.89$ & 8.10 , respectively; both $p < .003$): subjects felt more alert and calm later

in the session. A significant *Sex by Time* effect was found for feelings of contentedness, females feeling less and males more content later in the session. Separate comparisons showed that all three THC doses produced significantly reduced feelings of alertness ($F_{1,22}=12.46, 28.94$ & 24.80 for the 100, 200 and $300 \mu\text{g/kg}$, respectively; $p < .002, .001$ & $.001$; $p_c = .05, .025$ & $.017$). Only the two higher doses produced significantly reduced feelings of contentedness ($F_{1,22}=8.70$ & 15.05 for the 200 and $300 \mu\text{g/kg}$, respectively; $p < .007$ & $.001$; $p_c = .025$ & $.017$) and calmness ($F_{1,22}=14.29$ & 11.70 for the 200 and $300 \mu\text{g/kg}$, respectively; $p < .001$ & $.002$; $p_c = .017$ & $.025$).

Critical Tracking Test

Subjects' tracking performance, i.e. λ_c , was not affected by THC. Males performed significantly better than females ($F_{1,21}=12.61$; $p < .002$) and performance of all subjects was worse at the second than at the first assessment ($F_{1,21}=10.89$; $p < .003$), but these observations are not of great concern.

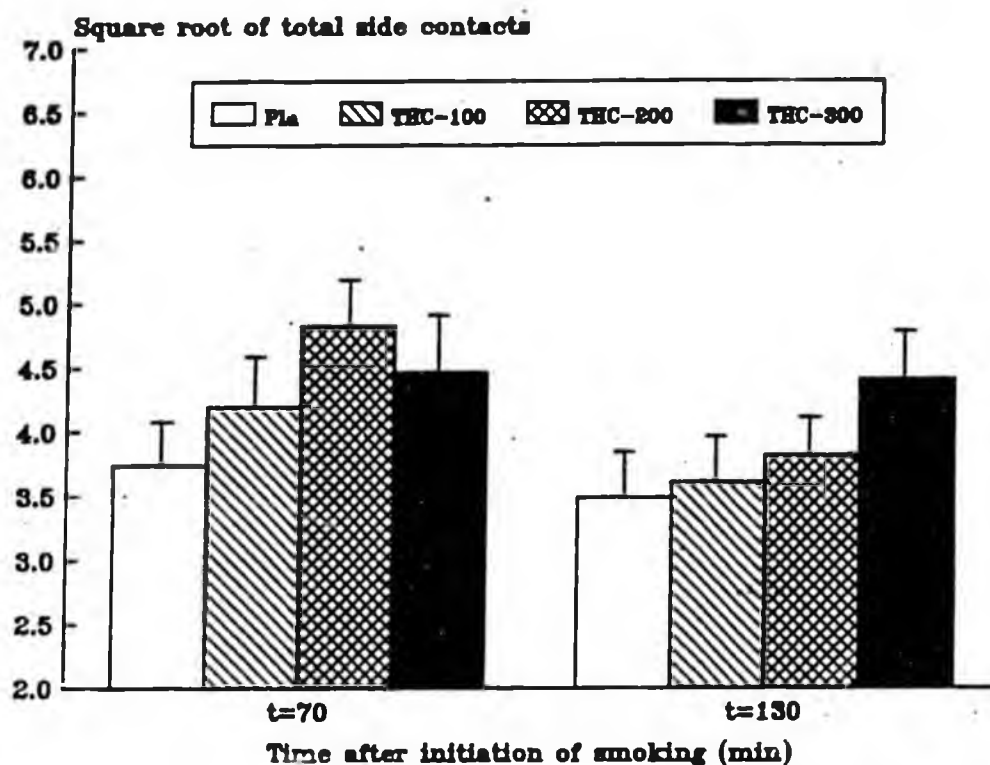


Figure 4.5 Mean (+SE) square root of total number of side contacts in the hand steadiness test by *Dose* and *Time*.

Hand Steadiness Test

Figure 4.5 demonstrates that hand steadiness diminished after all THC doses. MANOVA revealed a significant *Dose* ($F_{3,19}=5.04$; $p < .01$) and *Time* ($F_{1,21}=8.61$; $p < .008$), but no *Dose by Time* effect. This means that marijuana's impairment was still persistent two hours after

smoking. Separate comparisons showed that both higher THC doses, but not the lowest, diminished hand steadiness ($F_{1,22}=7.67$ & 11.76 for the 200 and 300 $\mu\text{g/kg}$, respectively; $p<.011$ & $.002$; $p_c=.025$ & $.017$).

Heart Rate and Blood Pressure

Heart rate and blood pressure were measured 70 and 130 minutes after the initiation of smoking. Yet as Figure 4.6 demonstrates, heart rate was still elevated in a dose related manner at both assessments. MANOVA confirmed this observation revealing a significant *Dose* effect ($F_{3,19}=7.71$; $p<.001$). Heart rate was always lower at the second assessment resulting in a significant *Time* effect ($F_{1,21}=24.34$; $p<.001$). *Dose by Time* interaction was not significant. Separate comparisons revealed that all three THC doses produced significant heart rate elevations relative to placebo ($F_{1,22}=9.00$, 13.62 & 20.61 for the 100, 200 and 300 $\mu\text{g/kg}$, respectively; $p<.007$, $.001$ & $.001$; $p_c=.05$, $.025$ & $.017$).

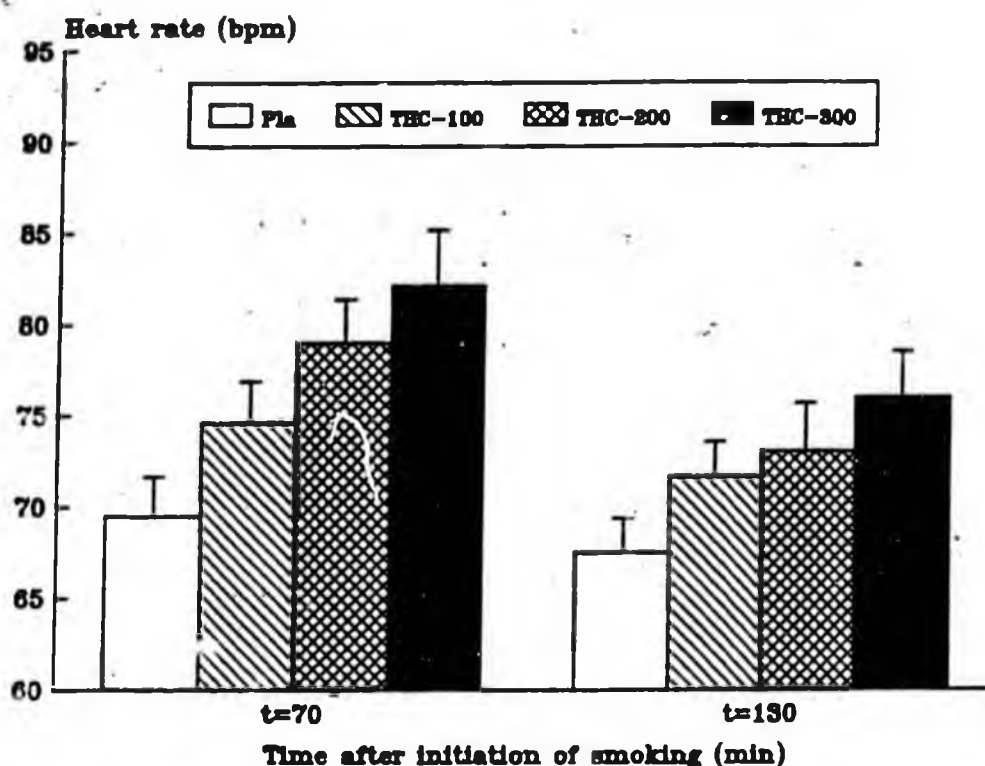


Figure 4.6 Mean (+SE) heart rate by *Dose* and *Time*.

Systolic and diastolic blood pressure measurements were simultaneously analyzed in one "doubly" repeated measures design. This means that both measures are analyzed in one multivariate design. Univariate effects of THC on systolic and diastolic pressures were only tested for significance, separately, if the multivariate *Dose* effect was significant. The lowest THC dose produced slightly lower blood pressure relative to placebo, whereas the highest dose had the opposite effect. Changes in blood pressures varied between -2.0 to $+5.8$ mmhg. MANOVA failed, however, to reveal either a significant *Dose* or *Dose by Time* effect. The only

significant factor was *Time* ($F_{1,21}=6.92$; $p<.005$), indicating that blood pressure decreased significantly from the first to the second assessment: this occurred in both the systolic ($F_{1,21}=12.92$; $p<.002$) and diastolic blood pressure ($F_{1,21}=4.77$; $p<.05$).

Intra-Subject Relations between Variables

Table 4.4 shows the average intra-subject correlations of [THC], [THC-COOH], and SDLP with each of the other variables. The averages were computed from 23 intra-subject correlations, calculated from data obtained at eight sampling times (twice in each condition). The table shows that higher plasma levels of the drug were associated with increased feelings of perceived "high"; higher levels of effort to accomplish the driving test, decreased ratings of subjective driving quality, and increased heart rate. There was no strong relationship, within subjects, between plasma levels of the drug and SDLP. This was because drug concentrations declined between the first and second sampling time, whereas SDLP scores hardly changed. When average intra-subject correlations were computed for the first and second sampling times separately, the correlations between [THC] and SDLP were 0.59 ($p<.01$) and 0.42 ($p<.05$), respectively.

Table 4.4 Average intra-subject correlations (* $p<.05$ ** $p<.01$; 2-tailed).

	[THC]	[THC-COOH]	SDLP
Perceived "high"	.83**	.80**	.41
Perceived Effort	.53**	.58**	.30
Perceived Driving Quality	-.43*	-.44*	-.29
SDLP	.23	.35	1.00
SP	-.35	-.34	.05
SDSP	-.02	.05	.16
λ_c	.11	.07	-.22
Side Contacts	.26	.20	.14
Heart Rate	.49*	.39	.27

Inter-Subject Relations between Variables

Relationship between Drug Levels and Performance. Inter-subject correlations between plasma concentrations of the drug and performance were calculated to determine whether subjects with higher plasma levels of the drug performed poorer than those that had lower plasma levels. Correlations between driving performance and performance in the laboratory were also calculated. The results are presented in Table 4.5. It appeared that correlations involving plasma concentrations were greater when logarithmic values of THC values were used in the computation (1 ng/ml was added to all THC values before the transformation in order to avoid negative log values). Correlations with THC-COOH were generally smaller than those with log THC values; therefore only correlations with log THC values are shown in the table.

Table 4.5 Inter-subject correlations between drug concentrations in plasma and raw performance scores in marijuana conditions (* $p < .05$, ** $p < .01$; 2-tailed).

	100 $\mu\text{g/kg}$		200 $\mu\text{g/kg}$		300 $\mu\text{g/kg}$	
	1 st	2 nd	1 st	2 nd	1 st	2 nd
$r(\text{Log}([\text{THC}] + 1), \text{SDLP})$	-.23	-.32	-.26	.01	.13	.07
$r(\text{Log}([\text{THC}] + 1), \text{SP})$	-.68**	-.72**	-.45*	-.39	-.52	-.58**
$r(\text{Log}([\text{THC}] + 1), \text{SDSP})$	-.37	-.57**	-.52*	-.38	-.27	-.22
$r(\text{Log}([\text{THC}] + 1), \lambda_c)$	.33	.51*	.24	.35	.08	.33
$r(\text{Log}([\text{THC}] + 1), \text{Side Contacts})$	.16	.24	.04	-.19	.31	.47*
$r(\text{SDLP}, \lambda_c)$	-.47*	-.50*	-.42*	-.56**	-.47*	-.27
$r(\text{SDLP}, \text{Side Contacts})$	.41	.38	.10	.41	.27	.38

Table 4.5 shows that SDLP was not related to prevailing plasma levels of THC. Another driving performance measure, mean speed, was only moderately, yet consistently, related to THC; subjects having high [THC] values drove slower than those having low [THC] values. Driving performance was moderately related to critical tracking; poorer tracking performance on the road (higher SDLPs) concurred with poorer tracking performance in the laboratory (lower λ_c s).

Five percent of the driving tests undertaken in this experiment yielded SDLP scores above the normal limit of 35 cm (Table 4.6). This limit was established by several hundred young and middle-aged volunteers and psychiatric patients who uniformly failed to achieve higher scores in the same test after being treated with placebo in all of the Institute's studies since 1986. It is illuminating to examine the present drivers who drove over the limit with respect to their prior treatments and the plasma concentrations of THC and its metabolite they exhibited at these times.

Table 4.6 Drug levels and SDLPs from those subjects whose SDLPs exceeded 36.0 cm.

Subject	Condition	Trial	[THC] (ng/ml)	[THC-COOH] (ng/ml)	SDLP (cm)
1523	100 $\mu\text{g/kg}$	2	2.5	3.2	38.7
1503	200 $\mu\text{g/kg}$	2	1.7	5.1	36.3
1523	200 $\mu\text{g/kg}$	1	8.8	6.7	39.2
1523	200 $\mu\text{g/kg}$	2	4.3	4.3	37.0
1527	200 $\mu\text{g/kg}$	2	10.0	16.2	39.4
1506	300 $\mu\text{g/kg}$	2	9.8	3.8	36.6
1523	300 $\mu\text{g/kg}$	1	18.0	11.5	36.9
1523	300 $\mu\text{g/kg}$	2	5.2	9.2	39.3
1526	300 $\mu\text{g/kg}$	2	6.7	16.2	36.6

These data are important in two respects. Aberrant driving performance never occurred after placebo smoking, only once after the lowest THC dose and with equal frequency (4x) after both

of the higher doses. Moreover, aberrant driving generally occurred during the second and not the first ride in direct opposition to the trend in plasma THC concentrations. From this, it's easy to infer the futility of predicting changes in SDLP, and presumably other aspects of driving performance, from a single [THC] estimation.

Correlations were also computed between drug plasma concentrations and changes in driving performance from placebo to marijuana conditions. These correlations were generally smaller than those involving the raw scores. Thus, [THC] does not predict changes in that performance.

Relationship between Driving Performance and Frequency of Current Use. Subjects were classified into two categories according to the frequency of reported cannabis consumption. Twelve subjects were infrequent users; i.e., between once weekly to once monthly; eleven subjects were classified as frequent users; i.e. at least once weekly but less than daily. SDLP values then entered a repeated measures MANOVA with *Frequency* of use as a between-groups factor, and *Dose* and *Time* as within-subjects factors. MANOVA failed to show a main effect of *Frequency*; interactions of *Frequency* and the other factors were also not significant.

Relation between Driving Performance and Driving under the Influence Experience. Subjects were classified into two categories according to the frequency of reported driving within one hour of cannabis consumption (see Table 3.1). SDLP values then entered a repeated measures MANOVA with *Experience* as a between-groups factor, and *Dose* and *Time* as within-subjects factors. Neither *Experience* nor any interaction was significant.

Relation of Willingness to Drive to Perceived "high" and Driving Performance. The relationship between willingness to drive and changes in SDLP and perceived "high" was determined as follows. Groups were defined by their willingness to drive; i.e., two groups were defined comprising those subjects who would not have driven and those who would, for each combination of condition (4x), sampling time (2x) and urgency of circumstance (3x), separately. Student's 2-tailed t-test for independent means was employed to determine whether the groups had significantly different change scores (drug minus placebo) of SDLP and perceived "high". Thus, 18 different t-tests were performed for each variable, SDLP and perceived "high". Criterion for statistical significance was set at .01 because of the large number of tests. No significant differences in SDLP change were found between subjects willing and those reluctant to drive. With respect to changes in perceived "high", only two significant effects were found. Subjects willing to drive under the imagined circumstance B ("important but avoidable") at both sampling times in the 200 $\mu\text{g/kg}$ condition felt less "high" than those who would not drive. However, this observation is not of major concern, since it was not supported in the other conditions and circumstances. From these results, it can therefore be concluded that subjects' willingness to drive was not related to either perceived "high" or driving performance.

DISCUSSION

This study demonstrated that marijuana impairs driving performance as measured by an increase in SDLP; all three THC doses significantly affected SDLP relative to placebo. It is remarkable that driving impairment was about the same after the two higher doses. This cannot be due to a ceiling effect, since greater deterioration in road tracking performance has been found after

many prescription drugs (e.g. Robbe *et al.*, 1989) and also high doses of alcohol (Louwerens *et al.*, 1987). One possible explanation for the lack of a clear dose related impairment may be that subjects were able to mitigate the effects of the highest dose by "trying harder". Indeed, subjects reported putting more effort in performing the test after smoking the highest THC dose. In other words, subjects tried to overcome the perceived disparity between their actual state and the one required to drive the car efficiently; the higher the THC dose, the greater the disparity between the actual and required states, and the harder they tried to compensate for it.

Though marijuana's adverse effects on SDLP were somewhat smaller in the second test than in the first, no significant interaction was found between the treatments and repetition of the test. This means that the driving performance decrement after smoking marijuana persisted almost undiminished for two hours after smoking.

What is the practical relevance of the size of the effects of marijuana upon lateral position variability? This can be inferred by comparing marijuana's effects to those of alcohol in the same test. As cited above, Louwerens *et al.* (1985, 1987) conducted a study to establish the dose-effect relationship of alcohol. Their study resembled the present one in many aspects: they applied exactly the same driving test, the study was performed on a closed road, and involved the participation of 12 male and 12 female volunteers. They were able to derive an empirical equation for predicting the change in SDLP from placebo levels with increasing blood alcohol concentrations. Mean SDLP began to change significantly at blood alcohol concentration of 0.03 g% and increases exponentially to the point where the vehicle's lateral motion can no longer be restricted to within lane boundaries (at about BAC=0.12-0.15 g%, on the average).

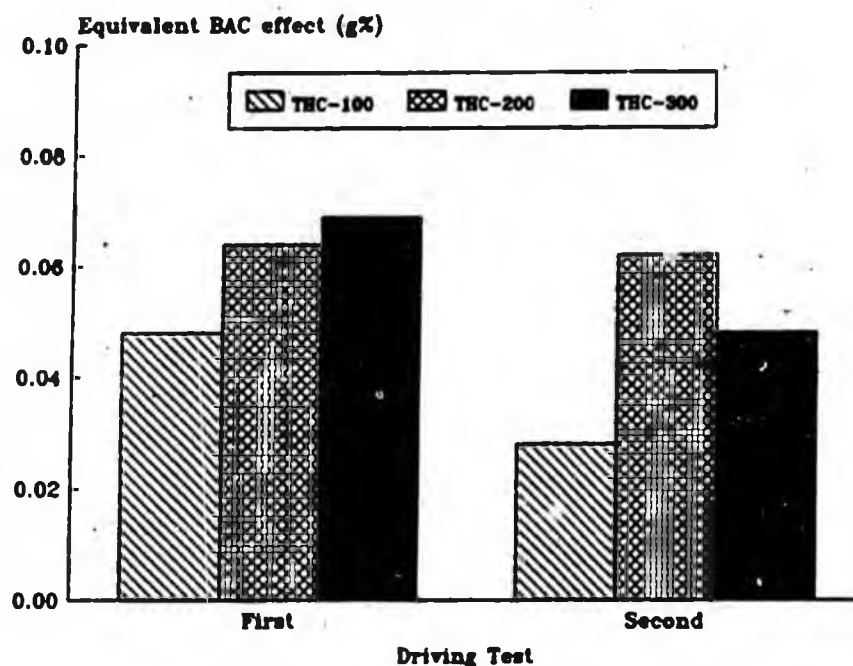


Figure 4.7 Comparison of mean SDLP changes after marijuana smoking to those associated with BAC.

Elevations of the group's mean SDLP in the first and second test after smoking 100, 200 and 300 µg/kg are presented in Figure 4.7, but now as their respective BAC equivalent

producing the same driving impairment. Two tentative conclusions can be drawn from these data: first, small doses of THC are capable of impairing driving performance; secondly, performance deterioration is only little worse, yet equivalent to BACs over the Dutch legal limit of 0.05 g%, when much higher doses are smoked.

As mentioned above, mean SDLP values did not change greatly over time. The same can be said of mean subjective driving quality ratings. Yet other parameters did change over time; THC in plasma, perceived "high", heart rate elevation and perceived effort to accomplish the driving test were all less in the second test than in the first. Another important observation was made when the 5% highest SDLPs were examined in greater detail. Nearly all of these scores were recorded in the second rather than the first driving test after smoking higher THC doses. It may be that subjects did not try to compensate as much during the second ride because they felt less intoxicated. Whatever the reason, these results clearly indicate that the behaviorally toxic effect of THC had not yet dissipated. This means that "behavioral intoxication" may outlast physiological and subjective marijuana intoxication, a phenomenon already reported by other investigators (e.g. Reeve *et al.*, 1983; Yesavage *et al.*, 1985). On the other hand, subjects' perceived driving performance, measured retrospectively, did not change from the first to the second test when compared to placebo. Thus, while they felt less intoxicated in the second test they realized that their driving impairment was still the same as in the first test. Subjective feelings of "high" should therefore not be equated with subjective feelings of impairment, as is often done.

Some investigators (Klonoff, 1974; Hansteen *et al.*, 1976) found that marijuana impairs lateral position control as measured by number of cones hit in slalom tests. Others (Casswell, 1979; Attwood *et al.*, 1981) did not find any effect of marijuana upon lateral position control as measured in a similar way as in the present study, presumably due to the low THC dose (6.25 mg in Casswell's study) or the small number of subjects (eight in Attwood's study). Peck *et al.* (1986) found that the number of cones hit decreased after smoking marijuana, probably due to a reduction in speed. Most of these studies also measured alcohol's effects (BACs between 0.04 and 0.10 g%) on lateral position control. It was generally concluded that marijuana's effects were less than alcohol's, especially at BACs of 0.08 g%. Marijuana's effects on lateral position variability were significant, yet not dramatic, in the present study and always less than or equal to the equivalent BAC effect of 0.07 g%. The reduction in mean speed, though small, fits also well with previous findings. It can therefore be concluded that this study's results are in close accordance with previous closed-course driving studies of THC effects on vehicle handling parameters. This implies that simple psychomotor functions involved in driving are impaired by normally consumed THC doses, though not to such an extent that traffic safety is seriously compromised.

Yet disturbing observations of two individuals' attentional deficits were observed; a sudden loss of the ability to shift attention from the prescribed task to an unexpected event (screwdriver on the road) and the lack of anticipation for a normal event (end of circuit). Since perception and attention are important aspects of actual driving, these instances may indicate an unusually hazardous property of THC when the drug is consumed shortly before operating a vehicle. Therefore, the revised conclusion must be: what was measured was only moderately affected by THC, but another major deficit may have existed after the highest dose which bears further examination. One can not conclude whether the standard driving test applied in this study measures the most important deficits.

Important practical implications of the study are whether driving performance decrements can be predicted by prevailing plasma concentrations of the drug. Though average [THC] and [THC-COOH] values were clearly dose-related, driving impairment reached a ceiling before the highest concentrations were achieved. Inter-subject correlations between plasma concentrations of the drug and driving performance after every dose were essentially nil, partly due to the peculiar kinetics of THC. It enters the brain relatively rapidly, although with a perceptible delay relative to plasma concentrations. Once there, it remains even at a time when plasma concentrations approach or reach zero. The conclusion is that driving impairment cannot be predicted by prevailing plasma concentrations of THC or THC-COOH.

Another way of predicting driving impairment was explored; namely, by performance in laboratory tests that might be potential "roadside" tests. Hand steadiness was impaired by marijuana after high doses but not after 100 $\mu\text{g/kg}$. Performance in this test was not related to driving performance. Previous studies employing the same test (Clark *et al.*, 1970; Milstein *et al.*, 1975) showed greater sensitivity to marijuana-induced impairment of hand steadiness. In those studies subjects were not allowed to rest their hands on the table, which is probably the major reason for the observed difference. In fact, the present and the preceding study merely measured finger rather than hand steadiness. The conclusion must be that hand steadiness was not properly tested, but the results suggest that it is not possible to predict driving impairment by means of hand steadiness performance.

Critical tracking performance was another candidate for being a good "roadside" test. Yet this test failed to show any effect of marijuana which is in conflict with prior research conducted by Sharma and Moskowitz (1975) and more recently Moskowitz *et al.* (1981). They demonstrated that a THC dose of 200 $\mu\text{g/kg}$ impairs critical tracking performance for at least up to 4 hours post-smoking. Peck *et al.* (1986), however, also reported a failure of marijuana alone (1.0 g cigarette containing 1.9% THC) to affect λ_c scores. They hypothesized that their conflicting results could be explained by their subjects' greater cannabis experience and tolerance. Although the same argument could be applied in the present study, it is suspected that the failure to detect significant changes in λ_c after marijuana smoking is due to the particular version employed in this and the pilot study (this group's mean values after placebo were also considerably lower than those commonly found in healthy volunteers). The device used was a commercial PC/AT version of CTT which was originally programmed on a Commodore-64 computer. The latter has been successfully applied in psychopharmacological research by the authors and their colleagues and hitherto appeared as a very sensitive test for drug-related impairment (e.g. Robbe *et al.*, 1989; Ramaekers *et al.*, 1992a). This study was the first in which the commercial PC/AT version was employed, so the conclusion that the software or hardware was not well designed seems inevitable.

All subjects were willing to undertake the driving tests. But test conditions were artificial and the same individuals may or may not have been willing to drive under normal circumstances. Therefore, one questionnaire inquired into the subject's willingness to drive an automobile when experiencing the same drug effect under "normal" conditions. Subjects' willingness to drive was related both to consumed THC dose and urgency. After smoking a low THC dose, nearly all were willing to drive, especially for urgent reasons. After higher doses, fewer were willing to drive under all circumstances. According to what subjects said, they did not become less cautious after inhaling increasingly large doses (unlike what is often reported about alcohol). On the contrary, their caution increased with intoxication. Still, 50% of the subjects reported that they would have driven for an unimportant reason shortly after smoking the two highest THC

doses. Since willingness to drive was not related to objective driving impairment, it may be concluded that at least some of the subjects either were not able to appraise their driving performance before they had actually driven or did not consider their impairment as critical.

It is interesting to compare plasma concentrations of THC found after smoking the highest THC dose in this study with those found in the pilot study. The highest dose administered in the present study was comparable to the average dose the same subjects consumed in the pilot study. Mean plasma concentrations of THC after the highest dose in the present study, determined 30 and 90 minutes after initiation of smoking, were 50 and 40% higher than those measured in the pilot study after 40 and 100 minutes. This large difference can only be partially explained by the 10 minutes delay between the two studies' blood sampling schedule. Apparently, subjects smoked more efficiently in this than the previous study. Since most volunteers were used to smoking hashish instead of marijuana, the increased efficiency compared to that in the pilot study may be explained by familiarization with the particular formulation of the drug.

One of the objectives of this study was to determine whether or not the same experimental conditions could be implemented in a study on marijuana's effects on driving on a primary highway public for other traffic. All subjects were willing and able to finish the driving tests without great difficulty. In cases of the exceptional events, the driving instructor was able to control the situation, safely. The effects of marijuana on SDLP were never so large as after many other drugs that had been safely studied in the presence of other traffic. Furthermore, it can be inferred from what subjects said and did that they would not be expected to seek dangerous situations and would be responsive to the instructor's advice. Normal safeguards were deemed sufficient to ensure safety. Hence, the final conclusion was that it would be safe to repeat this study on a normal highway in the presence of other traffic.

CHAPTER 5 - MARIJUANA AND DRIVING ON A NORMAL HIGHWAY IN TRAFFIC

INTRODUCTION

The preceding study showed that the average driving impairment on a closed highway segment was never particularly great after doses of 100, 200 and 300 $\mu\text{g/kg}$ THC (equivalent to impairment at 0.05 to 0.07 g% BAC) making it ethically acceptable to test the same doses' effects on performance in a more natural environment. It seemed essential to do so because the extent to which one can generalize from closed-course testing to the real world is presently unknown. Therefore, the same approach was applied for testing THC's effects on driving performance in a more realistic situation. In particular, the same THC doses were administered to a new group of subjects undertaking similar driving tests, though now on a highway in the presence of other traffic.

The present study was only the second wherein subjects drove in real traffic after receiving THC treatments. It was the first in which subjects inhaled higher "street doses" of THC before driving. Though the preceding study on a closed highway failed to show dramatic effects of high THC doses on high-speed driving, a conservative approach was chosen in designing the present study in order to satisfy the strictest safety requirements. This approach is unique in traffic science but closely follows the procedure used to determine the tolerability of medicinal drugs in human pharmacological research. It is to test THC's effects on actual driving performance in an ascending dose series (below). If any subject would have reacted in an unacceptable manner to a lower dose, he/she would not have been permitted to receive a higher dose.

The major objective of this study was to confirm the relationship between inhaled THC dose and lateral position variability in the context of a standard road tracking test. A secondary objective was to measure performance in another actual driving test (i.e. car following) to determine whether degrees of impairment would correlate between the two tests in a manner indicating a general influence of THC on driving behavior. The third objective was to continue efforts to correlate plasma concentrations of THC and THC-COOH with driving performance impairment as measured in both tests.

METHODS

Subjects

Sixteen new subjects, equally comprised of men and women, were selected according to the same inclusion/exclusion criteria as before. They were individually trained to perform the driving tests in a preliminary "dress rehearsal". Training at laboratory tests continued until each subject achieved satisfactory, asymptotical performance levels.

Plasma analyses after conclusion of the study showed that one female's plasma contained neither THC nor THC-COOH in any sample. It was concluded that this subject had not inhaled smoke, so her data were excluded from further analyses. Characteristics of the remaining 15 subjects are given in Table 5.1. T-tests for independent samples showed that males were heavier smokers than females ($p < .007$). There were no other significant differences between the sexes.

Table 5.1 Mean $\pm$ SD (range) of subjects' characteristics.

	Males (N=8)	Females (N=7)
Age (yrs)	28.3 $\pm$ 7.4 (22-42)	25.0 $\pm$ 4.6 (21-34)
Weight (kg)	70.8 $\pm$ 7.0 (61.0-83.5)	66.7 $\pm$ 7.9 (55.5-79.0)
Weight (lb)	156 $\pm$ 15 (134-184)	147 $\pm$ 17 (122-174)
Smoking Experience (yrs)	8.3 $\pm$ 6.5 (2-21)	6.3 $\pm$ 5.9 (1-16)
# Joints/Month	8.3 $\pm$ 5.0 (1-16)	2.0 $\pm$ 1.4 (1-4)
Driving Experience (yrs)	6.8 $\pm$ 5.7 (2-20)	4.9 $\pm$ 4.6 (1-15)
Driving Experience (km x 1000)	78 $\pm$ 101 (10-320)	38 $\pm$ 66 (5-188)
Driving Experience (mi x 1000)	48 $\pm$ 63 (6-199)	24 $\pm$ 41 (3-117)
# of Subjects Having Driven within 1 Hour following Cannabis Consumption:		
less than 5 times	4	7
5 times or more	4	0

Design, Doses and Administration

The study was conducted according to an ascending dose series design where both active drug and placebo conditions were administered, double-blind, at each of three THC dose levels. THC doses were the same as those used in the previous study, namely 100, 200 and 300 μ g/kg.

The lowest dose and placebo were administered in separate First Level treatment conditions spaced a week apart. Half the group received these treatments in the same order, the others in reverse order. Subjects proceeded to the next dose only if, in the driving instructor's opinion, no severe and potentially unsafe drug effects had occurred; and, if the subject was willing to go on to the next level. The intermediate dose and placebo were administered the same way in the Second Level conditions and the decision to proceed was made on the same grounds. The highest dose and placebo were administered the same way in the Third Level conditions to conclude the study.

Marijuana cigarettes were prepared from batches supplied by NIDA, containing 1.77% THC for the lowest, 2.64% THC for the intermediate, and 3.58% THC for the highest dose. Doses were administered by smoking and cigarettes appeared identical at each level of treatment conditions. Cigarettes were smoked through a plastic holder in a fashion determined by the subject but with the constraint that smoking had to be finished within ten minutes. After cessation of smoking, cigarettes were retained for subsequent gravimetric estimation of THC consumed. These analyses revealed that the average ($\pm$ SD) amount of consumed THC in the three marijuana conditions was 6.9 ($\pm$ 0.7), 13.8 ($\pm$ 1.4) and 20.7 ($\pm$ 2.2) mg, or 100 ($\pm$ 4), 204 ($\pm$ 7) and 299 ($\pm$ 7) μ g/kg, respectively.

Testing Procedures

Upon arrival at the laboratory, subjects' breath and urine were tested for the presence of alcohol and cannabinoids. If cannabinoids were found in the urine, a blood sample was taken for later verification of the presence of THC. Two subjects at a time commenced smoking at $t=0$ (Table

5.2). Thirty minutes after onset of smoking the subjects performed a battery of laboratory tests (tracking, hand steadiness and body sway) and yielded a blood sample. They were then transported to a primary highway (A76, different than in the previous study) between the Dutch cities of Maastricht and Heerlen where the driving tests were performed. Two instrumented vehicles, the same as those in the previous study, were employed in this study. One subject started the car following test (below) in the eastward direction whilst the other subject was sitting in the passenger's seat of the preceding car involved in the same test. The test was conducted on a 16 km (9.9 mi) circuit of the highway and lasted about twelve minutes. At the end of the circuit the car turned at a signalized intersection and parked at a service station, whereupon the subjects reversed roles to repeat the test running in the opposite direction. The new driver reentered the highway and began his/her car following test. After conclusion of the car following test, the subject left the highway at an exit ramp and reentered in the opposite direction on the associated entrance ramp. Thereupon both vehicles parked on the paved shoulder.

Table 5.2 Schedule of activities on test-days.

Relative Time (min)	Activity
0-10	Smoking
30-40	Tracking, Hand Steadiness and Body Sway Tests
40-45	Blood Sampling
55-70	Car Following Test (1st Subject)
70-85	Car Following Test (2nd Subject)
85-135	Standard Driving Test (Both Subjects)
140-155	Car Following Test (1st Subject)
155-170	Car Following Test (2nd Subject)
190-195	Blood Sampling
195-205	Tracking, Hand Steadiness and Body Sway Tests

Both subjects then commenced the standard driving test (below) in separate instrumented vehicles at $t=85$ and $t=88$, respectively. The test circuit was the same as for the car following test. Subjects drove twice around the circuit (in total, 64 km or 40 mi) without stopping in about 50 minutes. At the conclusion of this test, both subjects participated again in the car following test in the same order as before. Subjects were then transported back to the laboratory where they yielded a blood sample and repeated the test battery.

Two pairs of subjects were tested per test night. One pair performed the driving test in daylight, i.e. between 19.30 and 21.30 hours; the other pair commenced driving at 21.30 hours and finished at 23.30 hours in darkness.

Driving Tests

The standard test was the same as described in the previous study (Chapter 4) except for its duration and the presence of other traffic. Subjects were instructed to maintain a constant speed of 95 km/h (59 mph) and a steady lateral position between lane boundaries in the right traffic

lane. They were allowed to deviate from this only if it would become necessary to pass a slower vehicle in the same lane. Data from the standard test were analyzed to yield the same performance measures as in the previous study; namely, standard deviation of lateral position (SDLP), mean and standard deviation of speed (SP and SDSP), and standard deviation of steering wheel angle (SDST).

The car following test measures drivers' ability to perceive changes in a preceding vehicle's speed and to react in a manner maintaining a constant headway. It began as the preceding and the following vehicle, respectively driven by one of the driving instructors and the subject, operated in tandem on the slower traffic lane while travelling at a speed of 100 km/h (62 mph). The subject was instructed to maintain a 50 m (164 ft) headway however the preceding vehicle's speed might vary. After driving in this manner for about one minute, the operator of the preceding vehicle released the accelerator pedal allowing its speed to fall to 80 km/h (50 mph). Immediately thereafter, the operator of the preceding vehicle accelerated to 100 km/h (62 mph). The duration of one deceleration and acceleration maneuver was approximately 50 seconds and six to eight, depending upon traffic density, were executed during one test.

The velocity of the leading vehicle was transmitted via telemetry to a receiver in the following vehicle. This signal, along with the following vehicle's own velocity were recorded in parallel, time-coded files on computer files. These data entered a power spectral analysis for yielding phase-delay, modulus or gain and coherence between the vehicle's velocities at the maneuver cycle frequency (i.e. $1/50 \text{ s} = 0.02 \text{ Hz}$). The average phase-delay between frequencies of 0.01 and 0.03 Hz., encompassing the frequency of the deceleration and acceleration maneuvers, was then calculated and transformed to the time domain to yield a measure of the subject's average reaction time to the movements of the leading vehicle (RT; in seconds). This was taken as the primary dependent variable from the car following test. Gain and coherence were recorded for control purposes. If the test was performed according to instructions, gain should have a value of about 1.0, and coherence, $> .90$.

During the trials, 3 to 6 direct measurements of separation distance between the following and leading vehicle were made by means of a S-VHS video recording system which was mounted between the following vehicle's front seats facing forward through the windshield. Images of the rear of the preceding vehicle were acquired prior to each deceleration/acceleration maneuver. The camera's internal clock signal was recorded with the video imagery and also converted in an electronic pulse code for simultaneously computer recording along with the two vehicles' speed.

Video imagery recorded throughout the trials were analyzed off-line using an interactive software routine implemented on a IBM-AT computer. A single frame would show the appearance of the preceding vehicle at the moment it begins to decelerate. Next the coordinates of two target markers, spaced 119 cm apart on the rear of the leading vehicle were identified on the display. From this information the distance separating the two vehicles or "headway" was calculated according to the equation,

$$d(\text{in m}) = k (1 \text{ m} / \tan (\Theta/2))$$

where k is a proportionally constant and Θ the horizontal angle subtended by the camera lens. Once the starting distance was determined from a single measurement, headway changes during the maneuver were calculated using differential speed according to the equation,

$$H(t) = \int V_p dt - \int V_f dt + H_0$$

where headway varies as a function of time (t) according to the difference between integrals of velocities of preceding and following vehicles (V_p, V_f) plus the headway (H_0) that existed at the beginning of the maneuver. Headway and coefficient of variation of headway (CV-Headway) during maneuvers were taken as secondary dependent variables. The α efficient of variation of headway, and not standard deviation, is preferable because of the latter's confounding by mean headway.

Questionnaires

The same subjective questionnaires used in the previous study were administered to the subjects in the present study. Subjective feelings of "high", present cognitive and emotional state, and subjects' willingness to drive were assessed before the onset and after the conclusion of the driving tests ($t=50$ and 175). Subjects were also asked about their perception of the administered treatment, whether it was THC or placebo. At the end of each driving test, subjects were required to retrospectively rate the effort given in performing the test and perceived driving quality. Questionnaires are enclosed in Appendix A.

Laboratory Tests

Three tests were administered to the subjects: critical tracking, hand steadiness and body sway. These were also administered in the preceding studies, but the equipment or procedures were changed in this study.

1. Equipment, not procedures, changed in case of the critical tracking test (CTT). The test had shown no sensitivity to treatments administered in the preceding studies, in spite of the fact that other investigators had used the same test for showing significant effects of much lower THC doses. The validity of the particular MS-DOS version used in the preceding studies was doubtful. Therefore an older Commodore-64 version was employed in the present study. This version of the CTT had proven its sensitivity to drug-induced sedation in several previous studies conducted by the authors and their colleagues (e.g. Robbe *et al.*, 1989; Ramaekers *et al.*, 1992a). Test duration was approximately 5 minutes and mean λ_c was the dependent variable.
2. As discussed in the previous chapter, the hand steadiness test examined finger rather than hand steadiness because subjects were allowed to rest their hands on the table. Subjects were not allowed to do this in the present study. The modification was expected to induce greater instability. Therefore, the diameters of holes were increased to avoid ceiling effects of the number of contacts between their sides and the hand-held stylus. The diminishing diameters of the five circular holes were now set to 6.30, 4.70, 3.90, 3.05 and 2.70 mm (0.25, 0.19, 0.15, 0.12 and 0.11 in) respectively. The dependent variable was again the square root of the total number of contacts of the stylus with any side. The test lasted about 3 minutes.
3. Postural instability, or body sway, was measured using the stabilometry method (Kapteyn *et al.*, 1983). It involved the use of a balance platform that measures the location of the vector of force which extends vertically downward from the body's center of gravity and its movement over time. Analog output of force transducers within the platform were digitized

and analyzed to yield simultaneous measures of lateral and sagittal motion around the vertical axis. Subjects were instructed to maintain a static posture while standing over the center of the balance platform with their feet together. Two, 30-second recordings followed. The first with the subject's eyes open, the second with eyes closed. While standing with the eyes open, the subject was required to fixate on a target mounted on the wall from a distance of 2.0 m (6.6 ft). The mean area circumscribed by the vertical vector of force (i.e. curve surface, in mm²) was taken as the dependent variable (CS-O and CS-C for eyes open and closed, respectively).

Physiological Assessments

The electrocardiogram (ECG) was measured from precordial leads (RC₃), and the interbeat interval (IBI) times were registered continuously during the driving tests. Cardiac interval times were analyzed to yield three different parameters, mean IBI, the coefficient of variation (CV-IBI), and relative amplitude in the power density spectrum between the frequencies of .07 and .14 Hz (PWR-HR).

CV-IBI, is defined as standard deviation of IBI divided by the mean. It is the best measure of IBI variability in the time domain. The coefficient of variation, and not the standard deviation, of IBI is preferable because of the latter's confounding by mean IBI.

PWR-HR is a variability measure within a restricted region of the frequency domain and calculated from the time series of instantaneous heart rates, which are computed at each successive heart beat. It is defined as the integrated amplitude in the power density spectrum between 0.07 and 0.14 Hz.

Mean interbeat interval, and more frequently its reciprocal, mean heart rate, is frequently used for measuring THC's chronotropic cardiac effect. As shown in the previous study, the measure is valuable for assessing the course of the drug's activity over time. However the other measures, CV-IBI and PWR-HR, possess greater psychological significance. They are alternatively used for estimating relative changes in an individual's mental workload, or more correctly the amount of mental effort he must exert for handling a particular workload. In general, both measures vary inversely with the imposed mental workload or the increase in mental effort which is required to cope with a constant workload while maintaining the same level of performance efficiency under the influence of drugs or fatigue (Mulder, 1980; Mulder and Mulder, 1981).

Blood Sampling

Blood samples were obtained from the subjects by venepuncture immediately before they were transported to the test site and immediately after their return, or approximately 35 and 190 minutes after initiation of marijuana smoking. Two aliquots containing 10 ml each were heparinized and centrifuged, and the plasma fractions were placed in frozen storage for later assays to determine [THC] and [THC-COOH]. The analytical procedures were the same as those employed in the preceding studies.

Data Analysis

The first step executed was determining the reliability and consistency of performance and subjective parameters measured in the successive placebo treatment conditions. Test-retest reliability coefficients were determined and mean differences between data collected in successive conditions were tested for significance using repeated measures MANOVA. Previous studies wherein unmedicated subjects performance was repeatedly measured in the standard test have failed to show any significant changes over time intervals as long as one week; and, test-retest reliability coefficients for the SDLP measure have always been higher than $r = .80$. However, intervals separating successive placebo tests were longer in the present study and the reliabilities of measures obtained in the car following test had yet to be determined. For these reasons it appeared necessary to check the consistency of the subjects' performance in the present study.

Subsequently, data from drug and placebo conditions on the first, second and third levels were analyzed separately. Performance variables recorded on ratio or interval scales were subjected to repeated measures MANOVA with *Sex* as a between-groups and *Drug* (placebo versus marijuana) as a within-subjects factor. The effect of *Time* of testing (2 levels) was, if pertinent, simultaneously tested as a within-subjects factor in the same analyses.

It appeared that marijuana's effects on reaction time in the car following test were confounded by mean headway. Reaction times were therefore also analyzed by means of covariance analysis, using headway as the covariate. Covariance analysis estimates what the scores on one variable (in this case, reaction time) would have been if the same "average" score on another variable (in this case, mean headway) would have occurred in all conditions. It allows one to estimate the effects of THC on reaction time independently of those on headway.

Willingness to drive data were analyzed in the same manner as the parametric data. That is, data from drug and placebo conditions on the first, second and third levels were analyzed separately. Thus, data from both sampling times in a drug condition and its respective placebo condition were simultaneously tested for assessing differences in the proportion of subjects willing to drive for a particular reason.

Separate dose effects were tested using the "Sequential Bonferroni" procedure for adjusting the α -probability criterion (p_c) in accordance with the number of separate comparisons in a given set (Overall and Rhoades, 1987). For the largest of three differences tested at once, p had to be less than $.05/3 = .017$ to be judged significant. For the second, it had to be $< .05/2 = .025$; and for the smallest difference, $p < .05$. The adjustment had the effect of holding the probability of making a type I error at $p \leq .05$ over the entire set of comparisons.

Though data from both the marijuana and respective placebo condition entered MANOVA, figures illustrating the results display mean difference scores (drug - placebo) and standard errors of the difference (SED). The former are depicted by the height of the bars, the latter by the vertical lines above or below the bars. Difference scores were used in order to keep the figures as simple as possible. As a consequence, main effects of *Time* could not be depicted in the figures: a parallel rise or fall in the mean levels of a variable over time would not affect their difference. This is, however, not a major problem, since it is not very interesting to know whether subjects' performance changed in both conditions in the same manner. More interesting is a *Time by Drug* effect, which means that the difference between effects of marijuana and placebo changed over time. This effect would be obvious in the figures.

Significant *Sex* effects were generally absent. Results pertaining to differences between the sexes are therefore mentioned only in the exceptional cases where these were significant.

RESULTS

No subject dropped out during the experiment, neither on their own initiative nor on the driving instructor's. Therefore, the results presented below include data from fifteen subjects at each level of treatment. It was impossible to obtain every blood sample from one woman, even after repeated attempts. Her data were therefore excluded from all analyses involving drug and metabolite plasma concentrations. However, assays of what samples were obtained indicated that she did inhale THC. Consequently, her data were not excluded from other analyses.

Test-Retest Correlations and Consistency of Performance

Correlations between measurements obtained from the successive placebo treatment conditions are shown in Table 5.3. Correlations between repeated SDLP's were somewhat lower than those obtained in earlier studies for "normal" subjects, but were still both highly significant and consistent. Mean and standard deviation of speed were also quite reliable. Steering wheel variability, however, was not a reliable measure.

Table 5.3 Correlations between parameters measured at the same time in the successive placebo treatment conditions (* $p < .05$ ** $p < .01$; one-tailed).

	1 st and 2 nd placebo		2 nd and 3 rd placebo		1 st and 3 rd placebo	
	1 st test	2 nd test	1 st test	2 nd test	1 st test	2 nd test
<u>Standard Driving Test:</u>						
SDLP	.75**		.76**		.72**	
SP	.61**		.84**		.77**	
SDSP	.66**		.69**		.55*	
SDST	-.21		.17		-.62	
Subj. Driv. Quality	.24		.24		.30	
Perceived Effort	.72**		.50*		.56*	
<u>Car Following Test:</u>						
Headway	.73**	.31	.60**	.90**	.67**	-.01
CV-Headway	.48	.19	.36	.40	.55*	.07
RT	.61**	.45*	.81**	.68**	.64**	.09
Subj. Driv. Quality	.51*	.06	.64**	.28	.61**	-.06
Perceived Effort	.72**	.80**	.67**	.69**	.33	.71**
<u>Laboratory Tests:</u>						
λ_c	.68**	.70**	.73**	.87**	.67**	.78**
Side Contacts	.75**	.80**	.84**	.66**	.63**	.63**
CS-O	.43	.49*	.20	.62**	.04	.31
CS-C	.25	.56*	.71**	.18	.37	.41
<u>Other Subjective Feelings:</u>						
Alertness	.44*	.92**	.88**	.78**	.59*	.75**
Contentedness	.52*	.79**	.76**	.77**	.46*	.59**
Calmness	.71**	.34	.87**	.41	.51*	.22

Subjective driving quality ratings were also unreliable, probably due to restriction of range; i.e. most subjects naturally rated their driving performance as about normal (100%) following placebo treatment. Perceived effort ratings were somewhat more reliable, indicating that driving under the conditions of this study was consistently a more effortful occupation for some subjects than others.

Car following parameters were not as reliable as those measured in the standard driving test. Performance in the second ride in the first placebo condition was not related to that in the second ride of the second and third placebo conditions. This means that the test still needs further standardization to reduce the error variance of the measures tested. Ratings of perceived effort in the car following test were only slightly more reliable than those obtained in the standard test. Remarkably, ratings of subjective driving quality were highly reliable in the first car following test, but not in the second.

Hand steadiness and λ_c , but not body sway measures, were highly reliable. Ratings of alertness, contentedness and calmness were moderately reliable. Surprisingly, alertness and contentedness ratings were generally more reliable when measured after driving, in contrast to calmness ratings which were more reliable before the driving tests commenced. Correlations between perceived ratings of "high" were not computed since they were generally very low or zero following placebo.

Mean differences between data collected in successive placebo treatment conditions were tested for significance using repeated measures MANOVA. Only λ_c changed nearly significantly over successive placebo treatment conditions ($F_{2,12}=3.81$; $p<.052$); subjects' performance in this test improved during the study ($\lambda_c=4.6, 4.8$ & 5.0 , for the respective placebo conditions, averaged across both sampling times). Obviously performance had not reached an asymptotic level during practice trials which preceded the beginning of experimental sessions.

Plasma Concentrations of the Drug

Table 5.4 shows mean, median and range of [THC] and [THC-COOH] by *Dose* and *Time*. Placebo values were not used in the statistical analyses since these were zero in most cases. Therefore, data from all THC conditions were analyzed in one MANOVA. The tabular data indicate that [THC] was related to inhaled THC dose, and fell to about the same level three hours after smoking.

Table 5.4 Mean, median and range of [THC] and [THC-COOH] in ng/ml (N=14).

		100 μ g/kg		200 μ g/kg		300 μ g/kg	
		t=35	t=190	t=35	t=190	t=35	t=190
[THC]	mean	7.9	0.7	12.0	1.1	16.1	1.5
	median	6.5	0.9	10.0	1.0	15.8	1.5
	range	0.8-17.2	0.0-1.3	1.5-27.1	0.0-2.7	4.7-30.9	0.4-3.2
[THC-COOH]	mean	8.2	4.1	12.2	7.61	15.3	10.0
	median	7.4	4.1	11.2	6.4	13.0	8.2
	range	1.4-19.4	0.0-12.0	2.0-37.2	0.0-32.2	4.2-39.6	1.5-36.3

MANOVA confirmed this impression with significant *Dose* ($F_{2,11}=20.75$; $p<.001$) and *Time* ($F_{1,12}=54.81$; $p<.001$) effects, and *Dose by Time* interaction ($F_{2,11}=17.80$; $p<.001$). Males had somewhat higher [THC] than females and the *Sex* effect approached significance ($F_{1,12}=4.60$; $p<.053$); *Sex by Dose* interaction was not significant.

Plasma levels of the metabolite, THC-COOH, were about the same as those of THC 35 minutes after initiation of smoking, but did not decline as rapidly. Table 5.4 shows that [THC-COOH] was also dose-related at both sampling times. Significant *Dose* ($F_{2,11}=14.49$; $p<.001$) and *Time* ($F_{1,12}=62.50$; $p<.001$) effects, but no *Dose by Time* interaction, were shown by MANOVA.

Perceived "high"

Ratings of "high" after placebo were near zero in most cases. Therefore changes occurring after marijuana smoking, relative to placebo, instead of the raw values, were analyzed by MANOVA. Average subjective feelings of "high" were dose-related and greatest just before the first driving test (Figure 5.1). Relative to maximum personal experience, peak levels of intoxication were

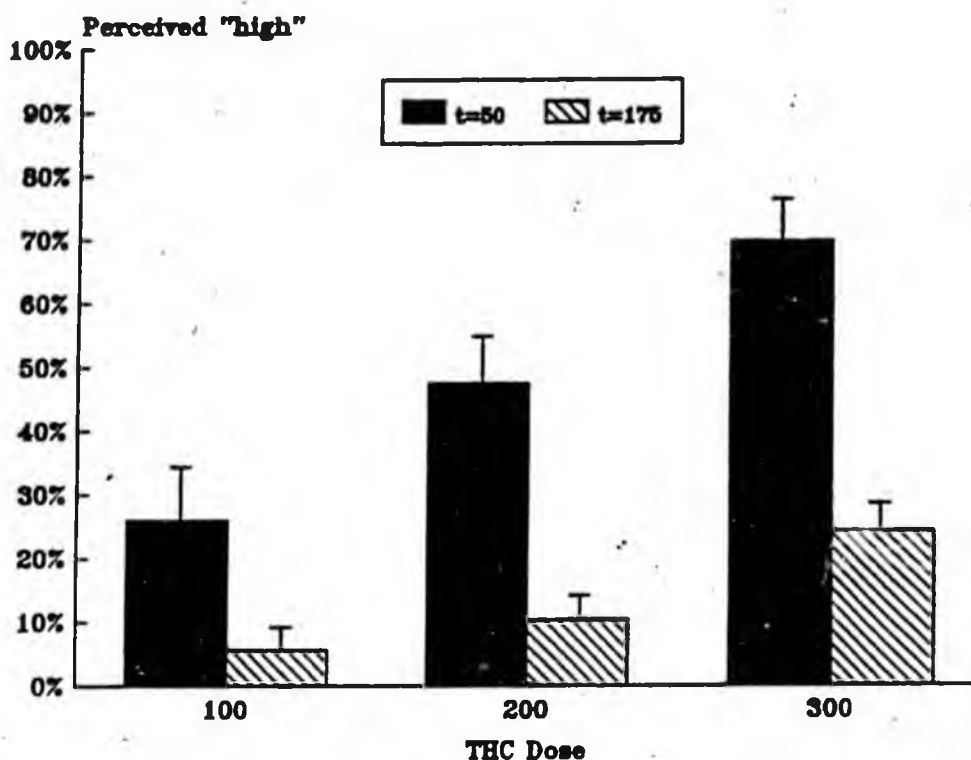


Figure 5.1 Mean (+SED) changes in perceived "high" by *Dose* and *Time*, relative to placebo.

about 30%, 50% and 75% after 100, 200 and 300 $\mu\text{g/kg}$ doses. The approximately linear correspondence between the administered dose and average subjective response was impressive.

Change scores were significantly dose-related ($F_{2,12}=35.07$; $p<.001$) and time-related ($F_{1,13}=40.25$; $p<.001$). The decline in feelings of "high" over time was also dose-related, resulting in a significant *Dose by Time* interaction ($F_{2,12}=7.87$; $p<.007$).

Driving Performance in the Standard Driving Test

All subjects undertook and completed each test in a safe manner; the driving instructors neither terminated any ride prematurely nor intervened while subjects were driving. In other words, the subjects' safety was never compromised.

Figure 5.2 shows the mean changes in SDLP from placebo to marijuana conditions. Performance after consuming THC was worse than after the respective placebo treatment; mean changes in SDLP were 1.1, 1.8 and 2.9 cm for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively. MANOVA showed that SDLP was significantly elevated after inhaling both the higher, but not the lowest, THC doses relative to placebo ($F_{1,13}=2.66, 6.63$ & 10.16 for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p < .13, .023$ & $.007$; $p_c = .05, .025$ & $.017$). No significant differences between males and females were discovered.

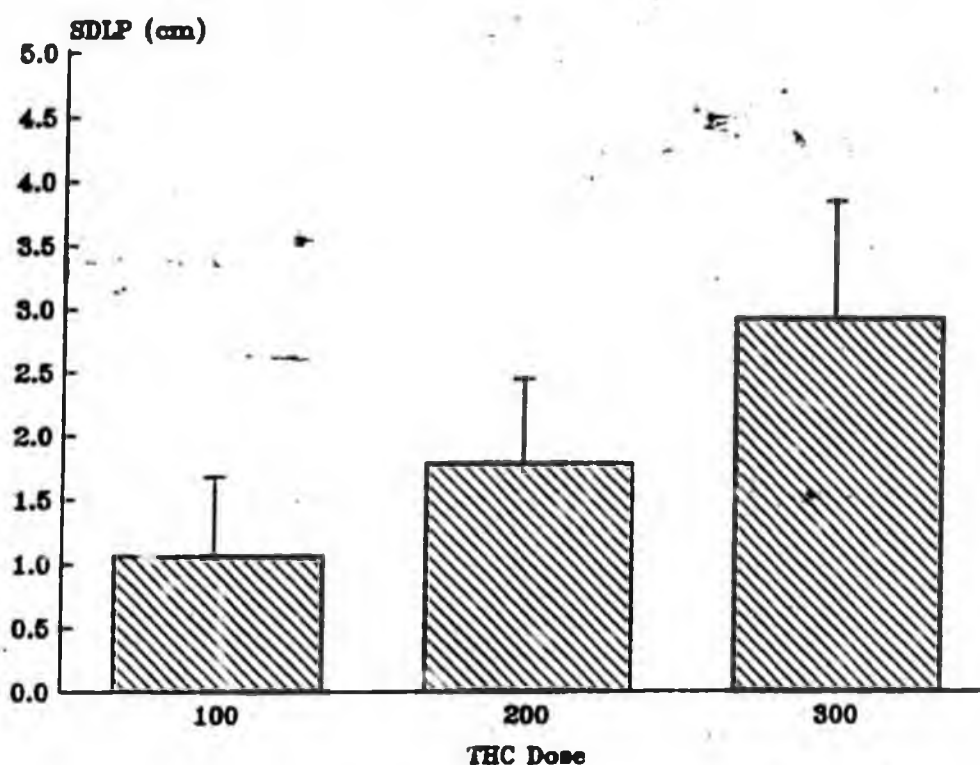


Figure 5.2 Mean (+SED) changes in standard deviation of lateral position in the standard driving test by *Drug*, relative to placebo.

Mean speed was very close to that established as the target by instructions and varied between conditions from 94.5 to 96.1 km/h (58.7 to 59.7 mph). Subjects drove slower following marijuana than following placebo, but the mean differences were quite small: 0.3, 1.1 and 0.5 km/h (0.2, 0.7 and 0.3 mph) for 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively. MANOVA showed that only the change after the intermediate dose was significant ($F_{1,13}=8.05$; $p < .014$; $p_c = .017$).

Standard deviation of speed was very small in each condition, on average 2.5% of mean speed. Though speed variability increased after smoking THC, the effects were minor and not

significant. Standard deviations of steering wheel movements were also not affected by THC; mean changes after smoking THC were essentially nil.

Subjects rated their driving performance in the standard test as about "normal" after smoking placebo and after the lowest dose of THC. Ratings were 90% and 77% of "normal" driving performance following the 200 and 300 $\mu\text{g}/\text{kg}$ conditions, respectively. Changes relative to placebo are shown in Figure 5.3. MANOVA demonstrated that changes in perceived driving quality approached the levels of significance required by the "Bonferroni" adjustment after the two higher THC doses ($F_{1,13}=5.29$ & 5.42 for the 200 and 300 $\mu\text{g}/\text{kg}$ conditions, respectively; $p<.039$ & $.037$; $p_c=.025$ & $.017$), but were not significantly different from placebo after the lowest THC dose.

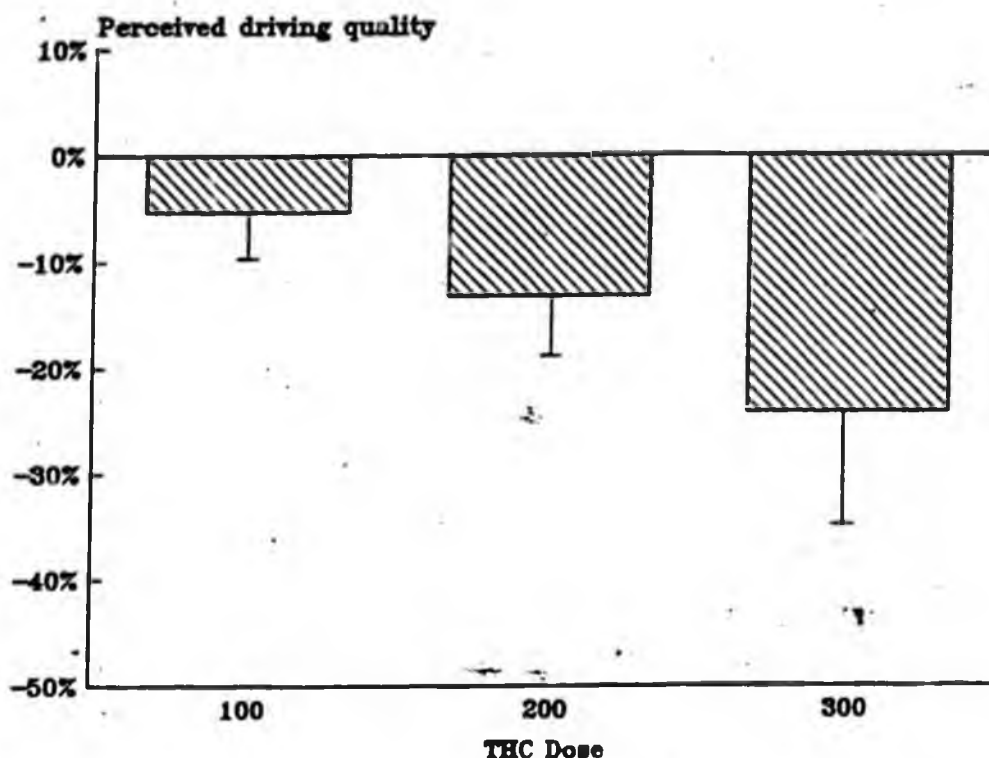


Figure 5.3 Mean (+SED) changes in perceived driving quality in the standard driving test by *Drug*, relative to placebo. Raw scores were expressed as percentage of "normal".

Changes in perceived effort ratings were trivial after the two lower THC doses. Effort did increase from 29% after placebo to 39% following the highest dose. MANOVA failed, however, to reveal any significant effects of THC on perceived effort.

Half of the subjects performed the driving tests in darkness, the other half under daylight conditions. Therefore, repeated measures analysis was again applied to the data, but now with *Light/Darkness* as a between-groups factor. No significant differences were found between the groups for any variable.

Driving Performance in the Car Following Test

All subjects were capable of performing the car following test in each treatment condition. There was no need for the driving instructors to ever intervene or prematurely terminate the test. In one instance, a subject needed the driving instructor's help after smoking the highest THC dose. The subject appeared confused when he took his seat in the car prior to the first car following test. The driving instructor noticed the subject's uncertainty as to what he should do and advised him to turn the engine on. Thereafter, the subject had no problems following the instructions and completing the ride.

Mean headway varied between conditions from 44.5 to 54.9 m (146 to 180 ft); changes relative to placebo are shown in Figure 5.4. It is interesting to note the inverse relationship between THC dose and headway: the lower the dose the greater the headway, especially in the first test after smoking. MANOVA showed that mean headway was significantly increased after smoking the lowest THC dose, relative to placebo ($F_{1,13}=7.57$; $p<.016$; $p_c=.017$); the two higher doses had no significant effect on headway. No significant *Time* or *Drug by Time* effects were found in either THC condition.

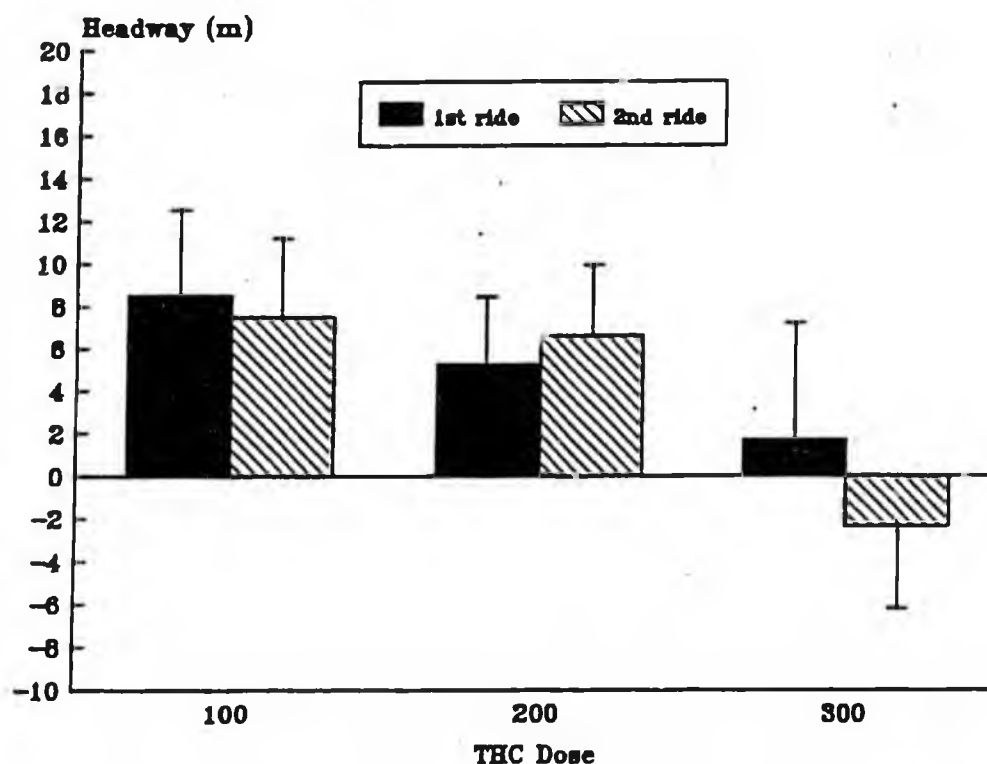


Figure 5.4 Mean (+SED) changes in headway in the car following test by *Drug* and *Time*, relative to placebo.

Coefficients of variation of headway, expressed as a percentage, were high and varied between conditions from 18.8% to 23.7%. Figure 5.5 shows an inverse relationship between CV-Headway and administered dose, with the exception of the first ride after the highest dose. MANOVA revealed a significant effect following the lowest dose ($F_{1,13}=16.62$; $p<.001$;

$p_c = .017$), but not the higher doses. *Drug by Time* interaction approached significance following the highest dose ($F_{1,13} = 4.85$; $p < .046$; $p_c = .017$); 300 $\mu\text{g/kg}$ THC produced an increased headway variability in the first test after smoking, but not in the second.

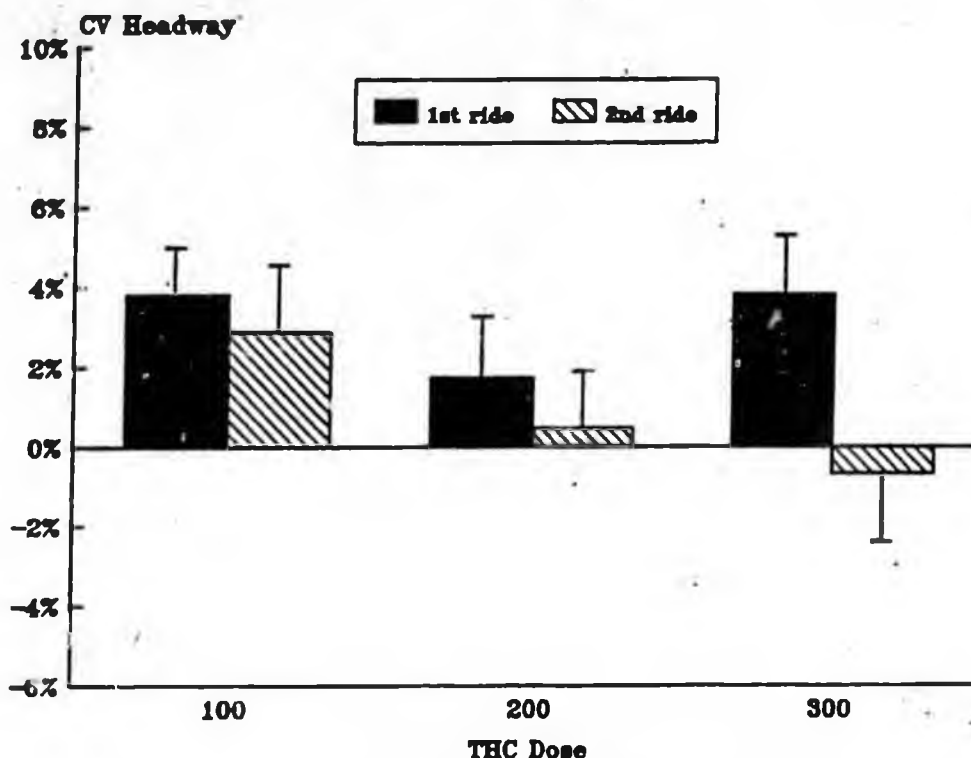


Figure 5.5 Mean (+SED) changes in coefficient of variation of headway in the car following test by *Drug* and *Time*, relative to placebo.

Mean reaction time to perceived changes in the preceding car's speed varied from 1.56 to 2.30 s, between conditions. The changes, shown in Figure 5.6, followed a similar pattern as those of headway; the greatest increase of reaction time occurred after the lowest THC dose, and the smallest after the highest dose. Reaction times were significantly increased after smoking both 100 $\mu\text{g/kg}$ and 200 $\mu\text{g/kg}$ THC, but not 300 $\mu\text{g/kg}$ ($F_{1,13} = 10.78, 6.26 \& 1.8$, respectively; $p < .006, .027 \& .193$; $p_c = .017, .025 \& .05$). Reaction times were, however, strongly related to mean distance ($r = 0.76$, across all conditions). This is understandable: the further apart two cars are, the more difficult it becomes for the subject to perceive changes in the preceding vehicle's velocity.

One may question what the effect of THC on reaction time would have been if subjects had driven at the same mean headway in all conditions? Covariance analysis of reaction time with headway as covariate was applied to answer this question. Figure 5.7 shows the mean changes in adjusted reaction times, from placebo levels. The figure makes clear that the differences in the adjusted reaction times were much less than those in the original ones. Though each THC dose increased reaction time, none did significantly. This means that the elevation in the raw reaction times following the lowest THC dose were simply due to a longer headway.

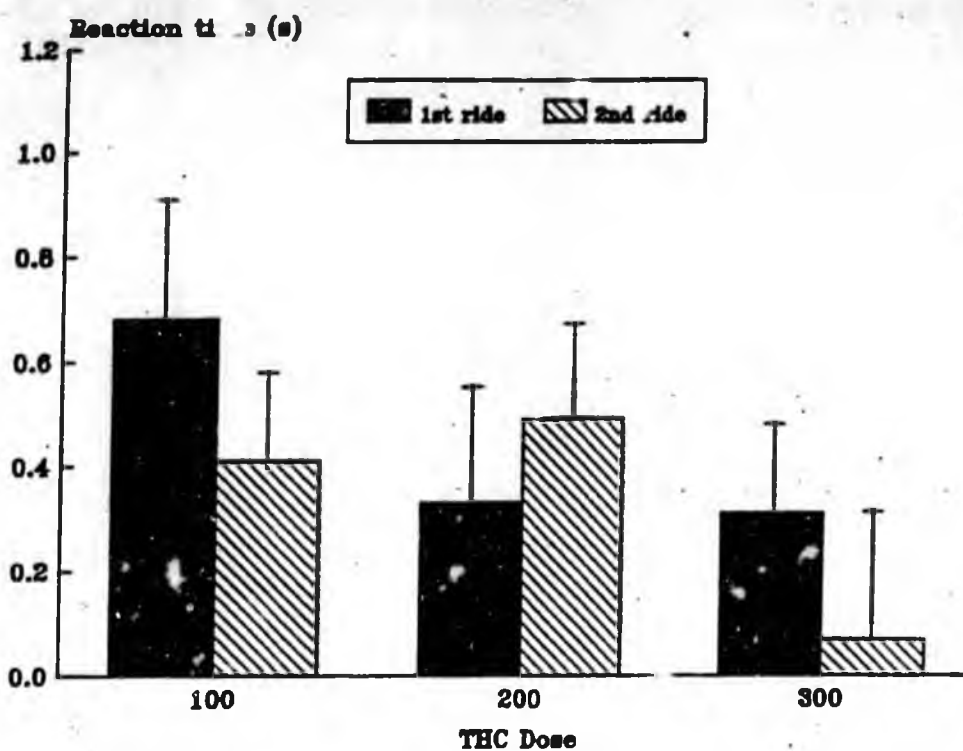


Figure 5.6 Mean (+SED) changes in reaction time in the car following test by *Drug* and *Time*, relative to placebo.

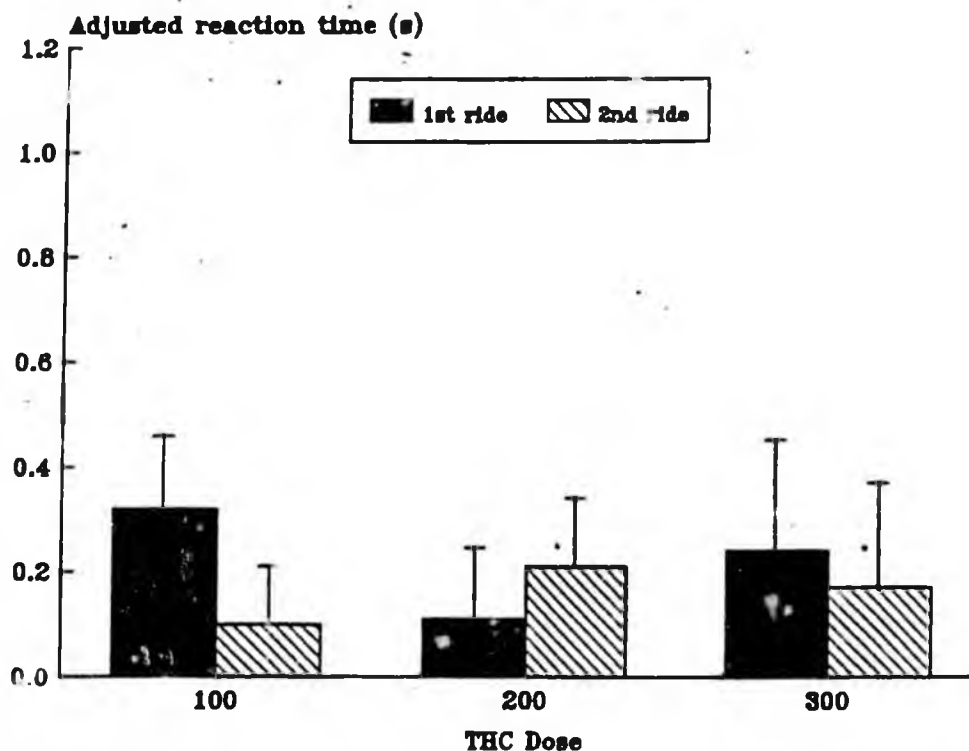


Figure 5.7 Mean (+SED) changes in reaction time, adjusted for changes in headway, in the car following test by *Drug* and *Time*, relative to placebo.

Subjects rated their driving quality in the car following test as somewhat better than normal following each placebo, and worse following each THC dose. Changes from placebo to drug are displayed in Figure 5.8. As for headway and reaction time, there was no clear dose-response

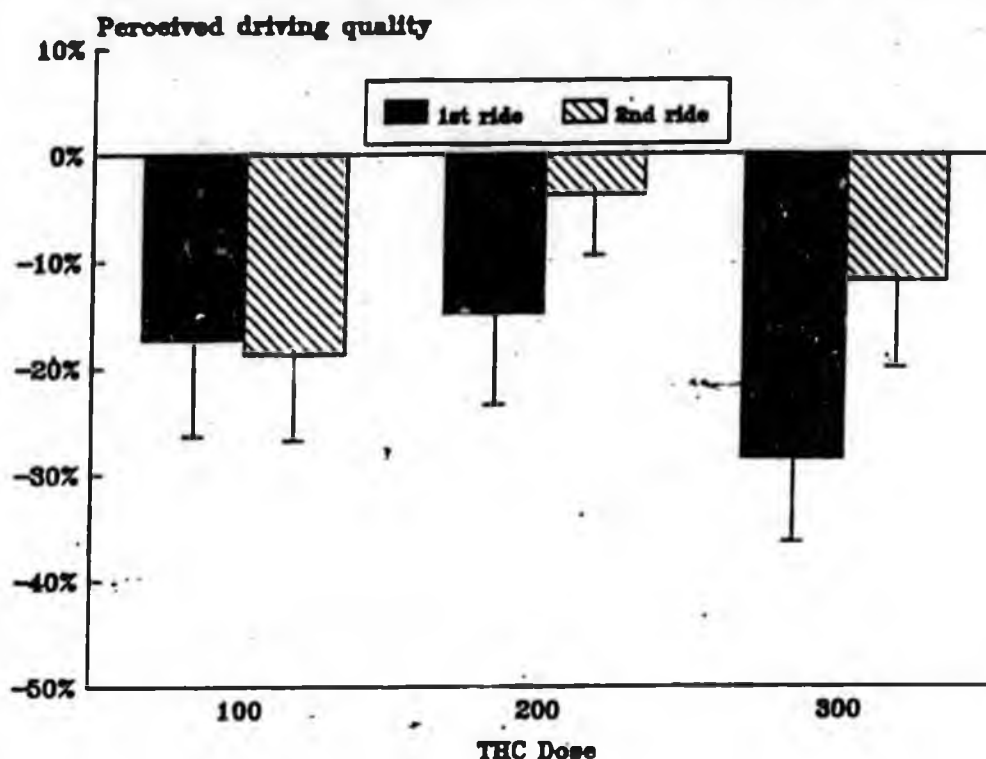


Figure 5.8 Mean (+SED) changes in perceived driving quality in the car following test by *Drug* and *Time*, relative to placebo. Raw scores were expressed as percentage of "normal".

relationship that determined how subjects rated their driving quality. Though they rated it the worst after the highest dose overall their judgement after the lowest dose was nearly as critical. MANOVA demonstrated that driving quality ratings after the highest dose were significantly different from placebo, but those after the lower doses were not ($F_{1,13}=6.04, 3.19$ & $13.8'$, for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p < .029, .097$ & $.003$; $p_c = .025, .05$ & $.017$). Neither *Time* nor *Drug by Time* effects were significant.

Though perceived effort ratings were generally higher following THC than placebo, MANOVA failed to show any significant drug effect.

Willingness to Drive

Table 5.5 presents the percentage of subjects willing to drive under specified conditions of different urgencies (*A.* unimportant though gratifying; *B.* important but avoidable; and *C.* urgent). Subjects' responses were similar to those in the previous study. The lower the administered THC dose and the more urgent the reason for driving, the more subjects declared that they would be willing to drive.

Table 5.5 Percentage of subjects willing to drive under circumstances A, B & C (see text) by treatment condition and sampling time.

		0 µg/kg	100 µg/kg	0 µg/kg	200 µg/kg	0 µg/kg	300 µg/kg
A	<i>t</i> =50	93	53	53	47	93	27
	<i>t</i> =175	93	80	80	87	93	53
B	<i>t</i> =50	100	73	100	60	100	40
	<i>t</i> =175	100	80	100	100	100	67
C	<i>t</i> =50	100	93	100	93	100	73
	<i>t</i> =175	100	93	100	93	100	87

Cochran's test showed that the numbers of subjects who would have driven for an unimportant reason following every THC dose were significantly less than after placebo ($Q_{df=3}=12.0, 13.4$ & 21.6 for the 100, 200 and 300 µg/kg conditions, respectively; $p < .008, .004$ & $.0001$; $p_c = .05, .025$ & $.017$). The same held true for the somewhat more important reason ($Q_{df=3}=10.2, 18.0$ & 21.4 for the 100, 200 and 300 µg/kg conditions, respectively; $p < .02, .0004$ & $.0001$; $p_c = .05, .025$ & $.017$). In contrast, the numbers of subjects who would have driven for an urgent reason after every THC dose were not significantly different from placebo ($Q_{df=3}=3.0, 3.6$ & 9.4 for the 100, 200 and 300 µg/kg conditions, respectively; $p < .40, .40$ & $.024$; $p_c = .05, .025$ & $.017$).

Perceived Alertness, Contentedness and Calmness

Table 5.6 shows the mean subjective ratings of alertness, contentedness and calmness, presented as the percentage of maximum scale. Mean subjective ratings generally declined after smoking marijuana, relative to placebo, indicating that subjects then felt less alert, content and calm. MANOVA showed that subjects felt significantly less alert after smoking THC ($F_{1,13}=12.57, 6.48$ & 21.24 for the 100, 200 and 300 µg/kg conditions, respectively; $p < .004, .024$ & $.001$; $p_c = .025, .05$ & $.017$). Furthermore, a significant *Drug by Time* interaction was found for the 100 µg/kg condition ($F_{1,13}=13.78$; $p < .003$; $p_c = .017$), due to the recovery in feelings of alertness from the first to the second time of testing.

Contentedness ratings were only significantly reduced after smoking the highest THC dose ($F_{1,13}=10.20$; $p < .007$; $p_c = .017$). *Drug by Time* interaction was significant in the 100 µg/kg condition ($F_{1,13}=7.71$; $p < .016$; $p_c = .017$). Calmness ratings also declined after the higher THC doses ($F_{1,13}=6.05$ & 14.65 for the 200 and 300 µg/kg conditions, respectively; $p < .029$ & $.002$; $p_c = .025$ & $.017$), and *Drug by Time* interaction approached significance in all conditions ($F_{1,13}=4.33, 6.62$ & 5.10 for the 100, 200 and 300 µg/kg conditions, respectively; $p < .058, .023$ & $.042$; $p_c = .05, .017$ & $.025$).

In summary, subjects felt less alert, content and calm after smoking each THC dose, relative to placebo. The effects were strongest and persisted throughout the testing session after smoking the highest dose.

Table 5.6 Mean (SE) ratings of alertness, contentedness, and calmness by treatment condition and sampling time.

		0 $\mu\text{g/kg}$	100 $\mu\text{g/kg}$	0 $\mu\text{g/kg}$	200 $\mu\text{g/kg}$	0 $\mu\text{g/kg}$	300 $\mu\text{g/kg}$
Alert	$t=50$	78.3 (3.7)	59.0 (4.3)	76.0 (4.4)	63.9 (4.1)	80.0 (3.4)	57.7 (4.6)
	$t=175$	69.6 (5.0)	64.7 (4.9)	72.4 (5.5)	66.1 (3.6)	70.6 (4.3)	56.9 (6.2)
Content	$t=50$	79.3 (2.7)	66.2 (5.1)	77.6 (3.3)	73.6 (3.6)	78.3 (3.4)	67.2 (4.4)
	$t=175$	72.4 (3.4)	70.3 (4.3)	74.9 (4.4)	73.1 (3.5)	76.7 (3.2)	65.7 (4.9)
Calm	$t=50$	78.2 (4.2)	64.2 (5.2)	79.5 (4.4)	61.7 (6.8)	79.5 (3.6)	59.6 (5.8)
	$t=175$	72.5 (5.0)	72.4 (3.8)	75.9 (4.1)	71.3 (4.0)	77.5 (3.5)	70.5 (4.8)

Critical Tracking Test

As shown in Figure 5.9, mean λ_c measured 30 minutes after initiation of smoking diminished in a dose-related manner. Measured 3 1/4 hours after initiation of smoking, λ_c remained low after

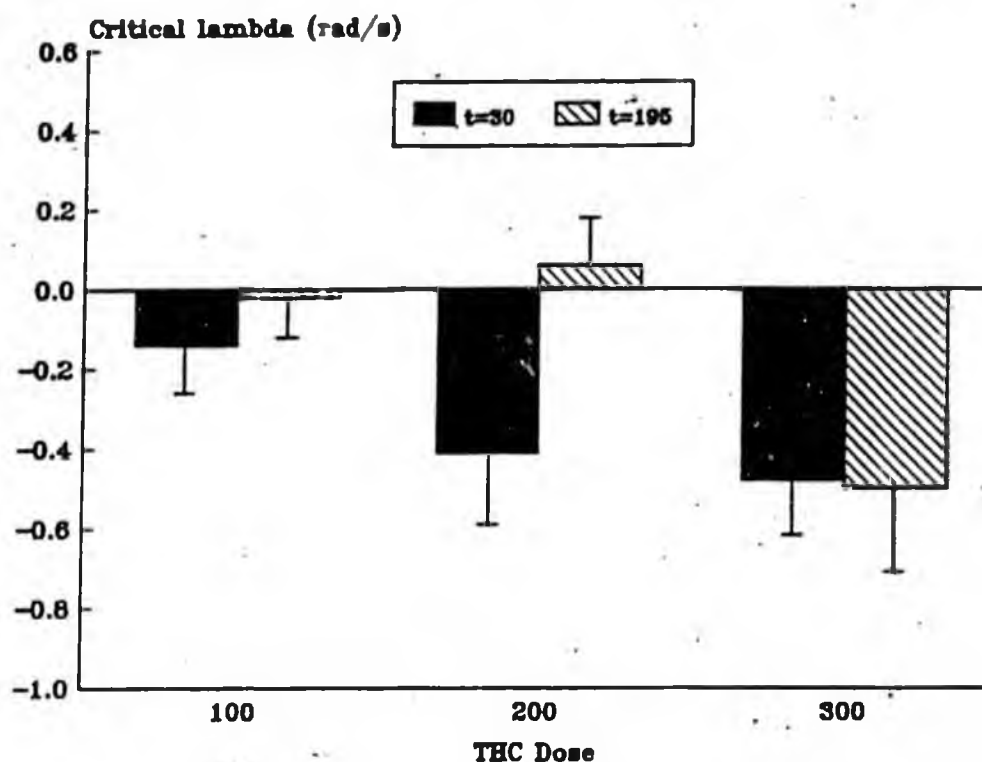


Figure 5.9 Mean (+SED) changes in λ_c in the critical tracking test by Drug and Time, relative to placebo.

the highest, but not the two lower doses. The lowest THC dose did not affect λ_c significantly. A nearly significant *Drug by Time* interaction was found in the 200 $\mu\text{g/kg}$ condition ($F_{1,13}=4.69$; $p<.05$; $p_c=.017$); i.e. that dose diminished λ_c shortly after smoking, but the effect dissipated

after three hours. The highest dose had a significant effect on λ_c ($F_{1,13}=9.03$; $p<.01$; $p_c=.017$), both shortly after smoking and three hours later.

Hand Steadiness Test

Hand steadiness diminished in relation to the dose after marijuana smoking (Figure 5.10). All doses produced significantly greater instability ($F_{1,13}=6.72, 13.05$ & 45.33 for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p<.022, .003$ & $.001$; $p_c=.05, .025$ & $.017$).

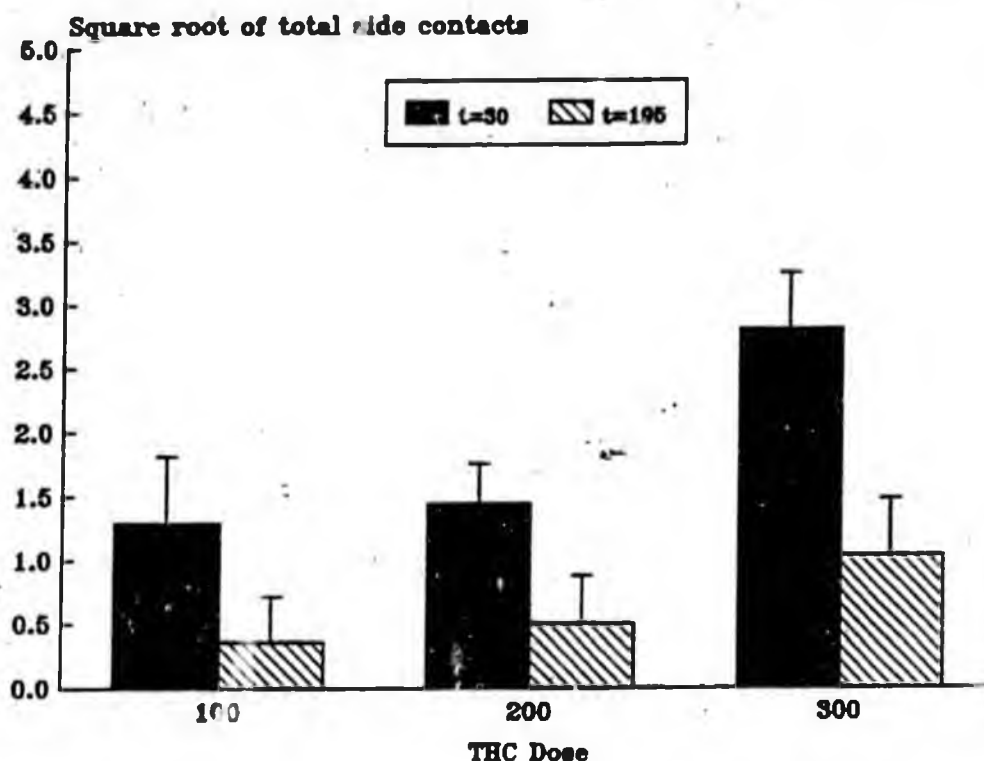


Figure 5.10 Mean (+SED), changes in the square root of total number of side contacts in the hand steadiness test by *Drug* and *Time*, relative to placebo.

Instability diminished after three hours, irrespective of the dose, resulting in significant *Time* effects in each drug-placebo comparison. *Drug by Time* interaction was not significant after the lowest dose, but approached significance after the higher doses ($F_{1,13}=4.51$ & 6.28 for the 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p<.053$ & $.026$; $p_c=.025$ & $.017$).

Body Sway

Mean values for the area circumscribed by the vertical vector of force (i.e. curve surface) are displayed in Table 5.7. Curve surface for subjects standing with eyes open (CS-O) increased after THC, relative to placebo. These effects approached significance ($F_{1,13}=4.67, 5.20$ & 4.95 for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p<.050, .040$ & $.044$; $p_c=.050, .017$ & $.025$). The greatest change from placebo to marijuana smoking was observed in the 200 $\mu\text{g/kg}$

condition, but only in the first test after smoking, resulting in a significant *Drug by Time* interaction ($F_{1,13}=9.23$; $p<.015$; $p_c=.017$).

Table 5.7 Mean (SE) curve surface (mm²) in the body sway test, both with eyes open (CS-O) and closed (CS-C), by treatment condition and sampling time.

		0 µg/kg	100 µg/kg	0 µg/kg	200 µg/kg	0 µg/kg	300 µg/kg
CS-O	<i>t</i> =50	29.2 (4.5)	38.7 (4.8)	26.7 (3.2)	42.3 (4.4)	32.5 (4.0)	39.1 (4.3)
	<i>t</i> =175	32.1 (3.8)	43.3 (5.4)	35.5 (5.7)	37.3 (4.8)	31.7 (4.1)	38.5 (3.5)
CS-C	<i>t</i> =50	27.9 (3.9)	53.0 (8.6)	33.7 (6.8)	55.2 (8.8)	36.1 (6.2)	57.7 (11.2)
	<i>t</i> =175	43.3 (6.5)	43.9 (8.3)	40.1 (7.7)	35.2 (5.4)	32.0 (5.5)	36.3 (5.6)

Mean curve surface for the subjects standing with eyes closed (CS-C), increased markedly in the first but not in the second test. The main effect of *Drug* approached significance ($p<.10$) in all three conditions, but *Drug by Time* interactions were significant for the two lower THC doses ($F_{1,13}=8.86$, 7.82 & 3.55 for the 100, 200 and 300 µg/kg conditions, respective y ; $p<.011$, .015 & .082; $p_c=.017$, .025 & .05). Analysis of variance of only the first measurements after smoking revealed that curve surface increased significantly after all THC doses, relative to placebo ($F_{1,14}=8.66$, 10.45 & 4.96 for the 100, 200 and 300 µg/kg conditions, respectively; $p<.011$, .006 & .043; $p_c=.025$, .017 & .05).

In summary, body sway was affected by all three THC doses, but this effect had dissipated three hours after smoking. Body sway parameters did not discriminate between different THC doses.

Heart Rate

ECG data could not be obtained from every subject in all conditions due to recurrent equipment failures. Though the problem was solved in time to obtain complete data from all 15 subjects in the highest dose conditions, analyses could only be conducted using data from 14 and 9 subjects in the middle- and low-dose conditions. The results of those analyses are summarized in Tables 5.8 and 5.9 for the standard and car following tests, respectively.

Both tables show that driving under the influence of THC is accompanied by shorter interbeat intervals (i.e. increased heart rates) and decreased variation both in the time domain (CV-IBI) and frequency domain between 0.07 and 0.14 Hz (PWR-HR). No clear dose-response relationship was found, except in mean IBI in the car following test.

With respect to the standard driving test, MANOVA showed that all THC doses produced significantly shorter IBIs relative to placebo ($F_{1,7}=9.07$, $F_{1,12}=7.63$ & $F_{1,13}=21.61$ for the 100, 200 and 300 µg/kg conditions, respectively; $p<.02$, .017 & .001; $p_c=.05$, .025 & .017). CV-IBI was significantly diminished after the two higher doses ($F_{1,12}=11.52$ & $F_{1,13}=28.90$ for the 200 and 300 µg/kg conditions, respectively; $p<.005$ & .001; $p_c=.025$ & .017), but not the lowest. PWR-HR, on the other hand, was significantly diminished by all THC doses ($F_{1,7}=18.62$, $F_{1,12}=12.20$ & $F_{1,13}=28.47$ for the 100, 200 and 300 µg/kg conditions, respectively; $p<.004$,

.004 & .001; $p_c = .025, .05 \text{ \& .017}$). Thus, the more specific measure, PWR-HR, which includes only one source of heart rate variability, is more sensitive to THC's effects than CV-IBI, a measure of total variability. In conclusion, both mean IBI and heart rate variability were significantly reduced by all THC doses. Since the latter measure is interpreted as a parameter of mental effort, it can be concluded that subjects needed to invest more effort in driving after smoking marijuana than after placebo.

Table 5.8 Mean interbeat interval time (IBI), coefficient of variation of IBI (CV-IBI), and power density of heart rate (PWR-HR) in the frequency band between 0.07 and 0.14 Hz during the standard driving test.

	N=9		N=14		N=15	
	0 $\mu\text{g/kg}$	100 $\mu\text{g/kg}$	0 $\mu\text{g/kg}$	200 $\mu\text{g/kg}$	0 $\mu\text{g/kg}$	300 $\mu\text{g/kg}$
IBI (ms)	792	721	805	743	797	709
CV-IBI (%)	5.97	4.91	5.40	4.48	5.41	4.15
PWR-HR	1114	666	877	570	862	499

With respect to the car following tests, MANOVA showed that mean IBI decreased significantly after the two higher doses ($F_{1,9}=9.66$ & $F_{1,7}=26.24$ for the 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p < .013$ & .001; $p_c = .025$ & .017), but not after the lowest. Mean IBI was always larger during the second ride relative to the first resulting in a significant *Time* effect in all conditions ($F_{1,9}=52.92$, $F_{1,9}=57.02$ & $F_{1,7}=79.07$ for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p < .001$, .001 & .001; $p_c = .05, .025$ & .017). *Drug by Time* interaction was not significant. This means that subjects were more relaxed when they performed the second than the first car following test, whether they had inhaled THC or placebo.

Table 5.9 Mean interbeat interval time (IBI), coefficient of variation of IBI (CV-IBI), and power density of heart rate (PWR-HR) in the frequency band between 0.07 and 0.14 Hz during the car following tests. Data from the first and second tests are separated by a slash.

	N=9		N=14		N=15	
	0 $\mu\text{g/kg}$	100 $\mu\text{g/kg}$	0 $\mu\text{g/kg}$	200 $\mu\text{g/kg}$	0 $\mu\text{g/kg}$	300 $\mu\text{g/kg}$
IBI (ms)	739/821	697/801	778/859	697/790	750/841	646/755
CV-IBI (%)	5.48/6.31	4.69/4.86	5.18/5.83	3.85/5.25	4.67/5.41	4.05/4.57
PWR-HR	983/1347	608/807	909/1094	438/967	726/993	405/633

CV-IBI was diminished after smoking THC in each condition relative to placebo and these effects were only nearly significant ($F_{1,9}=7.09$, $F_{1,9}=8.40$ & $F_{1,9}=6.21$ for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p < .026$, $.018$ & $.041$; $p_e = .025$, $.017$ & $.05$). As in the standard test, PWR-HR was more sensitive to drug induced variability reduction; MANOVA showed that PWR-HR was significantly affected by all doses ($F_{1,9}=10.46$, $F_{1,9}=6.04$ & $F_{1,9}=9.01$ for the 100, 200 and 300 $\mu\text{g/kg}$ conditions, respectively; $p < .010$, $.036$ & $.020$; $p_e = .017$, $.05$ & $.025$). Though PWR-HR was generally higher in the second than in the first test, a significant *Time* effect was only found in the 200 $\mu\text{g/kg}$ condition ($F_{1,9}=8.58$; $p < .0168$; $p_e = .017$). Though subjects felt more relaxed in the second car following test than the first, as measured by IBI, both rides required much the same mental effort, as measured by heart rate variability.

Intra-Subject Relations between Variables

The average intra-subject correlation between [THC] and perceived "high" was, as in the previous study, very high ($R=0.90$; $p < .01$). The correlation between measured SDLP and [THC] measured before driving was 0.63 ($p < .05$), individual correlations ranging from $-.14$ to $.96$; between SDLP and [THC] measured after driving 0.57 ($p < .05$), individual correlations ranging from $-.10$ to $.92$. These correlations closely resemble those found in the previous study where SDLP correlated 0.59 and 0.42 in the first and second tests, respectively. This means that the change in driving performance, as measured by SDLP in the standard driving test, is, within individuals, moderately related to the existing [THC]. Performance in the car following test was not significantly correlated with [THC].

The square root of the number of side contacts in the hand steadiness test was significantly correlated to [THC] and perceived "high" (both $r = .66$; $p < .01$). SDLP scores were significantly related to hand instability measured before driving ($r = .52$; $p < .05$), but not with scores obtained after driving ($r = .35$; ns). None of the other laboratory performance measures were either related to plasma concentrations of the drug or to driving performance.

In summary, as [THC] varied within a given individual so did that individual's perceived "high", hand steadiness and SDLP or road tracking error in the standard test.

Inter-Subject Relations between Variables

Relationship between Drug Levels and Performance. Inter-subject correlational analysis between [THC] and [THC-COOH] on one hand and performance parameters on the other failed to reveal any consistent relationship. The most consistent, yet still not strong, relationships found were those involving [THC] on one hand and mean speed in the standard driving test and CTT performance in the laboratory on the other (Table 5.10). Correlations with Log [THC] were generally the same as with [THC]; those with [THC-COOH] were, except a few, generally lower than those with [THC].

The correlations presented in Table 5.10 were derived from raw scores. Another question is whether changes in performance from corresponding placebo levels were related to prevailing [THC]. Correlational analyses showed, however, that these correlations were even smaller than those with the raw scores. Thus, neither [THC] nor [THC-COOH] predicted performance or performance impairment.

Table 5.10 Correlations between [THC] and raw performance scores in the marijuana conditions. If performance was measured only once (like SDLP), then the same scores were correlated with [THC] values as measured before and after the driving tests.

	100 $\mu\text{g/kg}$		200 $\mu\text{g/kg}$		300 $\mu\text{g/kg}$	
	1 st	2 nd	1 st	2 nd	1 st	2 nd
<u>Standard Driving Test:</u>						
SDLP	-.33	.02	-.13	.09	-.25	-.18
SP	-.26	-.18	-.50	-.20	-.55*	-.61
SDSP	-.22	-.14	-.34	-.32	-.20	-.15
<u>Car Following Test:</u>						
Adjusted RT	-.18	.20	.41	.24	.04	.05
Headway	.32	.15	.39	-.02	.18	.05
CV-Headway	-.21	.40	.27	.43	-.29	-.09
<u>Laboratory Tests:</u>						
λ_c	.63*	.31	.48	.27	.45	.18
Side Contacts	.45*	-.38	.54*	.32	.44	.50
OC-O	-.25	-.13	.43	.02	-.38	.06
OC-C	-.05	-.02	.36	-.25	-.26	-.37

Relationship between Driving Impairment and Willingness to Drive. In general, the average road tracking impairment in the standard test of those subjects, who indicated before the driving tests commenced that they would normally not have driven under the imagined circumstances, was greater than of those who would have driven. Statistically, these effects were neither significant when willingness to drive for "unimportant though gratifying" reasons was used as the grouping factor, nor when willingness to drive for "urgent" reasons was used. This was probably due to the small number of subjects who would not have driven under the former condition, and would have driven under the latter condition. When willingness to drive for "important, but avoidable" reasons was used as the grouping factor, no significant difference in road tracking impairment was found between the groups after the highest THC dose; but, following the two lower doses, subjects who would not have driven were significantly more impaired than those who would have driven ($F_{1,13}=10.38$ & 6.93 for the 100 and $200 \mu\text{g/kg}$ conditions, respectively; $p < .007$ & $.021$; $p_c = .017$ & $.025$).

Relationship between Driving Performance and Other Measures. In the previous study, SDLP was moderately correlated with λ_c from the CTT. The present study showed the same pattern of correlations i.e. $-.41$ and $-.50$ in the $100 \mu\text{g/kg}$ condition, $-.49$ and $-.37$ in the $200 \mu\text{g/kg}$ condition, and $-.58$ ($p < .05$) and $-.54$ ($p < .05$) in the $300 \mu\text{g/kg}$ condition. Despite the interesting theoretical aspects of these consistent results, correlations of such magnitude are generally considered too low for predictive purposes. Performance in the car following test was not significantly correlated with λ_c . Neither hand steadiness nor body sway were related to performance in the standard driving test or the car following test.

As in the previous study, repeated measures analysis of SDLP in the standard test was repeated with reported *Frequency* of cannabis smoking as a between-subjects factor. MANOVA failed to reveal any significant effect.

The relationship between test performance and previous experience of driving under the influence could not be determined: too few indicated having driven in that condition more than a few times (Table 5.1).

DISCUSSION

The conservative approach of administering THC according to an ascending, placebo controlled, dose series achieved its purpose of ensuring the subjects' safety. All were able to complete the series without suffering any untoward reaction while driving. However it is fair to ask whether this approach could have conceivably biased the results toward minimization of the drug's effects. We have three reasons for believing that this was not the case. Driving performance during successive repetitions of the standard highway driving test after placebo smoking was relatively constant, so that the reference for judging effects of every dose's effects was essentially the same. The measured mean changes in SDLP after the lowest and highest THC doses in the present study were about what they had been in the previous study where dose orders were counterbalanced. Finally, there was apparently one dose sequence effect on car following performance but it was the opposite of any which could bias the results toward minimizing THC's effects. Such a bias would have existed if the subjects choose to operate more cautiously as doses ascended. Yet as described below, they appeared to operate most cautiously in the car following test after the lowest dose. If any bias existed in this test it was toward maximizing, rather than minimizing THC effects.

Road tracking performance in the standard test was impaired in a dose-related manner by THC. The 100 $\mu\text{g/kg}$ dose produced a slight elevation in mean SDLP (1.1 cm), albeit nearly significant. The 200 $\mu\text{g/kg}$ dose produced a significant elevation (1.8 cm), of dubious practical relevance. The 300 $\mu\text{g/kg}$ dose produced a highly significant elevation (2.9 cm) which may be viewed as practically relevant but unexceptional in comparison with similarly measured effects of many medicinal drugs.

For example, diazepam given for one week in its lowest therapeutic dose (5 mg, thrice daily) caused anxious patients to drive with a mean SDLP about 7 cm higher than their premedication baseline (Van Laar *et al.*, 1992). Furthermore, THC's effects on SDLP were, after the 100, 200 and 300 $\mu\text{g/kg}$ doses in this study, about the same as those of BACs = 0.02, 0.04 and 0.06 g% according to the empirical equation described by Louwerens *et al.* (1985, 1987). The comparison reinforces our impression of the relevance of SDLP changes after THC. The two lower doses produced elevations less than the lowest BAC associated with intoxication and an elevated risk of causing a traffic accident (i.e. 0.05 g%; Borkenstein *et al.*, 1964; Council on Scientific Affairs, 1985), whereas the highest dose, and one preferred by the drug's users, produced a marginally greater elevation. But even this change in SDLP can not, by itself, be taken to indicate exceptional impairment.

It is often reported that subjects compensate for THC's adverse effects on driving abilities by operating at slower than normal speeds, especially through curves or slaloms. Our subjects were instructed to maintain a speed of 95 km/h (58 mph) unless compelled to slow down for safety reasons. Following marijuana smoking they drove with an average speed that was only

slightly lower (maximum, 1 km/h or 0.6 mph) than after placebo and very close to the prescribed level. They apparently felt that it was within their capability to safely perform this relatively simple task while operating at the normal highway speed.

The objective of confirming results obtained in the previous closed highway study was achieved in this one. It should be recalled that subjects' SDLPs were measured twice on the former occasion; i.e. in 22 km (13.7 mi) trials beginning 40 and 100 minutes after the initiation of smoking. The timing of the second trial most closely corresponded to that in the present study so their respective results will serve as the basis for comparison. Mean SDLP elevations after the lowest and highest doses differed little between the two studies: 100 $\mu\text{g/kg}$, 1.4 and 1.1 cm; and 300 $\mu\text{g/kg}$, 2.4 and 2.9 cm, respectively. Mean SDLP elevations after the 200 $\mu\text{g/kg}$ dose differed somewhat between studies, being 3.3 cm in the first case and 1.8 in the second. Yet the results of the first study were anomalous in two respects. Not only did the former group's reaction in the 2nd trial exceed that in the 1st trial following the 200 $\mu\text{g/kg}$ dose, it was also greater than their 2nd trial reaction after the 300 $\mu\text{g/kg}$ dose. Both results were in contradiction to plasma THC concentrations measured at these times. Thus the peculiar elevation in mean SDLP during the 2nd trial after the intermediate dose was probably a consequence of sampling error. That it was not replicated in the present study should dispel any notions to the contrary.

The car following test was implemented for the first time in the present study. In it, subjects maintained a headway of 45-50 m (148-164 ft) while driving in the successive placebo conditions. They lengthened mean headway by 8, 6 and 2 m (26.2, 19.7 and 6.6 ft) in the corresponding THC conditions after 100, 200 and 300 $\mu\text{g/kg}$, respectively. The initially large drug-placebo difference and its subsequent decline is a surprising result in need of an explanation. If one considers that changes in headway after THC results from impaired distance perception, the inverse relationship between administered dose and mean headway defies explanation. But if one considers these differences as the results of the subjects' caution in approaching the task under the influence of THC on successive occasions, another explanation seems plausible.

Performing the car following test in the company of investigators while under the influence of THC was a novel experience for all subjects. Neither the investigators nor the subjects could predict how the latter would be able to operate the vehicle. The former were somewhat apprehensive and it would not be surprising if the latter were also, particularly, on the first occasion the test was performed after THC inhalation. Subjects were required to match their vehicle's speed with that of the preceding vehicle's and so were unable to reduce velocity as a compensatory action. They could however maintain a longer headway and thereby slightly increase their margin of safety which might be needed if THC retarded their reactions. We believe they did so after receiving the lowest THC dose. When nothing untoward happened and the subjects' confidence in their ability to control the vehicle grew, they apparently tended to diminish headway after each of the succeeding doses so that it came progressively closer to the distance measured after all of the placebo treatments. Thus our explanation for the initial difference between headways maintained after THC and placebo, and why it diminished in subsequent pairs of these conditions, is that the subjects' caution was greatest the first time they undertook the test under the influence of THC and progressively less thereafter.

The only other plausible explanation is that lower THC doses induce a greater sense of caution than higher doses. There is of course no way to determine which of the two explanations is valid from the results of this study. But the fact that the subjects reported feeling less calm and content as the doses increased seems to contradict the notion that they simultaneously

became less cautious. Whatever explanation is favored, it is clear that large doses of THC have little effect on mean headway during car following.

Reaction time to changes in the preceding vehicle's speed increased following THC treatment, relative to placebo. The administered THC dose was inversely related to the change in reaction time, as it was to headway. Mean increases in reaction time were 0.55, 0.41 and 0.19 s following the 100, 200 and 300 $\mu\text{g/kg}$ dose, respectively. However, reaction time data were confounded with headway. That is, increased reaction times were partly due to longer headway. Statistical adjustment for this confounding resulted in smaller and non-significant increases in reaction time following marijuana treatment, the greatest impairment (0.32 s) being observed in the first test following the lowest THC dose. Headway variability followed a similar pattern as mean headway and reaction time; the greatest impairment was found following the lowest dose.

A secondary objective of the study was to determine whether degrees of impairment would correlate between the two tests in a manner indicating a general influence of THC on driving behavior. The results obtained in this study showed that this was not the case; a significant dose-related impairment was found with road tracking, but not with car following. Test duration can not have been the critical point, since the standard test in the previous study was of the same duration as the present car following test.

The car following test was both less sensitive and reliable than it could be following the removal of certain procedural flaws. Intervals between successive maneuvers were practically constant and the preceding vehicle's deceleration was both abrupt and stereotyped. Thus the occurrence and nature of the maneuvers were highly predictable for the subjects.

Greater irregularity in both the timing of maneuvers and the profile of velocity changes would probably increase the sensitivity of the test. After the fact we recognized that the indirect and discontinuous method used for measuring headway produced a degree of error variance which appreciably reduced the reliability of these data. Equipment has become available since the initiation of this study which now makes it possible to measure headway directly and continuously (i.e. an inexpensive pulsed laser reflection recording system). Use of this equipment should increase the reliability of headway measurement in future applications of this test. Finally, the greatest source of error variance was the procedure of allowing the subject to assume, within limits, whatever headway he/she chooses. Whether this is a flaw or not depends upon one's desire to measure or control headway at the beginning of maneuvers. However the subject's choice of headway is certainly a factor which inflates reaction time error variance. Adjusting the data statistically to overcome the confounding effect of headway on reaction time is only a partial solution to the problem. We would probably have been wiser to strictly enforce headway control in order to increase the reliability of reaction time measurements and their sensitivity to drug effects.

Without trying to minimize the impact of procedural errors on the data, it is doubtful whether any flaw or all in combination seriously obscured a practically important THC effect. SDLP recorded in the standard highway driving test was about as sensitive to low-dose THC effects as any of the traditional laboratory performance measures taken in the study. Moreover the average intra-subject correlation between [THC] and SDLP was as high or higher than any measured between the drug's plasma concentration and another performance variable. This relationship could not have been measured if SDLP were not one of the most sensitive parameters known for measuring the effects of THC. The fact that car following performance

was less sensitive does not mean that it would have failed to reveal effects of practical importance if these truly existed. SDLP showed no such effects even after the highest dose.

The reasons why SDLP and not car following performance showed the modest impairing effects of THC may have less to do with the inadequacy of the latter test than to the difference between what the two tests measure. SDLP is controlled by a very fast and high capacity human information processing system which operates in a wholly "automatic" manner. That is, outside of conscious control. The process is relatively impervious to environmental changes as shown again by the high reliability of SDLP under repeated placebo conditions in the present study. It is, however, highly vulnerable to internal factors that retard the flow of information through the system. THC and other drugs are among these factors. When they interfere with the process to elevate SDLP there is very little the afflicted individual can do in way of compensation. Car following performance on the other hand depends upon more discrete perception of events leading to a conscious decision, a response selection and its execution. Performing the test involves far more sustained attention and conscious effort than does road tracking in the standard test. Because car following performance is under conscious control and well within the speed limitations of "cognitive" compensatory mechanisms it is possible for individuals to recognize their deficiencies and correct them by effort that increases attention. In short, any deficiencies that THC might have otherwise produced may have been overcome by the subjects' compensatory effort. The cost of effort focused on accomplishing a task is however accompanied by less capacity left for performing another in parallel. The subjects indeed related that their investment of effort in the first car following test increased with the administered dose, and relative to corresponding placebo levels, more so than in the standard driving test. Though these differences were not statistically significant in either case, they were in line with the significant reduction in heart rate variability, that occurred independently of mean rate changes after every THC dose, including the lowest. Together the findings support the premise that THC increases the requirement for compensatory effort during car following which maintains constant performance, but possibly reduces the capacity for undertaking any activity in parallel. Coupled with THC's reputedly adverse effect on the ability to divide attention between tasks performed simultaneously (Smiley, 1986), the net effect might constitute a more serious impediment to safe driving than any observed in this study. It will be interesting to explore this possibility in further research.

Subjects' report of their willingness to drive under specified conditions of different urgencies were similar to those in the previous study. The lower the administered THC dose, and the more urgent the reason for driving, the more subjects declared that they would be willing to drive. Furthermore, there was a tendency for subjects who would normally not have driven to be more impaired in road tracking than those who would. Apparently these subjects recognized their respective degrees of impairment while under the influence of every THC dose. This is supported by the subjects' judgments of their own driving quality which changed in a realistic dose related manner after marijuana smoking.

Critical tracking and hand steadiness tests were more sensitive to THC induced impairment than in the previous study. This confirms our impression that the earlier CTT version was poorly conceived. It also indicates that applying the correct procedures for measuring hand steadiness is very important; i.e. subjects should not be allowed to rest their hand on the table while performing the test. Both tests showed dose-related impairment shortly after cessation of smoking. When the tests were repeated three hours later, hand instability was still present though to a lesser degree. The effect of the highest but not the two lower doses on CTT performance persisted undiminished from the first to the second test, or over a 3-hour period after smoking.

These results partially confirm results obtained by Sharma and Moskowitz (1975). They found that THC 200 $\mu\text{g/kg}$ had a virtually undiminished effect on tracking performance for up to four hours. The time course of postural instability after marijuana smoking followed a different profile. All THC doses increased body sway to the same extent shortly after cessation of smoking but none did three hours later.

An important practical objective of this study was to determine whether degrees of driving impairment can be accurately predicted from either measured concentrations of THC in plasma or performance measured in potential roadside "sobriety" tests of tracking ability or hand and posture stability. These results, like many reported before, indicate that none of these measures accurately predicts changes in actual driving performance under the influence of THC. CTT performance came closest but even its correlation with driving was only $r = .50$. However, that test might well be included in a battery of similarly predictive tests, measuring different abilities, to collectively yield a single more predictive index of impairment.

CHAPTER 6 - MARIJUANA, ALCOHOL AND URBAN CITY DRIVING

INTRODUCTION

In the previous study THC doses of 200 $\mu\text{g/kg}$, and higher, produced significant impairment of road tracking, but not car following, performance. The lowest dose, 100 $\mu\text{g/kg}$, failed to produce significant effects on road tracking, but increased headway during car following. The latter observation was interpreted as the result of increased caution, since mean headway did not change following subsequent higher THC doses. It therefore seems that low doses of THC do not, or only slightly, impair driving performance. Yet normal driving is far more complex and varied than simply maintaining a safe lateral position and headway during uninterrupted travel on a highway. A THC dose having no effect on these parameters might still impair driving performance in more complex urban driving situations.

There were logical and safety reasons for restricting the THC dose in the third driving study to that which had failed to produce significant impairment in the second. Both the 200 and 300 $\mu\text{g/kg}$ doses impaired performance on the highway and could be expected to do so again in the urban driving environment. There the consequences of high dose THC effects are more difficult to predict and therefore safely control. The 100 $\mu\text{g/kg}$ dose had some significant effects on the highway but none that could rightfully be called dangerous. This dose might still cause impairment in more complex city driving, but the risk was judged to lie within the realm of the acceptable. For that reason it was given to a group of regular cannabis users, along with placebo in the present study.

For comparative purposes another group of regular alcohol users were treated with a modest dose of their preferred recreational drug, and again placebo, before undertaking the same test. It was hoped that this addition would not only verify the sensitivity of the test but also allow a comparison between effects of recreational drugs that Dutch society considers as illicit and licit when both are given in relatively low doses. The comparison was not designed to show that one drug is "safer" for use by drivers than the other. Surely neither are safe when consumed before driving in high doses. However if respective low dose effects are comparable then one would be justified to conclude that THC may be considered as posing a traffic safety hazard which is in some respects similar to alcohol's.

The only study that has been conducted in actual traffic before this program started was also a city driving study. Klonoff (1974) assessed the effects of two THC doses, 4.9 and 8.4 mg THC which are equivalent to 70 and 120 $\mu\text{g/kg}$ for a 70 kg (154 lb) person. Aspects of subjects' driving performance were scored by a professional examiner using an abbreviated version of the British Columbia Department of Motor Vehicles' standard driver's licencing test. The results showed that subjects performed less competently when under the influence of the highest, but not the lowest, dose. In particular, they scored lower on judgement and concentration scales. Moskowitz (1985) and Smiley (1986) criticized the method of measuring driving performance on the grounds that the examiners' reliability was never determined and that the scoring instrument had never been shown to provide measures related to driving safety. Smiley questioned, for example, whether ratings of posture and irritability are relevant for good driving performance. These are sound criticisms but one has to assume that Klonoff's approach should

have been sensitive to serious driving performance impairment, related to safety, if it had in fact occurred.

Two scoring methods were employed in the present study. The first was in fact a method similar to that applied by Klonoff; i.e. the driving instructor acting as the safety controller during the tests retrospectively rated the driver's performance using a standard scale. This method has been applied previously to show the impairing effects of alcohol (De Gier, 1979) and diazepam (De Gier *et al.*, 1981) in similar situations. Jones (1978) criticized this use of driver licensing assessment procedures. She opposed the lack of precise definitions for many of the behaviors rated by examiners and the requirement for rating all of them at once. In contrast to this "molar" approach, she developed a more "molecular" one for evaluating driving proficiency. Her method was also applied in the present study. It involves the employment of specially trained observers who apply simple and strict criteria for recording when the driver makes or fails to make each in a series of observable responses at predetermined points along a chosen route.

The professional observer's global ratings are inherently less reliable than the scores obtained by the molecular rating scheme. Still the molar approach has some advantages. The professional's experience with many drivers operating in all traffic situations provides him with the ability to integrate far more information than is possible to obtain from limited performance sampling. He has internalized a broad concept of acceptable driving performance and applies more flexible criteria for judging when it is unsafe within a particular test situation. Of course the danger that a professional's biases may influence his judgments needs to be overcome by training and his adherence to structured rules which are specific for the investigation. But when this is done, he may provide a more valid estimation of the overall safety of a subject's driving performance. If this were not the case it would be difficult to explain how every developed society relies upon the professional's and not a traffic scientist's opinion of whether a particular individual should be licensed to drive.

The objective of this study would be satisfied in one way if neither observer rating method yielded a significant difference between driving performance after 100 $\mu\text{g/kg}$ THC and placebo. These results would confirm those obtained in the previous study by indicating that the selected dose lies below that capable of impairing driving performance. This conclusion would only be warranted, however, if it could be shown that the tests were sensitive enough to measure significant driving performance impairment after alcohol relative to placebo. If that were not the case, test insensitivity could be judged as the factor responsible for negative results, rather than the lack of a THC effect.

The objective would be satisfied in another way if either or both rating methods showed significant impairment after THC. Such results would indicate that any dose likely to be consumed before driving should be considered hazardous, regardless of whether alcohol's effects were the same, more or less. In the event that significant impairment occurred after THC, we were prepared to determine its relationship with plasma concentrations of THC and THC-COOH measured at about the same time.

METHODS

Subjects

Two groups of sixteen new subjects apiece, equally comprised of men and women, participated in the study. The groups will be referred to by the alcohol and marijuana group. Subjects in both groups were recruited according to the same inclusion/exclusion criteria as before with one exception. Subjects in the alcohol group were regular users of alcohol but not marijuana (see below). All subjects were individually trained to perform the city driving test in a preliminary "dress rehearsal" and were familiarized with the other tests and questionnaires.

Plasma analyses after conclusion of the study showed that two males' plasma contained neither THC nor THC-COOH in any sample. It was concluded that these subjects had not inhaled smoke so their data were excluded from further analyses.

Characteristics of the remaining subjects are given in Table 6.1. Except for the reported incidence of marijuana use, there were no significant differences between any of the groups' characteristics.

Table 6.1 Mean $\pm$ SD (range) of subjects' characteristics.

	Alcohol Group	Marijuana Group
N	16	14
Age (yrs)	23.7 $\pm$ 2.7 (20-28)	22.4 $\pm$ 3.5 (20-34)
Weight (kg)	68.1 $\pm$ 7.9 (60.0-86.1)	67.9 $\pm$ 8.9 (54.0-90.5)
Weight (lb)	150.1 $\pm$ 17.4 (132.2-189.8)	149.7 $\pm$ 19.6 (119.0-199.5)
# Alcoholic Drinks/Week	8.3 $\pm$ 6.2 (1-21)	10.6 $\pm$ 8.4 (1-30)
Smoking Experience (yrs)	0	3.1 $\pm$ 2.1 (1-10)
# Joints/Month	0	2.3 $\pm$ 2.5 (1-8)
Driving Experience (yrs)	4.8 $\pm$ 2.6 (2-10)	4.1 $\pm$ 3.3 (2-15)
Driving Experience (km x 1000)	35.3 $\pm$ 28.3 (5-90)	28.6 $\pm$ 45.7 (6-180)
Driving Experience (mi x 1000)	21.9 $\pm$ 17.6 (3-56)	17.8 $\pm$ 28.4 (4-112)

Design, Doses and Administration

The study was conducted according to a mixed between-groups within-subjects design, one group drinking alcohol and placebo alcohol and the other smoking marijuana and placebo marijuana.

Alcohol was administered as 99.8% ethanol mixed with orange juice and Grand Marnier essence to a volume of 250 ml. The dose was 0.43 g/kg lean body mass (On average, this resulted in a dose of 0.36 g/kg body weight in males, and 0.31 g/kg in females). Lean body mass was calculated by subtracting the percentage of fat, determined by skinfold thickness (Durnin and Womersley (1974), from total body weight. The dose was chosen to yield a Blood Alcohol Concentration (BAC) approaching 0.05 g% when the driving test commenced 45 minutes after onset of drinking. Subjects were instructed to fast 2½ hours before drinking and to ingest the dose within 5 minutes. Alcohol in the subjects' expired air was monitored using a Lion S-D3 Breath-Alcohol Analyzer to ensure that subjects would not drive with BACs that were higher than 0.05 g%, which is the legal limit in The Netherlands.

Marijuana and placebo cigarettes were obtained from the same source as before. The subjects were treated on separate occasions with THC doses of 0 and 100 $\mu\text{g/kg}$. Placebo cigarettes were prepared by ethanol extraction of THC from the plant stock. Marijuana cigarettes were prepared from batches containing 1.77% THC. Cigarettes were cut to different lengths to provide the doses appropriate for the individuals' body weights. Cigarettes appeared identical in both treatment conditions and were smoked through a plastic holder in a fashion determined by the subject but with the constraint that smoking had to be finished within five minutes. After cessation of smoking, cigarettes were retained for subsequent gravimetric estimation of THC consumed. These analyses revealed that the average ($\pm\text{SD}$) amount of consumed THC in the marijuana condition was 6.9 (± 1.0) mg or 101 (± 6) $\mu\text{g/kg}$.

Half of both groups received the treatments in the same order, the others, in reverse order. The driving instructor and observer who rated subjects' driving performance were blind regarding both the administered drug (active or placebo) and the subject's group membership.

Testing Procedures

Upon arrival at the laboratory, subjects were tested for the presence of alcohol in breath. Subjects in the marijuana group were further tested for the presence of cannabinoids and other drugs in urine (as described in Chapter 2). If cannabinoids were found, a blood sample was taken for later verification of the presence of THC. The schedule of further activities on test-days is shown in Table 6.2.

Table 6.2 Schedule of activities on test-days.

Alcohol Group		Marijuana Group
Relative Time (min)	Activity	Relative Time (min)
0-5	Drinking / Smoking	0-5
30-35	Hand Steadiness and Time Perception Tests	15-20
35-40	Blood Sampling and Questionnaires	20-25
45-95	City Driving Test	30-80
95-100	Blood Sampling and Questionnaires	80-85
105-110	Hand Steadiness and Time Perception Tests	90-95

Driving Test and Scoring Methods

Driving tests were conducted in daylight over a constant 17.5 km (10.9 mi) route within the city limits of Maastricht (population ca. 115,000). The route was constructed through business and residential areas on 2-lane undivided streets and included a 6 km (3.7 mi) 4-lane divided segment on a major cross-city thoroughfare (Figure 6.1). Subjects drove their placebo and active drug rides through heavy, medium and low density traffic on the same day of the week, and at the same time of day. Maneuvers included left and right turns at some intersections and driving through others, left and right lane changes, and responding to traffic control devices (i.e. stop signs and signals). There was one special maneuver, repeated twice; i.e. executing a Y-turn on a residential street. A schematic representation of the standard route is shown in Figure 6.1 and the symbols used for maneuvers and road densities are shown in Table 6.3 (the performance variables will be discussed below).

Driving tests were conducted in a dual control 2-door sedan (Volkswagen Golf) normally used for driving instruction/examination. Two persons accompanied the subject: a licensed driving instructor sitting in the front passenger's seat and an trained observer sitting in the center of the rear seat. The former had access to redundant controls and his primary responsibility were controlling safety and giving the route instructions; and, to rate the driver's performance retrospectively (below) after the ride. The observer in the rear seat scored the driver's performance "on-line" and timed the duration of the ride.

As described above, two different procedures were employed for determining a driver's proficiency from observer ratings; i.e. the molecular and the molar methods. The major difference between both methods is that performance variables are repeatedly measured on-line at different points along the route using the molecular approach; and, only once, retrospectively, in the molar approach.

The molecular approach was adopted from Jones (1978) who simplified the scoring of driving behavior so that the trained observer, sitting in the rear seat, attends to only one event at a time. The events observed at specific points along the route are only few aspects of total driving behavior. Thus, the observer is enabled to attend completely to the occurrence of each event in sequence while ignoring all other behavior which would in any case vary between tests. All aspects of a maneuver, such as a left turn, will be scored a number of times over the course of the whole route, but never more than a single aspect at a given moment.

Jones defined twelve aspects, called performance variables (Table 6.3), which were repeatedly scored, 156 times in total, at specific points along the route. The route was designed to fulfill Jones' requirements concerning maneuvers and road densities. The scoring sheet consisted of the schematic route map with symbols indicating the driver behavior to be scored at each point (reproduced in Figure 6.1 with symbology defined in Table 6.3). The observer moved his finger along the route and attended only to the behavior indicated, comparing it with a predefined standard of performance, and circled (if correct), crossed (if wrong) or underlined (if not observed) the symbol. If, for example, the observer were to score *Path* (P) at a lane change (↗) the correct response was defined as: 1. maintains straight path while scanning, 2. signals before the lane change, 3. steers smoothly with gradual angular movement, 4. straightens vehicle in new lane, and 5. cancels signal. If the driver failed to make one or more of these responses *Path* was scored as fail, otherwise pass. A complete description of all maneuvers is included in Appendix B.

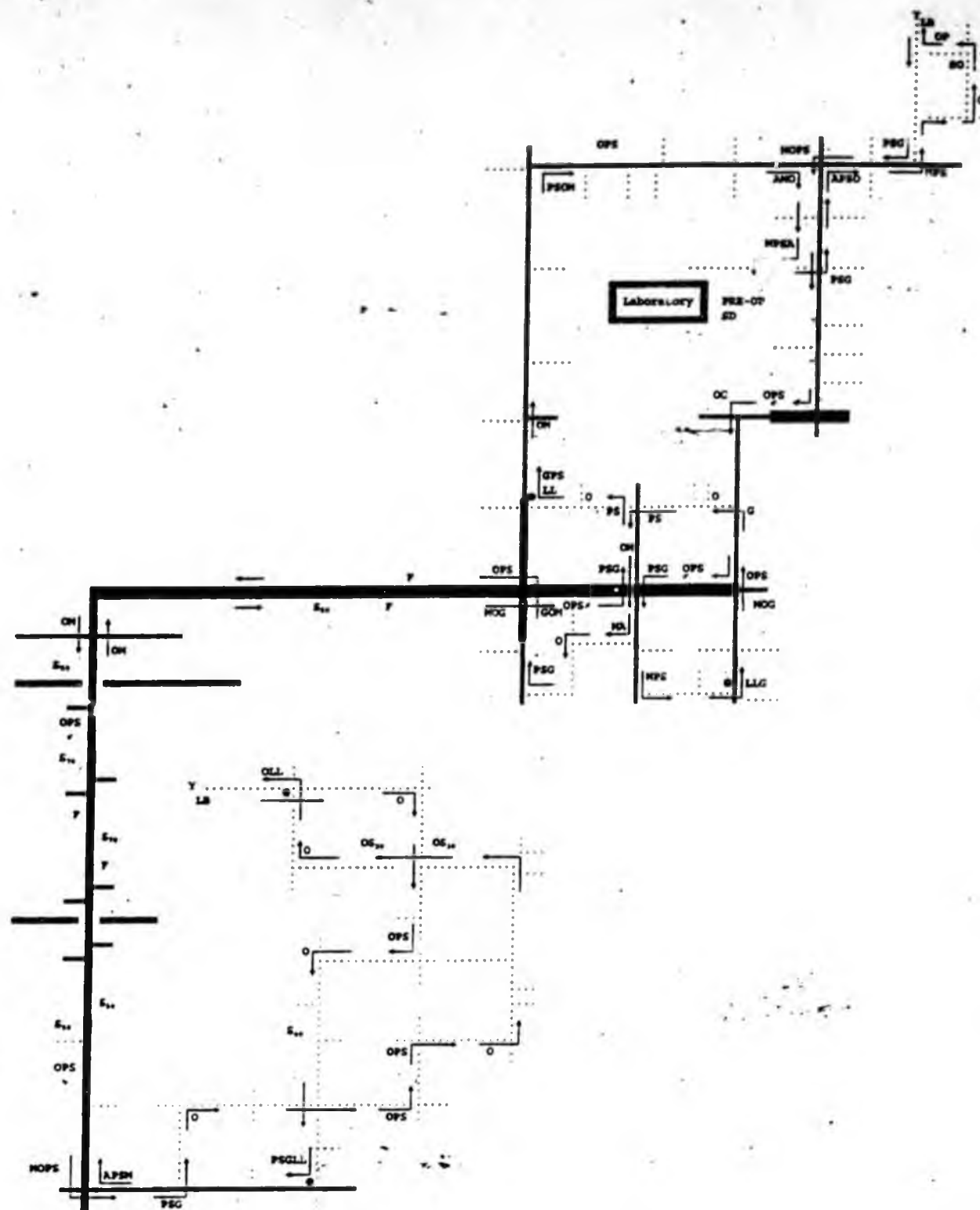


Figure 6.1 Scoring sheet for molecular approach, consisting of the schematic route map with symbols indicating the driver behavior to be scored at each point (for explanation of the symbols, see Table 6.3).

Table 6.3 Maneuvers, road densities, performance variables and their symbols.

Maneuvers:		Road Density:	
Right Turn			Heavy Density Traffic
Left Turn			Medium Density Traffic
Driving Through			Low Density Traffic
Right Lane Change			
Left Lane Change			
Y-Turn			
		Halt-Line: ●	

Performance Variables:		# of times scored:
O	Observation	38
G	Gap Acceptance	14
M	Mirror Check	16
P	Path	30
S	Speed	39
A	Approach at Intersection	5
F	Following Distance	4
LL	Limit Line (stopping at halt-line)	4
L	Location at Y-Turn	2
B	Backing at Y-Turn	2
Pre-op	Pre-operations	1
SD	Shut-Down	1

At the end of the test, the *Total Score* was calculated by summing all passing items and dividing by the total number of observed items. Subscores were also calculated for *Observing*, *Car Control*, *Judgment* and *Other* (Table 6.4). Three additional scores were obtained from the driving instructor; 1. *Instructor Control*, the number of times the instructor took control, either orally or physically, 2. *Hazard Score*, the number of times the driver responded correctly to hazards divided by the total number of hazards encountered, and 3. *Instructions*, the number of times the driving instructor had to repeat a route instruction. All scores, except *Instructor Control* and *Instructions*, were expressed as per cent correct.

The molar approach required the driving instructor to retrospectively rate the driver's performance using a shortened version of the Royal Dutch Tourist Association's (ANWB) Driving Proficiency Test (Appendix B). This instrument is normally applied for practical purposes; e.g. remedial training, driver's licensing, qualifying for a reduction in insurance premiums, etc. Items that did not apply to the driving test, e.g. those regarding railway crossing and special maneuvers like driving backwards and parking, were dropped from the normal list. In total, 108 items were dichotomously scored, as either pass or fail. Total test performance was measured by the percentage items scored as "pass". Subscores were calculated for *Vehicle Checks*, *Handling of Vehicle*, *Action in Traffic*, *Observation and Understanding of Traffic*, and *Turning* (Table 6.5).

Table 6.4 Dependent variables, and their operationalization, measured by the molecular approach.

Dependent Variable	Operationalization
<i>Total Score</i>	% correct of all 156 items
<i>Observing</i>	% correct of 68 items comprising Observation, Gap Acceptance, and Mirror Check
<i>Car Control</i>	% correct of 69 items comprising Path and Speed
<i>Judgment</i>	% correct of 13 items comprising Approach, Following Distance and Limit Line
<i>Other</i>	% correct of 6 items comprising Y-turn Location and Backing, Pre-Operations and Shut-Down
<i>Hazard Score</i>	% of correct responses to hazards encountered along the route
<i>Instructor Control</i>	# of times instructor took control, either orally or physically
<i>Instructions</i>	# of times the driving instructor had to repeat a route instruction

Table 6.5 Dependent variables, and their operationalization, measured by the molar approach.

Dependent Variable	Operationalization
<i>Total Score</i>	% correct of all 108 items
<i>Vehicle Checks</i>	% correct of 13 items regarding preparations for driving and driving away
<i>Handling of Vehicle</i>	% correct of 23 items regarding posture and steering, controls handling, speed adjustment and stopping, and driving through curves
<i>Action in Traffic</i>	% correct of 60 items regarding straight driving, behavior near and at intersections, right turns, left turns, overtaking, driving in lanes and lane changing, driving through traffic circles, and on highways
<i>Observation and Understanding of Traffic</i>	% correct of 8 items regarding perception and traffic insight
<i>Turning</i>	% correct of 4 items regarding Y-turns
<i>Driving Time</i>	time duration (s) of ride

Questionnaires

Questionnaires used in the previous studies were administered to the subjects in the present study. Subjective feelings of intoxication ("high" or "drunkness"), present cognitive and

emotional state, and subjects' willingness to drive were assessed before the onset and after the conclusion of the driving tests. Subjects were also asked about their perception of the administered treatment, whether it was an active or placebo. At the end of each driving test, subjects were required to retrospectively rate the effort given in performing the test and perceived driving quality. Questionnaires are enclosed in Appendix A.

Laboratory Tests

Subjects performed two laboratory tests before and after driving. The hand steadiness test was used since it had shown a significant effect of the 100 $\mu\text{g/kg}$ THC dose in the previous study and confirmation of this result would indicate the equivalent sensitivities of the present and previous groups to the drug. In addition a time perception test (method of interval production; Fraisse, 1963) was used to satisfy the investigators' curiosity about an oft-reported effect of THC. The former followed the same procedures as described in Chapter 5. The latter required the subjects to stand with eyes closed and indicate when he/she thought that 30 seconds had elapsed since a starting signal. The verbal response was timed to the nearest second by stopwatch.

Blood Sampling

Blood samples were obtained by venepuncture immediately prior to and following all placebo and drug driving tests. Two aliquots containing 10 ml each were heparinized and centrifuged, and the plasma fractions were placed in frozen storage for later assays to determine [THC] and [THC-COOH], in the marijuana group; and, [EtOH], in the alcohol group. The analytical procedures regarding THC and THC-COOH assays were the same as in previous studies. As before, samples obtained in conjunction with placebo marijuana tests were only analyzed if the urine test had been positive. Plasma samples obtained from subjects in the alcohol condition were analyzed using gas-chromatography.

Data Analysis

For each variable measured on interval or ratio level, except plasma concentrations, change scores were computed by subtracting raw scores obtained in the placebo condition from those in the drug condition. In the figures, the mean change of the variable is depicted by the height of the bar and its standard error (SED) by the height of the vertical line above or below the bar. Change scores were expressed in absolute and not relative units. This means that if a performance measure fell from 80% after placebo to 70% after active drug; the change score would be 10% and not 12.5%. Mean drug-placebo changes were tested for significant departure from zero by 2-tailed t-tests, for each group separately. Differences between the groups' mean changes were tested by 2-tailed t-tests for independent samples. Willingness to drive data were again analyzed for assessing differences between drug and placebo conditions using Cochran's Q-test. Differences between the respective groups' willingness to drive after drug treatments were analyzed by Mann-Whitney's U-test. Correlations were computed by Pearson's r and tested for significant departure from zero by 2-tailed t-tests.

Preliminary analyses were executed to determine whether change scores were significantly different between subjects who received placebo in the first, and active drug in the second

condition and those who received treatments in reversed order. Significant differences were generally absent and are therefore mentioned only in the exceptional cases where these were significant.

RESULTS

Plasma Concentrations of the Drugs

Table 6.6 shows mean, median and range of [THC] and [THC-COOH] in the marijuana group and [EtOH] in the alcohol group. In the marijuana group, [THC] and [THC-COOH] were in the expected range. In the alcohol group, mean [EtOH] at $t=35$ was somewhat lower than expected. Furthermore, the fall in [EtOH] to $t=95$ was less than expected from alcohol's pharmacokinetics; a fall of .02 % per hour is commonly seen during the elimination phase in subjects who fast prior to alcohol intake. This probably means that peak [EtOH] generally occurred during the driving test and was not much higher than measurements taken before and after. This situation contrasts to that for the subjects in the marijuana group whose [THC] reached its peak before the test and fell much more rapidly during it. Average plasma concentrations were significantly different from zero in all cases ($p < .001$).

Table 6.6 Mean, median and range of [THC] and [THC-COOH] in ng/ml ($N=14$), and of [EtOH] in g % ($N=16$).

	[THC]		[THC-COOH]		[EtOH]	
	$t=20$	$t=80$	$t=20$	$t=80$	$t=35$	$t=95$
mean	10.5	2.3	7.5	5.6	.034	.028
median	7.8	1.9	6.1	4.3	.034	.028
range	4.3-31.2	1.1-4.9	2.9-18.9	1.7-15.1	.013-.050	.018-.036

Perceived "high" and "drunkness"

Mean levels of intoxication reported by both groups varied from placebo to drug conditions in a remarkable manner. Few subjects in either group reported feeling intoxicated after placebo and their average levels were about 5% of maximum personal experience. After both THC and alcohol these levels rose to about 35% when the respective groups were about to begin driving, then declined to 25% at the end of driving. Means and standard errors of differences (SED) in reported intoxication are shown in Figure 6.2.

T-tests showed that ratings of intoxication after active drugs were significantly different from zero in the marijuana and alcohol groups, both before ($T_{13}=4.36$ & $T_{15}=5.20$, respectively; $p < .001$) and after driving ($T_{13}=3.44$ & $T_{15}=5.23$, respectively; $p < .001$).

Subjects' responses to the question of whether they thought the administered drug was active or placebo showed that they were well aware of what they smoked or drunk. In the marijuana group, 93% of the subjects correctly identified the placebo cigarette when it was administered, and 79%, the active drug. In the alcohol group, 94% of the subjects correctly identified the placebo alcohol when it was administered, and 87%, the active drug.

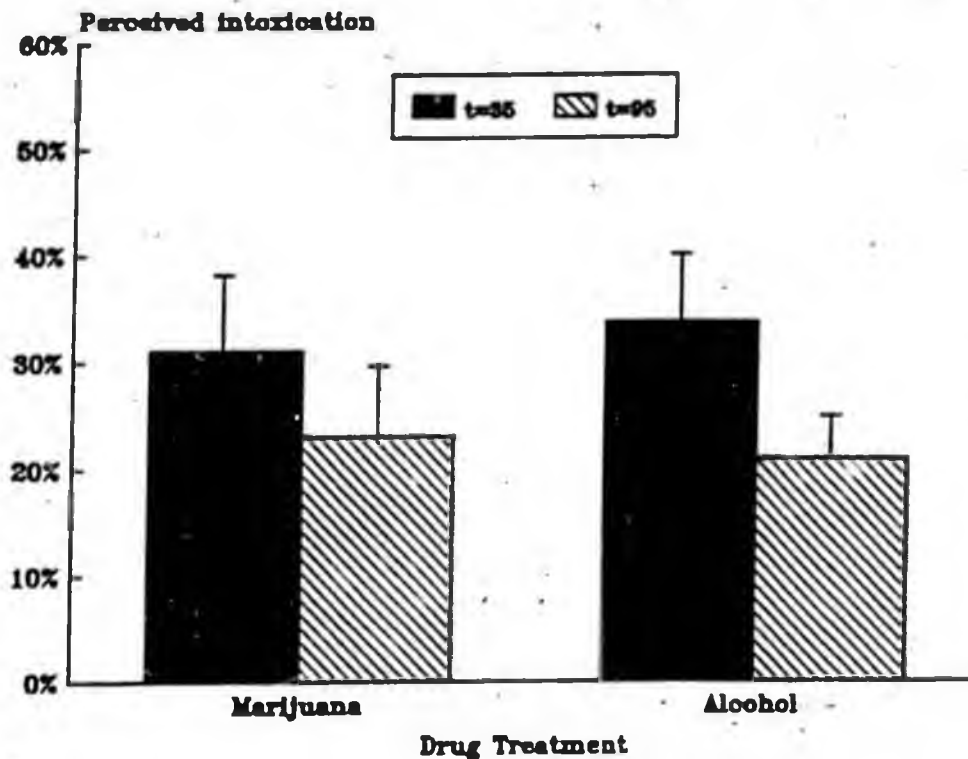


Figure 6.2 Mean (+SED) changes in perceived intoxication by *Drug* and *Time*, relative to placebo. Raw scores were expressed as percentage of maximum personal experience.

Driving Performance Measured by the Molecular Approach

Though some of the changes were positive, indicating better performance after drug and some were negative, showing the opposite, no mean change was significant (Table 6.7). Differences between the two groups' changes were also not significant, although one came close: the difference between improvement shown by the marijuana group and impairment shown by the alcohol group in *Car Control* approached significance ($p < .059$). In general, the effects of both drugs on driving performance, as measured by the molecular approach were very small or absent.

Driving Performance Measured by the Molar Approach

Mean *Total Score* obtained using the molar approach varied between 82.8% and 89.5% over the conditions of the study. Groups' mean change scores on all dependent variables are given in Table 6.8. It is apparent that THC did not significantly affect *Total Score* or any of the component scores. On the other hand, alcohol significantly diminished the *Total Score* as well as two components, *Handling of Vehicle* and *Action in Traffic*. Mean *Driving Time* was, within two seconds, the same for both groups following placebo, namely about 41½ minutes. Subjects drove 46 s slower after THC and 42 s faster after alcohol, but neither change was statistically significant.

Table 6.7 Mean ($\pm$ SED) changes in driving performance scores measured by the molecular approach for the marijuana (N=14) and alcohol group (N=16); and, the significance of each change and difference between changes.

Dependent Variable	Marijuana Group		Alcohol Group		Marijuana vs Alcohol
	Δ	$p <$	Δ	$p <$	$p <$
<i>Total Score</i>	1.6 ($\pm$ 1.7)	ns	-1.5 ($\pm$ 1.7)	ns	ns
<i>Observing</i>	2.4 ($\pm$ 3.1)	ns	-0.3 ($\pm$ 2.8)	ns	ns
<i>Car Control</i>	2.7 ($\pm$ 2.1)	ns	-2.6 ($\pm$ 1.8)	ns	.059
<i>Judgment</i>	-8.3 ($\pm$ 4.8)	ns	-2.2 ($\pm$ 4.0)	ns	ns
<i>Other</i>	-3.6 ($\pm$ 4.3)	ns	1.3 ($\pm$ 4.4)	ns	ns
<i>Hazard Score</i>	6.3 ($\pm$ 17.6)	ns	14.6 ($\pm$ 9.4)	ns	ns
<i>Instructor Control</i>	0.5 ($\pm$ 0.4)	ns	0.4 ($\pm$ 0.5)	ns	ns
<i>Instructions</i>	0.1 ($\pm$ 0.6)	ns	0.8 ($\pm$ 0.6)	ns	ns

Table 6.8 Mean ($\pm$ SED) changes in driving performance scores measured by the molar approach for the marijuana (N=14) and alcohol group (N=16); and, the significance of each change and difference between changes.

Dependent Variable	Marijuana Group		Alcohol Group		Marijuana vs Alcohol
	Δ	$p <$	Δ	$p <$	$p <$
<i>Total Score</i>	-0.7 ($\pm$ 2.7)	ns	-6.8 ($\pm$ 1.8)	.002	.065
<i>Vehicle Checks</i>	-0.6 ($\pm$ 1.5)	ns	0.5 ($\pm$ 1.3)	ns	ns
<i>Handling of Vehicle</i>	3.7 ($\pm$ 2.8)	ns	-8.4 ($\pm$ 2.2)	.002	.002
<i>Action in Traffic</i>	-2.7 ($\pm$ 3.1)	ns	-8.4 ($\pm$ 2.3)	.003	ns
<i>Observation and Understanding of Traffic</i>	1.8 ($\pm$ 8.7)	ns	-6.3 ($\pm$ 7.0)	ns	ns
<i>Turning</i>	-1.8 ($\pm$ 4.9)	ns	3.1 ($\pm$ 7.5)	ns	ns
<i>Driving Time</i>	45.6 ($\pm$ 51.8)	ns	-42.0 ($\pm$ 32.4)	ns	ns

Differences between the groups' mean change scores were also significant or nearly so. The greater drop in *Total Score* caused by alcohol was almost significantly different from that caused by THC ($p < .065$). The difference between groups' changes in *Handling of Vehicle*, a component score, was significant ($p < .002$): whereas the marijuana group's performance improved slightly, that of the alcohol group deteriorated under the influence of their respective drugs. In particular, 6 items checked under the category of *Handling of Vehicle* discriminated between the groups' reactions to the drugs. These all pertained to how well the driver handled the vehicle through curves. Whereas THC had little effect on this ability, alcohol seemed to affect it

strongly. This more than any other factor was responsible for the difference between the instructor's ratings of how the two groups were affected by the respective drugs.

Perceived Driving Quality and Effort to Accomplish the Test

Both groups rated their driving performance following placebo as somewhat better than "normal". Following the active drug, ratings were about 35% lower in the marijuana group, but only 5% lower in the alcohol group (Figure 6.3). This striking mean difference was substantiated by the statistical analysis. Mean change of driving quality ratings was significantly lower in the marijuana ($T_{13} = -3.05$; $p < .009$), but not in the alcohol group. The difference between the groups' mean changes approached significance ($T_{24} = -1.97$; $p < .058$).

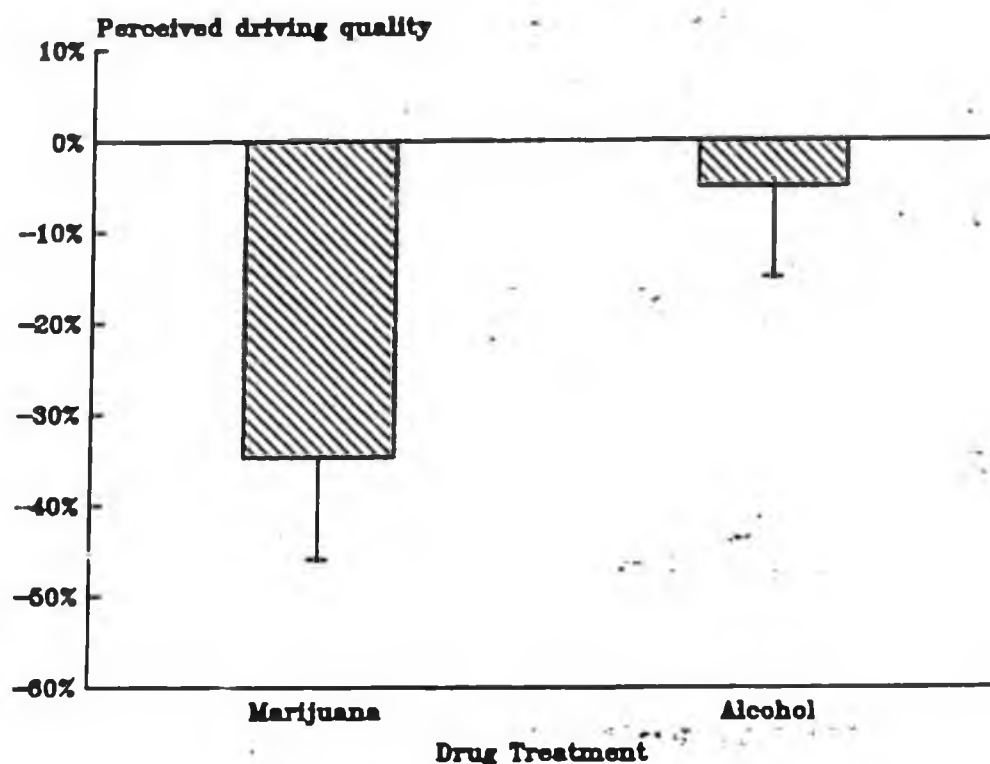


Figure 6.3 Mean (+SED) changes in perceived driving quality by Drug, relative to placebo. Raw scores were expressed as percentage of "normal".

Perceived effort to accomplish the driving test was about the same in both groups following placebo. Following the active drug, a greater increase in perceived effort was reported by the marijuana group than the alcohol group (Figure 6.4). Statistical analysis showed that increased effort ratings following the drug were only significant in the marijuana group ($T_{13} = 2.39$; $p < .033$). No significant difference between the groups' mean changes was found.

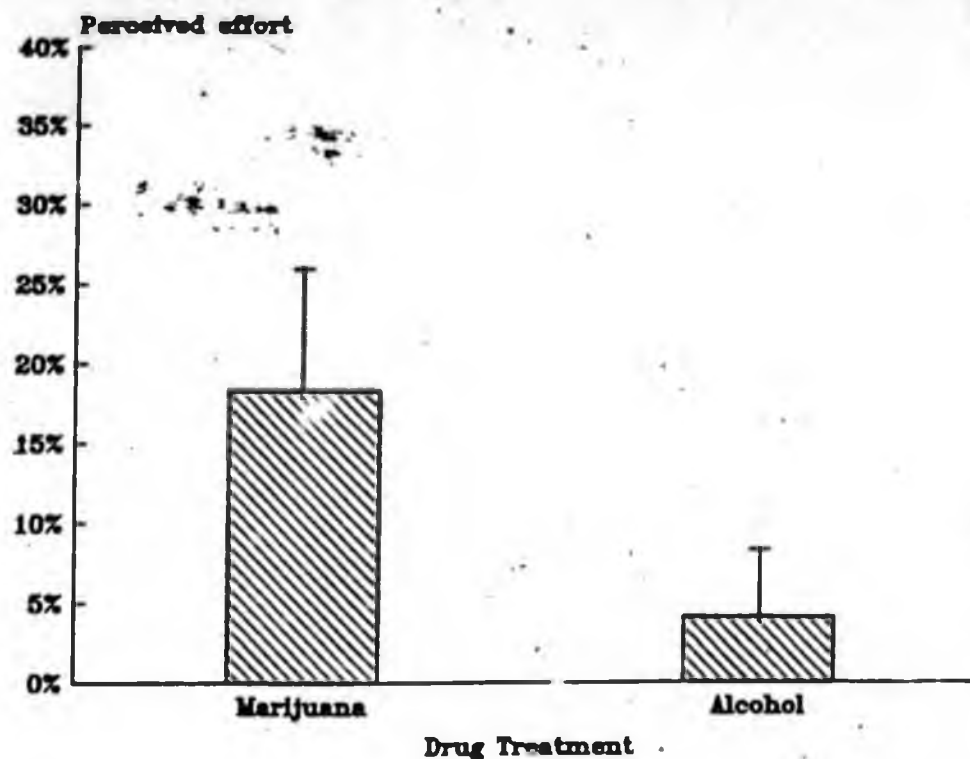


Figure 6.4 Mean (+SED) changes in perceived effort to accomplish the driving test by *Drug*, relative to placebo. Raw scores were expressed as percentage of maximum of scale.

Willingness to Drive

Table 6.9 presents the percentage of subjects willing to drive under specified conditions of different urgencies (*A*. unimportant though gratifying; *B*. important but avoidable; and *C*. urgent). The more urgent the reason for driving, the more subjects declared that they would be willing to drive.

Table 6.9 Percentages of subjects willing to drive under circumstances *A*, *B* & *C* (see text) by treatment condition and sampling time; and, the significance of each difference between placebo and active drug condition, tested by Cochran's Q-test.

		Alcohol Group			Marijuana Group		
		placebo	alcohol	<i>p</i> <	placebo	marijuana	<i>p</i> <
A	<i>t</i> =50	100	38	.006	86	50	.044
	<i>t</i> =175	100	50	.012	93	57	.044
B	<i>t</i> =50	100	44	.008	93	57	.044
	<i>t</i> =175	100	75	.07	100	57	.03
C	<i>t</i> =50	100	94	ns	100	93	ns
	<i>t</i> =175	100	94	ns	100	100	ns

Cochran's Q-test showed that the numbers of subjects who would have driven for an unimportant reason following the active drug were significantly less than after placebo, in both groups. The same held true for the somewhat more important reason. In contrast, nearly all subjects indicated that they would have driven for an urgent reason, irrespective of the administered drug. Mann-Whitney's U-test failed to reveal any significant difference between the groups' percentages following the active drug.

Perceived Alertness, Contentedness and Calmness

Changes in subjective feelings of alertness, contentedness and calmness are shown in Table 6.10. Feelings of alertness were significantly diminished in both groups and at both time points following the active drug relative to placebo. Subjects felt also less content and calm following the active drugs, but the effects were smaller. Statistical tests revealed only one significant effect: alcohol producing significantly diminished feelings of contentedness measured after termination of the driving test.

Table 6.10 Mean ($\pm$ SED) changes in subjective feelings of alertness, contentedness and calmness (raw scores being expressed as percentages of maximum) for the marijuana (N=14) and alcohol group (N=16); and, the significance of each change and difference between changes.

Dependent Variable		Marijuana Group		Alcohol Group		Marijuana vs Alcohol
		Δ	$p <$	Δ	$p <$	$p <$
Alertness	$t=35$	-15.4 (± 4.2)	.003	-18.9 (± 3.6)	.001	ns
	$t=95$	-15.1 (± 5.3)	.014	-20.1 (± 3.0)	.001	ns
Contentedness	$t=35$	-6.2 (± 4.0)	ns	-5.8 (± 4.3)	ns	ns
	$t=95$	-5.7 (± 3.6)	ns	-8.9 (± 2.3)	.002	ns
Calmness	$t=35$	-7.5 (± 4.4)	ns	-1.2 (± 4.2)	ns	ns
	$t=95$	-10.0 (± 5.2)	.077	-7.3 (± 5.3)	ns	ns

Hand Steadiness Test

Mean square root of total number of side contacts were about the same in the placebo conditions for both groups. The active drugs, however, affected hand steadiness differently; the number of side contacts increased after THC whereas the opposite occurred after alcohol (Figure 6.5). Statistical analysis showed that the impairment following THC was highly significant, both shortly after smoking and more than one hour later ($T_{13}=3.96$ & 3.40 ; $p < .002$ & $.005$, respectively), whereas the improvement following alcohol was only significant shortly after drinking ($T_{15}=-2.29$; $p < .037$). The differences between the groups' mean changes were significant both before and after the driving test ($T_{28}=4.71$ & 3.35 ; $p < .001$ & $.002$, respectively).

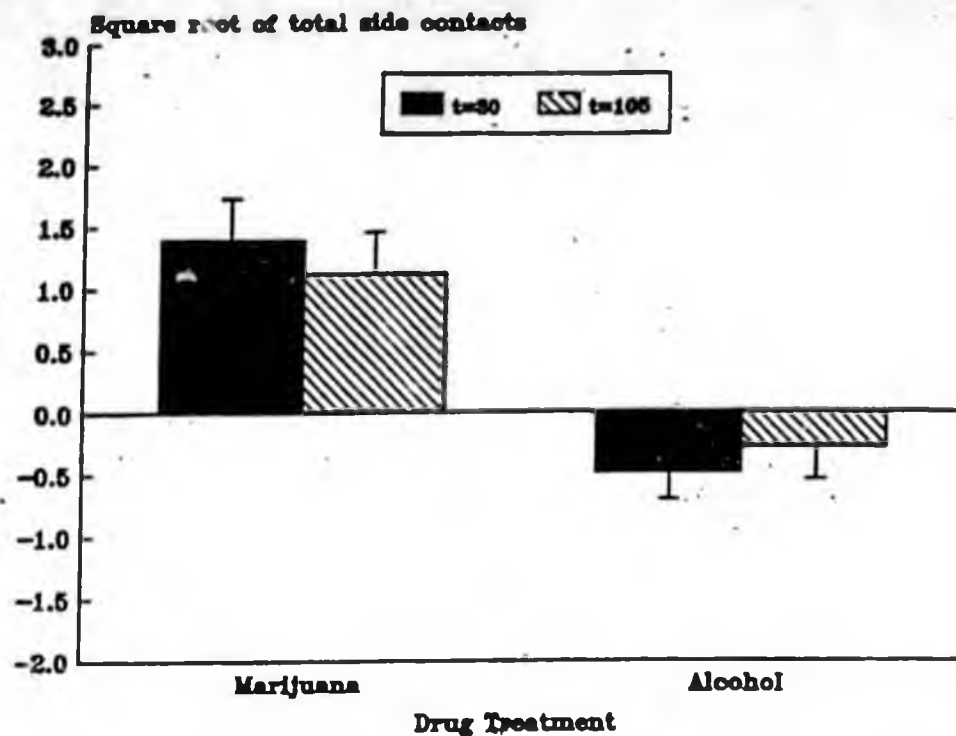


Figure 6.5 Mean (+SED) changes in the square root of total number of side contacts in the hand steadiness test by *Drug*, relative to placebo.

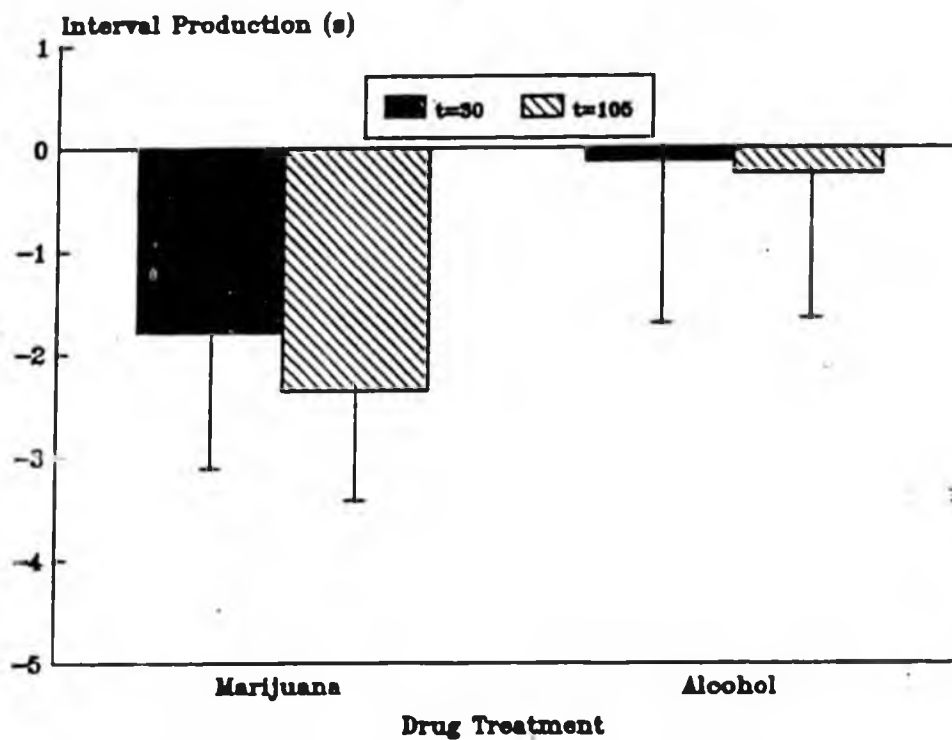


Figure 6.6 Mean (+SED) changes in attempted production of a 30-second interval by *Drug*, relative to placebo.

Time Perception Test

Mean attempted production of a 30-second interval was close to the target for the alcohol group, both after placebo and active drug yielding very small, and non-significant, changes (Figure 6.6). Subjects in the marijuana group produced a foreshortened interval in both conditions, but foreshortening was greater following THC. The change in interval production was, however, only significant after, and not before, the driving test ($T_{13} = -2.36$; $p < .045$).

Inter-Subject Relations between Variables

Relationship between Plasma Concentrations and Driving Performance. Correlational analyses were performed to determine whether driving performance was related to plasma concentrations of the drugs, measured both before and after the driving tests. The first step involved correlational analysis between raw variables; the second step, between changes in driving performance and plasma concentrations. Neither analysis yielded significant results.

Relationship between the Molecular and Molar Approach. Correlations were also computed between the raw *Total Scores* obtained by both the molecular and molar approach. These correlations were computed in each condition separately. For the marijuana group, the correlation between the Total Scores were 0.71 ($p < .005$; 2-tailed) and 0.54 ($p < .044$) in the placebo and active drug condition, respectively. For the alcohol group, the corresponding correlations were 0.71 ($p < .002$) and 0.79 ($p < .001$), respectively. Differences between these correlations were not significant. The second step involved correlational analysis of change scores. This analysis revealed that changes in *Total Scores* of both methods were not significantly correlated, neither in the marijuana ($r = 0.05$) nor in the alcohol group ($r = 0.08$).

Relationship between Driving Performance and Driving Experience. Correlations were also computed between driving experience on one hand, and driving performance and changes in driving performance following the active drug on the other. Neither analysis revealed significant correlations. This means that driving experience of the subjects in the present study could neither predict driving performance per se nor changes following the active drug.

Relationship between Plasma Concentrations and Perceived Intoxication. Correlations of perceived "high" following THC with [THC] were 0.65 ($p < .013$) shortly after smoking and 0.47 ($p < .093$) following termination of the driving test. Correlations with [THC-COOH] were 0.74 ($p < .002$) and 0.62 ($p < .018$), respectively. Correlations of perceived intoxication following alcohol and [EtOH] were not significant ($r = 0.27$ & 0.39 , respectively). Correlations of plasma concentrations with changes in perceived intoxication were nearly the same as those with the raw scores, because intoxication ratings were generally zero following placebo.

DISCUSSION

The present study showed that alcohol, administered in a dose of 0.43 g ethanol per kg of lean body mass yielding an average plasma alcohol concentration of about 0.04 g%, produced a significant impairment in city driving as measured by the molar approach, relative to placebo. Significant impairment was shown by changes in *Total Score*, and subscores describing *Handling of Vehicle* and *Action in Traffic*. Marijuana, administered in a dose of 100 μ g THC per kg of whole body weight, on the other hand, did not significantly change mean driving performance

as measured by this approach. Neither alcohol nor marijuana significantly affected driving performance measures obtained by the molecular approach.

The first conclusion one might draw is that the methods applied for measuring driving performance did not yield exactly the same results. Yet both methods similarly measured individual differences in driving proficiency. Correlations between the total scores in all four conditions were between 0.54 and 0.79, and as such, highly significant. Obviously both methods were able to discriminate the relatively large re-existing differences in the subjects' respective abilities to operate the vehicle in urban traffic. Change scores were, however, not correlated; i.e. $r=0.05$ & 0.08 in the marijuana and alcohol group, respectively. Since the molar, and not the molecular, approach was sensitive to alcohol's adverse effects, it is tempting to conclude that the latter may fail to measure some important driving deficits. That is, the molecular approach seems relatively insensitive to drug-induced changes.

The second conclusion one might draw is that the molar method, having proven its sensitivity by detecting impairment associated with a low BAC, should be sensitive to any similar impairment occurring after a correspondingly low THC dose. That it failed to show any significant change in the marijuana group's driving performance leads to the third and most important conclusion:

The 100 µg/kg THC dose these subjects received shortly before the test did not impair their city driving performance.

The different effects of alcohol and marijuana on driving performance can not be explained by the subjects' reported driving experience. Although subjects in the alcohol group were somewhat more experienced drivers than those in the marijuana group, the difference was not significant. Furthermore, correlational analysis showed that neither driving performance nor driving impairment was significantly related to previous driving experience. The different effects of alcohol and marijuana on driving performance can also not be explained by differences in the groups' subjective feelings. There was a remarkable correspondence between the two groups' feelings of intoxication, i.e. "high" or "drunkness". Prior to the driving test, both groups reported intoxication levels of about 35% of the highest ever experienced, and 25%, after its termination. THC's significant impairing effect on hand steadiness also showed that the subjects in the marijuana group were sensitive to THC's effects.

The difference between the drugs' effects on driving may be explained, however, by compensational mechanisms, such as increased effort. Both groups reported about the same amount of effort in accomplishing the driving test following placebo. Yet only subjects in the marijuana group reported significantly higher levels of invested effort following the active drug. Previous on-road driving studies indicate that subjects may compensate for THC's adverse effects by slowing down (Hansteen *et al.*, 1976; Casswell, 1979; Peck *et al.*, 1986). Results of the present study were in the same direction: it took the marijuana group an average of 46 s longer to complete the circuit after THC than following placebo. That this difference was not significant was probably due to the real-life character of the test: unforeseen obstructions and variable traffic density probably increased the error variance of this measure over what it would have been on a closed course. Thus, there was evidence that subjects in the marijuana group were not only aware of their intoxicated condition but were also attempting to compensate for it.

There were other striking differences between the groups' reactions to their respective drugs. As stated, subjects in the marijuana group invested more effort in the test while driving under the influence of THC. The alcohol group apparently made no greater effort after the drug than placebo. Yet for all of their effort, the marijuana group rated their driving performance as being significantly worse after THC than placebo. The alcohol group who invested no special effort after the drug, not surprisingly, thought they had driven as well as following placebo. They were nonetheless driving in a deficient manner according to the instructor's ratings. These seem to be important findings. They support both the common belief that drivers become overconfident after drinking alcohol and investigators' suspicions that they become more cautious and self-critical after consuming low THC doses by smoking marijuana.

These impressions were seemingly contradicted by the similarity in the groups' responses indicating their willingness to drive after the respective drugs. About 50% of both groups said they would have been unwilling to drive for less than very urgent reasons. This profession of caution seems a bit odd for the alcohol group who knew that they could not be given a dose which would produce BACs over the legal limit during the test. The "contradiction" in this case seems to be a reflection of the group's desire to give "socially desirable" answers to the questionnaire, whether the same was true for the marijuana group in the present and preceding studies is a moot point.

The laboratory performance tests also discriminated between the drugs' effects. Hand steadiness was impaired following THC and improved following alcohol, relative to placebo. The difference between the drugs' effects was significant, both before and after the driving test. Impairment after THC was about as much as that produced by the same dose in the previous study, indicating equivalent sensitivities of the present and previous groups. Production of time intervals was not affected by alcohol, but THC significantly shortened interval production, relative to placebo. This confirms the common finding that THC affects time estimation (Hollister and Gillespie, 1970; Bech *et al.*, 1973). As usual, THC accelerated the subjects' perception of time passing. They arrived at a foreshortened production of 30 s and would have estimated the duration of the actual interval as longer than it actually was. Changes in driving performance were not correlated with changes in performance in either laboratory test. Nevertheless, both tests should be seriously considered for inclusion in any test battery for measuring these drugs' effects, mainly because of the different pattern of results they produced.

Plasma concentrations of THC and THC-COOH were comparable to those obtained in the previous studies. Plasma concentrations of ethanol were somewhat lower than predicted, and the fall in plasma concentration during the driving test was less than expected. This probably means that peak plasma concentrations generally occurred during the driving test. If so, it probably was about 0.04 g%. Ratings of "high" were significantly related to plasma concentrations of THC and THC-COOH but those of "drunkness" were not significantly related to plasma concentrations of ethanol. Drug plasma concentrations were neither related to absolute driving performance scores nor to the changes that occurred from placebo to drug conditions. With respect to THC, these results confirm the findings in previous studies. They are somewhat surprising for alcohol but may be due to the restricted range of ethanol concentrations in the plasma of different subjects.

How do the present results relate to those reported by Klonoff (1974)? He also assessed the effects of relatively low THC doses on aspects of subjects' driving performance in a city driving test using a similar molar approach. His subjects commenced driving immediately after cessation of smoking. They scored lower on judgment and concentration scales when under the influence

of the highest, but not the lowest, dose. Behaviors that were more directly related to driving performance, e.g. lane changing, compliance with traffic signals and posted speed advisories, were not affected by the drug. Subjects in the present study commenced driving 30 minutes after initiation of smoking. The molar method applied in the present study did not include ratings of judgment or concentration. With the exception of these two items, neither study indicated significant effects of THC on driving performance and are, therefore, in complete agreement.

CHAPTER 7 - GENERAL DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

INTRODUCTION

It is commonly assumed that marijuana smoking in real-life social situations delivers THC doses that seriously degrade the ability to safely operate motor vehicles; and, that the drug's users frequently drive shortly after smoking. If these premises are correct, it would follow that marijuana users are, while intoxicated, at increased risk of traffic accident involvement and constitute a safety hazard for other road users. However, the foremost impression one gains from reviewing the literature is that no clear relationship has ever been demonstrated between marijuana smoking and either seriously impaired driving performance or traffic safety. The epidemiological evidence, as limited as it is, shows that the combination of THC and alcohol is over-represented in injured and dead drivers and more so in those who actually caused the accidents. Yet there is little if any evidence to indicate that drivers who have used marijuana alone are any more likely to cause serious accidents than drug free drivers. To a large extent, the results from driving simulator and closed-course tests corroborate the epidemiological findings by indicating that THC in single inhaled doses up to about 250 $\mu\text{g/kg}$ has relatively minor effects on driving performance, certainly less than BACs in the range 0.08-0.10 g%.

But how well do these findings relate to the actual driving performance of regular marijuana users? If previous experience is any guide, little of crucial importance will emerge from experimental research until it is conducted in a more realistic manner. Therefore, a series of studies were conducted to determine the dose-response relationship between THC and objectively and subjectively measured aspects of real world driving. A variety of driving tasks were employed, including maintenance of a constant speed and steady lateral position during uninterrupted highway travel, adjusting velocity to the movements of a leading car on a highway, and city driving. The purpose of applying different tests was to determine whether similar changes in performance under the influence of THC occurs in all thereby indicating a general drug effect on driving safety.

However real these tests might appear, the circumstances in which the subjects smoked the drug and drove the car were still somewhat artificial. First, the subjects consumed the drug in a neutral setting, alone or in the presence of a stranger. This was of course different from the situation wherein they normally smoke marijuana, i.e. in the company of friends who might reinforce a certain type of behavior not normally considered as conservative or prudent. Marks and Pow (1989) found that marijuana smokers derived slightly greater pleasure from THC in the company of friends than strangers from which one might infer a social amplification of the pharmacological effect. However, neither they nor any other investigators ever indicated that social amplification outlasts the situation which gives rise to it. In the absence of such evidence, we tend to discount the possibility that the unusual setting for drug administration had any effect upon subsequent driving performance. Social amplification of THC's adverse effects on driving performance might well occur if the driver were accompanied by similarly intoxicated passengers. We must therefore restrict generalizations from the studies' results to those situations

where the intoxicated driver is doing his best to perform efficiently and is uninfluenced by friends or any other factor which might amplify the drug's adverse effects.

Secondly, subjects were aware of the fact that their driving behavior was being observed and that the accompanying driving instructor would intervene if necessary. The former is hardly avoidable in experimental studies but possibly provoked the subjects to do their utmost; the latter is a prerequisite for ensuring safety in actual driving studies and may or may not have produced nonchalance on the subjects' part resulting in poorer than normal performance. Yet according to what the subjects declared, they drove normally after placebo indicating that the experimental situation had not seriously altered their performance. Whether they drove in the test as they normally would after smoking marijuana remains open to question. The correspondence between experimental and epidemiological studies regarding THC's effects on driving performance suggests that this artificiality is also of minor concern.

The present series of studies are about the best simulation of real world driving one can reasonably achieve and have gone further toward defining the effects of marijuana smoking on actual driving performance than any of its predecessors. The results found in the successive studies were discussed at full length in the respective chapters. In this chapter, results of the separate studies will be integrated to provide answers to some important questions concerning marijuana's influence on driving performance. First however, the implications of the pilot study's major result will be discussed, i.e. the THC dose that marijuana users prefer to achieve their desired "high". In the following section, the driving tests will be discussed in terms of the kinds of mental operations they require. Some further remarks provided in that section concern the relevance of the driving tests for traffic safety. The major part of this chapter will be addressed to the most important issue, i.e. what the results indicate as the real effects of marijuana smoking on driving performance. Finally, attention will focus on the relationship between plasma drug concentrations and drug-induced driving impairments. This chapter will end with a list of conclusions and recommendations.

THC DOSES

To avoid arbitrarily selecting an unrealistic maximum THC dose for the driving studies, it was necessary to establish the dose which marijuana users actually prefer for achieving their desired "high". A pilot study met this requirement. The study showed that marijuana users prefer higher THC doses than those previously administered in experimental studies. Previous THC doses were generally between 100 and 200 $\mu\text{g/kg}$, including the remaining butt, whereas the subjects in the pilot study preferred an average dose of 300 $\mu\text{g/kg}$, excluding the butt. This either means that today's marijuana users prefer higher doses than in the past or that investigators failed to administer realistic doses in previous studies, or both.

Ohlsson *et al.* (1980) compared THC's effects after three different routes of drug administration. In the smoking condition, subjects were allowed to smoke a marijuana cigarette containing 19 mg THC in their own manner such as to obtain the maximum desired "high". Comparing the weight of the remaining butt with the unlit cigarette revealed that the eleven males participating in the study had smoked 13.0 mg THC on the average. Ohlsson *et al.* failed to report the subjects' mean weight but, assuming that it was 70 kg (154 lb) on average, this would equal to a THC dose of nearly 200 $\mu\text{g/kg}$. Perez-Reyes *et al.* (1982) compared THC's effects after smoking marijuana cigarettes of three different potencies. Three males and three

females participated in that study and the same procedures were applied to determine the amount of THC consumed as in Ohlsson's study. It appeared that the amount of THC consumed was proportional to the THC content, or potency, of the cigarette. The subjects consumed 9.7, 12.8 and 16.9 mg THC when smoking cigarettes containing 1.32%, 1.97% and 2.54% THC, respectively. Perez-Reyes *et al.* also failed to report the subjects' mean weight but, for a 70 kg (154 lb) person, the weight calibrated amount of THC consumed would have been 140, 180 and 240 $\mu\text{g/kg}$, respectively. These results indicate that the potency of the marijuana cigarette is a major contributor to the preferred dose. Ohlsson failed to mention the potency of the marijuana cigarettes they used which makes a comparison with the data of Perez-Reyes impossible. The potency of the cigarettes used in the present pilot study was 2.57%, nearly the same as the highest in Perez-Reyes' study, and our subjects smoked on the average a THC dose of 20.8 mg, or 308 $\mu\text{g/kg}$. This might be an indication that users presently prefer higher doses than in the early eighties. However, there is one important distinction between these earlier studies and the present one that may account for the increase. Our subjects were allowed to smoke a second, and even a third, cigarette to achieve their desired "high". Subjects in previous studies were given only one cigarette, maybe out of ignorance but probably because it was not the investigators' primary objective to determine the subjects' preferred dose. Consequently, the preferred dose of subjects who smoked one cigarette completely but not yet achieved their desired "high" was under-estimated. Thus, whether current users indeed prefer higher doses than ten years ago is hard to say. What is clear from the pilot study's results, is that higher THC doses than those usually administered in previous studies should be included in future ones.

The relation between preferred dose and the potency of the drug found by Perez-Reyes *et al.* (1982) raises two questions that might have implications for interpreting the present studies' results. The first question is, how do people regulate their THC consumption? Apparently they do not titrate brain THC concentrations to within a narrow range as tobacco smokers reliably do with nicotine (Jaffe, 1990). It's also doubtful that marijuana smokers integrate their THC concentrations over time to cease consumption when the cumulative effect approaches a certain threshold. In the earlier study the subjects may have simply ceased smoking after consuming the same volume of cigarettes, regardless of the delivered dose. But this could not have occurred in the pilot study for the present series since our subjects smoked ad lib. The probable explanation is that our subjects were somewhat aware of both the momentary brain concentration and its rate of increase and ceased smoking before the expected rise would shortly exceed the preferred effect. This procedure was accurate enough to limit the drug's effects to below what they had previously experienced as an unpleasant maximum. It was not accurate enough to attain homogeneity in the subjects' achievement of the preferred "high" in relation to the maximum (coefficient of variation: 25%). In real life, marijuana users are usually more aware of the potency of the material they smoke, from prior experience, upon the advice of other users or even from its "street" price. The material presented to the subjects in the pilot study was definitely unfamiliar and they may have suddenly become prudent smokers. Confirmation of this supposition came from the same subjects' consumption of THC in the subsequent driving study. Though treated with the same average dose they had preferred in the pilot study, their plasma drug concentrations were now higher. This difference was interpreted as the result of increased smoking efficiency due to familiarization with the potency of the material containing the drug.

If familiarization plays a major role in smoking efficiency and, consequently THC plasma concentrations, THC's adverse effects on performance may also be dependent on this factor. That being the case, the second and third driving studies' results would under-estimate THC's

adverse effects on driving performance since new groups of subjects were recruited in both. However, the remarkable resemblance between effects of every THC dose on SDLP in the first and second driving studies indicates that familiarization is not a very important factor. Nevertheless, we recommend that subjects in future studies be familiarized with the potency of the drug before the beginning of performance testing.

The second question raised by the apparent relationship between the drug's potency and the preferred dose is, what the latter would have been if marijuana of much higher potency were smoked. This is an important question since potencies of marijuana are increasing rapidly. At present, potencies of marijuana cultivated in The Netherlands may contain 5-20% THC, and, in exceptional cases, 30%. It is hard to imagine that subjects would consume as much of a cigarette containing a very high THC concentration as one containing a very low one. Future research determining marijuana users' preferred dose should also include marijuana with much higher potencies. It may then appear that Perez-Reyes *et al.*'s findings were attributable to their subjects' inability to discriminate among potencies spanning a narrow range. A broader range of cigarette potencies would probably allow regular marijuana users to discriminate well enough to alter their consumption and thereby come closer to administering the same preferred dose after every one.

On the basis of the pilot study's results, the highest dose of THC administered in subsequent driving studies was defined as 300 $\mu\text{g/kg}$; other doses were 100 and 200 $\mu\text{g/kg}$, and placebo. Marijuana cigarettes were prepared from batches obtained from NIDA with potencies varying from 1.75% to 3.58%, the highest that were then available. If future research shows that current users of marijuana prefer much higher THC doses when they smoke very potent marijuana, the results of the current program can only serve as an indication of the minimal effects the drug may have on actual driving performance. If, on the other hand, it shows that users prefer a THC dose of about 300 $\mu\text{g/kg}$ to reach their desired "high" irrespective of the potency of the drug, the results presented in this report are truly valid estimates of what may happen in daily life after smoking THC doses that induce a preferred "high".

THE DRIVING TESTS

Three different tests were applied in the experiments that progressively increased in the number of skills employed by the driver: road tracking, car following and city driving. The first is now a standardized test which, in more than 40 studies, has proven to be very sensitive to sedation produced by a variety of medicinal and social drugs, including alcohol. The car following and city driving test were developed following the recognition that parameters measured in the standard test fail to represent all abilities considered important for safe driving. This section will describe the differences between the driving tests and the relevance of each to traffic safety.

The difference between the three driving tests can be characterized in many ways. The one described here is that in terms of the type of information processing each requires. Two distinct types of human information processing can be distinguished (Shiffrin and Schneider, 1977): "automatic" and "controlled". The former is capable of accepting an enormous volume of perceptual information at a relatively high rate to mediate coordinated multi-effector responding in a normally stable input-output relationship. This process is not generally under voluntary control, proceeds in parallel with the stream of consciousness and involves no decision making. Controlled information processing is much slower but highly adaptive. It begins with the

conscious perception of a discrete event or situation. Identification of the meaning of that perception is made by comparing it with information stored in memory. A decision involving the selection and execution of a particular series of motor responses and/or the suppression of a motor routine in progress occurs next. This process can proceed in parallel with an automatic process and the integrity of both are essential for safe driving.

Aspects of both types of information processing are present in most well practiced tasks. Most would agree that skilled performance is the integrated sum of automatic and controlled information processing and that their respective weights vary constantly with the task requirements. The more controlled information processing a task requires, the more it is experienced as demanding effort. According to this concept, lateral position control in the road tracking test depends principally upon automatic information processing. The car following test requires somewhat more controlled information processing and driving in urban traffic, even more. The concept can be illustrated by the ease of having a conversation with other occupants of a vehicle while driving. It is easy to converse with them while driving on a highway in light traffic. It becomes somewhat more difficult when driving in heavy traffic and maintaining a safe headway behind cars travelling in a platoon. Conversing while driving in urban traffic is even more difficult and, at times, even impossible for most drivers. Thus, the more controlled processing involved in a particular situation, the more effort the driving task demands and the less "spare capacity" is left for having a conversation with other occupants. This concept of effort relates to task or computational demands, and often, to the allocation of attention. There exists, however, also another concept of effort which relates to brain arousal mechanisms (Kahneman, 1973; Pribram and McGuinness, 1975) or the required psychological state (Hockey, 1986). If one perceives a discrepancy between his actual state of arousal and that required to efficiently accomplish the task, he will first attempt to resolve the difference by compensatory effort, e.g. focussing attention. Failing that, he will try to reduce task demands to what can be efficiently accomplished in the deficient arousal state. The latter can be accomplished during driving by reducing speed or assuming a greater headway to compensate for slower reaction times.

It is sensible to keep the relevance of the separate driving tests for driving and traffic safety in mind while discussing THC's effects on driving performance. It is obvious that the road tracking test measures only a few aspects of driving behavior. Yet proper road tracking is a general prerequisite for safe driving. Consequently, drugs that substantially impair a driver's fundamental road tracking ability possess a real potential for adversely affecting driving safety. Whether this means that drivers under the influence of such drugs have also a greater probability of becoming involved in a traffic accident seems plausible but has yet to be determined. The same kind of reasoning applies to the car following test. It measures only a few additional aspects of driving behavior, but their impairment is also incompatible with safe driving. The city driving test measures most aspects of driving behavior and therefore comes closest to reality. Driving in urban traffic is so common in daily life that any drug-induced impairment found with this test should be considered as the most important, though not necessarily the earliest, sign that the drug possesses properties that adversely affect traffic safety.

EFFECTS OF THC ON DRIVING PERFORMANCE

One of the issues addressed by the first driving study was whether it would be safe to continue using the same approach for subsequent on-road studies in traffic. The first group complied with all instructions, even after high doses of THC. Changes in mood were often reported but changes in personality were never observed. Most importantly, the subjects were always able to complete every ride without major interventions by the driving instructors and their safety was never compromised. The same occurred in the subsequent studies showing that it is possible to safely study marijuana's effects on actual driving performance in the presence of other traffic. In this respect, the drug is no different from many others studied by the same investigators and their colleagues.

The standard test measured the subjects' ability to maintain a constant speed and a steady lateral position between the lane boundaries. Standard deviation of lateral position, SDLP, increased after marijuana smoking in a dose-related manner. The lowest dose, i.e. 100 $\mu\text{g/kg}$ THC, produced a slight elevation in mean SDLP, albeit significant in the first driving study. The intermediate dose, i.e. 200 $\mu\text{g/kg}$ THC, increased SDLP moderately; and, the highest, i.e. 300 $\mu\text{g/kg}$ THC, substantially. It is remarkable how well the changes in SDLP following THC in the first driving study were replicated in the second, in spite of the many differences in the ways they were designed. The replication of THC's effects on SDLP substantiates the generality of these results. Other objective measures obtained by this test were much less affected by THC. Mean speed was somewhat reduced following the higher THC doses, but the effects were relatively small (max. 1.1 km/h or 0.7 mph). Standard deviations of speed and steering wheel movements were unaffected by the drug. Subjective ratings of perceived driving quality followed a similar pattern as SDLP indicating that the subjects were well aware of their diminished ability to control the vehicle after marijuana smoking.

The car following test measured the subjects' ability to follow a leading car with varying speed at a constant distance. All THC doses increased mean headway, but according to an inverse dose-response relationship. This type of relationship was unexpected and probably due to the particular design of the second driving study, i.e. the ascending dose series. It means that subjects were very cautious the first time they undertook the test under the influence of THC (i.e. after the lowest dose) and progressively less thereafter. As a consequence of this phenomenon, mean reaction time to changes in the preceding car's speed also followed an inverse dose-response relationship. Statistical adjustment for this confounding by analysis of covariance indicated that reaction times would not have increased significantly if the mean headway were constant. Coefficient of headway variation increased slightly following THC. Together, these data indicate that there is no more than a slight tendency towards impairment in car following performance after marijuana smoking. They also show that subjects try to compensate for anticipated adverse effects of the drug by increasing headway, especially when they are uncertain of what these might be. As in the standard test, subjects' ratings of driving quality corresponded to the objective changes in their performance.

The city driving study measured the subjects' ability to operate a vehicle in urban traffic. For reasons mentioned in the respective chapter the THC dose in that study was restricted to 100 $\mu\text{g/kg}$. For comparative purposes another group of subjects was treated with a modest dose of alcohol, producing a mean BAC of about 0.04 g%. Results of the study showed that the modest dose of alcohol, but not THC, produced a significant impairment in driving performance, relative to placebo. Alcohol impaired driving performance but subjects did not perceive it. THC

did not impair driving performance yet the subjects thought it had. After alcohol, there was a tendency towards faster driving and after THC, slower.

The results of these studies corroborate those of previous driving simulator and closed-course tests by indicating that THC in single inhaled doses up to 300 $\mu\text{g/kg}$ has significant, yet not dramatic, dose-related impairing effects on driving performance. They contrast with results from many laboratory tests, reviewed by Moskowitz (1985), which show that even low doses of THC impair skills deemed important for driving, such as perception, coordination, tracking and vigilance. The present studies also demonstrated that marijuana can have greater effects in laboratory than driving tests. The last study, for example, showed a highly significant effect of THC on hand unsteadiness but not on driving in urban traffic.

It is a natural question why the effects of marijuana on actual driving performance appear to be so small. As in many previous investigations, subjects attempted to compensate for anticipated adverse effects of marijuana smoking. Our subjects were aware of the impairing effects of THC as shown by lower ratings of perceived driving quality. Consequently, they invested more effort to accomplish the driving tests following THC than placebo. Furthermore, in the car following test, they drove at a greater headway after marijuana smoking; and, in both road tracking and city driving tests, they slightly reduced their driving speed. Yet despite their effort, subjects were unable to fully compensate for THC's adverse effects on lateral position variability. This is because SDLP is primarily controlled by an automatic information processing system which operates outside of conscious control. The process is relatively impervious to environmental changes, as shown by the high reliability of SDLP under repeated placebo conditions, but highly vulnerable to internal factors that retard the flow of information through the system. THC and many other drugs are among these factors. When they interfere with the process that restricts SDLP, there is little the afflicted individual can do by way of compensation to restore the situation. Car following and, to a greater extent, city driving performance depend more on controlled information processing and are therefore more accessible for compensatory mechanisms that reduce the decrements or abolish them entirely.

This still leaves the question open why performance appears to be more affected by THC in laboratory than actual driving tests. Many researchers defend the primacy of laboratory performance tests for measuring drug effects on skills related to driving on the basis of superior experimental control. Certainly some control is always necessary to reduce the confounding influence of extraneous factors that would otherwise so increase measurement error as to totally obscure the drug's effects. However, only some extraneous factors are truly sources of measurement error and others either attenuate or amplify drug effects in real driving and must be considered as relevant to a test's predictive validity. Simply eliminating all of them, first, removes their normal mediating influence on the drug effect, and secondly, affects the subject's motivation to perform the test by making it appear "unreal". Controlling the test usually involves drastic simplification and restriction of response options. The desire in doing this is to isolate a particular driving skill and determine how it changes under the influence of drugs. However, drivers always apply numerous skills in parallel and series. Should one become deficient, they are often able to compensate in a number of ways to achieve a satisfactory level of proficiency. Thus the demonstration of some particular skill decrement in the laboratory in no way indicates that this would ultimately reduce driving safety in reality. Finally there are some skills that simply can not be measured in laboratory tests, at least not easily enough to make it a routine matter. The acquisition of any skill which depends upon automatic information processing requires practice over weeks or months. After learning to drive, subjects possess such skills in

abundance and one can only demonstrate how they vary with drug effects in the real task or a very close approximation thereof.

Profound drug impairment constituting an obvious traffic safety hazard could as easily be demonstrated in a laboratory performance test as anywhere else. But THC is not a profoundly impairing drug. It does affect automatic information processing, even after low doses, but not to any great extent after high doses. It apparently affects controlled information processing in a variety of laboratory tests, but not to the extent which is beyond the individual's ability to control when he is motivated and permitted to do so in real driving. In short, it would appear as if over-control in laboratory performance tests has resulted in a misimpression of THC's effect, incomplete in some respects and exaggerated in others. The actual driving tests may provide a more realistic impression of the drug's effects, albeit still incomplete and perhaps tending to minimize them with respect to more complex driving situations that come closer to "worst case".

The degree of experimental control also varied between driving tests in this series in ways affecting the subjects' motivation. This is illustrated by a comparison between the first and second driving study. The standard road tracking test was applied in both, first in the absence and then in the presence of other traffic. It was only during the former that disturbing observations of two individuals' attentional deficits caused the driving instructor to intervene. Driving in the presence of other traffic, subjects were always able to complete the rides without intervention. Lateral position control, an automatic process, did not change as a consequence of the absence or presence of other traffic. What did change was the subjects' motivation to focus attention, a controlled process. Motivation in the second study was very probably affected by recognition of the increased risk of the untoward consequences of wandering attention. This means that the intrinsic motivation produced by the reality of the test situation is an important mediator of THC's effects on performance.

Compensatory mechanisms help the driver under the influence of marijuana to maintain an effective level of performance but with an associated cost. If drivers compensate for THC's adverse effects by diminishing driving demands (e.g. by reducing speed and/or increasing headway), this will occur without a reduction in spare capacity. But if they increase effort as well (e.g. by focusing attention), it will occur at the expense of spare capacity. Less capacity would be left for simultaneously performing another task, such as conversing with passengers, using a car telephone, or handling emergency situations. The information processing capacity these situations demand may well go beyond the driver's spare capacity with the result of impaired and perhaps dangerous driving. Results of the present program show that THC increases the mental load of driving, as shown by increased effort ratings and reduced heart rate variability, and consequently reduces spare capacity. This corroborates results from previous simulator and closed-course studies that with reasonable consistency show an adverse THC effect on subsidiary task performance (Smiley, 1986). Further research is required to determine marijuana's effects on *actual* driving performance when the driver is simultaneously performing another task or suddenly confronted with a situation that requires a rapid adaptive response. The latter was occasionally encountered during the city driving test, but only after a low THC dose. The city driving test should therefore be repeated with subjects consuming higher THC doses.

Hazardous driving can also occur in situations that demand very little of the driver's information processing capacity. If the driving task is very monotonous and the demand is low, wandering attention may result in negligent monitoring with disastrous results. This is in fact what happened twice during the driving study on the closed road. After the highest THC dose,

one subject failed to shift attention from the prescribed task to an unexpected event (screwdriver on the road); another failed to anticipate a normal event (end of circuit). Though even sober experienced drivers may experience similar deficits, the fact that it happened twice after the highest THC dose, and never after a lower dose or placebo, strongly suggests that drivers under the influence of THC would be unusually susceptible to attentional deficits during prolonged and monotonous driving.

How do marijuana's effects on driving performance compare to those of alcohol? There are two sources from which one can draw to answer the question. Information can be directly obtained from studies comparing THC and alcohol effects in the same experiment; and, indirectly, from studies wherein alcohol's effects were assessed using the same methods as applied in the present THC studies. As mentioned in Chapter 1, most closed-course studies on THC also measured alcohol's effects (BACs between 0.04 and 0.10 g%). It was generally concluded that THC's effects were less than alcohol's, especially at BACs above 0.08 g%. The city driving study in the present program also compared the effects of modest doses of alcohol and THC. For doses administered in that study, alcohol produced the greater effects. Indirect evidence concerning the relative effects of THC and alcohol can be obtained from three studies. First, the alcohol calibration study by Louwerens *et al.* (1985, 1987) which resembled our first driving study in many respects. According to their empirical equation, THC's effects on SDLP were equal to or less than that of BAC=0.07 g%. More recently, studies by Riedel *et al.* (1989) and Ramaekers *et al.* (1992a) measured the effects of low doses of alcohol (BACs of 0.05 and 0.03 g% respectively) on SDLP. Both groups applied the standard test in the presence of other traffic, as in our second driving study, but on another highway. Mean SDLPs were respectively about 5.0 and 2.5 cm higher while driving after alcohol than placebo. The former elevation is greater than that produced by the highest THC dose in our study. The latter lies between the effects of 200 and 300 µg/kg doses, which were 1.8 and 2.9 cm respectively. There was some discrepancy between alcohol's effects on SDLP in the more recent studies and those predicted by the empirical equation: the former were higher than predicted. The discrepancy appears to be related to the difference between alcohol's effects on the ascending and descending phases of its pharmacokinetic profile. Louwerens measured alcohol's effects at the time when BAC was at the ascending but Riedel and Ramaekers measured them during the descending phase. Notwithstanding methodological differences among studies, both direct and indirect evidence converge on the conclusion that THC's effects after doses up to 300 µg/kg never exceed alcohol's at BACs of 0.08 g%.

How do marijuana's effects on driving performance compare to those of drugs other than alcohol? No direct comparisons have ever been made, but many studies employing the standard road tracking test were conducted for measuring other drugs' effects on SDLP during the last decade. The results from a few will be mentioned. Diazepam (Valium®) given for one week in a low therapeutic dose (5 mg, thrice daily) caused anxious patients to drive with a mean SDLP about 7 cm higher than their premedication baseline (Van Laar *et al.*, 1992). The same drug and dose given over the same period caused healthy volunteers to drive with a mean SDLP about 6 cm higher than placebo (Van Veggel and O'Hanlon, 1993). Lorazepam (Ativan®), another anxiolytic, given twice daily for one week in a 1.5 mg dose to healthy volunteers (Volkerts *et al.*, 1988) and a 2 mg dose to patients (Vermeeren *et al.*, 1993), produced an elevation of SDLP of about 10 cm in both cases. Amitriptyline (Elavil®), a widely prescribed antidepressant, given in a dose of 50 mg at night and 25 mg in the morning caused healthy volunteers to drive with a mean SDLP about 6 cm higher than placebo (Robbe *et al.*, 1989). Flurazepam (Dalmane®),

a hypnotic, was administered to insomniacs and its "hang-over" effects on SDLP were measured 10-11 hours after ingestion. A 15 mg dose of flurazepam elevated mean SDLP by about 4 cm; a 30 mg dose, 7 cm. Antihistamines also cause sedation and, consequently, impair road tracking performance. Triprolidine (Actifed[®]) increased SDLP by 3.5 cm after a single 5 mg dose (Riedel *et al.*, 1990); and, diphenhydramine 50 mg (Benadryl Kapseals[®]) increased SDLP by 4.5 cm (Ramaekers *et al.*, 1992b). This is not to say that all psychotropic drugs produce greater elevations of SDLP than THC. Many in the same and other experiments had less effect than THC did in our studies. These examples are merely cited to indicate that THC's effects as measured in the standard test were in no way unusual. In so far as its effects on SDLP are concerned, THC was just another moderately impairing drug.

The foregoing comparisons might be misleading. THC's effects differ qualitatively from many other drugs, especially alcohol. For example, subjects drive faster after drinking alcohol and slower after smoking marijuana (Hansteen *et al.*, 1976; Casswell, 1979; Peck *et al.*, 1986; Smiley *et al.*, 1987). Moreover, the simulator study by Ellingstad *et al.* (1973) showed that subjects under the influence of marijuana were less likely to engage in overtaking maneuvers, whereas those under the influence of alcohol showed the opposite tendency. Very importantly, our city driving study showed that drivers who drank alcohol over-estimated their performance quality whereas those who smoked marijuana under-estimated it. Perhaps as a consequence, the former invested no special effort for accomplishing the task whereas the latter did, and successfully. This evidence strongly suggests that alcohol encourages risky driving whereas THC encourages greater caution, at least in experiments. Another way THC seems to differ qualitatively from many other drugs is that the former's users seem better able to compensate for its adverse effects while driving under the influence. Weil *et al.* (1968) were among the earliest authors who mentioned the possibility that marijuana users can actively suppress the drug's adverse effects. They presumed that THC's effects were confined to higher cortical functions without any general stimulatory or depressive effect on lower brain centers. According to them, the relative absence of neurological, as opposed to psychiatric, symptoms in marijuana intoxication suggests this possibility. More recently, Moskowitz (1985) concluded that the variety of impairments found after marijuana smoking could not be explained by decrements in sensory or motor functions which led him to hypothesize that some important central cognitive process is impaired by THC, without saying what it is. Identification of THC's site of action would greatly enhance our understanding of the drug's psychopharmacological effects.

Epidemiological research has shown that THC is infrequently detected in the blood of fatally injured drivers as the only drug present. In most cases alcohol is also detected. The effects of the combination of THC and alcohol on actual driving performance have never been studied in the presence of other traffic. Closed-course studies have shown that the effects of both drugs, when taken in combination, are generally additive (Attwood *et al.*, 1981; Peck *et al.*, 1986). This may only be so for those behaviors that are similarly affected by both drugs given separately. Closer examination of the combined use is warranted in those driving situations where both drugs produce qualitatively different effects. It may well be so that alcohol reduces drivers' insight or motivation to the point where they would no longer attempt to compensate for the THC effect. As a result, the combined effects on drivers' performance could well be greater than the sum of either drug acting separately. There is therefore a great need for further research on marijuana and actual driving research, but now extended to the combination of marijuana and alcohol.

In summary, this program of research has shown that marijuana, when taken alone, produces a moderate degree of driving impairment which is related to the consumed THC dose. The impairment manifests itself mainly in the ability to maintain a steady lateral position on the road, but its magnitude is not exceptional in comparison with changes produced by many medicinal drugs and alcohol. Drivers under the influence of marijuana retain insight in their performance and will compensate where they can, for example, by slowing down or increasing effort. As a consequence, THC's adverse effects on driving performance appear relatively small. Still we can easily imagine situations where the influence of marijuana smoking might have an exceedingly dangerous effect; i.e., emergency situations which put high demands on the driver's information processing capacity, prolonged monotonous driving, and after THC has been taken with other drugs, especially alcohol. We therefore agree with Moskowitz' conclusion that "any situation in which safety both for self and others depends upon alertness and capability of control of man-machine interaction precludes the use of marihuana". However, the magnitude of marijuana's, relative to many other drugs', effects also justify Gieringer's (1988) conclusion that "marijuana impairment presents a real, but secondary, safety risk; and that alcohol is the leading drug-related accident risk factor". Of the many psychotropic drugs, licit and illicit, that are available and used by people who subsequently drive, marijuana may well be among the least harmful. Campaigns to discourage the use of marijuana by drivers are certainly warranted. But concentrating a campaign on marijuana alone may not be in proportion to the safety problem it causes.

DRUG PLASMA CONCENTRATIONS AND DRIVING PERFORMANCE

One of the program's objectives was to determine whether it is possible to predict driving impairment by plasma concentrations of THC and/or its metabolite, THC-COOH, in single samples. The answer is very clear: it is not. Plasma of drivers showing substantial impairment in these studies contained both high and low THC concentrations; and, drivers with high plasma concentrations showed substantial, but also no impairment, or even some improvement. The first driving study showed that impairment in the road tracking test was nearly the same in the first and second test, executed between 40-60 and 100-120 minutes after initiation of smoking, respectively. Plasma concentrations of THC and THC-COOH, however, were not the same during the tests: both were lower during the second than the first. The same pattern was found for ratings of perceived "high". It has been said that behavioral signs of intoxication, though small, outlast physiological and subjective reactions to THC (Reeve *et al.*, 1983; Yesavage *et al.*, 1985). To examine this hypothesis, future research should extend actual driving performance measurements to 4, 8, 16 and 24 hours after smoking. If driving impairment still occurs after THC disappears from plasma, it could mean that previous epidemiological research has underestimated the proportion of drivers who were driving under the influence of marijuana at the times their accidents occurred.

Mean speed was the only measure of driving performance that was even moderately related to plasma concentrations of the drug. Subjects with higher THC concentrations in plasma drove slower in the standard road tracking test (correlations varying from $r = -.18$ to $r = -.72$ between conditions). This effect might have been even more pronounced if the subjects had not been instructed to drive at a particular speed, and if they had had no feedback from the speedometer.

CONCLUSIONS

The major conclusions from the present program are summarized as follows:

- Current users of marijuana prefer THC doses of about 300 $\mu\text{g/kg}$ to achieve their desired "high".
- It is possible to safely study the effects of marijuana on driving on highways or city streets in the presence of other traffic.
- Marijuana smoking impairs fundamental road tracking ability with the degree of impairment increasing as a function of the consumed THC dose.
- Marijuana smoking which delivers THC up to a 300 $\mu\text{g/kg}$ dose slightly impairs the ability to maintain a constant headway while following another car.
- A low THC dose (100 $\mu\text{g/kg}$) does not impair driving ability in urban traffic to the same extent as a blood alcohol concentration (BAC) of 0.04 g%.
- Drivers under the influence of marijuana tend to over-estimate the adverse effects of the drug on their driving quality and compensate when they can; e.g. by increasing effort to accomplish the task, increasing headway or slowing down, or a combination of these.
- Drivers under the influence of alcohol tend to under-estimate the adverse effects of the drug on their driving quality and do not invest compensatory effort.
- The maximum road tracking impairment after the highest THC dose (300 $\mu\text{g/kg}$) was within a range of effects produced by many commonly used medicinal drugs and less than that associated with a blood alcohol concentration (BAC) of 0.08 g% in previous studies employing the same test.
- It is not possible to conclude anything about a driver's impairment on the basis of his/her plasma concentrations of THC and THC-COOH determined in a single sample.

RECOMMENDATIONS FOR FUTURE RESEARCH

The recommendations for future research are summarized as follows:

- Future studies on marijuana's effects on driving performance should include the THC dose that current users of marijuana prefer to achieve their desired "high", i.e. 300 $\mu\text{g}/\text{kg}$.
- Subjects in future studies should be familiarized with the potency of the material providing THC before the beginning of tests designed to measure its effects on performance.
- Future research determining marijuana users' preferred dose should involve administering THC in different marijuana preparations that encompass a wide range of potencies.
- Further research is required for determining marijuana's effects on actual driving performance in the presence of other traffic when the driver is simultaneously performing another task or suddenly confronted with a situation that requires a rapid adaptive response.
- The city driving test should be repeated with subjects consuming THC doses over 100 $\mu\text{g}/\text{kg}$.
- Further research on marijuana and actual driving research should be extended to include combinations of marijuana and alcohol.
- Future research should extend actual driving performance measurements to 4, 8, 16 and 24 hours after smoking.

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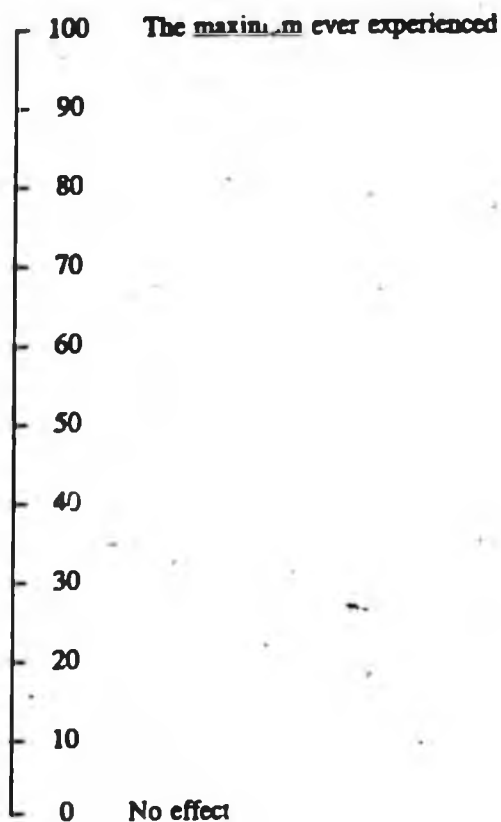
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APPENDIX A

Questionnaires

Subjective Intoxication and Willingness to Drive Questionnaires

Please rate your feeling of "high" (or "drunkness" after drinking alcohol) as a percentage of the maximum ever experienced.



Would you attempt to drive for a set distance if the reasons were:

A. unimportant though gratifying, such as for transporting a friend to another party	Y / N
B. <u>important</u> but avoidable, such as for transporting a mildly sick friend home when he would otherwise have to call a taxi	Y / N
C. urgent, such as transporting a severely sick infant to the hospital	Y / N

Mood Rating Scale (Bond and Lader, 1974)

This form is a mood rating scale and the intention is to measure your feelings as they are at this moment. The instructions are given below. Please read them carefully and proceed. Have you any questions?

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as presenting the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	Drowsy (1)
Calm	_____	Excited (2)
Strong	_____	Feeble (3)
Muzzy	_____	Clear headed (4)
Well-coordinated	_____	Clumsy (5)
Lethargic	_____	Energetic (6)
Contented	_____	Discontented (7)
Troubled	_____	Tranquil (8)
Mentally slow	_____	Quick witted (9)
Tense	_____	Relaxed (10)
Attentive	_____	Dreamy (11)
Incompetent	_____	Proficient (12)
Happy	_____	Sad (13)
Antagonistic	_____	Amicable (14)
Interested	_____	Bored (15)
Withdrawn	_____	Sociable (16)

Do you think you received placebo or active drug ? Placebo / Active

Scores on these scales were grouped to form 3 cluster scores for measuring the corresponding factors: alertness (1,3,4,5,6,9,11,12,15), contentedness (7,8,13,14,16) and calmness (2,10).

Perceived Effort Scale (Zijlstra and Van Doorn, 1985)

Please rate the effort made while performing the driving test.

A vertical scale with 11 horizontal tick marks. The labels are positioned to the right of the scale, aligned with specific tick marks. The labels, from top to bottom, are: 'extreme effort', 'very great effort', 'great effort', 'considerable effort', 'rather much effort', 'some effort', 'a little effort', 'almost no effort', and 'absolutely no effort'. There are also two tick marks at the top of the scale without labels, and one tick mark at the bottom without a label.

Effort Level
extreme effort
very great effort
great effort
considerable effort
rather much effort
some effort
a little effort
almost no effort
absolutely no effort

Perceived Driving Quality Scale (translated from Dutch)

Please rate the quality of your driving in the test you just finished.

I drove exceptionally well

I drove normally

I drove exceptionally poorly

Translation of the Royal Dutch Tourist Association's original "Verslag Rijvaardigheidstest".

The following categories did not apply to the driving test and were dropped from the scoring sheet: "Condition of the Car" (Category I.01), "Railway Level Crossing" (Category III.16), and several Special Maneuvers (Categories V.19 to V.26, V.28 to V.30).

I VEHICLE CHECKS

02 Preparing to drive off

- 02-1 Passing in front of car and observing traffic
- 02-2 Clear view and clean windows
- 02-3 Position of driver's seat
- 02-4 Instrument check
- 02-5 Starting the engine
- 02-6 Use of safety belt(s)
- 02-7 Checking mirrors
- 02-8 Proper use of lights

03 Driving off

- 03-1 Checking position of hand-brake
- 03-2 Looking ahead, to the side and to the rear before driving off
- 03-3 Selecting correct position in traffic lane
- 03-4 Adapting speed immediately to traffic flow
- 03-5 Re-checking mirrors

II HANDLING OF VEHICLE

04 Manner of sitting behind the wheel, and steering

- 04-1 Manner of sitting behind the wheel when driving
- 04-2 Position of hands on the wheel
- 04-3 Steering through curves
- 04-4 Position of head whilst talking to passengers

05 Handling of controls

- 05-1 Accelerator
- 05-2 Foot-brake
- 05-3 Hand-brake
- 05-4 Clutch-pedal
- 05-5 Gear-lever

06 Speed control, deceleration and stopping

- 06-1 Choice of speed in view of circumstances
- 06-2 Use of accelerator and brake
- 06-3 Use of mirrors before and during deceleration
- 06-4 Indication of deceleration in good time by use of stop-lights
- 06-5 Correct sequence of maneuvers for deceleration
- 06-6 Declutch at the correct stage and put gear-lever in neutral
- 06-7 Come to a stop smoothly
- 06-8 Clutch not depressed whilst waiting

07 Taking corners

- 07-1 Safe starting speed
- 07-2 Selecting correct gear before entering corner
- 07-3 Without slipping clutch or foot on the clutch-pedal
- 07-4 No braking in corner
- 07-5 No free-wheeling
- 07-6 Correct driving line

III ACTION IN TRAFFIC

08 Driving straight

- 08-1 Keeping to the right
- 08-2 Adapting speed to that of other similar traffic
- 08-3 Looking into side streets
- 08-4 Taking into account blind spots caused by car design and passengers
- 08-5 Taking into account limitation of mirrors
- 08-6 Keeping distance from traffic in front
- 08-7 Driving in offset position with regard to preceding vehicle
- 08-8 Pedestrian crossings
- 08-9 Watching for pedestrians crossing the road (at other places than at zebra crossings)

09 Behavior at or near crossroads

- 09-1 Judging the situation beforehand
- 09-2 Behavior at the approach to traffic lights
- 09-3 Driving in traffic lanes marked with arrows, and according to other indications on road surface
- 09-4 Taking position in traffic lanes marked with arrows
- 09-5 Bicycle and bus lanes
- 09-6 Consideration of other drivers
- 09-7 Complying with priority rules

10 Right-hand turn

- 10-1 Taking position in good time when filtering (selection of correct lane)
- 10-2 Looking behind and to the right
- 10-3 Switching on direction indicators
- 10-4 Positive filtering and in good time, adapting speed
- 10-5 Looking over right shoulder
- 10-6 Not impeding traffic that continues straight ahead
- 10-7 Final check
- 10-8 Taking corner as closely as possible

11 Left-hand turn

- 11-1 Taking position in good time when filtering (selection of correct lane)
- 11-2 Looking to the rear, rear left and left
- 11-3 Switching on direction indicators
- 11-4 Positive filtering and in good time, adapting speed
- 11-5 Not impeding traffic that continues straight ahead
- 11-6 Correct timing of wheel turning and position on wide crossings
- 11-7 Final check
- 11-8 Taking a sufficiently wide corner

12 Overtaking

- 12-1 Judging traffic flow correctly and in time (oncoming, behind and to the left)
- 12-2 Switching on direction indicators
- 12-3 Moving out smoothly and in good time
- 12-4 Canceling direction indicators
- 12-5 Observing vehicle that will be overtaken
- 12-6 Overtaking quickly and safely
- 12-7 Keeping well clear of overtaken cyclists
- 12-8 Reverting to the right
- 12-9 Overtaking on the right when permitted

13 Traffic lane technique

- 13-1 Keeping well within lane
- 13-2 Checking traffic before leaving lane
- 13-3 Changing traffic lanes one at a time
- 13-4 Driving straight, avoiding minor deviations
- 13-5 Driving in lines abreast
- 13-6 Overhead traffic lane control

14 Driving on roundabouts

- 14-1 Observation (dividing attention)
- 14-2 Using direction indicators during the entire maneuver
- 14-3 Correct positioning for turning in good time
- 14-4 Selecting and driving in the correct traffic lane
- 14-5 Weaving out of the traffic flow correctly and in good time

15 Driving on highways

- 15-1 Using acceleration lane, observing traffic on highway
- 15-2 Choice of speed and lane
- 15-3 Correct distance to vehicle in front
- 15-4 Stopping and parking in emergency stopping lane (if permitted)
- 15-5 Leaving emergency stopping lane
- 15-6 Use of lay-bys
- 15-7 Behavior at approach to intersections
- 15-8 Use of deceleration lane

IV OBSERVATION AND UNDERSTANDING OF TRAFFIC

17 Observation

- 17-1 Observation technique
- 17-2 Observation of overall picture of traffic, road and surroundings
- 17-3 Conscious observation of traffic signs
- 17-4 Use of direction signs

18 Understanding of traffic

- 18-1 Anticipation
- 18-2 Making allowance for any traffic situations that may occur
- 18-3 Reactions to observations made
- 18-4 Strategy

Proceeding Through
Intersection

Speed (S)

Low Traffic Density

Correct Response

The driver will reduce speed before entering a four-way blind uncontrolled intersection.

1. Brakes gently, to 10 to 15 mph, one car length before the corner and continues to cover brake pedal until the traffic checks have been completed.
2. Does not stop or go slowly once into the intersection.
3. Accelerates through the intersection.

Normal Transit
Between Intersections

Speed Control (S)

High-medium or Low

Traffic Density

Correct Response

The driver will select the appropriate speed for conditions, be guided by speed limit signs, laws, and traffic conditions.

1. Does not exceed the legal speed limit at any time between the beginning of the (S) coding and the start of coding the next maneuver.
2. Does not exceed the speed of the traffic flow by more than 4 mph.
3. Does not fall below the speed limit by more than 4 mph unless traffic or potential hazards require it.

Following Distance

(F)

High Traffic Density

Correct Response

The driver must maintain at least a 2-second interval from traffic ahead at all times.

Unless there is a significant amount of traffic, there is no opportunity to observe this. If the situation is favorable, there is ample opportunity to observe following distance in normal transit on high density streets. Following distance can also be coded if the driver comes up on slow traffic or traffic stopped at an intersection. Interrupt assessment of following distance to observe mirror check before driver slows down, but then return to following distance as he comes up on traffic. The driver must anticipate slowing of traffic ahead. He must brake gradually enough that he does not throw passengers forward. He must maintain a 2-second distance at all times. Following distance (F) is necessarily indicated on the scoring sheet at specific locations but refers to the entire segment of the route between two turns. If two F's occur, attempt to code it twice in that segment. Do not code following distances of more than four seconds. If it cannot be coded, underline the F's.

Stop Sign

Limit Line (LL)

Correct Response

Stop sign for the driver's vehicle, but none for cross traffic. The driver must stop behind the limit line (and then continue when traffic permits). If there is no physical limit line, the stop should be made behind a line connecting the two near corners of the street the vehicle is on. The vehicle must not enter the intersecting street.

1. Stops behind limit line.

Mirror Check

(M)

The driver will check rear view mirror before any speed reduction or lateral movement and when approaching a traffic light. The coder must attend to the mirror check as soon as the previous coding has been completed, since driver may check early and, if there is no traffic, may not need to repeat.

Gap Acceptance
(G)

Correct Response

Gap ~~acceptance~~ is coded on some turns where path and speed on the turn are also called for. The novice should decline the smallest gaps that an experienced driver might accept but should not wait when there is ample time.

1. Accepts a 10-second gap; does not accept a gap smaller than 9 seconds*. The coder should check his judgment by counting seconds (1001, 1002, etc.). If driver accepts too small a gap, code it as X. (Examiner may also code Hazard, X, or Instructor Control, I.)
2. Gap is also wrong if there is no traffic and driver does not move promptly.
3. If there is no traffic and the driver moves promptly, underline G (i.e., a judgment cannot be made).

Pre-operation
(Pre-op)

Correct Response

The driver will perform these pre-operation checks before starting the engine:

1. Adjusts seat.
2. Fastens seat belt and shoulder harness.
3. Checks and insures that all passengers are also buckled up.
4. Adjusts both mirrors correctly. If driver must make head adjustments, or adjusts mirrors later, then go back and mark Pre-op wrong.

Shut Down
(S.D.)

Correct Response

The driver will perform these shut-down checks:

1. Puts gear selector lever in Park (or gear shift in neutral).
2. Turns ignition off.
3. Sets parking brake.

Y Turnabout
Low Density Traffic
(residential)
Location (L)

Correct Response

Driver will choose a safe location for the Y turnabout (three-point turnabout).

1. Chooses a point at least 200 feet from any intersection.
2. Does not start a Y turnabout when pedestrians or vehicles are nearby.
3. If there is no safe place to turn and the driver traverses the whole block without attempting to turn, underline Location (L) and Backing (B). (The instructor will tell the driver how to get back on the route.)

Backing (B)

Correct Response

Driver will look left, right, and back before moving the car in reverse.

1. Looks left and right before backing.
2. Turns head around and looks straight back over right shoulder when moving the car in reverse. Failure to be looking straight back at all times that the car is moving backwards is disqualifying, except for brief checks left, right, and forward.

* Experience drivers may accept smaller gaps, but must not throw passengers off balance nor clear on-coming car by less than 4 seconds.

Right Turn
Path (P)
Low Density
Traffic
Correct Response

The driver must select a path that will allow him to start his turn two to three feet from the curb and finish his turn in the middle of the right half of the street.

1. Begins turning when vehicle is two to three feet from the curb and front wheels are even with the beginning of the bend of the curb.
2. Turns steering wheel smoothly and follows a smooth curve to the center of the right lane on the new street.

Right Turn
Speed Control (S)
High and Medium
Density Traffic
Correct Response

The driver will decelerate smoothly before the turn and accelerate smoothly when clearing the intersection.

1. Decelerates smoothly before the turn to 8-10 mph, or less if traffic warrants.
2. Accelerates smoothly two-thirds of the way through the turn, increasing speed quickly enough so that following traffic in new path would not have to slow down or change lanes for driver's vehicle. (The coder must turn around and observe traffic.)
3. Adjusts speed to flow of traffic.
4. Accelerates promptly; if driver hesitates or starts and stops without cause, speed is coded X.

Right Turn
Speed Control (S)
Low Density
Traffic
Correct Response

Driver must control his speed by braking before the turn and resuming normal speed after completing his turn.

1. Before one car length from the corner, brakes to a speed of 8 to 10 mph.
2. Accelerates smoothly as soon as driver is two-thirds of the way through the turn.
3. Accelerates promptly; if driver hesitates or starts and stops without cause, speed is coded X.

Right Turn
Observing (O)
High, Medium &
Low Density Traffic
Correct Response

Driver will scan the intersection for potential conflicts with vehicles and pedestrians prior to initiating turn.

1. Turns head to the right and looks for pedestrians or vehicles that could block intended path. If a pedestrian is on right near corner, head movement must indicate check of the spot (75° head movement).
2. Turns head to the left and looks for approaching cross traffic.
3. Turns head to the right again and looks at turn path just prior to the execution of the turn.
Order of checks is important. (Note: forward scan will usually not be noticeable.)
4. Completes these checks quickly and does not look for more than 2 seconds (count of 1001, 1002) at any spot unless there is traffic and the driver's vehicle is stopped.

Lane Change
Path (P)
High or Medium
Density Traffic
Correct Response

The driver must maintain a straight lane position during scanning procedures (mirrors and blind spot). He must signal before he moves and cancel after the move is completed. The driver then steers smoothly with a gradual angular movement into the middle of the new lane without swerving to either side of the lane.

1. Maintains straight path while scanning.
2. Signals before the lane change.
3. Steers smoothly with gradual angular movement.
4. Straightens vehicle in new lane.
5. Cancels a signal.

Lane Change
Speed (S)
High or Medium
Density Traffic
Correct Response

Driver will decrease, increase, or maintain speed according to traffic conditions.

1. If flow of traffic of new lane is faster, increases speed when entering new lane.
2. If flow of traffic of new lane is slower, decreases speed when entering new lane.
3. If flow of traffic of new lane is of equal speed, maintains speed when entering new lane.

Lane Change
Observing Traffic (O)
High or Medium
Density Traffic

The driver will scan one or both mirrors, as appropriate, and check blind spot before changing lanes. He will observe traffic ahead in both present and intended lanes for possible slowing. Lane change (right or left) is necessarily indicated on the scoring sheet at specific locations but refers to the entire segment of the route between two turns. If two lane change arrows occur within a segment (between turns), both of them should be coded whenever they occur. Ignore aborted lane changes. (If they are dangerous, the examiner will code hazard, and mark it wrong.)

Correct Response

1. Checks traffic ahead in present and intended lanes.
2. Checks rear view mirror.
3. Checks outside mirror for left hand change.
4. Checks blind spot by turning the head briefly (appr. 1 second: if the coder counts 1002, it is too long) in the direction of the lane change and then before steering into the new lane, again checks forward traffic. Driver must not look through back window when checking blind spot. If he does, check is wrong (X).

Proceeding Through
Intersection
Observing Traffic (O)
Correct Response

The driver will scan the intersection before entering.

1. The driver will look left and right before entering a four-way controlled intersection.
2. At a four-way uncontrolled blind intersection, the driver will look left and right before entering the intersection. If blind at that point for less than 200 yards, checks left again.
3. At a blind tee intersection, the driver will look briefly in the direction of the adjoining street.
4. For all checks at intersections, the driver will not look in any direction for more than 2 seconds (count of 1001, 1002) at any spot unless there is traffic and the driver's vehicle is stopped.

Maneuvers in Molecular Approach (from Jones, 1978).

Left Turn

Path (P)

High, medium or low traffic density.

Correct Response

The driver will follow a standard path. A standard path runs from the center of the left-most lane of the original street to the center of the left-most lane of the intersecting street*. The turn must commence at a point one-third to one-half of the way into the intersection. The path passes just to the left of the center of the intersection. If the light is red, the driver must stop clearly behind the crosswalk line.

1. Enters intersection in the center of the left-most lane of a 4 (or more) lane street, or center of lane if single lane in each direction, and remains in the center until turning begins.
2. Begins turning when one-third to one-half of the way into the intersection.
3. If the car must stop for oncoming traffic in the intersection, the wheels must remain straight until the turn is started. (After stop, if vision is blocked by a left-turning truck, the driver may move forward into the turn but if he enters the oncoming travel lane and forces vehicles to compensate, examiner will score Hazard or Instructor Control and coder should underline P.)
4. Passes just to left of center of the intersection.
5. Completes turn in center of the left-most lane of intersecting street*. (If that lane is blocked or otherwise inaccessible, for example, a roadwork crew or a disabled vehicle, and the driver selects another lane, the examiner will code as Hazard or Instructor Control (see Examiner's Manual) and coder should underline P.)
6. Stops well behind nearest crosswalk line if light is red.

Left Turn

Speed (S)

High and Medium Density Traffic

Correct Response

The driver will decelerate smoothly before the turn and accelerate smoothly when clearing the intersection. Failure to accelerate promptly is a frequent error of novice drivers.

1. Decelerates smoothly, coming to a stop or near stop if there is traffic. At no time should the tires squeal or the passengers be thrown.
2. Accelerates smoothly, soon after he passes the one-third mark in the turn, steadily increasing to traffic speed.
3. Adjusts speed so that vehicle does not interfere with oncoming traffic.
4. Accelerates promptly; if driver hesitates or starts and stops without cause, speed is coded X.

Left Turn

Speed (S)

Low Density Traffic

Correct Response

The driver will control his speed before the turn by braking to 10-12 mph one car length from the corner. He will accelerate smoothly two-thirds of the way through the turn. (Driver must approach between 20 and 25 mph).

1. Before the turn, brakes to 10-12 mph.
2. Two-thirds of the way through the turn, accelerates smoothly out of the turn.
3. Accelerates promptly; if driver hesitates or starts and stops without cause, speed is coded X.

* For experienced drivers, it is acceptable to end in any open lane if it is safe to do so. This is not acceptable for novice drivers.

V SPECIAL MANEUVERS

27 Turning

- 27-1** Stopping at the correct place
- 27-2** Driving slowly, while turning steering wheel rapidly; no use of steering wheel while stopped
- 27-3** Looking alongside the car when approaching the kerb
- 27-4** Observing traffic during the entire maneuver

69 of 100 DOCUMENTS

National Library of Medicine MEDLINE Database

TITL: Marijuana use and depression.

AUTH: Green B E; Ritter C

ORGA: Department of Sociology, Ohio State University, Columbus 43210, USA, green.446@osu.edu

PUB TYPE: Journal Article.

CITE: *J Health Soc Behav.* 2000 Mar; 41 (1): 40-9.

LANG: ENG; English

ABST: The primary goal of this study is to examine the association between marijuana use and adult depressive symptomatology. The key independent variables examined are age of marijuana initiation, frequency of current marijuana use, the use of other licit and illicit drugs, and whether marijuana was used to cope with problems. The relationships among these variables are assessed using data from the Young Men and Drugs Survey (n = 1,941), a nationally representative sample of men from the 1944-1954 birth cohort. Results show that early marijuana initiation appears to be weakly associated with increased depression in adulthood. This effect, however, is mediated by educational attainment, employment status, marital status, and other drug use, notably alcohol and tobacco use. Adult frequency of marijuana use is not significantly associated with increased depression in adulthood. Finally, marijuana users who use the drug to cope with problems are more depressed than those who do not use to cope with problems.

MJTR: Depression, complications. Marijuana Smoking, adverse effects.

MNTR: Adaptation, Psychological. Adult. Depression, psychology. Humans. Male. Research Support, U.S. Gov't, P.H.S..

GEOT: UNITED STATES

IDEN: ISSN: 0027-1465. JOURNAL-CODE: 0103130. ENTRY-DATE: 20000427. NIH-GRANT-NUMBER: 5T32-MH14592/MH/NIMH. DA-02646/DA/NIDA. SPECIAL-LIST: IM. JOURNAL-SUBSET: IM.

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MARIJUANA AND MEDICINE: ASSESSING THE SCIENCE BASE

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11 a.m. EST**

PLEASE CITE AS A REPORT OF THE
INSTITUTE OF MEDICINE

Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr., *Editors*

Division of Neuroscience and Behavioral Health

INSTITUTE OF MEDICINE

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Preface

Why study the medical value of marijuana now? What circumstances provoked this analysis and report? There have been a variety of influences since the IOM Report of 1982. First, advocates of personal choice with a growing distrust of scientific medicine sought alternatives congruent with their values about health and life. This view was expressed at the ballot box in recent state referenda. Proponents claimed their own "scientific evidence" of marijuana's safety and effectiveness. Others, distressed by the societal ravages of drug abuse, especially among young people, view legalized medical marijuana as a subterfuge enabling liberalization, the potential "gateway" to even more harmful substance abuse. Meanwhile, there have been remarkable and accelerating advances of relevant knowledge in molecular and behavioral neuroscience, in particular newly elaborated systems of transmitters, receptors, and antagonists—all illuminating the physiological effects of cannabinoids, both those found in nature and those normally found in the brain. (Cannabinoids are the group of compounds related to THC, the primary psychoactive ingredient in marijuana.) The new science could inform policies responding to the public divide.

In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. That review began in August 1997 and culminates with this report.

Information for this study was gathered through analysis of the relevant scientific literature, scientific workshops, site visits to cannabis buyers' clubs and HIV/AIDS clinics, and extensive consultation with biomedical and social scientists. Three 2-day workshops—in Irvine, California; New Orleans, Louisiana; and Washington, DC—were open to the public and included scientific presentations and also reports, mostly from patients and their families, about their experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics. In addition, advocates for and against the medical use of marijuana were invited to present scientific evidence in support of their positions. Finally, the Institute of Medicine appointed a panel of nine experts to advise the study team on technical issues.

Public outreach included setting up a Web site that provided information about the study and asked for input from the public. The Web site was open for

comments from November 1997 until November 1998. Some 130 organizations were invited to participate in the public workshops. Many people in the organizations—particularly those opposed to the medical use of marijuana—felt that a public forum was not conducive to expressing their views; they were invited to communicate their opinions (and reasons for holding them) by mail or telephone. As a result, roughly equal numbers of persons and organizations opposed to and in favor of the medical use of marijuana were heard from.

Advances in cannabinoid science of the last 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, nausea, and appetite stimulation. For patients, such as those with AIDS or undergoing chemotherapy, who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad spectrum relief not found in any other single medication.

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, the harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically-active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons, the report concludes that the future of cannabinoid drugs lies not in smoked marijuana, but in chemically-defined drugs that act on the cannabinoid systems that are a natural component of human physiology. Until such drugs can be developed and made available for medical use, the report recommends interim solutions.

John A. Benson, Jr., M.D.
Stanley J. Watson, Jr. M.D., Ph.D.
Principal Investigators

EXECUTIVE SUMMARY

Public opinion on the medical value of marijuana has been sharply divided. Some dismiss medical marijuana as a hoax that exploits our natural compassion for the sick; others claim it is a uniquely soothing medicine that has been withheld from patients through regulations based on false claims. Proponents of both views cite 'scientific evidence' to support their views and have expressed those views at the ballot box in recent state elections. In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids (see box: *Statement of Task*). That review began in August 1997 and culminates with this report.

The ONDCP request came in the wake of state "medical marijuana" initiatives. In November 1996, voters in California and Arizona passed referenda designed to permit the use of marijuana as medicine. Although Arizona's referendum was invalidated five months later, the referenda galvanized a national response. In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana. (The Colorado vote will not count, however, because after the vote was taken a court ruling determined there had not been enough valid signatures to place the initiative on the ballot.)

Can marijuana relieve health problems? Is it safe for medical use? Those straightforward questions are embedded in a web of social concerns, most of which lie outside the scope of this report. Controversies concerning the nonmedical use of marijuana spill over onto the medical marijuana debate and obscure the real state of scientific knowledge. In contrast with the many disagreements bearing on social issues, the study team found substantial consensus among experts in the relevant disciplines on the scientific evidence about potential medical uses of marijuana.

This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Throughout this report, *marijuana* refers to unpurified plant substances, including leaves or flower tops whether consumed by ingestion or smoking. References to "the effects of marijuana" should be understood to include the composite effects of its various components; that is, the effects of THC, the primary psychoactive ingredient in marijuana, are included among its effects, but not all the effects of marijuana are necessarily due to THC. *Cannabinoids* are the group of compounds related to THC, whether found in the marijuana plant, in animals, or synthesized in chemistry laboratories.

EXECUTIVE SUMMARY

Three focal concerns in evaluating the medical use of marijuana...

- Evaluation of the effects of isolated cannabinoids.
- Evaluation of the health risks associated with the medical use of marijuana.
- Evaluation of the efficacy of marijuana.

EFFECTS OF ISOLATED CANNABINOIDS

Cannabinoid Biology

Much has been learned since a 1982 IOM *Marijuana and Health* report. Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. Additionally, too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That all changed with the identification and characterization of cannabinoid receptors in the 1980s and 1990s. During the last 16 years, science has advanced greatly and can tell us much more about the potential medical benefits of cannabinoids.

CONCLUSION: At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multifaceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals, but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium®).

CONCLUSION: The different cannabinoid receptor types found in the body appear to play different roles in normal human physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.

RECOMMENDATION 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Efficacy Of Cannabinoid Drugs

The accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation. The therapeutic effects of cannabinoids are best established for THC, which is generally one of the two most abundant of the cannabinoids in marijuana. (Cannabidiol, the precursor of THC, is generally the other most abundant cannabinoid.)

The effects of cannabinoids on the symptoms studied are generally modest, and in most cases, there are more effective medications. However, people vary in their responses to medications and there will likely always be a subpopulation of patients who do not respond well to other medications. The combination of cannabinoid drug effects (anxiety reduction, appetite stimulation, nausea reduction, and pain relief) suggests that cannabinoids would be moderately well suited for certain conditions, such as chemotherapy-induced nausea and vomiting and AIDS wasting.

Defined substances, such as purified cannabinoid compounds, are preferable to plant products which are of variable and uncertain composition. Use of defined cannabinoids permits a more precise evaluation of their effects, whether in combination or alone. Medications that can maximize the desired effects of cannabinoids and minimize the undesired effects can very likely be identified.

Although most scientists who study cannabinoids agree that the pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public for medical use. Cannabinoid-based drugs will only become available if public investment in cannabinoid drug research is sustained, and if there is enough incentive for private enterprise to develop and market such drugs.

EXECUTIVE SUMMARY

CONCLUSION: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

Influence Of Psychological Effects On Therapeutic Effects

The psychological effects of THC and similar cannabinoids pose three issues for the therapeutic use of cannabinoid drugs. First, for some patients—particularly older patients with no previous marijuana experience—the psychological effects are disturbing. Those patients report experiencing unpleasant feelings and disorientation after being treated with THC, generally more severe for oral THC than for smoked marijuana. Second, for conditions such as movement disorders or nausea, in which anxiety exacerbates the symptoms, the anti-anxiety effects of cannabinoid drugs can influence symptoms indirectly. This can be beneficial or can create false impressions of the drug effect. Third, in cases where symptoms are multifaceted, the combination of THC effects might provide a form of adjunctive therapy; for example, AIDS wasting patients would likely benefit from a medication that simultaneously reduces anxiety, pain, and nausea while stimulating appetite.

CONCLUSION: The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations, and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug effect.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

RISKS ASSOCIATED WITH MEDICAL USE OF MARIJUANA

Physiological Risks

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications. The harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse. When interpreting studies purporting to show the harmful effects of marijuana, it is important to keep in mind that the majority of those studies are based on *smoked* marijuana, and cannabinoid effects cannot be separated from the effects of inhaling smoke of burning plant material and contaminants.

For most people, the primary adverse effect of *acute* marijuana use is diminished psychomotor performance. It is, therefore, inadvisable to operate any vehicle or potentially dangerous equipment while under the influence of marijuana, THC, or any cannabinoid drug with comparable effects. In addition, a minority of marijuana users experience dysphoria, or unpleasant feelings. Finally, the short-term immunosuppressive effects are not well established but, if they exist, are not likely great enough to preclude a legitimate medical use.

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking, and the effects of THC. Marijuana smoking is associated with abnormalities of cells lining the human respiratory tract. Marijuana smoke, like tobacco smoke, is associated with increased risk of cancer, lung damage, and poor pregnancy outcomes. Although cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer, proof that habitual marijuana smoking does or does not cause cancer awaits the results of well-designed studies.

CONCLUSION: Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.

RECOMMENDATION 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

EXECUTIVE SUMMARY

Marijuana Dependence And Withdrawal

A second concern associated with chronic marijuana use is dependence on the psychoactive effects of THC. Although few marijuana users develop dependence, some do. Risk factors for marijuana dependence are similar to those for other forms of substance abuse. In particular, antisocial personality and conduct disorders are closely associated with substance abuse.



CONCLUSION: A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short-lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping.

Marijuana As A "Gateway" Drug

Patterns in progression of drug use from adolescence to adulthood are strikingly regular. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana—usually before they are of legal age.

In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a "gateway" drug. But because underage smoking and alcohol use typically precede marijuana use, marijuana is not the most common, and is rarely the first, "gateway" to illicit drug use. There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs. An important caution is that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes. It does not follow from those data that if marijuana were available by prescription for medical use, the pattern of drug use would remain the same as seen in illicit use.

Finally, there is a broad social concern that sanctioning the medical use of marijuana might increase its use among the general population. At this point there are no convincing data to support this concern. The existing data are consistent with the idea that this would not be a problem if the medical use of marijuana were as closely regulated as other medications with abuse potential.



CONCLUSION: Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs, and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

USE OF SMOKED MARIJUANA

Because of the health risks associated with smoking, smoked marijuana should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern. Further, despite the legal, social, and health problems associated with smoking marijuana, it is widely used by certain patient groups.

RECOMMENDATION 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months); be conducted in patients with conditions for which there is reasonable expectation of efficacy; be approved by institutional review boards; and collect data about efficacy.

The goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but rather as a first step towards the possible development of nonsmoked, rapid-onset cannabinoid delivery systems. However, it will likely be many years before a safe and effective cannabinoid delivery system, such as an inhaler, will be available for patients. In the meantime, there are patients with debilitating symptoms for whom smoked marijuana might provide relief. The use of smoked marijuana for those patients should weigh both the expected efficacy of marijuana and ethical issues in patient care, including providing information about the known and suspected risks of smoked marijuana use.

Statement of Task

The study will assess what is currently known, and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

The study will also include an evaluation of the acute and chronic effects of marijuana on health and behavior; a consideration of the adverse effects of marijuana use compared with approved drugs; an evaluation of the efficacy of different delivery systems for marijuana (e.g., inhalation vs. oral); and an analysis of the data concerning marijuana as a gateway drug; and an examination of the possible differences in the effects of marijuana due to age and type of medical condition.

Specific Issues

Specific issues to be addressed fall under three broad categories: the science base, therapeutic use, and economics.

Science Base

- Review of neuroscience related to marijuana, particularly relevance of new studies on addiction and craving
- Review of behavioral and social science base of marijuana use, particularly assessment of the relative risk of progression to other drugs following marijuana use
- Review of the literature determining which chemical components of crude marijuana are responsible of possible therapeutic effects and for side effects

Therapeutic Use

- Evaluation of any conclusions on the medical use of marijuana drawn by other groups
- Efficacy and side-effects of various delivery systems for marijuana compared to existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Differential effects of various forms of marijuana that relate to age or type of disease.

Economics

- Costs of various forms of marijuana compared with costs of existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Assessment of differences between marijuana and existing medications in terms of access and availability

These specific areas, along with the assessments described above will be integrated into a broad description and assessment of the available literature relevant to the medical use of marijuana.

EXECUTIVE SUMMARY

Recommendations

RECOMMENDATION 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural functions of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Scientific data indicate the potential therapeutic value of cannabinoid drugs for pain relief, control of nausea and vomiting, and appetite stimulation. This value would be enhanced by a rapid onset of drug effect.

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

The psychological effects of cannabinoids are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence perceived medical benefits, should be evaluated in clinical trials.

Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory diseases, but the data that could conclusively establish or refute this suspected link have not been collected.

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Recommendations, continued

RECOMMENDATION 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues.

RECOMMENDATION 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months); be conducted in patients with conditions for which there is reasonable expectation of efficacy; be approved by institutional review boards; and collect data about efficacy.

If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, nonsmoked cannabinoid delivery systems.

RECOMMENDATION 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- failure of all approved medications to provide relief has been documented;
- the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;
- such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness;
- and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

EXECUTIVE SUMMARY

RECOMMENDATION 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

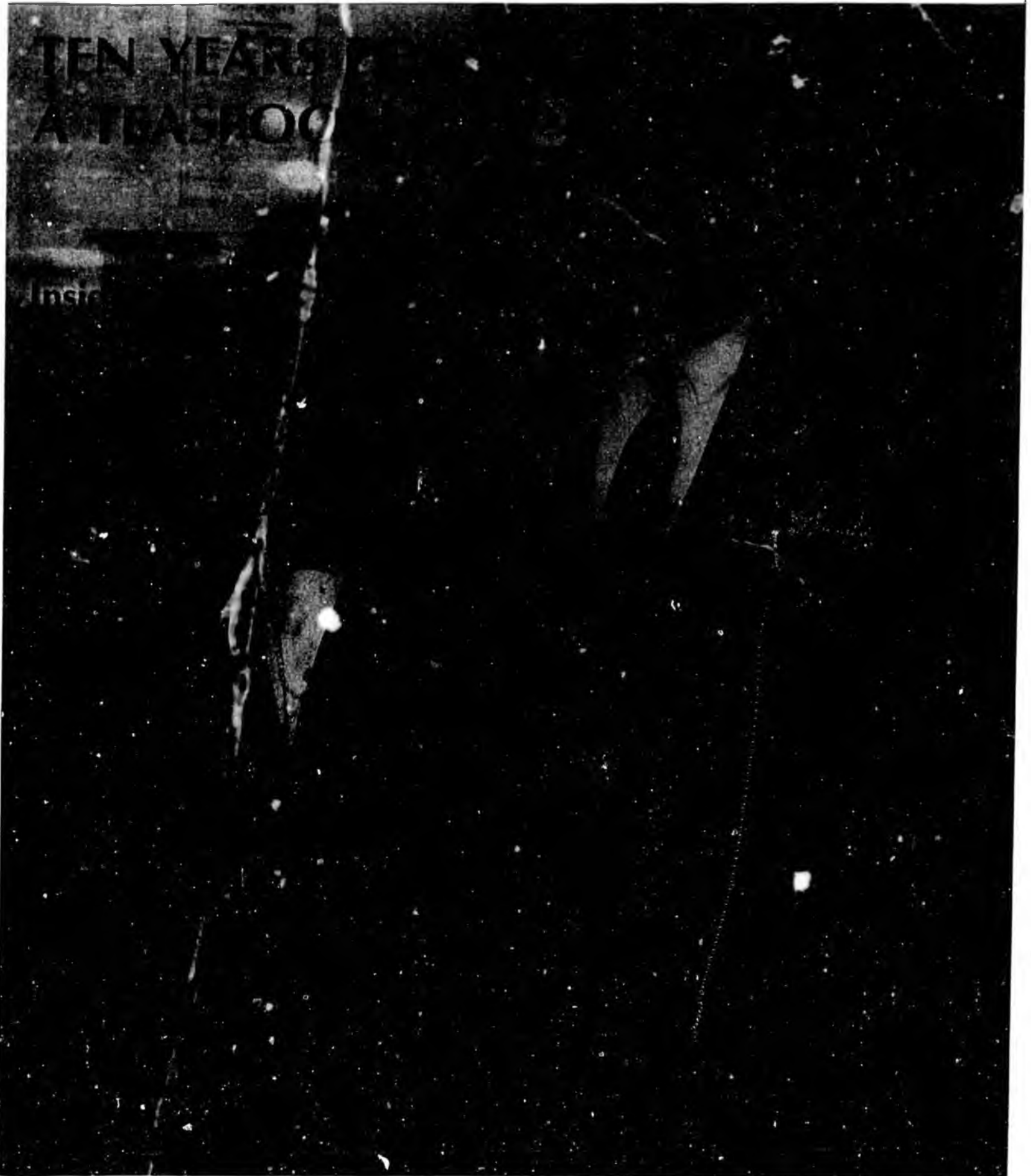
- failure of all approved medications to provide relief has been documented;
- the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs;
- such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness;
- and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

Until a non-smoked, rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as n-of-1 clinical trials, in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system, and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions.

The Drug Policy Letter

number 24

fall 1994



MARIJUANA HAS 'MODERATE' EFFECT ON DRIVING, ALCOHOL BIGGEST DANGER ON THE ROAD

The National Highway Traffic Safety Administration (NHTSA) released two studies this year on drug use and driving.

"The Incidence and Role of Drugs in Fatally Injured Drivers" is dated October 1992, but was released February 1994. The study found that, out of a sample of 1,882 drivers killed in car, truck and motorcycle accidents from 1990 to 1991, alcohol was found in just over half the cases. By comparison, only 17.8 percent of the fatally injured drivers showed traces of other drugs, the majority of whom also had intoxicating levels of alcohol in their system. (A person with a blood/alcohol content (BAC) greater than 0.1 percent is considered intoxicated in most states.) Of the drugs that showed up in the fatally injured drivers, the most frequent was cannabis, in 6.7 percent of the drivers. Other drugs that showed some prevalence were cocaine (5.3 percent), benzodiazepines (2.9 percent), amphetamines (1.9 percent) and barbiturates (1.5 percent).

In addition to measuring for drug presence, the study also attempted to measure causal contributions to the accidents by the various drugs. This was accomplished by conducting a "responsibility analysis" of each accident, and comparing the

responsibility rates of those with a drug or drugs in their system with the "drug-free" control group. The responsibility rates were as follows:

- alcohol with a BAC greater than 0.1 percent, 93.9 percent;
- alcohol with a BAC under 0.1 percent, 75.8 percent;
- amphetamines, 83.3 percent;
- drug-free, 67.7 percent;
- benzodiazepines, 66.7 percent;
- THC, the active ingredient in marijuana, 57.9 percent; and
- cocaine, 57.1 percent.

TWO STUDIES RATE DRUG TREATMENT A BARGAIN OVER LAW ENFORCEMENT

What's the best way to fight drug abuse? There is plenty of room for debate, but two recent reports concluded that drug treatment provides more bang for the buck.

The nonprofit RAND Corporation released a report on how to control cocaine markets and treat the drug's users. They concluded that too much money was spent on "attack" type supply-reduction strategies and far too little was available for treatment programs. The study established that one dollar spent on a drug treatment program would save seven dollars' worth of supply reduction efforts.

Even though the responsibility rates in the THC and cocaine-only groups were lower than the drug-free group, the differences were rated as statistically insignificant because of the low number of persons in these categories.

The report concluded: "Although drugs other than alcohol were the basic focus of this study, the dominance of alcohol in fatal crashes was inescapable.... No single drug, nor all the drugs combined, approached the prevalence of alcohol."

The second report, "Marijuana and Actual Driving Performance," reached similar conclusions. Just as the previous

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The report, "Controlling Cocaine: Supply versus Demand Programs," weighed the positive and negative aspects of supply control techniques. Authors C. Peter Rydell and Susan S. Everingham from RAND's Drug Policy Research Center demonstrated that treatment pays for itself by reducing the costs of crime and lost productivity, whereas supply-side techniques end up costing the taxpayer more money. As Rydell and Everingham discovered: Source eradication operations save only about \$.15 per dollar, interdiction is worth \$.32 per dollar and domestic

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SOURCES FOR "WAS KEVIN ELDERS SET UP? YOU BE THE JUDGE" (p. 8)

1, 3, 5: Prosecution. 2, 4: Defense. 6: Walraven testimony; sources to *The Drug Policy Letter*. 7: Walraven testimony. 8: Friend of Walraven to DPL. 9: Sources to *Arkansas Democrat-Gazette*. 10: Friends of Walraven to DPL. 11: Prosecution to DPL. 12: Police and friends of Walraven to DPL. 13: Walraven police statement. 14: Walraven testimony. 15: Police to DPL. 16: Walraven testimony. 17: Prosecution to DPL. 18: Dr. Elders' letter to Judge Plegge. 19: Prosecution to DPL. 20: Kevin Elders testimony.

SOURCES FOR THE DRUG INDEX (p. 16)

1, 2: Department of Justice. 3-5: Office of National Drug Control Policy. 6-8: DOJ. 9: Peter D. Hart Research Associates poll. 10: CBS News/America Tonight poll. 11: Louis Harris & Associates poll. 12: CBS News/America Tonight poll. 13: DOJ. 14, 15: *Congressional Quarterly Researcher*. 16, 17: DOJ.

PHOTO CREDITS

p. 5: Stanton Breidenthal, *Arkansas Democrat-Gazette*. pp. 6, 7, 9: Cynthia Cotts. p. 12: James Kelly. p. 14: Scripps Howard News Service. p. 15: Robert Chapman, Office of Baltimore Mayor Kurt Schmoke. p. 17: Washington Convention and Visitors Association. p. 24: Dupont Photographers. p. 33: MTV Networks.

LETTERS TO THE EDITOR

[continued from page 3]

jurisdiction in an Article III Court is supposedly provided in § 801 of Title 21. The Congress molded the language of the preamble to the U.S. Constitution, using "We the People of the United States, in Order to ... promote the general Welfare..." to mean, "we the government." The Constitution was written to protect "we the people" against overbroad government. The language of the preamble has been subverted to justify the prosecution of state citizens in federal courts.

In summary, § 801 argues that the Congress cannot tell the difference between drugs which have traveled in interstate commerce and those which have not. Therefore, because Congress *wanted* to create a federal prohibition, it *needed* jurisdiction over all drugs, in the interest of promoting the public welfare. I am unable to find any authority in the Constitution which allows Congress to pass a law because it wants to.

Perry McCullough
Phoenix, AZ

MARIJUANA HAS 'MODERATE' EFFECT ON DRIVING

[continued from page 29]

study found that there was no indication that marijuana by itself was a cause of fatal accidents," this study found that "THC's adverse effects on driving performance appear relatively small."

The study, conducted in the Netherlands and sponsored by NHTSA, measured the effects of marijuana on drivers on a closed road, but with traffic, and compared the effects of a modest dose of THC to alcohol (BAC of 0.04 percent). The report concluded that:

1) "Marijuana, when taken alone, produces a moderate degree of driving impairment, ... manifesting itself mainly in the ability to maintain a steady lateral position on the road,"

2) "The magnitude of impairment is not exceptional in comparison with changes produced by many medicinal drugs and alcohol,"

3) "It is not possible to conclude anything about a driver's impairment on the basis of his/her plasma concentrations of THC," and

4) When comparing the effects of alcohol with marijuana, marijuana's effects on driving, even at the highest

dosage tested (300 micrograms/kg), never exceeded alcohol's effects at BACs of 0.08 percent. The marijuana users also tended to overestimate the adverse effects of the drug on their driving quality and compensated for this by increasing effort and/or slowing down. Alcohol had the opposite effect: Drivers under its effect tended to underestimate the adverse effects of the drug and did not "invest compensatory effort."

As the researchers stated: "THC's effects differ qualitatively from many other drugs, especially alcohol. For example, subjects drive faster after drinking alcohol and slower after smoking marijuana.... This evidence strongly suggests that alcohol encourages risky driving whereas THC encourages greater caution, at least in experiments. Another way THC seems to differ qualitatively from many other drugs is that the former's users seem better able to compensate for its adverse effects while driving under the influence."

It would be a mistake to infer from either report that it is safe to drive under the influence of any drug.

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TREATMENT STUDIES

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enforcement equals \$.52 per dollar. By contrast, drug treatment programs reduced crime and productivity to save \$7.46.

The authors recommend developing more demand reduction programs in the United States. They point out that even if the treatment does not completely alter drug use rates, 80 percent of the people enrolled in treatment do not use drugs during that time.

To reach their conclusions, the RAND researchers created a mathematical model of cocaine users and how much cocaine they consume. They used the mathematical models to project several likely directions in which the phenomenon of cocaine use could move.

Meanwhile, an August study commissioned by the state of California found, as did RAND, that treatment was more cost-effective than law enforcement.

The report, "Evaluating Recovery Services: The California Drug and Alcohol Treatment Assessment (CALDATA)," interpolated population data and concluded, in part, that:

- each day of treatment pays for itself by the end of the day because of the cost of crime avoided during that time.

- The benefits from different treatment programs outweigh the costs, depending upon the type of program, at ratios ranging from 4:1 to 12:1.

- A two-thirds reduction in the amount of crime within the population sample selected occurred during the time from before to after treatment.

This report, which was commissioned in 1992, found that treatment yielded a \$7 return on every dollar spent. Further, by treating 150,000 people at a cost of \$2 million, the taxpayers saved about \$1.5 billion, mostly from the reductions in crime.

To acquire a copy of the RAND report, write RAND Distribution Services, 1700 Main St., P.O. Box 2138, Santa Monica, CA 90407-2138, call (310) 451-7002, fax (310) 451-6915, or e-mail via the Internet: order@rand.org.

To acquire a copy of the report, "Evaluating Recovery Services: The California Drug and Alcohol Treatment Assessment (CALDATA)," write the California Department of Alcohol and Drug Programs Resource Center, 1700 K Street, Sacramento, CA 95814, or call (800) 879-2772 or (916) 327-3728.

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as phenothiazines and butyrophenones. It usually occurs early in treatment and rarely during maintenance treatment. It develops in up to 3% of patients started on antipsychotics. Risk is increased in agitated male patients who have received large and rapidly increased doses. No genetic component is apparent. Its pathophysiologic basis is believed to be blockade of central dopamine receptors. Characteristic signs are muscle rigidity, hyperpyrexia, tachycardia, hypertension, tachypnea, change in mental status, and autonomic dysfunction. Laboratory abnormalities include respiratory and metabolic acidosis, myoglobinuria, elevated CK, and leukocytosis. Mortality approaches 30%.

Treatment includes cessation of antipsychotic drugs, supportive care, and aggressive treatment of myoglobinuria, fever, and acidosis. The dopamine agonist bromocriptine 2.5 to 20 mg tid or dantrolene up to 10 mg/kg IV q 4 h may be used as a muscle relaxant. Treatment is usually in an ICU. After recovery, reintroduction of the antipsychotic drug retriggers the syndrome in up to 1/3 of patients.

Malignant hyperthermia, induced by inhalation of potent anesthetics or suc-

cinyllcholine, is clinically similar to neuroleptic malignant syndrome; however, the pathophysiology and susceptibility appear to be different in most cases (see under PHARMACODYNAMIC VARIATION in Ch. 301). When patients with neuroleptic malignant syndrome require anesthesia, trigger agents for malignant hyperthermia should be avoided, although malignant hyperthermia has not been reported in these patients or their family members.

Legal Considerations

In most states, when a patient expresses the intention to harm a particular person, the evaluating clinician is required to warn the intended victim and notify a specified law enforcement agency. Specific requirements vary by state. Typically, state regulations also require reporting suspected abuse of children, the elderly, and spouses.

Criteria and procedures for involuntary hospitalization vary by jurisdiction. Usually a physician or psychologist and one additional clinician must certify that the patient has a psychiatric disorder, is a danger to himself or others, and refuses treatment.

195 / DRUG USE AND DEPENDENCE

(Substance Use Disorders; Drug Addiction; Drug Abuse; Drug Habituation)

A single definition for drug dependence is neither desirable nor possible. Some illicit drug use, although considered abuse because it is illegal, does not involve dependence of any kind. Drug dependence of a specific type (eg, cocaine dependence) emphasizes that different drugs have different effects, including type and risk of dependence.

Two concepts contribute to the definition of drug dependence: **tolerance**, which describes the need to progressively increase the dose to produce the effect originally achieved with smaller doses, and **physical dependence**, a state of physiologic adaptation to a drug, manifested by a withdrawal

(abstinence) syndrome. In a withdrawal syndrome, untoward physiologic changes occur when the drug is discontinued or when its effect is counteracted by a specific antagonist that displaces the agonist from its binding site on cell receptors. Physical dependence does not accompany all forms of drug dependence.

Psychologic dependence is accompanied by feelings of satisfaction and a desire to repeat the drug experience or to avoid the discontent of not having it. This anticipation of effect is a powerful factor in the chronic use of psychoactive drugs and, with some drugs, may be the only obvious factor associated with intense craving and apparent

compulsive use. Drugs that cause chiefly psychologic dependence include cocaine, marijuana, amphetamine, and hallucinogens, such as lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), and peyote.

Drugs that produce strong physical dependence (eg, heroin, alcohol) are prone to abuse, and dependence is difficult to treat. If a drug does not cause physical dependence, discontinuing the drug does not cause a major stereotypical withdrawal syndrome. However, most psychoactive drugs cause tolerance, and in some cases, reactions after discontinuation resemble a withdrawal syndrome (eg, depression and lethargy after withdrawal of cocaine or amphetamine; characteristic changes in the EEG after withdrawal of amphetamine). Commonly used psychoactive drugs vary in their potential for different types of dependence (see TABLE 195-1).

Drugs that produce dependence act on the CNS and have one or more of the following effects: reduced anxiety and tension; elation, euphoria, or other mood changes pleasurable

to the user; feelings of increased mental and physical ability; altered sensory perception; and changes in behavior.

Addiction, a concept without a consistent, universally accepted definition, is used here to refer to a lifestyle characterized by compulsive use and overwhelming involvement with a drug; it may occur without physical dependence. Addiction implies the risk of harm and the need to stop drug use, whether the addict understands and agrees or not.

Drug abuse is definable only in terms of societal disapproval. It may involve experimental and recreational use of drugs, which is usually illegal with risk of arrest; unsanctioned use of psychoactive drugs to relieve problems or symptoms; or use of drugs first for the previous two reasons but later because of dependence and the need to continue at least partially to prevent the discomfort of withdrawal. Abuse of prescription and illegal drugs occurs in all socioeconomic groups, including among persons with advanced education and professional status. However, the most devastating use of psy-

TABLE 195-1. POTENTIAL FOR DEPENDENCE WITH COMMONLY USED DRUGS

Drug	Physical Dependence	Psychologic Dependence	Tolerance
CNS depressants			
Alcohol	+++	+++	++
Barbiturates	+++	+++	++
Ethchlorvynol	+++	+++	++
Glutethimide	+++	+++	++
Methaqualone	+++	+++	++
Methypylon	+++	+++	++
Opioids	++++	++++	++++
Synthetic opioids	++++	++++	++++
Anxiolytics			
Alprazolam, oxazepam, temazepam (short-acting)	++	+++	+
Chlordiazepoxide, diazepam (long-acting)	+	+++	+
Stimulants			
Amphetamine	?	+++	++++
Cocaine	0	+++	++
Methamphetamine	?	+++	++++
Hallucinogens			
LSD	0	++	++
Marijuana			
(low-dose Δ^9 -THC)	0	++	0
(high-dose Δ^9 -THC)	0	++	+
Mescaline, peyote	0	++	+

0 = lysergic acid diethylamide; THC = tetrahydrocannabinol; 0 = no effect; + = slight effect to +++ = marked effect

TABLE 195-2. PHYSICAL DEPENDENCE WITH SOME COMMON SEDATIVES AND ANXIOLYTICS

Drug	Doses Producing Dependence (mg/day)	Time Necessary to Produce Dependence (days)	Dose Equivalent to Phenobarbital 30 mg (mg/day)*
Amobarbital ("blues")	500-600	30	100
Amobarbital-secobarbital combination ("rainbows")	500-600	30	100
Chloral hydrate	2000-2500	30	500
Chlordiazepoxide	200-300	60	25
Diazepam	60-100	40	10
Ethchlorvynol	1500-2000	60	500
Glutethimide	1250-1500	60	500
Meprobanate	2000-2400	60	400
Methaqualone	1800-2400	30	300
Methypyrrolon	1200-1500	60	300
Pentobarbital ("yellow jackets")	500-600	30	100
Secobarbital ("reds")	500-600	30	100

*Drugs on which a patient is dependent can be replaced by a dose of phenobarbital equivalent to 1/3 the average dose of that drug.

ance level can be determined by repeating the test q 3 to 4 h with a larger dose. Severe anxiety or agitation may increase the patient's tolerance. Once the 24-h dose still tempered by tolerance is determined, that dose is usually given qid for 2 or 3 days to stabilize the patient and is then decreased by 10% a day.

Alternatively, phenobarbital can be used. It does not produce the "high" of more rapidly acting drugs, and it is the anticonvulsant of choice. Rapid-onset barbiturates, other sedative-hypnotics, or minor anxiolytics can be replaced by a dose of phenobarbital equivalent to 1/3 the average daily dose of the drug on which the patient is dependent (see Table 195-2); eg, for secobarbital 1000 mg/day, the stabilizing dose of phenobarbital is 300 mg/day or 75 mg q 6 h. Phenobarbital is given orally qid, and the initial phenobarbital dose is reduced by 30 mg/day until the patient is drug-free. Because the initial daily dose must be estimated from the patient's history, a potential for error exists, and the patient must be observed closely for the first 72 h. If he remains agitated or anxious, the dose should be increased; if he is drowsy or dysarthric or has nystagmus, the dose should be decreased. While patients are being detoxified, other sedatives and psychoactive drugs should be avoided. However, if the patient is

also taking antidepressants, especially tricyclics, the antidepressant should not be abruptly discontinued; the dose should be reduced over 3 to 4 days.

CANNABIS (MARIJUANA) DEPENDENCE

Chronic or periodic use of cannabis producing some psychologic dependence but no physical dependence.

Any drug that causes euphoria and diminishes anxiety can cause dependence, and cannabis is no exception. However, heavy use and complaints of inability to stop are unusual. Cannabis can be used episodically without evidence of social or psychologic dysfunction. The term dependence probably is misapplied to many users. No withdrawal syndrome occurs when the drug is discontinued, but some heavy users report disrupted sleep and nervousness when they stop.

Use of cannabis is widespread. Surveys that showed diminishing prevalence of use from 1979 to 1991 show an increase in use by persons 12 to 17 yr old until 1995. Prevalence may have leveled recently. Of the 65 to 70 million Americans who have tried cannabis, about 2 to 3% are daily or near-daily

users. Not all daily users are addicts. Use of cannabis is a drug problem (as indicated by the increase in prevalence and in the number of persons seeking help to control its use), although its toxicologic importance is unclear. The number of users who have sought treatment or counseling to help them stop may be exaggerated because persons who test positive in the workplace are often ordered to seek treatment, then followed with compulsory testing.

In the USA, cannabis is commonly smoked in cigarettes made from the flowering tops and leaves of the dried plant or as hashish, the pressed resin of the plant. Dronabinol, a synthetic form of Δ -9-tetrahydrocannabinol (the principal active constituent of marijuana), is used to treat nausea and vomiting associated with cancer chemotherapy and to enhance appetite in AIDS patients. This form does not appear on the street.

Symptoms and Signs

Smoked cannabis produces a dreamy state of consciousness in which ideas seem disconnected, unanticipated, and free-flowing. Time, color, and spatial perceptions may be altered. In general, a feeling of well-being and relaxation (a "high") results. These effects last 2 to 3 h after inhalation. There is no persuasive evidence of a prolonged or hangover effect. Tachycardia, conjunctival injection, and dry mouth occur regularly. Many of the psychologic effects seem to be related to the setting in which the drug is taken. Panic reactions have occurred, particularly in naive users, but have become unusual as the culture has become more familiar with the drug. Communicative and motor abilities are decreased, depth perception and tracking are impaired, and the sense of timing is altered—all hazardous in certain situations (eg, driving, operating heavy equipment). Schizophrenic symptoms may be exacerbated by marijuana, even in patients being treated with antipsychotic drugs (eg, chlorpromazine). Appetite often increases.

Critics of marijuana cite much scientific data regarding adverse effects, but most of the claims regarding severe biologic impact are unsubstantiated, even among relatively heavy users and in areas intensively investigated, such as immunologic and reproductive function. However, high-dose smokers of marijuana develop pulmonary symptoms (episodes of acute bronchitis, wheezing,

coughing, and increased phlegm), and pulmonary function may be altered. This is manifested by large airway changes of unknown significance. Even daily smokers do not develop obstructive airway disease. Pulmonary carcinoma has not been reported in persons who smoke only marijuana, possibly because less smoke is inhaled than during cigarette smoking. However, biopsies of bronchial tissue sometimes show precancerous changes, so carcinoma may occur. In a few case-control studies, some tests detected diminished cognitive function in small samples of long-term high-dose users; this finding awaits confirmation. Studies in newborns have not found evidence of fetal harm due to maternal use of cannabis. Decreased fetal weight has been reported, but when all factors (eg, maternal alcohol and tobacco use) are accounted for, the effect on fetal weight disappears. Δ -9-Tetrahydrocannabinol is secreted in breast milk. Although no harm to breastfed babies has been shown, breastfeeding mothers, like pregnant women, are advised to avoid using cannabis.

Because cannabinoid metabolites persist, urine tests after one-time use remain positive for days or weeks after discontinuation in regular users. Tests that identify an inactive metabolite identify use only, not dysfunction; the smoker may be free of drug effect by the time his urine is tested. The test can detect extremely small amounts and so is of little value in identifying the pattern of use.

COCAINE DEPENDENCE

Psychologic dependence, sometimes leading to profound psychologic addiction, produced by high doses of cocaine, which can cause euphoric excitement.

Tolerance occurs, but physical dependence has not been confirmed; no stereotypical withdrawal syndrome occurs when the drug is discontinued. However, the tendency to continue taking the drug is strong.

Most users are episodic recreational users who voluntarily curtail their use. However, cocaine use and the development of addictive behavior in some users has increased in North America, although recent declines are recorded.

Although most cocaine in the USA is snorted intranasally, smoking crack cocaine has become widely publicized. The imported hydrochloride salt is converted to a more

Psychoactive substance use and the risk of motor vehicle accidents

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Abstract

The driving performance is easily impaired as a consequence of the use of alcohol and/or licit and illicit drugs. However, the role of drugs other than alcohol in motor vehicle accidents has not been well established. The objective of this study was to estimate the association between psychoactive drug use and motor vehicle accidents requiring hospitalisation.

A prospective observational case-control study was conducted in the Tilburg region of The Netherlands from May 2000 to August 2001. Cases were car or van drivers involved in road crashes needing hospitalisation. Demographic and trauma related data was collected from hospital and ambulance records. Urine and/or blood samples were collected on admission.

Controls were drivers recruited at random while driving on public roads. Sampling was conducted by researchers, in close collaboration with the Tilburg police, covering different days of the week and times of the day. Respondents were interviewed and asked for a urine sample. If no urine sample could be collected, a blood sample was requested.

All blood and urine samples were tested for alcohol and a number of licit and illicit drugs. The main outcome measures were odds ratios (OR) for injury crash associated with single or multiple use of several drugs by drivers.

The risk for road trauma was increased for single use of benzodiazepines (adjusted OR 5.1 (95% CI: 1.8–14.0)) and alcohol (blood alcohol concentrations of 0.50–0.79 g/l, adjusted OR 5.5 (95% CI: 1.3–23.2) and ≥ 0.8 g/l, adjusted OR 15.5 (95% CI: 7.1–33.9)). High relative risks were estimated for drivers using combinations of drugs (adjusted OR 6.1 (95% CI: 2.6–14.1)) and those using a combination of drugs and alcohol (OR 112.2 (95% CI: 14.1–892)). Increased risks, although not statistically significantly, were assessed for drivers using amphetamines, cocaine, or opiates. No increased risk for road trauma was found for drivers exposed to cannabis.

The study concludes that drug use, especially alcohol, benzodiazepines and multiple drug use and drug–alcohol combinations, among vehicle drivers increases the risk for a road trauma accident requiring hospitalisation.

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1. Introduction

The Grand Rapids Study convincingly showed that driving under influence of alcohol is an important risk factor for traffic accidents (Borkenstein et al., 1974). The role of drugs other than alcohol in motor vehicle accidents, however, has not been well established. Many medicines (prescription or over-the-counter) and illicit drugs affect the nervous system (Ramaekers, 1998). Driving under the influence of drugs

other than alcohol is considered to be an increasing cause of traffic accidents worldwide (Morland, 2000).

Several classes of drugs, including amphetamines, anti-histamines, cannabis, hypnotics, tranquillizers and tricyclic antidepressants, have been shown to impair driving skills in laboratory tests and driver-simulation studies (O'Hanlon and Volkerts, 1986; Smiley, 1987; Robbe, 1998). These studies are restricted in various ways, e.g. with regard to subject selection and divergent behaviour or sample size. Their generalization to a 'real' traffic situation is debated. Many observational studies have shown that drug use as determined by biological sampling among drivers is prevalent and increasing (Gjerde et al., 1993; Soderstrom et al., 1997; Morland, 2000). Several studies tried to provide

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accident risk estimates related to drug use by linking drug prescription records to hospital admission records involving motor vehicle accidents, police reports, or health insurance records (Skegg et al., 1979; Ray et al., 1992; Leveille et al., 1994; Neutel, 1995; Hemmelgarn et al., 1997; Barbone et al., 1998; McGwin et al., 2000). In addition, a few studies have been conducted in which non-trauma patients were included as controls (Honkanen et al., 1980; Marquet et al., 1998). These studies provided risk estimates, but a limitation is that the control groups were not taken from moving traffic.

The objective of our study was to estimate the association between the use of various psychoactive substances and serious traffic injuries needing hospitalisation by comparing exposure frequencies (prevalences) of these substances in injured and non-accident involved drivers.

2. Methods

2.1. Setting

The study was conducted in co-operation with a large general teaching hospital (St. Elisabeth Hospital) and the police department located in the Dutch city of Tilburg, covering a population of approximately 350,000 persons. The hospital has all the facilities comparable with a highly equipped trauma centre. The source populations of our study were injured and non-accident involved drivers throughout the period from May 2000 until August 2001. The hospital's Medical Ethics Committee approved the study protocol and informed consent was obtained for the use of medical records from patients or their relatives.

2.2. Study design

A prospective case-control study was conducted to assess the relationship between drug use and trauma injuries requiring hospitalisation caused by motor vehicle accidents. Only injured car or van drivers were included in the study.

2.3. Selection of cases

All injured car or van drivers who were admitted to the emergency room of the hospital were prospectively identified. Demographic, accident and injury characteristics were obtained from medical and ambulance records, and the emergency's department electronic medical data system (Vles et al., 2000). The physicians at the emergency department were trained to fill in a detailed questionnaire about the crash circumstances. The severity of injuries was graded according to the Injury Severity Scale (ISS) (Baker et al., 1974). Urine and/or blood samples were taken directly in the emergency room.

2.4. Selection of controls

Control patients were randomly selected from moving traffic during 20 roadside survey sessions. In order to be able to construct a representative control sample, the week was systematically divided into 6 h periods. Each survey session covered a 6 h period because of work-time reasons. The survey was conducted among a representative sample of locations along main roads in the Tilburg police district, which covers the area of the St. Elisabeth Hospital. Frequent change of location was intended to minimize the predictability of the surveys with respect to time and place.

The police stopped cars and the drivers were asked to co-operate on a voluntary basis. The survey sessions were combined with normal police enforcement activities regarding drink-driving. Respondents were interviewed on their drug and medicine use and subsequently requested to produce a urine specimen. If they were not able or willing to urinate they were requested to deliver a blood specimen. A trained research nurse performed the vena-puncture. Subjects who delivered a urine or blood specimen were compensated by a small amount of 10 Dutch guilders (approximately € 5). The interview and specimen sampling took place in a specially equipped mobile research unit with a private toilet. After the interview and specimen sampling, all subjects were breath tested for alcohol by a police officer, using a Dräger Alcotest 7410 Plus screening device. The breath test was compulsory for all drivers who were stopped. Data collection also comprised date and time of selection, gender and age of the driver, and signs of intoxication.

2.5. Drug exposure assessment

Both cases and controls were tested for the presence of alcohol, amphetamines, barbiturates, benzodiazepines, cannabis, methadone, opiates, and tricyclic antidepressants.

Urine samples were screened at the Dutch Laboratory for Drugs Doping, Tilburg, The Netherlands. Screening was performed by enzyme multiplied immunoassay technique (EMIT[®] II Plus). For benzodiazepines, a special high sensitivity protocol was used with on-line deglucuronidation. The risk for false-positive results was avoided by confirmation analysis of the positive urine samples (amphetamines and opiates) with appropriate gas chromatography mass spectrometry (GC-MS) techniques.

Drug screening in serum was performed by The Netherlands Forensic Institute (NFI), Rijswijk, The Netherlands. Opiates and cannabis screening was performed by Cozart[®] enzyme immunoassay (EIA). Confirmation was performed using GC-MS. For the other drugs and pharmaceuticals, a high-performance liquid chromatography (HPLC) method was used, which was developed by NFI.

Concerning the cases medical and ambulance records were examined to control for drugs administered during transport and at the emergency department. When urine or blood specimens were positive for drugs given during

transport, or in the emergency room before sampling, the specimens were considered to be negative.

2.6. Potential confounders

The following covariates were studied as possible confounding factors: age, gender, blood alcohol concentration, concomitant drug exposure, season, and time of day. Time of day was categorised as day (10 a.m.–10 p.m.) or night (10 p.m.–10 a.m.).

2.7. Statistical analysis

For both cases and controls, the baseline characteristics were determined. An ANOVA/Student's *t*-test was performed to assess the significance of differences in the mean of continuous variables between cases and controls. Differences in proportions of categorical variables were tested for significance by a chi-square (χ^2) test. To estimate the association between drug use, and any other potential risk factor and road trauma requiring hospitalisation adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using multivariate unconditional logistic regression (Hosmer and Lemeshow, 1989). All potential confounding factors were entered in the logistic model. In this model the odds ratio can be interpreted as a relative risk. Unadjusted ORs are not presented because this study was not designed to determine a causal relationship for each single drug separately. Data were analysed using SPSS 10.0 statistical software.

3. Results

We were able to identify and include 110 injured motorists. The relatives of two deceased patients refused consent and their data were excluded from analysis. The mean ISS for the case patients was 14 (range 1–75) of the 1029 controls, 816 (79.3%) drivers complied to participate. In the case group 39% of the specimens consisted out of urine compared to 85% in the controls, respectively. Overall, 74% of the study subjects were men. The mean age was 38.6 years. Control subjects were older than case patients (39.1 versus 34.6, $P = 0.002$).

Table 1 shows the distribution of demographic variables and of the frequencies of drugs and alcohol use. Male patients were more frequently exposed to cannabis and cocaine. Drugs and/or alcohol were more frequently detected in injured drivers than in non-accident involved drivers.

Forty percent of all case patients were positive for one or more drugs and/or alcohol in comparison with 14% of the controls (Fig. 1). Eight percent of all case patients were both exposed to (multiple) drugs and alcohol. Only one control subject had used a drug–alcohol combination.

The use of benzodiazepines (adjusted OR 5.1 (95% CI: 1.8–14.0)) and alcohol was significantly associated with road

Table 1
Characteristics of cases and controls

Characteristics	Cases, N = 110 (%)	Controls, N = 816 (%)
Gender		
Male	81 (74)	602 (74)
Female	29 (26)	214 (26)
Age group (year)		
18–25	31 (28)	144 (18)
25–34	35 (32)	228 (28)
35–49	28 (26)	237 (29)
≥50	16 (14)	207 (25)
Season		
January–March	25 (23)	169 (33)
April–June	21 (19)	172 (21)
July–September	37 (34)	147 (18)
October–December	27 (25)	228 (28)
Time of day		
10 a.m.–10 p.m.	54 (49)	496 (61)
10 p.m.–10 a.m.	56 (51)	320 (39)
Drugs and alcohol		
Amphetamines	7 (6)	13 (2)
Barbiturates	2 (2)	0 (0)
Benzodiazepines	11 (10)	12 (1.5)
Blood alcohol concentration (g/l)		
<0.5	84 (76)	796 (97)
0.5–0.79	3 (3)	7 (1)
≥0.8	23 (21)	13 (2)
Cannabis	13 (12)	49 (6)
Cocaine	10 (9)	16 (2)
Methadone	1 (1)	0 (0)
Opiates	8 (7)	20 (3)
Tricyclic antidepressants	1 (1)	4 (0.5)

accidents (Table 2). Drivers with a blood alcohol concentration (BAC) ≥ 0.8 g/l were at the highest risk (adjusted OR 15.5 (95% CI: 7.1–33.9)). Users of amphetamines, cocaine, and opiates had a twofold increased risk, however, not statistically significant. No association was found for cannabis and tricyclic antidepressants, and no estimates could be calculated with regard to methadone and barbiturates.

A sixfold increased risk (adjusted OR 6.1 (95% CI: 2.60–14.10)) was found for the concurrent use of two, or more drugs compared with no drug use. This effect was even more pronounced in patients concomitantly exposed to alcohol and one or more drugs, which showed the highest risk for road accidents (adjusted OR 112.2 (95% CI: 14.1–892.9)).

4. Discussion

This study indicates that use of alcohol, amphetamines, benzodiazepines, cocaine, and opiates places drivers at increased risk for motor vehicle accidents requiring hospitalisation. Users of drug–drug combinations were at a sixfold increased risk. Vehicle drivers who were exposed

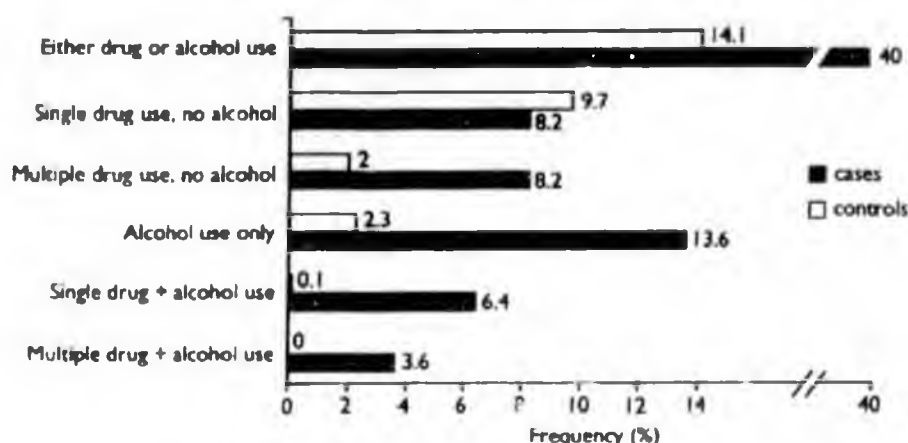


Fig. 1. Use of drugs and/or alcohol (≥ 0.5 g/l) for cases and controls.

to drug–alcohol combinations were at the highest risk of experiencing injurious road accidents.

The prevalence for drug and alcohol found in this study is consistent with literature on impaired drivers, or drivers injured or killed in road accidents. However, prevalence figures are hard to compare because of time trends and local differences in drug use habits, patterns, and legislation (Morland, 2000). Our study confirms the well-known association between alcohol and traffic accidents (Borkenstein et al., 1974).

For drivers using benzodiazepines, a fivefold increased injury risk (95% CI: 1.8–14.0) was found, which is in concordance with other studies. In the late 70s, Skegg and co-workers linked drug prescription records with hospital admission and showed that people who used minor tranquilizers had a fivefold higher risk of a serious road accident (Skegg et al., 1979). A similar result was concluded in a related study, which found a four times increased risk for per-

sons taking benzodiazepines within 4 weeks of receiving the prescription (Neutel, 1995). Also more recent data showed that users of benzodiazepines were at increased risk of experiencing road accidents (Barbone et al., 1998). In contrast, other studies using a comparable methodology showed no increase of accident risk with the use of benzodiazepines and sedatives (Jick et al., 1981; Leveille et al., 1994). However, Honkanen and others found a twofold increased accident risk among car drivers using benzodiazepines compared to controls. They selected controls randomly from car drivers at petrol stations, which comes closest to the methodology used in our study (Honkanen et al., 1980). Further research is necessary to establish whether within the group of benzodiazepines specific substances or doses bear a higher or lower risk than others due to differences in pharmacokinetic and pharmacodynamic properties.

The most common therapeutically used opioids studied in relation to traffic accidents are morphine and codeine. In our study, a twofold increased risk was found, which is in concordance with the literature (Ray et al., 1992; Leveille et al., 1994). We found a relatively high prevalence of opiates in injured drivers. After analytical confirmation 6-monoacetylmorphine (6-MAM) the first heroin metabolite was found in the urine of only one case, and two control patients. This figure may underestimate the real number of heroin users because 6-MAM is very rapidly metabolised into morphine and can therefore not always be detected.

The use of amphetamines (including ecstasy) and cocaine has been related with driving impairment (Dussault et al., 2001; Logan and Couper, 2001). In our study, we found that use of amphetamines or cocaine, and opiates places drivers at a twofold increased risk for motor vehicle accidents, however, not statistically significantly. The differences in the prevalence's of these drugs among drivers involved in an accident and non-accident drivers possibly indicates that these drugs are important risk factor for traffic accidents.

In our study, no association was found between exposure to cannabis and road accidents. Experimental and epidemiological studies have provided conflicting data about the

Table 2

Risk for personal injury in road accidents associated with current use of psychoactive substances in real moving traffic

Substance	OR ^a	95% CI
Amphetamines	2.10	0.66–6.73
Benzodiazepines	5.05	1.82–14.04
Cannabis	1.22	0.55–2.73
Cocaine	2.04	0.69–6.09
Opiates	2.35	0.87–6.32
Blood alcohol concentration (g/l)		
<0.5	1.00 ^b	
0.5–0.79	5.46	1.28–23.22
>0.8	15.5	7.09–33.90
Multiple drugs vs. no drug	6.05	2.60–14.10
Drug–alcohol combination vs. no drug	112.22	14.10–893

Adjusted in the multivariate logistic model for age, gender, alcohol, amphetamines, benzodiazepines, cannabis, cocaine, opiates, season, and time of day.

^a OR: odds ratio.

^b Reference category.

role of cannabis to impair a driver's performance to that extent that it will comprise traffic accidents (Morland, 2000). However, the combination cannabis with alcohol is known to have serious effects on the driving performance (Robbe, 1998).

The potentials for bias must be considered as in every epidemiological study and the presented relative risks should be interpreted with caution. We sampled controls from moving traffic. Although the willingness to participate was high (79%), the non-response may have led to selection bias. Theoretically, potential drug addicts might have refused to participate in our study. However, all motorists were by law compelled to undergo a breath test for alcohol. No major differences in age, sex, and alcohol levels were found when comparing controls who delivered a urine or blood specimen to motorists who did not. Thus, no indications of substantial selection bias in the control group were found.

The different distribution in the urine and blood specimens between the cases and controls may have led to information bias. The main strategy in our study was to get urine or blood as a biological sample and not to limit the inclusion of cases as well as controls by specifying one biological fluid. An advantage of urine over blood analysis is the longer persistence and higher concentrations of drugs and its metabolites (e.g. cannabis). However, this is also its major drawback as persistence for cannabis may vary from 1 day to several weeks after the pharmacological effect has disappeared. In that case, it is most unlikely that a positive drug result is related to an increased risk for road accidents. Because of the much larger share of urine specimens in the control group compared to the cases an underestimation of the relative risk for cannabis is possible. However, in this study it seems unlikely because overall 6.3% of all the urine specimens and 7.3% of all the blood specimens were positive for cannabis, respectively.

On the other hand, if the applied analytical method is not sensitive enough, drugs might escape detection. However, in our study this analytical bias is thought to be random; thus, there is no reason to believe that the level of error would differ between the study groups. Such bias will finally underestimate the study results (Hennekens and Buring, 1987).

Another limitation of this study is the sample size. The wide confidence intervals around some of the odds ratios are a reflection of this phenomenon. However, to our consideration expanding the number of cases would not change the main findings of our study. Expanding the sample size will decrease the confidence intervals around the estimates but will not majorly affect the point estimates in question.

The causal directions of the associations found in this study need to be considered. From a non-experimental study, it is difficult to unravel whether the drug (e.g. benzodiazepine), the reason for taking it or associated risk taking behaviour led to an increased accident risk (Neutel, 1995). Some underlying conditions, e.g. sleeping difficulties, may themselves lead to increased accident risks and become the causal factor itself, and not the benzodiazepine prescribed

for this indication (Connor et al., 2002). However, there is substantial evidence from experimental placebo-controlled studies with patients previously diagnosed as insomniacs, that two nights of hypnotic drug use did cause a substantial impairing effect on real driving behaviour, whereas treatment significantly improved sleep quality (O'Hanlon and De Gier, 1986). Some benzodiazepine hypnotics caused effects in the morning after the second night and in the following afternoon that exceeded the effects of 0.5, 0.8 and 1.0 g/l blood alcohol concentrations, which are used as legal limits in several countries around the world (Brookhuis, 1998). Also other risk taking behaviour, associated with drug use like overestimation of capabilities, macho attitude, habitual speeding, and other indecent driving behaviour, could be the causal factor (Petridou and Moustaki, 2000).

Generally, determining the relation between drug use and road trauma accidents is extremely complex because of many important selection factors that are doubtlessly present. Many reports have demonstrated a high rate of drug use among injured motorists, but few studies have collected comparable drug use data from a control group of motorists who were not involved in a traffic accident (Honkanen et al., 1980). Some researchers tried to overcome the control group problem by using a case-cross-over design, as in the so-called culpability studies of (fatally) injured drivers (Robertson and Drummer, 1994; Lowenstein and Koziol-McLain, 2001). Important limitations of this type of studies are the generally small numbers of subjects, and subjective elements that are involved in evaluating culpability. Our study is an epidemiological study including a control group of non-accident drivers selected randomly from the moving traffic flow. The key advantage of this study is that the control (non-accident) drivers were legally stopped, tested for drug use and compared with a representative group of seriously injured drivers.

5. Conclusions

In conclusion, although a causal relationship between road trauma accidents and the use of drugs other than alcohol is not proven by the results of this study, it provides new insights in the role of these drugs in traffic crashes. Use of drug-drug combinations constitute a risk for drivers that will be at least as severe as the risk caused by the use of moderate quantities of alcohol. The impact on society is significant and actions related to reducing the use of these drugs by drivers are therefore needed. Still obvious gaps in our knowledge remain with respect to different effects of certain drugs within the same therapeutic class and drug combinations (multiple and with alcohol). Our study provides evidence that the use of drugs other than alcohol is associated with road traffic accidents. Users of these drugs should not drive a motor vehicle, especially not if taken in combination with alcohol. Legislators and health care providers will have to face this reality and act in

accordance with new knowledge in order to prevent drugged driving.

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Relation of the Pre-employment Drug Testing Result to Employment Status:

A One-year Follow-up

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All employees hired over a six-month period at a large hospital underwent pre-employment urinary toxicology screening. Results of the screening were kept confidential. After a year of employment, the personnel folders of all employees studied were reviewed. Twenty-two of 180 employees (12%) had tested positive for drug use. Employees in clerical/aide positions were significantly more likely to be positive than were employees in professional positions (17% vs. 6%). Drug-positive employees were also more likely to be young and male. Comparison of job performance variables, job retention, supervisor evaluations, and reasons for termination showed no difference between drug-positive and drug-negative employees. Eleven drug-negative employees were fired during the study; no drug-positive employee was fired. There was a strongly significant difference between clerical and professional employees on each of these variables. This study did not find a relation between drug use and job performance. The widespread use of drug screening prior to employment makes further studies of this issue important. Key words: pre-employment drug testing; urinary toxicology; screening. J GEN INTERN MED 1989; 4:44-47.

HOSPITALS AND OTHER EMPLOYERS have utilized urinary toxicology screens of potential employees for many years. The legality and validity of such testing have been questioned.¹ Federal employees have challenged a move to have all employees undergo screening; the court decisions in this case have found urinary drug screening in the absence of probable cause to be an invasion of privacy. The social value of screening programs has been the subject of reviews and editorials^{2,3} that raise questions regarding the accuracy of screening, the failure to include legal but abusable drugs such as alcohol, and the ethics of making employment decisions based on non-work-related behavior.

The research literature on drug screening focuses on technical aspects of screening. No studies could be found addressing the basic question of whether drug usage correlates with impairment of job performance. To assess the relationship between positive urinary toxicology and job performance, all persons hired over a six-month period at a hospital were screened. This report compares the job performance characteristics of employees who tested positive on the urinary toxicology screens with those of employees who tested negative.

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One hundred ninety-two employees underwent urinary toxicology screening. Samples were obtained in the Employee Health Clinic during the pre-employment physical examination. No attempt was made to directly observe specimen collection. The restroom used for collection is less than 10 feet from the examination room and the nurse's station; no attempt to submit a cold specimen or a diluted specimen was detected. Specimens were coded using a random number system and sent to the laboratory for analysis. Results were reported by the laboratory using only the random numbers assigned.

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	Subgroups by Job Category and Testing Status				Testing Status Totals		Job Category Totals		Total
	Professional		Clerical/Aide		Drug- positive (n = 22)	Drug- negative (n = 158)	Profes- sional (n = 78)	Clerical/ Aide (n = 102)	
	Drug Positive (n = 5)	Drug Negative (n = 73)	Drug Positive (n = 17)	Drug Negative (n = 85)					
Job retention									
Employed > 1 year	2 (40)	57 (78)*	10 (59)	45 (53)	12 (55)	102 (65)	59 (76)	55 (54)‡	114
Resigned									
With notice	2 (40)	12 (16)*	3 (18)	16 (19)*	5 (23)	28 (18)*	14 (18)	19 (19)†	33
Without notice	1 (20)	3 (4)	4 (24)	14 (16)	5 (23)	17 (11)	4 (5)	18 (18)	22
Fired	0 (—)	1 (1)	0 (—)	10 (12)	0 (—)	11 (7)	1 (1)	10 (10)	11
Total employed < 1 year	3 (60)	16 (22)	7 (41)	40 (47)	10 (45)	56 (35)	19 (24)	47 (46)	66
Supervisor evaluation									
None	4 (80)	28 (38)*	10 (59)	55 (65)	14 (64)	83 (53)	32 (41)	65 (64)‡	97
Poor	0 (—)	1 (1)	2 (12)	3 (4)	2 (9)	4 (3)	1 (1)	5 (5)	6
Good	0 (—)	17 (23)	4 (24)	19 (22)	4 (18)	36 (23)	17 (22)	23 (23)	40
Excellent	1 (20)	27 (37)	1 (6)	8 (9)	2 (9)	35 (22)	28 (36)	9 (9)	37
Other entries in personnel file									
Commendations	0 (—)	10 (14)*	2 (12)	10 (12)	2 (9)	20 (13)	10 (13)	12 (12)‡	22
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No entry	5 (100)	58 (79)	6 (35)	41 (48)	11 (50)	99 (63)	63 (81)	47 (46)	110

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†p = 0.04 comparing professional and clerical workers.

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(15%) than among drug-negative employees (35%). This difference was not significant. There was a strongly significant difference in the turnover rate of clerical (46%) versus professional employees (26%) (chi square = 8.98, $p = 0.003$). Clerical employees who tested positive for drugs had a lower turnover rate (41%) than did clerical employees who tested negative (47%).

There was a strongly significant difference in the qualities of evaluation received by clerical and professional employees (chi square = 21.74, $p < 0.001$). Professional employees were much more likely to receive favorable evaluations (36%) than were clerical employees (9%). A nonsignificant trend toward better evaluation among drug-negative employees as a total group resulted from the higher proportion of drug-positive employees in the clerical/aide category. Comparison of only clerical/aide employees showed no difference in the qualities of evaluation. The number of professional employees testing positive for drug use was too small to allow valid comparisons.

A comparison of other markers of job performance—commendations, warnings, promotions, and probation—showed a highly significant difference in likelihoods of receiving a warning between clerical/aide employees (42%) and professional employees (6%) (chi square = 29.92, $p < 0.001$). There was a nonsignificant increase in the likelihood of receiving a warning among drug-positive (41%) compared with

drug-negative (25%) employees. A comparison of drug-positive and drug-negative clerical/aide employees showed no difference. The warnings given were of several types. Many were for minor infractions related to arriving at work a few minutes early or late; few were for more serious behavior such as rudeness, poor job performance, and sleeping on the job. None of the warnings given drug-positive employees were serious infractions. Clerical employees were significantly more likely to be fired or to leave without notice than were professional employees (chi square = 6.2, $p = 0.043$). Eleven drug-negative employees were fired during the study; no drug-positive employee was fired. Reasons given for leaving were similar among drug-positive and drug-negative employees. However, most groups were too small for valid statistical comparisons to be made.

DISCUSSION

Drug use is common in the United States. Given the high frequency of use of drugs in the population, it is certain that hospitals and other major employers have significant numbers of employees who use drugs.

Drug use on the job is generally agreed to be detrimental to performance. Tests of motor and intellectual function while intoxicated support this perception. Drug addiction is frequently associated with impairment of job performance, usually related to family and economic stresses caused by addiction.

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TABLE 1
Analytic Methods Used for Drug Screening and Confirmation*

Drug(s) Tested for	Screening Method	Internal Confirmation	Reference Laboratory
THC (marijuana)	EMIT®-dau	TLC	GC/MS
Barbiturates	EMIT®-dau	TLC	GC or GC/MS
Codeine	TLC	TLC	GC/MS
Propoxyphene	TLC	TLC, metabolite	GC/MS
Barbiturates	EMIT®-dau	TLC	GC or GC/MS
Phenothiazines	EMIT®-dau	TLC	GC or GC/MS
Barbiturates	TLC	GC	GC or GC/MS
Phenothiazines	TLC	TLC	GC or GC/MS
Phenothiazines	TLC	TLC, metabolite	GC or GC/MS
Phenothiazines	EMIT®-dau	TLC	GC/MS

*Using internal confirmation prior to sending specimens to the reference laboratory resulted in no unconfirmed positives. TLC = thin-layer chromatography; EMIT = enzyme-multiplied immunoassay technique; GC = gas chromatography; MS = mass spectrophotometry.

†Cocaine screen done by TLC, metabolite by EMIT.

‡Alternate method for TLC utilized (HFTLC).

Characteristics of job performance were assessed by review of personnel files of study employees. The personnel department reviewed the files and extracted information on job evaluation, disciplinary actions, promotions, commendations, termination of employment, and absenteeism. The reviewer had no access to information concerning the individual employee's drug screening status. Summary information about each employee was forwarded to the author for compilation of results.

Each job was characterized as clerical/aide or professional based on the degree of training required for the job and amount of independent decision making required to perform the job. The categorization was made without knowledge of any individual's drug testing status.

Statistical calculations were performed using the SAS package (1985) run on a PRIME 50 computer.⁶ Comparisons were made using the chi-square statistic. Several subgroups included cell sizes too small to allow valid calculations to be performed.

RESULTS

One hundred ninety-two sequentially hired employees underwent urinary toxicology screening. Twelve employees were excluded from the study. Six had no results reported by the laboratory, four were excluded because of two instances of assignment of the same random number to two employees, and two never reported to work and therefore had no employee folder available to review.

The final study population was 180 employees. Twenty-two employees tested positive for drug usage, representing 12% of the study group. Drugs identified were THC (marijuana) (14), propoxyphene (3), barbiturates (3), phenothiazine (1), and multiple drugs (phenothiazine, barbiturates, codeine, and propoxyphene) (1).

Demographic characteristics are shown in Table 2.

The employees were representative of the racial makeup of the community at large. The high percentage of women in the study group (73%) reflects the high percentage of total hospital employees in female-dominated job categories (e.g., nursing, ward clerk, nurse's aide). The new employees tended to be young.

Employees testing positive were more likely to be young and male; this tendency is supported by population surveys of drug usage.⁷ Test-positive employees were significantly more likely to be in clerical/aide positions (chi square = 4.33, $p = 0.0037$). This finding is also in keeping with population surveys.⁸

Table 3 shows comparisons of the employees on the various job-related criteria assessed during the study. Comparison of job retention at one year revealed a higher turnover rate among drug-positive employees

TABLE 2
Demographic Characteristics and Job Categories by Drug-testing Status in 180 Employees

	Drug-testing Status		Total
	Positive No. (%)	Negative No. (%)	
Age (years)			
<30	16 (14)	96 (86)	112 (62)
>30	6 (9)	62 (91)	68 (38)
Race			
White	16 (13)	111 (87)	127 (71)
Black	6 (11)	47 (89)	53 (29)
Sex			
Male	9 (19)	39 (81)	48 (27)
Female	13 (10)	119 (90)	132 (73)
Job category*			
Professional	5 (6)	73 (94)	78 (43)
Clerical/aide	17 (17)	85 (83)	102 (57)
TOTAL	22 (12)	158 (88)	180 (100)

* $p = 0.04$ comparing professional and clerical workers.

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	Professional		Clerical/Aide		Drug- positive (n = 22)	Drug- negative (n = 156)	Profes- sional (n = 78)	Clerical/ Aide (n = 102)	
	Drug Positive (n = 5)	Drug Negative (n = 73)	Drug Positive (n = 17)	Drug Negative (n = 63)					
Job retention									
Employed > 1 year	2 (40)	57 (78)*	10 (59)	45 (53)	12 (55)	102 (65)	59 (76)	55 (54)*	114
Resigned									
With notice	2 (40)	12 (16)*	3 (18)	16 (19)*	5 (23)	28 (18)*	14 (18)	19 (19)*	33
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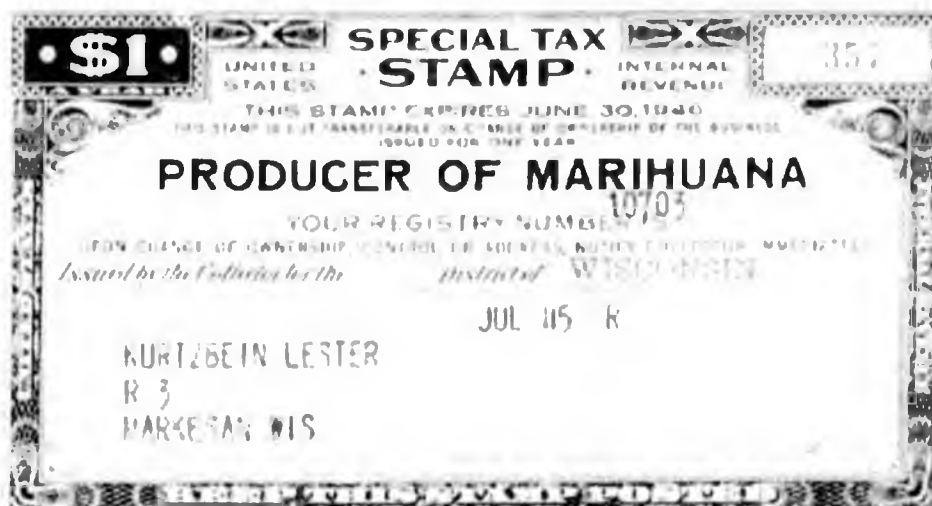
relationship of drug use off the job to overall performance is a subject of great heat and little light. There are few population surveys of drug use in workers; no studies comparing the job performance of non-job-related drug users with those of combatants were found. While drug abusers constitute a subset of the population of drug users, the relationship between use and abuse is complicated and not understood. Pre-employment drug screening presumes that drug users are less desirable than non-drug users. The National Institute on Drug Abuse estimated in 1986 that 40% of Fortune 500 companies use some form of urinary drug screening of employees.⁹ However, only three institutions reported the yields of their screening programs. Only one was done by the Employee Health Service at Presbyterian Hospital in New York. The others were done in private industry.¹¹ All had such low percentages of positive screens that the programs were discontinued. No known study prior to this report has hired all individuals tested to compare their performances. We found no significant difference in the performance of individuals who tested positive and those who tested negative using broad categories of job performance. The categories were drawn broadly to ensure consistency; review of routinely generated personnel records prevented any special handling of the group being studied. Further studies of the relation of drug use to job performance are needed. The size of the drug-positive group in this study was clearly not large enough to detect subtle differences in job performance or retention.

Other institutions should attempt to replicate this study and expand the range of job characteristics studied. If further studies show impairment in performance with certain drugs or in certain jobs, techniques of identifying relevant drug use could be supported. If no relation between drug use and job performance can be found, we should transfer the money now being spent on drug screening to other programs. The data presently available do not support the thesis that positive drug screening predicts poor job performance.

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The Economic Implications
of
Marijuana Legalization in Alaska



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Executive Summary

This study focuses on the economic effects of marijuana prohibition and the consequences of eliminating prohibition in Alaska. A central concern in this analysis was estimating the cost savings associated with justice system expenditures for:

- Law Enforcement
- Court System
- Incarceration and Parole/Probation

Following the methodology of Miron (2003) we find that a total of approximately \$16 million in direct expenditures is dedicated to marijuana prohibition annually by the State of Alaska (2004 dollars). Law enforcement is the least costly component of this expenditure, whereas adjudication by the courts is the most costly.

In addition to the above, consideration was given to indirect economic costs associated with prohibition, including:

- Lost economic output
- Impact on family and social service budgets
- Secondary justice system effects

The value of these three items is estimated at over \$8 million. An upper boundary is difficult to estimate without detailed survey data on the effects of prohibition on family and social services budgets.

The concern of disproportionate minority arrest and incarceration is raised, and although not a monetary cost, it is a social cost nonetheless.

Marijuana prohibition brings to the State of Alaska federal grants, fines and asset forfeitures which equal less than a million dollars per year, doing very little to offset its costs. Net direct plus indirect costs are thus in excess of \$24 million per year, plus additional criminal costs.

We found that marijuana prohibition causes additional crimes, although no estimate is provided of total prohibition-caused crimes and associated costs. Elimination of prohibition will, therefore, reduce crime. Even a 1% reduction in crime would produce budget savings in Alaska on the order of \$3.6 million dollars annually, as well as eliminating costs to victims.

Total costs of marijuana prohibition for Alaska are easily in the range of \$25 million to \$30 million per year.

Do these costs provide a commensurate benefit? Of central import in a cost-benefit framework is the question of whether prohibition "works" in its primary objective of reducing consumption. A literature search of peer-reviewed professional literature leads to the conclusion that one cannot state that prohibition significantly reduces consumption.

To the extent that consumption is curbed, the literature suggests a corresponding substitution of other substances. As with Alcohol Prohibition in the early 20th century, this substitution is, at least in part, towards more dangerous substances. In Alaska, the problem of inhalant abuse in remote areas is quite serious and may reasonably be regarded as a direct result of marijuana prohibition.

In sum, marijuana prohibition costs the State of Alaska well over \$24 million annually in direct and indirect costs of enforcement, not offset significantly by grants, fines or forfeitures. Prohibition does not succeed at its stated purpose, and in fact contributes to additional crime, and to use of other, more dangerous substances. Marijuana prohibition, using the most favorable figures in a cost-benefit analysis, is a costly failure.

Appendix I discusses the revenue potential of hemp in an atmosphere of state and federal legality. Were Alaska to tax sales of marijuana at a non-prohibitive rate, similarly to alcohol and tobacco products, it is estimated that \$10-12 million dollars in state revenue could be generated annually. This estimate is based upon consumption by Alaska residents and does not include revenues from tourist "coffee shop" trade, discussed separately. While estimates from other locations may suggest potentially greater tax revenues, taxing marijuana too heavily in Alaska could encourage continued home production, undermining tax revenues.

Industrial hemp and the marijuana tourism trade could generate more in sales revenue than the combined total of all prohibition enforcement savings and potential tax revenues. Estimates from locations such as Vancouver and Amsterdam suggest that tens of millions in sales revenue is easily achievable. This would in turn generate millions in property, licensing, and sales tax revenues. The potential size of these industries is speculative, but Alaska may possess unique advantages for such enterprises.

If Alaska ends marijuana prohibition, then, it will first eliminate \$25-\$30 million of costs. Were it further to tax residents for marijuana consumption, \$10-12 million in direct government tax receipts could be generated. Tens of millions in industrial hemp and marijuana coffee shop/tourist trade dollars could be generated as well, if Ballot Measure 2 is fully implemented, primarily from nonresidents.

Introduction

According to the International Centre for Prison Studies at King's College in London, the United States leads the world in incarceration of its citizens. This leadership is not by a small margin, and it is both in absolute terms as well as by proportion.¹ The U.S. surpasses the second place contender, the Russian Federation, by 20%. It leads European industrialized countries by approximately 500%. The Alaska incarceration rate exceeds the U.S. average.² It is therefore reasonable to assert that Alaska is a world leader in incarcerating its citizens.

Many factors affect incarcerations, but the war on drugs, in America, is a leading factor. The increase in incarcerations for drug offenses began in earnest about 30 years ago. Aggressive policing, combined with mandatory sentencing and the application of drug testing to parolees and probationers, has caused a substantial change in the composition of the American prison population. Whereas previously the majority of prisoners were incarcerated for violent crimes, now the majority are imprisoned for nonviolent crimes.

According to the Center for Juvenile and Criminal Justice (1999):

Contrary to the public perception that the incarceration of violent offenders has driven America's prison growth, the Institute found that 77% of the growth in intake to America's state and federal prisons between 1978 and 1996 was accounted for by nonviolent offenders. According to data collected by the United States Justice Department, from 1978 to 1996, the number of violent offenders entering our nation's prisons doubled (from 43,733 to 98,672 inmates); the number of nonviolent offenders tripled (from 83,721 to 261,796 inmates) and the number of drug offenders increased seven-fold (from 14,241 to 114,071 inmates). Justice Department surveys show that 52.7% of state prison inmates, 73.7% of jail inmates, and 87.6% of federal inmates were imprisoned for offenses which involved neither harm, nor the threat of harm, to a victim.

In this study we focused on one element of the war on drugs in Alaska — the prohibition of marijuana. In the approach taken, we did not evaluate whether marijuana is beneficial or harmful to the user, or to society. Rather, we focused on several measurable aspects of prohibition: What are the costs of prohibition? Does prohibition serve the ends it intends? Are there unintended consequences of prohibition, and what are they?

In Part I we address the direct costs of judicial system resources used in marijuana prohibition. Three areas of the justice system are affected by marijuana prohibition. The first and least costly is policing, or law enforcement. The second and most expensive is the court system. The third is incarceration and probation/parole. Following the methodology established by Miron (2003), we estimated the proportion of total resources in each area accounted for by marijuana prohibition. We then applied that proportion to the corresponding level of expenditures in order to estimate costs associated with marijuana prohibition.

Secondly, we investigated additional costs subsequent to enforcement and adjudication of marijuana prohibition. There is a lost economic output associated with incarcerating marijuana offenders. There is an impact on family and social services. Secondary offenses stemming from an initial marijuana

¹ http://www.kcl.ac.uk/depsta/rel/icps/worldbrief/highest_to_lowest_rates.php

² The U.S. Average is 701 per hundred thousand population. The most recent data available for Alaska is in the 2002 offender profile report. At 4599 average incarcerations for the year and estimated 2002 population of 643,786, it puts Alaska's incarceration rate at 714 per hundred thousand. That is, Alaska is about 2% above the average.

prosecution, including probation violations, or parole violations such as failing urinalysis or being in the presence of marijuana, can result in costly imprisonment.

Our attention then turns to a cost-benefit approach to prohibition, reported in Part II. After identifying the costs of prohibition, we investigated the effects of prohibition on behavior. The most direct question is the effect of prohibition on substance use. That question involves the impact of marijuana prohibition upon marijuana consumption, as well as on consumption of other substances. The literature also addresses the relationship between prohibition and crime. It is important to distinguish between cause and effect: do drugs cause crime, or is crime caused by prohibition?

In the course of this study, we relied on peer-reviewed professional literature. Often, proponents or opponents of prohibition cite casual or spurious statistical associations to advance their case. There are difficult statistical issues in such studies, and often an apparent association can be superficial. A study that is well done but not comparable to others might be cited out of context. A case in point is a study produced in 1988 which is often cited as evidence of dramatic increases in marijuana use by youths after Alaska decriminalization in 1975. That study is reviewed here.

In Appendix I, an investigation of tax revenue and hemp/marijuana industry potential is reported. Tax revenue potential is conservatively estimated, because the potential for home production is considered significant for Alaska. Were the technique cited for a California study to be used here, revenue potential would be on the order of 75% greater.

Industrial hemp's tax revenue potential is modest. Revenue potential for the coffee shop/tourist trade is more significant, if Alaska experiences anything like what existing international models have seen. In one 2002 study cited, shops in Amsterdam were earning \$1.2 million dollars in revenue per year, with the government receiving half of the money.

The Alaska laws and judicial decisions pertaining to marijuana are presented in Appendix II. Generally speaking, the current status is that the Alaska Court of Appeals has struck down a portion of a 1990 initiative that re-criminalized possession of less than four ounces. Alaska's Supreme Court has yet to rule on the question. But possession of more than four ounces and less than 1 pound can result in jail sentences of up to 1 year and a \$5,000 fine. Possession of over 1 lb. can result in a sentence of up to 5 years and a \$50,000 fine. Sale, or "manufacture", of less than 1 oz. can bring a sentence of up to 1 year and a \$5,000 fine. Sale of more than 1 oz. can result in a sentence of up to 5 years and \$50,000 fine. Sale to a minor can bring a sentence of 10 years and a \$100,000 fine.

Part I

Costs of Alaska Marijuana Prohibition

Justice System Costs

Costs of marijuana prohibition on the Alaska justice system must be estimated since there is no tracking of costs by offense category for the State of Alaska. The methodology used here follows closely that established by Miron (2003) in imputing police resources dedicated to marijuana prohibition. Law enforcement costs are based upon an estimate of "stand alone" arrests for marijuana. Court system costs are based upon an estimate of felony convictions. Costs of incarceration are based upon the estimate of marijuana offenders in the correctional system.

Law Enforcement Costs

We examined arrest data for marijuana offenses and compared that to total arrest data for all crimes. We utilized the resulting proportion, after adjusting for "stand-alone" vs. "incidental" arrests, to impute a budgetary figure for marijuana policing.

Arrest data by Census area for the State of Alaska are provided by the FBI Uniform Crime Statistics.⁸ The most recent year of data availability is 2001. Arrests are tabulated for possession and for "sale or manufacturing". Data are available for both adult and juvenile offenses. For purposes of this study, five years of data are averaged for analysis (1997 to 2001) and reported in Table 1 by total, adult, and juvenile offenses.

The table shows that, over this period, arrests for marijuana offenses constituted 3.5% of total arrests in Alaska. They constituted 2.9% of adult arrests and 6% of juvenile arrests, as there are numerous classes of offenses generally not committed by juveniles. (Conversely there are juvenile "status offenses", such as running away from home, which are not crimes if committed by adults. However, these are outweighed by adult offenses.) Total arrests for marijuana offenses averaged 1,233 annually, with most of them (1086) for possession and the remainder (147) for sale or manufacturing.

There is an additional consideration in imputing police resources devoted to marijuana prohibition. Often an individual is initially detained for some non-marijuana offense, and subsequently, during a search or questioning, the marijuana offense is recorded, so the marijuana offense is not a "stand alone" offense. Two "arrests" are recorded, and the marijuana "arrest" is incidental to the original reason for arrest. An incidental arrest is not as costly as a "stand alone" arrest, which may have required investigational and other resources.

The converse is also true: arrest for a marijuana offense can lead to other charges. Arrests for incidental charges are not "free", as they will incur evidentiary handling, laboratory testing, reporting and other costs. So it would not be appropriate to simply exclude everything except "stand alone" marijuana arrests. Doing so produces a conservative estimate of costs. "Incidental" marijuana arrests are also largely for possession rather than sale or manufacture, where the marijuana offense is often the focus of an investigation prior to arrest.

⁸ <http://fisher.lib.virginia.edu/collections/stats/crime/arrests94.html>.

Table 1: Average Number of Alaska Arrests 1997-2001
(totals may not add due to rounding)

<u>Total - All Offenders</u>	<u>Average</u>
Possession	1086
Sale or Manufacturing	147
Total	1233
Percentage of Total Alaska Arrests	3.5%
 <u>Adult</u>	 <u>Average</u>
Possession	776
Sale or Manufacturing	98
Total	874
Percentage of total Adult arrests	2.9%
 <u>Juvenile</u>	 <u>Average</u>
Possession	311
Sale or Manufacturing	49
Total	360
Percentage of Total Juvenile Arrests	6%

Source: FBI Uniform Crime Statistics as reported in:
<http://fisher.lib.virginia.edu/collections/stats/crime/>.

Miron (2003) indicated that the proportion of "stand-alone" arrests for marijuana possession may vary between 33% and 85%. No data are available on this question for Alaska. The average is assumed here (50%). If we concern ourselves strictly with "stand-alone" arrests for possession, the annual total is about 641. We would add to that figure the 147 for sale/manufacture, to arrive at an average of 818 "stand alone" arrests, constituting 2.2% of total arrests. For the reasons stated, this is a very conservative minimum for estimating costs.

The U.S. Bureau of Justice Statistics (USBJS) provides data on total justice system expenditures by state annually.⁴ This is accomplished through a comprehensive survey of state and local governments. The most recent year of data availability is 2001. According to the data, Alaska spent \$64 million on policing

⁴ www.ojp.usdoj.gov/bjs Justice Expenditure and Employment Abstracts file CJec0109.wk1

expenditures in fiscal year 2001. To convert 2001 dollars into 2004 dollars, the consumer price index is used.⁵ Total police expenditures for Alaska are estimated at \$68.1 million in 2004 dollars.

If we use the 3.5% figure for proportion of total arrests, then we arrive at a figure of \$2.4 million in 2004 dollars for police expenditures pertaining to marijuana prohibition. If we consider the adjustment for estimating "stand-alone" arrests, then the corresponding proportion would be 2.2%, or \$1.5 million. This is the least costly component of marijuana prohibition.

Drug Offenses vs. Marijuana Offenses in Alaska

Because the State of Alaska does not track "marijuana offenses" as a specific category through the remainder of the judicial system, it is necessary to discuss marijuana arrest data in relation to total drug offenses. Drug offenses as a group are tracked. Determining the relationship between marijuana arrests and total drug arrests assisted us in estimating prosecutorial and corrections burdens imposed by marijuana prohibition. We separated possession from sale or manufacture, because the first class of offense is primarily misdemeanors while the second class is primarily felonies.

Most marijuana felonies fall into the "misconduct with a controlled substance IV" category. Marijuana offenses are not found in the misconduct II or misconduct I categories at all. The misdemeanor categories of misconduct with a controlled substance apply to possession of small amounts of marijuana, but in reproducing studies pertaining to judicial costs we confined ourselves largely to the felony categories, as is discussed below.

Table 2 provides data on marijuana arrests as a proportion of total drug arrests, as well as arrests by category for the period 1997-2001 in Alaska. This is compared with the U.S. average for the same years. There are some important distinctions to note. First, the rate of total arrests for drug-related offenses of any kind is about twice as high nationally as in Alaska: 11% of total arrests nationally are for drug-related offenses as compared with 5.2% for Alaska. On the other hand, of the drug arrests made in Alaska, a significantly higher proportion is associated with marijuana offenses.

Less than half of all drug-related arrests nationally (45%) are for marijuana, as compared with 66% in Alaska. When we break this into categories of possession vs. sale or manufacture, the discrepancy holds true. Whereas 27.5% of arrests for sale or manufacture of a drug nationally are for marijuana, Alaska has a much higher rate at 38.5%. About half of all drug possession arrests nationally are for marijuana, whereas 73.4% of the drug possession arrests in Alaska are for marijuana.

Because the proportion of total drug-related arrests nationally is nearly twice that in Alaska, there is still a larger proportion of total national arrests (5%) associated with marijuana offenses. In Alaska, with half the national rate of drug arrests, but a much higher concentration of those in marijuana offenses, 3.5% of total arrests are marijuana related.

⁵ 2001 January index = 175.1; Feb. 2004 Index = 186.2. from: <http://www.economagic.com/em-egi/data.exe/blscu/CUUR0000SA0>

Table 2:
Proportion of Total Drug Offense Arrests Due to Marijuana

	Proportion of Drug Offenses Accounted for by Marijuana ⁶	
	<u>Alaska</u>	<u>USA</u>
Total Drug Arrests: Proportion Marijuana	66.1%	45.2%
Drug arrests for Sale/Manufacture Proportion Marijuana	38.5%	27.5%
Drug Arrests for Possession Proportion Marijuana	73.4%	49.6%
Marijuana Offenses- % of All Arrests	3.5%	5.0%

Source: Data for Alaska compiled from FBI Uniform Crime Statistics as Reported in: <http://fisher.lib.virginia.edu/collections/stats/crime/arrests94.html>. U.S. Data compiled from USDOJ "Crime in the United States", 1997-2001.

Disproportionate Arrest Rates Across Alaska

In reviewing the arrest data by census area, it is apparent that there is a disproportionate arrest rate between locations in Alaska⁷. In particular, according to the Uniform Crime Reports in 2001, about 1.5% of total arrests in the Anchorage census area were for marijuana. In the Prince of Wales/Outer Ketchikan area, the rate was five times higher at 6.7%. Generally speaking, it appears that the rural arrest rate for marijuana is far higher than that for the Anchorage census area. That in turn indicates a disproportionately higher arrest rate for Alaska Natives.

The Fairbanks-North Star census area arrest rate was also 6.1%, so there is not a uniformly rural/urban distinction. Nevertheless, there are substantial differences across locations, bringing to mind the question of disproportionate minority representation in the Alaska justice system. This issue is currently a concern of both the federal and state governments, in both the juvenile and adult systems.

⁶ Data for Alaska compiled from: <http://fisher.lib.virginia.edu/collections/stats/crime/arrests94.html>. From the USDOJ: Crime in the United States, 1997-2001.

⁷ Jon Gettman, PhD, and Senior Fellow at George Mason University School of Public Policy is acknowledged for pointing out these differentials.

Court System Costs

A similar cost estimation procedure was used to determine court costs of prohibition. We first estimated the burden on the legal and judicial system in terms of marijuana convictions as a proportion of the total. We then applied that proportion to the total expenditures in this area to arrive at a cost estimate for marijuana prosecutions. The previous work provided some guidance, as it established marijuana offenses as a proportion of total drug offenses.

Individual state data on marijuana prosecutions and convictions is not available through the U.S. Justice system. There is, however, aggregate data we may use to establish some key relations. In particular, we looked at the number of prosecutions or convictions in relation to the number of arrests. The relationship between arrests and convictions nationally will provide some direction in estimating that for Alaska. Only felony data is available nationally.

The State of Alaska uses a management information system known as the Offender Tracking Information System (OTIS). Although it does not specifically track marijuana offenses, it does break out categories that are somewhat specific to marijuana convictions. The Juvenile Offender Management Information System (JOMIS) is a similar system for juveniles in Alaska. Cases are not disaggregated sufficiently to extract marijuana offenses specifically.

Following the methodology established previously in Miron (2003), we estimated the proportion of *felony* convictions associated with marijuana offenses, as opposed to total offenses including misdemeanors. It is the proportion of felony convictions that is used as a proxy for the relative burden of prohibition on the judicial system.⁴

U.S. State Court Convictions

According to the USBJS, for the most recent year available (2000), state court felony sentences included 2.7% for known marijuana trafficking and 3.7% for known marijuana possession.⁵ The data are for "felons convicted" as opposed to the total number of felonies and refers to the most severe charge. Unfortunately, the largest single category among all of the drug felony sentences was "unspecified", at 13.4% of total felony sentences. There is little question that marijuana convictions are significantly more than this combined 6.4% total.

A total of 34.6% of state felony convictions were for drug offenses, with 13.4% of these unassigned to marijuana or any other specific drug. We assumed that marijuana cases constitute the same proportion of the unspecified cases as they do of specified ones. That would give a total of 10.4% of state felony convictions attributable to marijuana offenses nationwide.¹⁰

⁴ Felony prosecutions are much more expensive than misdemeanors and take up a disproportionate amount of state resources. For example, Iowa estimated that the cost for prosecuting a simple misdemeanor ranged from \$14-\$300, whereas a serious misdemeanor cost from \$100-\$5000, and the lowest felony charge, from \$2,000-\$8000. See Iowa Fiscal Services Division, Legislative Services Agency: Fiscal Note Dennis C. Prouty March 3, 2004.

⁵ Bureau of Justice Statistics Bulletin: Felony Sentences in State Courts, 2000.

<http://www.ojp.usdoj.gov/bjs/pub/pdf/fssc00.pdf> p 2.

¹⁰ 34.6% of total convictions are for drugs. 13.4% of convictions are for drugs but unknown type. That means 21.2% of drug convictions are known. Of these, 2.7% + 3.7% = 6.4% are known marijuana offenses. Therefore $(6.4/21.2) = 30.2\%$ of known drug convictions are marijuana. Assuming the same proportion for the unknown drug convictions results in $(.302) * (.134) = 4\%$ of convictions not classified are for marijuana. Adding all felony convictions for marijuana together results in $2.7\% + 3.7\% + 4\% = 10.4\%$.

We then noted the relationship between arrest data and felony conviction data. Nationwide, there are about 5% of total arrests associated with marijuana (misdemeanor plus felony), whereas 10.4% of total felony convictions are for marijuana offenses. There is nearly twice the rate of felony marijuana convictions as there are marijuana-related arrests, primarily because these offenses comprise a greater proportion of felony cases than misdemeanor cases.

It is also useful to note that about 20% of the U.S. state prison and jail population is incarcerated for drug offenses.¹¹ So, while 34% of felony convictions are for drug offenses, a considerably smaller portion of state incarcerations are for drug offenses. This may be accounted for by suspended and probated sentences. This ratio will also help serve as a guide for Alaska.

Alaska State Court Convictions

We knew that using the 10.4% U.S. marijuana felony conviction rate as an estimate for Alaska would over-estimate Alaska prosecutions, given the pattern of arrest data there vs. the U.S. Having established that 3.5% of total arrests in Alaska are for marijuana vs. 5% nationwide we reduced the 10.4% figure commensurately, or, $(3.5/5) \times 10.4 = 7.28\%$, as a guide for further discussion.

The State of Alaska provided an analysis of post-2002 conviction data upon request.¹² This data was based on the total Alaska corrections population, both those housed in-state and those housed by contract with other states. For that subset of total offenders, case convictions were extracted in order to examine the proportion incarcerated for all felonies, the proportion for felony drug offenses, and the proportion for the two categories consistent with marijuana felony convictions.

This subset omitted felony convictions that resulted in suspended imposition of sentence (SIS), probation, or release with time served, consistent with the national data used. Because marijuana convictions are often considered a lesser offense, and therefore more likely to fall in this category, we thus underestimated marijuana felony convictions.

We also saw that there are year-to-year variations in convictions data correlating to variations in arrests. Some years have a higher proportion of marijuana and drug offense arrests than others. The year 2002 was selected as it is both recent and may be compared with available arrest data. The average time required to process state drug cases is 158 days (USBJS 2003:34). According to the USBJS (1992:172), it is nine months for federal cases. So we compared 2001 arrest data with 2002 convictions data.

Marijuana arrest rates for 2001 were nearly 20% beneath the five-year average. We can be confident that, if anything, we again were conservative in our estimation. There would have been fewer marijuana cases in the judicial system in 2002 as compared with the average year. This should be recalled later when final estimates are made.

¹¹ See USBJS <http://www.ojp.usdoj.gov/bjs/prisons.htm> for 2001 State prison data (20%). See USBJS <http://www.ojp.usdoj.gov/bjs/pub/pdf/pji96.pdf> for State jail data (most recent year available 1996).

¹² Data extraction provided courtesy of Mary Collins, Alaska Department of Corrections, through Jerry Burnett, Commissioner 4/5/04.

Table 3: Alaska Felony Convictions since 2002 for Drug Related Offenses

Proportion of Convictions for Corrections Population	
Total Drug related	9.6%
Total Misconduct III, IV	8.6%

Source: Alaska Offender Tracking and Information System

Table 3 is the result of the data extraction from the State of Alaska OTIS system. Again, because multiple charges are often entered simultaneously against a single defendant, it is more appropriate to utilize felon data as opposed to the total number of charges. In addition, the conviction is associated with the most serious offense. These data are constructed in the same manner as the federal data in the preceding section.

We noted first that there are about half as many corrections inmates who have been convicted for drug offenses in Alaska as compared with the U.S. average (9.6% vs. 20%). This is almost precisely the same relationship as for arrests. Alaska has a little under half of the national average in terms of drug arrests, and it also has a little under half the national average for drug-related incarcerations.

It will be recalled, though, that Alaska has a much greater relative percentage of marijuana cases among drug offenses. Marijuana felony cases are found mostly in the misconduct IV category, although some could be misconduct III. There are no marijuana cases in the misconduct II or misconduct I categories. Note from Table 3 that the vast majority of the drug convictions are in the misconduct III and IV categories. In fact, the majority of these are misconduct IV.

Thus, the relationship between national arrest data and Alaska arrest data is basically upheld all the way through to convictions and incarcerations. While there are fewer total drug offense arrests in Alaska, they are more heavily concentrated in the marijuana category. There are few heroin, crack cocaine, and other hard drug arrests in Alaska relative to the rest of the nation.

By using the relationship between national felony convictions and national incarcerations to estimate the same for Alaska, we arrived at the figure of 16.6% of total felony convictions in Alaska being for drugs of any kind.¹³ We further estimate that 7.31% of felony convictions in Alaska are for marijuana as opposed to other drug offenses.¹⁴

So we have a couple of different estimates for the proportion of felony convictions for marijuana out of all Alaska felonies. By utilizing the national ratio of felony convictions to arrests and applying that to Alaska arrest data, we arrived at the figure of 7.28%. By working backwards from Alaska incarcerations data to felony convictions, utilizing the same relationship as found in national data, we found a rate of

¹³ Nationally $(34.6/20) = (X/9.6)$ for Alaska, where $X = 16.6$.

¹⁴ Nationally, the proportion of marijuana felony convictions out of total felony drug convictions $= (10.4/34.6)$. Alaska has a higher relative concentration of marijuana arrests $(66.1/45.1)$, so the national ratio is adjusted (multiplied) by this ratio. Then solve for $(10.9/34.6) * (66.1/45.1) = X/16.6$.

7.31%. We used the average of the two figures, 7.3%, to estimate the expenditures in the legal and judicial arena due to marijuana prohibition. According to the Department of Justice, total justice system expenditures in Alaska for the year 2001 were \$121.7 million¹⁵, including prosecution, courts, and public defense. Utilizing the same price index data, we estimated this in 2004 dollars at \$129.4 million. Applying the 7.3% figure to that total, we arrived at an estimate of \$9.45 million for the judicial costs of Alaska marijuana prohibition in 2004 dollars.

Corrections Costs

We used the same approach to estimate the proportion of Alaska's correctional population attributable to marijuana prohibition. There is one further consideration here, because the U.S. Justice Department survey correctional expenditure data is not broken down by type of institution. (It does include any agency concerned with corrections, including probation offices). Since correctional populations may be housed in different types of institutions, sometimes depending on type of offense or offender, there may be cost differentials associated with corrections for different types of offenses.

Correctional centers are more costly than community residence centers. If the majority of drug and marijuana offenders are housed in community residence centers, then we would be concerned about overestimating costs based on the simple average from the U.S. Justice Department data. On the other hand, if the majority is found in correctional institutions, then we have a conservative cost estimate for marijuana corrections.

According to the Alaska Department of Corrections, in 2002 there were 216 drug-related offenders out of a total 3,508 institutionalized (correctional center) offenders, or 4.3%.¹⁶ There were 90 drug-related offenders out of 902 housed in community residence centers, or 10%.¹⁷ The average across all institutions was 6.9%. This data is calculated based upon the most serious charge. Thus, although a greater fraction of the community residence center population is accounted for by drug offenders, there are more than twice as many drug offenders housed in correctional centers. Consequently, and also because we have demonstrated that marijuana offenses make up the bulk of drug offense convictions, there is little likelihood of over-estimating the cost of incarcerating marijuana offenders by using the Department of Justice Data.

In comparison to other states, Alaska has a lower proportion of incarcerated drug offenders. This is no surprise given the arrest and convictions data. Nationwide, an average of 20% of state correctional populations are drug offenders.¹⁸ In the previous section we noted that Alaska has about half that, but with a much higher proportion of marijuana offenses as compared to other drugs. Unfortunately, the corrections data is not broken down into type of drug, so we are unable to say exactly what proportion of these are marijuana offenders.

Because more severe offenses typically receive longer sentences, the population of offenders will be more heavily weighted toward those who have been convicted of more serious crimes. That is, the proportion of marijuana offenders in the correctional population will be lower than the rate of convictions determined previously, 7.3%.

Among the post-2002 institutionalized offender population, 50% of the total drug-related offenses are misconduct with a controlled substance IV, the category for most marijuana offenders. There were only

¹⁵ Justice Expenditure and Employment Abstracts file CJec0109.wk1, id.

¹⁶ State of Alaska Department of Corrections, 2002 Offender Profile p 13-16.

¹⁷ Ibid. p 26-28

¹⁸ <http://www.ojp.usdoj.gov/bjs/pub/pdf/p02.pdf>, table 15.

two misdemeanor (Misconduct V and VI) offenders housed in correctional institutions. There are also a sundry few in the "attempted drugs" categories.

In community residence centers we found that 46% of residents with drug related charges had a conviction for misconduct with a controlled substance IV. There were two misdemeanor offenders in community residence centers, and several more in the "attempted drugs" and conspiracy categories.

A total of 124 offenders were housed in institutions or community residence centers without any charge entered into the OTIS system. It is unclear how to assign these in our analysis, but it is doubtful that they diverge so dramatically from the general offender profile as to significantly distort any estimates.

We set as a benchmark the proportion of post-2002 incarcerated offenders in the misconduct IV category, the most particular for marijuana offenses, 3.4% of total incarcerations. Again, the misconduct IV category does not include misdemeanor marijuana offenders, or more serious marijuana felony charges. It would not include anyone in the attempted drugs or conspiracy categories. On the other hand, there are misconduct IV drug offenders who are not incarcerated for marijuana.

Although we have demonstrated that marijuana offenses make up the majority of drug arrests and prosecutions, it is the least serious drug offense and therefore receives lighter sentencing. We did not want to assign 66% of the corrections population serving drug offense sentences to marijuana, as that would be an overestimate. We instead rounded our benchmark misconduct IV figure down to 3%, on the assumption that the proportion of non-marijuana misconduct IV offenders significantly outweighs marijuana offenders charged with other (greater or lesser) offenses.

Having arrived at an estimate of the corrections population serving marijuana sentences, we applied that figure to corrections expenditures. According to the U.S. Department of Justice survey, the State of Alaska spent a total of \$172.6 million on corrections in 2001. In 2004 dollars, the figure would be \$183.5 million. Three percent of that figure indicates a cost of \$5.05 million for marijuana incarcerations.

Summary of Justice System Costs

A summary of total judicial system expenditures for prohibition is presented in Table 4, indicating a total of \$16 million.

Table 4
Total Judicial System Budget for Marijuana Prohibition in Alaska

<u>Item</u>	<u>\$ Millions</u>
Policing	1.50
Legal and Judicial	9.45
Corrections	5.05
Total	\$16.00

Additional Economic Considerations

There are several other areas of concern besides the direct costs calculated above. The most important of these is the lost economic output associated with incarcerating offenders. There are also costs to the family and social service budgets of the state, particularly when offenders have minor children. There are some secondary offenses to consider, such as probation violations that would not exist in the absence of prohibition. Finally, there are mitigations of costs from intergovernmental revenues. Fines and forfeitures are also discussed.

Lost Economic Output

DeSimone (2002:968) produced the most recent study of the effect of marijuana use on employment. According to his estimates, marijuana users are 15% less likely to be employed. We utilized these results to get an estimate of lost output from incarcerating marijuana offenders.

According to the Alaska Department of Labor, the employment rate statewide was 92% in 2003. Adjusted down to 85% to account for the differential probability of employment cited above resulted in a figure of 78.2%. That is, it is estimated that about three-quarters of the marijuana users and, by extrapolation, marijuana offenders, were employed.

Previously, we estimated that there were 132 persons in Alaskan correctional institutions of one kind or another for marijuana offenses. According to the U.S. Department of Labor, the average wage income for Alaska in 2002 was \$40,280.¹⁹ Assuming the employment percentage above gives a total lost wage income of \$4.2 million. Also according to the U.S. Department of Labor, the wage component of total compensation is approximately 71.4% of the total.²⁰ Adding in benefits results in total lost labor compensation of \$5.8 million. In 2004 dollars, the amount is \$6.08 million. Because labor produces more value than it is compensated for, we know that lost economic output is even higher.

There are some long run costs to consider as well. Young people, in particular, who have a conviction face losses in student loans, loss of employment advancement, and other forms of discrimination in the marketplace. The cumulative loss will, over time, significantly exceed their short run loss.

Family and Social Services

Because some portion of marijuana offenders have children, there are additional expenditures by various state agencies concerned with family and social services. With loss of employment from incarceration, there are impacts on agency budgets.

Parke and Clarke-Stewart (2001) indicated that in the year 2000, 56% of all incarcerated persons had minor children. This figure was stable relative to the previous decade. Needless to say, the effects on minor children of parental incarceration are negative. This can vary according to arrangements for alternative care, visitation, economic circumstance, whether the mother or the father is incarcerated, etc. In one estimate cited, 70% of young children with incarcerated mothers had emotional or psychological problems (Parke and Clarke-Stewart 2001:7).

Johnson and Waldfogel (2002:472) noted an increased burden on the foster care system from incarcerated parents, over 7% of the population in their sample. In this study, as with others, over 80% of the children

¹⁹ http://stats.bls.gov/oes/2002/oes_ak.htm#b00-0000

²⁰ <http://data.bls.gov/cgi-bin/dsxy> Data taken from the 4th quarter 2003, all workers.

of incarcerated fathers live with the mother, whereas when the mother is incarcerated only about 20% live with the father. Regardless of whether the mother stays at home with minor children or works and receives daycare assistance, there is an impact on state social services budgets. Although 90% of incarcerated parents are fathers, the war on drugs has a higher fraction of incarcerated mothers as compared with other offenses (Johnson and Waldfogel 2002:473).

There is little doubt, then, that marijuana prohibition has significantly increased the burden on the social welfare system. Without a detailed survey of inmates and family circumstances it would be difficult to render a precise figure. But a couple of different approaches give us an idea of the order of magnitude. One approach is to ask how much per inmate in various monthly social service costs would be required to equal \$1 million dollars per year. The answer is about \$631 per inmate.

The monthly AFDC (now called Temporary Assistance) maximum benefit is \$821 and the food stamp benefit is \$391 for one adult and one dependent (rural I figure). With half of all inmates having a minor child and with loss of employment during incarceration, those two services alone would cost over one million dollars per year. Then one must consider Medicaid, energy assistance, and so forth. Given the behavioral problems of children of incarcerated parents, significantly more than \$1 million per year in social service costs is doubtless incurred due to marijuana prohibition.

The FY 2004 State of Alaska Children's Services approved budget was \$127.5 million. The Public Assistance budget was \$244.1 million. Each 1% rise in these combined budgets results in \$3.7 million in additional operating expenditures for the state. The FY 2004 approved Health Care Services budget was \$671.6 million. It would appear again here that marijuana prohibition easily adds well over \$1 million dollars to the family and social services budgets of the state.

Secondary Offenses Stemming from an Initial Marijuana Charge

Some proportion of marijuana offenders re-appear in the judicial system due to probation or parole violations. In addition, testing positive for marijuana can be a parole violation for unrelated offenses. We note that 216 of 3,508 correctional center residents were in custody for either parole or probation violations. In addition, 113 of the 902 in residential centers were in custody for probation or parole violations. That is, 6.2% of the correctional population and 12.5% of the residential population (7.5% of the total) were incarcerated because of such secondary violations.

If parole, probation, and other violations subsequent to a marijuana offense (i.e., failure to appear, failure to comply, failure to adhere to conditions of release, fugitive from justice, etc.) were eliminated, there would be additional cost savings. It would appear that if such secondary offenses were equiproportional across all categories, the savings would be on the order of another 10% in incarcerations, or about \$500,000. An estimate of additional judicial cost savings is not attempted here.

Cost-Mitigating Factors

A portion of Alaska's marijuana policing expenditures is financed by grants from the federal government. In addition, there are some property seizures and fines associated with marijuana arrests. Federal grant funds mitigate costs of enforcement, as they come from outside the state. While it is true that, ultimately, these grants come from federal taxes, even if marijuana policing is done away with for Alaska, it will not change policy in other states. Those states would continue to receive grants whereas Alaska would lose them, and federal taxes would not be reduced for Alaskans.

Property seizures and fines are another matter. They are discussed here, but from the perspective of the state as a whole they do not provide resources. They take resources from a tiny portion of residents to pay for a program as opposed to its being paid for by the state's residents in general. If marijuana is legalized, the "loss" of revenue from property seizures will exactly equal the "gain" to persons who will no longer have their property taken from them. Fines are a similar situation.

According to the Alaska Bureau of Alcohol and Drug Enforcement (ABADE), there are three sources of grant funds that may be used for marijuana policing. Two of these grants are awarded by the U.S. Dept. of Justice, the Byrne Grant and the Alaska Illegal Drug and Alcohol Grant. Additional funds are also received through the U.S. Drug Enforcement Administration (DEA) for marijuana eradication.

The DEA grant, exclusively for marijuana policing, amounted to \$86,000 in FY 2004 (I. McKenzie, Coordinator, DEA Eradication, Anchorage, AK, personal communication, May 28, 2004). The other two were not exclusively for marijuana. Of these, the total Byrne grant request for 2004 was approximately \$1 million while the Illegal Drug and Alcohol grant was a multi-year program with an annual average of \$664,500. A request was made for an apportionment of these funds between marijuana, alcohol and other drug enforcement. An estimate of 10% for marijuana was provided, with the understanding it was no more than a guess (Capt. E. Harrington, ABADE, personal communication, June 17, 2004).

An alternative method for allocating these funds across enforcement categories is to look at arrest data, on the assumption that the allocation of funds is proportional to arrest data for alcohol and drugs. According to the Uniform Crime Report arrest data for Alaska, there were an average of 5,667 arrests for either drug or alcohol offenses for the years 1997-2001. Of these, 21.67% were for marijuana offenses.

We have one estimate from a cognizant official of 10%, and another of 21.67% based on arrest data. A conservative estimate of 15% was used, resulting in a \$249,675 figure for the two grants in question. We would add to this amount the \$86,000 DEA grant for marijuana eradication. The total amount of federal grant funding strictly for marijuana enforcement is therefore estimated at \$335,675.

The Alaska court system also received federal grant money in FY 2003, in the amount of approximately \$300,000, for "felony drug court" funding in Anchorage.²¹ The number of marijuana cases assigned to this specific court is unknown. As this funding is strictly concerned with felony charges, it would be appropriate to apply the 38.5% proportion of drug offenses for sale/manufacture of marijuana, obtaining an estimate of \$115,500, or, in 2004 dollars, \$117,500.

During calendar year 2003, there was approximately \$1.05 million in property seized by state alcohol and drug enforcement agencies (Capt. E. Harrington, ABADE, personal communication, June 17, 2004). About one-third of this amount was in cash. The remainder consisted of weapons, vehicles, real property, aircraft, vessels, and miscellaneous items. Values of such property are estimated by investigators.

One may allocate a portion of these seizures strictly to marijuana enforcement as opposed to alcohol and other drug offenses. It is appropriate to estimate property seizures using arrest data for sale and manufacture of marijuana, as opposed to simple possession, because seizure laws do not apply to most cases of simple possession. For the same reason, we excluded alcohol arrests, in which seizure actions would not apply.

Restricting our attention to drug offenses for sale and manufacture, we found that marijuana constituted 38.5% of these cases. So, although marijuana accounts for 66% of total drug related arrests, there is a

²¹ Office of National Drug Control Policy. Profile of Drug Indicators Anchorage, Alaska April 2004, p. 3.

much lower fraction to which seizure actions would apply. (Unfortunately, we do not have any type of proxy for alcohol cases in which seizure of property would apply.)

A reasonable approach would be to use the same proportion used earlier to estimate grant funds for marijuana enforcement, in consideration of the lower proportion of marijuana arrests subject to seizure actions. Assuming 15% of total seized property allocated to marijuana offenses results in a figure of \$157,500. In 2004 dollars the amount would be \$160,236.

Amounts of judicial fines for marijuana convictions are unknown. Alaska does not track fines by types of convictions. According to the State of Alaska Revenue Sources Handbook, in FY 2003 fines and forfeitures together totaled \$7 million for every form of civil and criminal fine and forfeiture action. This included traffic court and civil penalty fines for infractions such as lack of permits, as well as all criminal fines together. Marijuana convictions are a small fraction of criminal cases, and must be quite insignificant in comparison to all civil and criminal actions together. Most likely fines total, at most, something in the same ballpark as forfeitures.

Adding all of the grants and property seizure amounts together results in a figure of \$613,411 to mitigate costs of marijuana enforcement and adjudication. It is recognized that from year to year there are variations in grant funding. We argue that property seizures and fines are not, in fact, a net savings of resources for the state. Even including both of these sources of enforcement income gives cost mitigations well under \$1 million.

Many millions in indirect costs are associated with marijuana prohibition. The value of lost labor productivity is the most significant, at over \$6 million. Additions to family and social services budgets, and expenses associated with secondary offenses, appear to far outweigh any mitigating factors such as intergovernmental grants. Well over \$7 million in net additional costs has been identified here, and a figure of \$8 million is used in our summary, still quite conservative, as it seriously understates the extent of prohibition's impact on family and social services budgets.

Part II

A Cost-Benefit Approach to Prohibition

Effects of Prohibition

A host of reasons are employed to justify marijuana prohibition. The first of these is that prohibition "works." Does it? This question is less superficial than establishing a link between prohibition and consumption of the prohibited substance. It requires addressing whether the benefits are sufficient to outweigh the costs. An analysis of whether prohibition "works" requires addressing these points:

- 1) In order for prohibition to pass the first elementary test of cost/benefit analysis, it must be shown that prohibition significantly reduces consumption of the substance. It is not merely enough that consumption decreases, but that the decrease is significant enough to warrant the expenditure.
- 2) In a less superficial test of cost vs. benefit, it must also be demonstrated that the secondary effects of prohibition are positive rather than negative. Do other crimes increase or decrease under prohibition? Does consumption of other substances increase or decrease with prohibition? Are these substances more dangerous or less dangerous than the prohibited substance?
- 3) If prohibition passes these first two tests, then it also must compete with other alternatives for decreasing substance abuse. If there are superior alternatives to reducing substance abuse, then society's resources are better directed towards the alternatives. Such an analysis is not undertaken as a part of this study. We point out here that, when passing on such prohibitory legislation, this question is generally not addressed.
- 4) Prohibition has an opportunity cost in terms of justice system resources that can be directed elsewhere. Every dollar directed towards marijuana investigations, prosecutions, and incarcerations could have been spent on homicide, rape, assault, and other more serious crimes. The current allocation of resources implies that increased investigation and prosecution of homicide, rape, assault, and other serious crimes are less valuable to Alaska than investigations and prosecutions of marijuana offenders. Is this the actual preference of Alaskans, or would re-directing resources towards more serious crimes be more beneficial?

Does Prohibition Decrease Use?

There are two avenues by which prohibition may decrease consumption. The first is that prohibition can act to increase price and therefore reduce demand. The second is that prohibition imparts a penalty for use, and the threat of punishment, therefore, reduces demand. There are alternative assertions that prohibition itself makes the substance more attractive as "forbidden fruit." Regardless of theory, it is empirical work that demonstrates whether prohibition decreases use significantly, or, alternatively, if legalization increases use significantly.

There have been few studies relating marijuana use to price, and among those it is rare to find one using actual price data as opposed to asking hypothetical questions of users. Nisbet and Vakil (1972) surveyed UCLA students regarding hypothetical price changes. This study is often cited, but frankly, we are not interested in hypothetical responses but in quantifying observed behavior.

In Pacula et al. (2001:100), marijuana use was found to be extremely unresponsive to price. The elasticity of demand with respect to price was -0.06. That is, a 1% increase in price results in only a 0.06 percent decline in demand. Another way of saying this is that a 16.67% increase in price is required to reduce demand by just 1%.

The most recent study available was also the only other study using actual price and consumption data. DeSimone and Farrelly (2003:109) found that "adult marijuana demand was not related to its own price" and that for juveniles, price was also irrelevant. However, for both juveniles and adults, use decreased with increases in arrest probability. The question is, by how much?

Over the sample period (1992-1997), the arrest rate per user doubled for marijuana. According to the model estimates, if nothing else changed but the arrest rate, demand should have decreased by 3%. But according to the data, use increased, and use by juveniles increased by 13.5%. This led the authors to conclude, "Clearly, factors other than prices or arrests are important in determining changes in drug use across cohorts." (DeSimone and Farrelly 2003:112).

In an earlier study, DeSimone (2002: 966-967) estimated the increase in probability of marijuana use in states that decriminalized use. Two different years were studied. While one year revealed an increase in probability of use of 2-3%, the other showed no statistically significant impact.

Saffer and Chaloupka (1999) found that, "Marijuana decriminalization was found to increase the probability of marijuana participation by about 8%". In reviewing the literature, they report that, "The few prior studies of the effect of decriminalization on marijuana use generally find that marijuana decriminalization has no effect on participation. Pacula (1994), Thies and Register (1993), Dinardo and Lemieux (1992), and Johnston, O'Malley, and Bachman (1981) all used samples of young people and found no effect of marijuana decriminalization." However, "Model (1993) found that decriminalization increases marijuana use."

The National Academy of Sciences (1999) undertook an exhaustive study of many aspects of the marijuana question, including the effects of legalization. After analyzing numerous studies, in their section "Marijuana Decriminalization", they concluded that, "there is little evidence that decriminalization of marijuana use necessarily leads to a substantial increase in marijuana use."

Alaska and Decriminalization in 1975

Much has been written about Alaska's post-1975 decriminalization of marijuana and about a study of it performed in 1988. The Drug Enforcement Administration, for example, said:²²

The consequences of legalization became evident when the Alaska Supreme Court ruled in 1975 that the state could not interfere with an adult's possession of marijuana for personal consumption in the home. The court's ruling became a green light for marijuana use. Although the ruling was limited to persons 19 and over, teens were among those increasingly using marijuana. According to a 1988 University of Alaska study, the state's 12 to 17-year-olds used marijuana at more than twice the national average for their age group.

The only possible study such "citations" can reference is Segal (1988). The study makes no such finding, and the statement above is deceptive on a number of levels. Segal's study was undertaken, in part, because Alaska was not included in the 1988 National Household Survey on Drug Abuse (NHSA, now called the National Household Survey on Drug Use and Health). The Alaska and national studies are not comparable for several reasons.

²² <http://www.usdoj.gov/dea/demand/speakout/06so.htm>

The critical issue, however, in any analysis of Alaska substance use from the mid-1970's onward must be the Alaska pipeline boom, not marijuana decriminalization. Segal (1988:7) comments, "That the construction of the transalaska pipeline (1974 to 1978) had an effect on drug use in the state is undisputable. The effect is well illustrated in a report by the Alaska State Troopers in 1976 which described the problem of drug use as 'growing to such a magnitude that illicit drugs were coming into Alaska by every conceivable means imaginable, and the drugs were being distributed to virtually every city and village in Alaska' (P.2)."

Segal cited a previous study by Lanner (1983) demonstrating increased marijuana use among the young as a consequence of the pipeline, and pointed to an increase in available money as one of the reasons. (Segal 1988: 8). It is difficult to overstate the consequences of 25,000 pipeline workers "hitting town" with the highest wages in the nation, in a boomtown atmosphere, on the last frontier.

So "baseline" drug use in Alaska was not comparable to the rest of the nation to begin with; however, there was a possibly even more important difference in survey methodology. The Alaska survey was anonymous. The NHS was not only conducted by interview, but also in the home. The rates reported of "lifetime prevalence" (i.e., have you ever used in your lifetime) were 51.6% for Alaska and 23.7% for the national survey. As Segal (1988:81) notes, "It is possible that direct interviews, particularly when conducted in the interviewees' home, elicited more false negatives than responding anonymously in school."

Segal then compared results for his Alaska study with two other studies. The first was the 1987 National High School Senior Survey. In that survey, Alaska's 68.2% "lifetime prevalence" compared with 50.2% for the U.S. (Segal 1988:83). Alaska 8th graders had a user rate of 37.6% as compared with Oregon 8th graders' rate of 27.7%. What Segal concluded, after looking at surveys taken in California, Oregon, and Alaska, was that, "These findings suggest strongly that the national data may be underestimating drug taking behavior." Segal (1988:87).

Another problem besides the difference in survey methodology was the lack of comparable questions that actually reflect use. In the annual NHS, questions are asked about whether the individual has used a drug within the last month, and whether there is chronic dependency. It is unquestionably inappropriate to pretend that a "lifetime prevalence" question is reflective of who is "using" a substance.

Because there was no baseline to the pre-pipeline years, and no comparable data whatsoever until 1983, we cannot actually quantify anything until after that time. Segal (1988:96) compared "lifetime prevalence" with 1983 data for age 12-17 year olds, and found that it had increased from 49.4 to 53.0%. It is true that, over that time period, national use appears to have declined; again, the problem is that making statements about "use" requires questions about recent use, not whether one tried something once, several years earlier.

Lastly, it should be noted that alcohol abuse is high in Alaska, and that there are unique aspects of Alaska life not mirrored in the lower 48 states. Winters without sunshine, seasonal affective disorder, and seasonally different work schedules, are among many factors that would have to be modeled in a study seriously investigating social effects of decriminalization.

In fact, the Segal (1988) study drew no conclusions about the relationship between marijuana decriminalization and use. Segal (1988:135) states, "Any attempt to assess the impact of decriminalization is fraught with difficulty;" and, "Depending on one's views, several contrasting conclusions can be made about decriminalization." He did not find that decriminalization had caused an increase in use, yet that is the clear purpose to which proponents of prohibition have put his study.

For Alaska, we simply do not have comparable baseline and current-year numbers for either the effects of 1975 decriminalization or subsequent recriminalization in 1990. In recent years, Alaska has been included in the NHS exercises. We can compare current use numbers with the rest of the U.S. for survey questions that are the same and for methodologies that are consistently applied. Even then, year-to-year changes in survey methodology may cause significant differences in estimates of drug use.

Wright (2002) reported the distribution of use across age categories presented in Table 5, based upon the survey methodology used in the NHS for calendar year 2000. The question asked in this survey regarded use in the past month. Alaska numbers exceed those for the nation at large by a very small amount, for use by persons under 26 years of age. Since that time, the methodology of the survey has changed and this table is presented strictly for comparing Alaska vs. national use.

In 2002, the NHS has used an improved estimation technique²³. As a consequence, the estimate of current (within the last month) drug use increased by 22.6% nationally.²⁴ That is, drug use was significantly underestimated in the past, and the numbers in Table 5 are underestimates for Alaska. Revised estimates by state have not been published yet, but by using the same proportion for Alaska as for the rest of the nation, results are as illustrated in Table 6.

Table 5

Reported Use of Marijuana By Age Group in Alaska
(Old Survey Methodology - Year 2000)

	Age Category		
	<u>12-17</u>	<u>18-25</u>	<u>26 +</u>
Reported use in last month (Alaska)	8.65%	17.35%	3.76%
Number reporting use in last month	5,000	12,000	13,000
Reported use in last month (USA)	8.2%	17.3%	4.0%

Source: Wright (2002)

Given the population growth since 2002, there are roughly 42,000 "current" users of marijuana over the age of 12 in Alaska. Again, by "current" use is meant use within the last month. This is the best estimate available at the present time. There are nearly twice that number of Alaskans who have used marijuana in the last year, according to the improved survey methodology — roughly 75,000. But it would be more accurate to cite the 42,000 figure when referring to "users".

²³ See National Household Survey on Drug Use and Health: National Findings, p 7. Jon Gettman, PhD. and Senior Fellow at George Mason University School of Public Policy, pointed out the change in survey methodology to us.

²⁴ In the 2001 survey, an estimated 15.9 million Americans had used drugs within the last month. In the 2002 survey, the figure was 19.5 million. In 2001, 76% had used marijuana. In 2002, 75% had used marijuana.

Table 6
Estimated Current Users in Alaska by Age Group - 2002

	Age Category			
	<u>Over 12</u>	<u>12-17</u>	<u>18-25</u>	<u>Over26</u>
Past Month Marijuana Use - Percent	8.7%	12.1%	23.4%	5.0%
Past Month Marijuana use - Thousands	41,000	7,000	17,000	17,000

Sources: 2001 National Household Survey on Drug Abuse and 2002 National Household Survey on Drug Use and Health

The Office of National Drug Control Policy (2004:7) reported a different statistic, but the source was not referenced carefully enough to evaluate the data.²⁵ In that citation, marijuana use was reported by 47% of Alaska high school students, and 24% reported current use. One must ask how these numbers could be so much higher than in the annual household survey. But if the 47% figure is for "lifetime prevalence," that would demonstrate the drastic difference between "use" and experimentation.

The most comprehensive international study available is the European School Survey Project on Alcohol and Drugs (ESPAD). This survey compared use across 30 countries by surveying 95,000 10th grade students. Data are comparable to the United States, because the survey followed the *Monitoring the Future* (MTF) study that has been conducted at the University of Michigan for the past 26 years.

The U.S. had a higher experimentation rate for marijuana than any other country, at 41%.²⁶ Denmark, with the most lax policy of legality, compared favorably at 28%, and was also lower than other western European countries with more punitive legal regimes such as France, the UK, and Ireland. The U.S. experimentation rate was higher than that in most eastern European countries. Romania, for example, was the lowest, registering a mere 1%.

After reviewing the empirical work regarding marijuana prohibition, we must conclude that it is an ineffective means of reducing marijuana use. We cannot even state positively that prohibition decreases consumption *at all*. There are mixed results, but even those studies reporting an effect of prohibition find one so small as to leave room for debate. *Prohibition does not achieve its principal objective in any meaningful way.*

²⁵ Curiously, it did state that Anchorage was excluded. As Anchorage contains nearly half of Alaska's population, that is a rather strange omission.

²⁶ http://www.monitoringthefuture.org/pubs/espada_pr.pdf

What are the Secondary Effects of Prohibition?

The economics of prohibition are the same whether one is considering alcohol, marijuana, or other "vices". They differ in degree, but not in kind. The lessons learned during national alcohol prohibition provide important parallels for marijuana that should be considered. One of the most important is that prohibition creates crime of a more serious nature, particularly violent crime.

Under the well-known modeling of rational substance use, people perceive that they benefit from and manage their use of substances (Becker and Murphy: 1988). When one substance becomes more expensive or difficult to obtain, they substitute another in its place. We therefore also sought information on the substitutability of marijuana and other substances.

Prohibition and Crime

There have been many studies on the effects of prohibition on crime. Probably the most telling data is the impact of Alcohol Prohibition on the murder rate:

The homicide rate in large cities increased from 5.6 per 100,000 population during the first decade of the century to 8.4 during the second decade when the Harrison Narcotics Act, a wave of state alcohol prohibitions, and World War I alcohol restrictions were enacted. The homicide rate increased to 10 per 100,000 population during the 1920s, a 78 percent increase over the pre-Prohibition period.²⁷

Other serious crimes rose in the same period, including robbery, burglary, assault, etc. All fell with the repeal of Prohibition. One of the more important consequences of Prohibition was the rise of *organized* crime. All of these increases in crime came with minor effects on consumption (see, e.g., Miron and Zwiebel 1991, Friedman 1991 and Thornton 1991). Some have argued that consumption actually rose (Tillitt, 1932: 36).²⁸ It is apparent from all sources that consumption initially fell sharply, but then rose significantly as the underground "speakeasy" and black market economy developed.

It is common to cite a spurious association between "drugs and crime" exactly as the association between alcohol and crime was made during Alcohol Prohibition. Initially, the benefit of Prohibition was asserted to be decreases in crime consequent to "demon rum". But the result was the opposite. Ultimately it was the dramatic increases in crime and other negative effects of Prohibition that led to its repeal.

The parallel of Alcohol Prohibition causing more serious crime and prohibition of drugs causing more serious crime is an obvious case of history repeating itself. Miron (2001:1) and others have pointed out that "many of the harms typically attributed to drug use are instead due to drug prohibition." Moreover, "these outcomes would be reduced or eliminated under legalization." (see also Friedman 1991, Benson and Rasmussen 1991, Benson 1992 Duke and Gross 1993, and Miron 1999). The USBJS (1992:5-8) also gives ample evidence of the relationship between violent crime and drug prohibition, and again, specifically, homicides and drug trafficking. One wonders: since street drugs have nearly exact counterparts in legal prescription drugs, if drugs themselves cause crime, why there is no such link between prescription drug use, prescription drug trafficking, and violent crime.

²⁷ Quoted from Thornton (1991). This is one of the most widely cited documenting the ill effects from prohibition.

²⁸ In any such study, illegality necessarily causes an under-reporting problem. This is also true in issues such as alcohol-related deaths and health problems. For example, Tillitt (1932:114-115) reported that medical examiners and family physicians avoided citing alcohol on certificates during Prohibition.

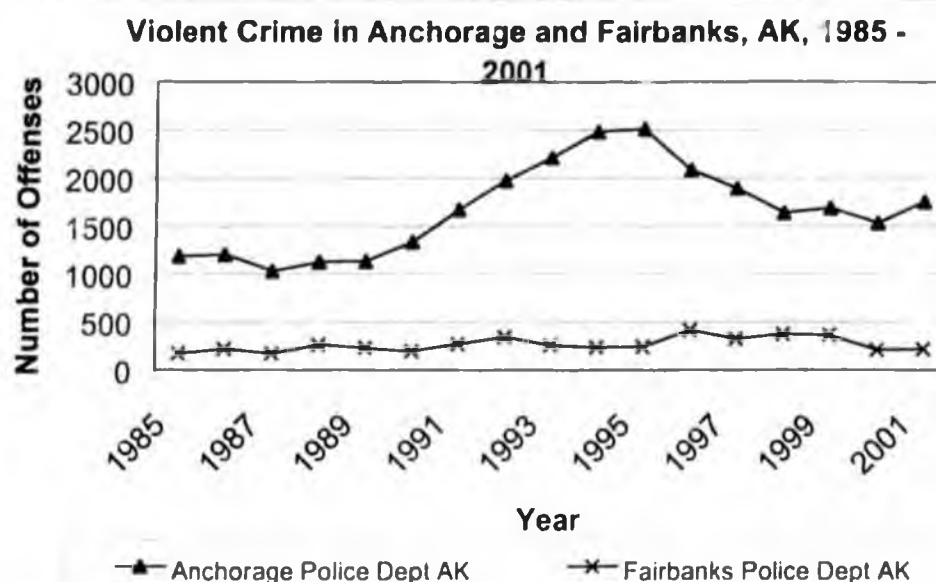
Violent crimes in Alaska increased dramatically after marijuana was recriminalized in 1990, as shown in figure 1. Data are available from 1985 onward only for Anchorage and Fairbanks reporting districts, so this is what was used. By 1995, violent crimes had increased *by just over 100%*. It appears that, after the concealed carry handgun bill was passed, violent crimes decreased, as they did in other states with concealed carry laws. But there are also other factors to consider, such as the economy.

While we do not pretend this is a definitive study of marijuana prohibition and crime in Alaska, it is impossible to argue that marijuana prohibition has reduced violent crimes. The evidence is the opposite, and rather dramatically so.

If prohibition *worked*, one might argue that these costs were tolerable. But because prohibition *fails*, these costs are in *addition to* any social costs that actually stem directly from marijuana use. Following Miron (2001), we may outline the effects of prohibition as follows:

- 1) Marijuana prohibition creates a black market in marijuana rather than eliminating it.
- 2) Prohibition increases violent crime by preventing black market participants from resolving their differences through standard nonviolent mechanisms.
- 3) By raising the price of marijuana, prohibition encourages income-generating crime such as theft, since additional income is needed to purchase marijuana.
- 4) In black markets, participants must either evade law enforcement authorities or pay them to look the other way, so the scope for corruption is substantial.
- 5) Making products illegal can make them less safe. United States experience with Alcohol Prohibition provides a classic example of this effect: deaths from adulterated alcohol soared (Miron and Zwiebel, 1991; Morgan, 1982).
- 6) Revenue is diverted from government and law-abiding citizens to criminals.
- 7) Prohibition breeds disrespect for the law.
- 8) It complicates or compromises other policy areas, for example, civil liberties and rights to privacy, and international relations.

Figure 1: Violent crimes in Anchorage and Fairbanks Reporting Districts



Source: Bureau of Justice Statistics

<http://bjsdata.ojp.usdoj.gov/dataonline/Search/Crime/Local/TrendsInOne/ar.cfm>

Prohibition and Use of Other Substances

Conlin et al. (2002), DiNardo Lemieux (1992; 2001), and others have studied the substitutability of alcohol and marijuana. In the latter study, "We find that increases in the legal minimum drinking age did slightly reduce the prevalence of alcohol consumption. We also find, however, that increased legal minimum drinking ages had the unintended consequence of slightly increasing the prevalence of marijuana consumption" (DiNardo Lemieux 2001:991).

Conlin, et al. (2002:13) found that, "allowing local alcohol access decreases crimes associated with illicit drugs." They also found that, "Prohibiting the sale of beer to persons under 19 and under 21 increases the fraction of drug related arrests attributed to juveniles more in wet counties than in dry counties."

Chaloupka and Laixuthai (1994), in particular, examined the effect of this substitutability on accidents due to teenage intoxicated drivers. They concluded that, "results imply that the reduction in accidents resulting from substitution away from alcoholic beverages and other intoxicating substances to marijuana as its full price is lower more than offsets the increase in accidents related to marijuana use."

This matches studies of adults where marijuana appears to impair driving ability substantially less than alcohol (U.S. Department of Transportation, 1993; Crancer, et al. 1969). Model (1993) demonstrated that rates of other illicit drug use were significantly higher for emergency room patients in states where marijuana prohibition was in effect.

There is suggested by some to be a complementarity of marijuana and other substances. Generally, this is suggested by the casual statistical observation that those who have used marijuana are also more likely to have used other substances.

At first glance, it might appear that the "substitutability vs. complementarity" stances are fundamentally in disagreement. One appears to say that marijuana is used in place of other substances, while the other appears to say that marijuana is used alongside other substances.

Imagine that the issue involves "use" of coffee and soda. It is quite true that one can demonstrate that people who drink coffee as a stimulant also tend to drink soda as a stimulant. The question is, what will happen to soda consumption if coffee is made illegal?

A related issue is the concept of a "gateway" effect of marijuana. Use of marijuana may precede use of other more dangerous substances. In a sense, it is argued that marijuana and other substances "go together" as complements in this additional way. The question, again, is, what happens when marijuana is made illegal?

The "gateway" assertion generally involves a sequence between cigarettes, alcohol, marijuana, and then other, "harder", drugs, as in Kandel and Yamaguchi (1993). There does indeed appear to be a pattern, which can be summarized quite simply: More immediately available and less expensive substances are used prior to those that are more difficult and more expensive to obtain.

The problem with such studies is that they no more demonstrate that marijuana causes harder drug use than that candy causes marijuana use. Virtually every marijuana user ate candy before they used marijuana. Therefore, candy is the gateway to marijuana. This sounds ridiculous when taken out of the context of the "stepping stone" preconception about drugs. We could make a similar assertion about bicycles causing motorcycle ownership.

A study of the gateway effect could be constructed in several ways. One would be to *remove* an element of the "stepping stones" for one set of subjects and not for the other. If it could be demonstrated that removing one of the stepping stones prevented the next step, then one could conclude a "gateway" effect had been observed. However, all of the substances above (cigarettes, alcohol, and illegal drugs) are already under prohibition for minors; thus, such a study cannot be legally or ethically undertaken.

The approach taken by Morral, et al (2002) is the "bad seed" or "common factor" approach. Given a propensity to use drugs in the first place, does use of marijuana increase the probability of progressing to other drugs? The answer was no: "We demonstrate that the primary evidence supporting the marijuana gateway effect can be explained completely by the order in which youths first have the opportunity to use marijuana and other drugs."

That is why the NHS data demonstrates that, for the majority of those who have tried marijuana, it is a "terminal" substance, with no harder drugs tried at all, and use generally ending after the late 20's. It may indeed be true that, for the population that has tried marijuana, there is a higher likelihood of trying other drugs. That does not demonstrate that marijuana is the *cause* of other drug use or that marijuana smokers will become heroin addicts.

Another possibility of assessing the gateway hypothesis is to re-arrange the order of the "stepping stones", to see if there are effects on final disposition. One such study has been completed. In Sen, et al. (2002), empirical study of 6,748 adolescents between the ages of 12 and 16 was undertaken for the purpose of identifying a "gateway" effect between cigarettes, alcohol, and marijuana. Ironically, it was discovered that initiation of marijuana use *decreased* the likelihood of subsequently using the other two. This was statistically significant at the 99% level of confidence.

The reverse was found to be true for cigarettes and alcohol: use of either one resulted in a *greater* likelihood of subsequent marijuana use. The conclusion regarding marijuana apparently prompted an attempt at alternative modeling in order to reach a different conclusion. The study recognized a "bad seed" effect; that is, that someone predisposed to risky behavior will try anything when it is available, as opposed to one thing leading to a specific other.

One speculative conclusion of that study was that, by curbing use of one of the three substances, use of the others might decrease as well. In order to reach such a conclusion, however, *one must study a situation in which it actually occurs*; that is, where use of one or the other has been successfully curbed. In the Sen, et al. (2002) study, all three substances were prohibited to minors, yet more than 50% of youths had experimented with at least one of them.

There are also other substances to consider. In rural Alaska, it would be wise to investigate the substitutability between marijuana and inhalation of volatile vapors. This practice is especially prevalent among Alaska Native youth and is discussed, for example, in Segal, et al (1999:35-36). Sniffing gasoline, glue, and other industrial solvents is widespread in remote villages. It causes permanent brain damage, and death by liver, kidney, or bone marrow damage. Inhaling such vapors can also cause sudden sniffing death. The problem is so severe that Alaska has the only Inhalant Abuse Treatment Center in the nation.²⁹

In evaluating the secondary effects of marijuana prohibition, we see an unambiguously negative set of results. We must remind ourselves first that prohibition is ineffective in curbing use. It is effective in raising price and creating black market activity that generates other crime. To the extent that use is decreased, the evidence indicates that there is a substitution of other substances, primarily alcohol.

Conclusion

In conclusion, we find that marijuana prohibition costs the State of Alaska well over \$24 million annually in direct and indirect costs of enforcement. These costs are not offset significantly by federal grant monies, fines or forfeitures. In addition, prohibition does not succeed at its stated purpose, and in fact contributes to additional crimes being committed, and to use of other, more dangerous substances. Marijuana prohibition, using the most favorable figures in cost-benefit analysis, is a costly failure.

²⁹ The Tundra Swan Inhalant Program, Yukon Kuskokwim Health Corporation - Bethel, Alaska

Appendix I: Tax Revenue Potential and Hemp Industry Analysis for Alaska

Tax Revenue Potential

We developed estimates for tax revenues derived from marijuana legalization in Alaska and from potential industrial hemp trade. Tax revenue potential from marijuana appears to be on the order of \$10-12 million. An industrial hemp trade and a tourist market trade would certainly generate sales values at a multiple of that. Given the quasi-legal status in countries where such tourist trade exists, it is difficult to assess exact figures. But even a 2% increase in travel and tourism in Alaska would be worth on the order of \$35 million.

Our estimate of tax revenue potential from legalization of marijuana in Alaska is offered for exploratory purposes, as legalization in Alaska will not cause legalization at the federal level. It is nonetheless a legitimate public policy question that has a place in the debate. It is not unrealistic to contemplate legalization with taxation in the future, and it is a question invariably addressed in other studies. In fact, the original 1937 federal "Marihuana Tax Act" did not make marijuana illegal, but provided for its production by purchase of a tax stamp.¹⁰

In Alaska, a comparison might be made between potential marijuana taxes and tobacco taxes; however, there are some very important differences. There are many more cigarette consumers, roughly 25% to 30% of the adult population.¹¹ At 30% of the adult population, there are in excess of 130,000 cigarette consumers alone as compared with 42,000 "regular" marijuana users¹². That means there are at least 90,000 more cigarette consumers than marijuana smokers. This does not include juvenile tobacco use, nor does it count smokeless tobacco.

Cigarette consumers also smoke much more, on average, than do marijuana smokers. In 2001, Alaskans consumed an estimated \$17 million cigarettes.¹³ Although the retail cigarette price is lower than that of marijuana, that is primarily because there is no "risk premium" from prohibition for tobacco. That distinction would disappear with legalization.

The Alaska statewide presumptive cigarette price, produced by the Alaska Department of Revenue, is \$41.69 per carton.¹⁴ This includes total federal plus state excise taxes of \$13.90, about 33% of the retail price. The tax on other tobacco products is 75% of the wholesale price.

State tax revenues from tobacco taxes were about \$46.9 million in FY 2003.¹⁵ Including federal and local revenues, tobacco sales generated close to \$70 million in total tax revenue. Governor Murkowski has proposed doubling the state tax. Although Alaska's is already the third highest such tax in the nation, about a dozen other states are also considering increases. Assuming Alaska and the other states all pass

¹⁰ Act of August 2, 1937 Public 238, 75th Congress. See cover illustration for an example.

¹¹ Estimates seem to differ. According to the Center for Disease Control (2004) it was 29.4% of Alaska adults. See: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5253a1.htm>. But according to the Alaska Department of Health and Social Services, it is 25%. http://health.hss.state.ak.us/dph/targets/PDFs/tobacco_hand-out.pdf

¹² Reported in table 6. "Regular" means within the last month.

¹³ http://health.hss.state.ak.us/dph/targets/PDFs/tobacco_hand-out.pdf That works out very roughly to seventeen cigarettes per day per consumer.

¹⁴ <http://www.tax.state.ak.us/programs/tobacco/reports/Cigarette%20Presumptive%20Min%20Price%20-%20Web%20Post.xls>

¹⁵ Alaska State Revenue Sources Book Spring 2004: <http://www.tax.state.ak.us/sourcesbook/2004/spr2004/non-oil.pdf>

these increases, Alaska would remain in third place. The proposed measure would boost total taxes to over 50% of retail, and bring in over \$100 million in total (state plus federal) taxes. Interestingly, the city of Anchorage has just imposed a tax increase of \$1⁰⁰ per pack, and plans to raise it again by the same amount over the next two years. Enforcement issues have already surfaced.

The price elasticity of demand for cigarettes is in the -.4 to -.6 range (Hersch, 2000). As we have noted previously, demand for marijuana is even more inelastic (i.e., less responsive to price). That means a marijuana tax can constitute an even higher proportion of the retail price. But, because the number of consumers and the amount used per consumer is so much lower, the total revenue potential is much less.

To get an idea of revenue potential from marijuana taxation, we first take from Miron (2003:8) the \$10.5 billion estimate of total marijuana expenditures in the U.S. and determine a proportionate share for Alaska. Although use is slightly higher in Alaska, according to the data provided earlier, we will use the relative population proportion for a conservative estimate. Adjusting for a year of inflation using the consumer price index, and using a proportion of national population of .0022, there will be about \$24 million spent for marijuana by Alaska consumers in 2004.

Let us ask if this is reasonable, given the total number of marijuana smokers estimated for Alaska. With an estimate of 42,000 that "used" marijuana within the last month of the most recent survey (Table 6), that comes to \$571 per year per marijuana consumer. At \$90 per quarter ounce, that would be roughly one and one-half ounces per year per marijuana consumer¹⁶, a figure that suggests use of less than one gram per week. Certainly, this is not a lot of use, only about one "joint" per week.¹⁷

We depart from the Miron (2003) model in two respects. First, we rely exclusively on empirical estimates of price responsiveness based on real data, as opposed to hypothetical questions asked of marijuana users. Second, the potential for tax evasion is considered to be more serious for Alaska as compared to the Massachusetts situation considered by Miron (2003). These work in opposing directions, but are believed to provide a more realistic estimate.

Empirical observations demonstrate that marijuana use is extremely unresponsive to price. This makes it a good candidate for taxation. If taxes significantly suppress use, it is not a good tax instrument, because there is little revenue potential. On the other hand, Alaska affords an easier environment for tax evasion because of its rural nature, and the difficulty of enforcement in comparison to the urban setting considered by Miron (2003).

The final element we considered was the effect of legalization on market price in the absence of a tax. Consider that industrial hemp production is on the order of 3-12 tons per acre and sells at under \$100 per ton (Ehrensing 1998). Industrial hemp is quite different from marijuana grown for its psychoactive compound content, but it is instructive to compare the two, as they are actually the same plant, *Cannabis sativa*. Because marijuana is no more difficult to grow than industrial hemp, marijuana's high price under prohibition is, obviously, mostly a risk premium.

¹⁶ An average price for small (quarter ounce) purchases over the last 20 years of \$89.21 was retrieved from the Office of National Drug Control Policy. *The Price of Illicit Drugs: 1981 through the Second Quarter of 2000*. Washington, DC. October, 2001, pg 46. While this figure is accurate for municipalities in Alaska according to knowledgeable sources, it is an understatement of rural Alaska prices. Thanks to Jon Gettman for citing the ONDCP source data.

¹⁷ Dr. Alexander Sumach, in Cannabis Calculations per day.

Cervantes (1999) provided "cost" estimates for different home operations that are also useful here, although they were not constructed in accordance with business accounting principles. (They did not include the value of the home cultivator's labor, nor were costs of floor space included.) All examples reported variable costs per ounce of under ten dollars. Capital costs were not calculated on a useful life of equipment basis, but simply attributed to the first "crop", with zero for subsequent crops. Even allocating the entire capital cost to the first crop resulted in a "cost" generally under \$100 per ounce, a fraction of current market prices.

The U.S. Drug Enforcement Agency (2000) estimated that British Columbian "bud" sold for \$1500 per lb. in Vancouver, as compared with \$3000 in California. Although this trade is illegal, and any intercepted B.C. exports or sizeable operations are prosecuted, a much more tolerant policy exists in British Columbia. Small-scale operations are generally not prosecuted, and there is a coffee shop trade in cities such as Vancouver similar to the Amsterdam approach. The price premium is reflective of relative risk.

There is little doubt that the price of marijuana will fall drastically with legalization, because the risk premium would be completely eliminated, and even "closet" operations produce at a small cost per unit relative to market price. Were marijuana to be grown commercially, with industrial methods utilizing scale economies, these small operations would be almost completely supplanted. This in turn would facilitate tax collection, so long as the tax is not so exorbitant as to keep production in the black market.

A balancing act is needed to set a tax high enough to create substantial revenue, but low enough to prevent widespread tax evasion. Even a tax constituting 50% of the retail price would result in market price below present levels, but bring production to larger scale commercial enterprises utilizing much more efficient technology, and make collection of taxes simple. No taxation of individual home production is envisioned, and none was considered here.

With an estimated \$24 million in present illegal marijuana expenditures, and the knowledge that a large fraction of this amount — much more than 50% — is reflective of a risk premium, it is likely that revenue potential from a tax is at least on the order of \$10 million after legalization. Fifty percent of \$24 million is \$12 million. The government could probably appropriate nearly the entire risk premium in tax revenues, perhaps somewhere between \$10-12 million. Significantly more than this, though, would begin to encourage tax evasion and substantial "cottage industry" production in the Alaskan environment.

The nation's tobacco taxes have not brought about significant evasion through home production¹⁸ because of the complications involved in growing, drying, curing, and processing tobacco products. More than a year is required for curing, and this alone discourages home production. Such complications are not present in marijuana processing and consequently the potential for home production and black market sale is significant. Despite empirical estimates suggesting that heavier taxation of marijuana is possible, it is probably not wise to suggest much more than \$10 million dollars in initial Alaska tax revenues.

If we compare this \$10 million dollar estimate to figures from a recent California study, we find that it is considerably lower.¹⁹ In that study, a \$1 per "joint" tax was presumed, and estimates of use were based on the National Household Survey, as well as a British individual consumer survey. Estimated annual tax revenues for California were \$1 billion. Using the relative proportions of Alaska and California users, a comparable amount for Alaska would be about \$17.7 million.

¹⁸ Tobacco tax evasion is primarily a different form, involving transportation between states with differing tax rates.

¹⁹ http://www.canorml.org/background/CA_legalization.html

In Miron (2003), only the prevailing sales and income taxes, 5% and 4.3%, respectively, were applied to marijuana expenditures, as opposed to the approaches taken both here and in the California study. We have considered a much heavier level of taxation, quite obviously a "sin tax."

Industrial Hemp and Cannabis Tourism

Industrial hemp would develop in Alaska mostly as an ancillary feature of marijuana legalization, as opposed to a stand-alone export trade. The coffee shop tourist trade has become significant in places such as Vancouver and Amsterdam, and consideration should be given to such development in Alaska for its strong revenue potential.

General U.S. Industrial Hemp Market Conditions

The U.S. industrial hemp market has grown from nothing to an estimated \$200 million since the 1980's⁴⁰. The USDA (2002) issued a report with incomplete data; however, it is instructive. Raw hemp fiber imports to the U.S. increased from zero to 1.6 million pounds between 1980 and 1999⁴¹. Total imports of fibers, yarn, and waste (excludes seed, oils, and finished products) rose from 0.2 million to nearly 1.9 million pounds in that time.

The USDA report focused on the existing "narrow" market for hemp products, and based estimates of U.S. markets on the last year of data. The problem with this approach is that decades of illegality, and continuing uncertainty over hempseed oil food products in particular, have hampered the market. One should view the market's growth as quite significant in light of the legal cloud and anticipate substantial growth following the 2004 Court of Appeals ruling in favor of the industry.⁴² Prior to this decision, legal uncertainty had stifled the industry. Hemp food products will represent an important market segment in the future.

Other potential hemp uses cited in the USDA (2002) report include fiberboard composites, paper products, molded automobile parts, fuel, and a substitute for fiberglass. Hemp hurds, the by-products of extracting the useful fiber from hemp, are an excellent bedding material for livestock, and are also used as cat litter. Hempseed oils appear to have the most immediate promise in food and body-care products. There are many uses of this versatile plant, some of which are being "rediscovered" now, lost since the prohibition era was initiated in 1937.

Marijuana is currently prescribed for the treatment of anorexia and resultant weight loss due to AIDS, and for refractory nausea and vomiting associated with cancer chemotherapy (Joy et al, 1999).⁴³ As medicinal properties of the plant are increasingly researched and accepted, the market for various medicinal hemp preparations will expand. New marijuana medicines for spasticity and chronic pain are already under investigation.

⁴⁰ Personal communication: C. Penn, Director, Hemp Industry Association, May 2004.

⁴¹ USDA (2002), Table 1.

⁴² L.A. Times Feb 7, 2004. *U.S. Ban of Hemp Foods is Rejected*. The U.S. DEA attempted to ban fledgling hemp foods in the U.S. beginning in 2001. The food products have no psychoactive properties. But for three years the judicial issue was battled in the courts by the industry and the DEA. The U.S. 9th District Court of Appeals struck down the ban in February of 2004.

⁴³ An Institute of Medicine (IOM) Report, by Joy, et al. in 1999, titled *Marijuana and Medicine: Assessing the Science Base*, was commissioned by the White House Office of National Drug Control Policy. The entire text of the IOM Report is available at: <http://books.nap.edu/html/marimed>

Hemp has been used for thousands of years in fabrics, rope, paper, medicines, and a multitude of other products. Synthetic fibers and other competitors to former hemp industry products, developed concomitantly with prohibition, have served with it to destroy hemp product industries in the U.S. Eliminating prohibition can remove the legal obstacles, but hemp must still compete in the marketplace with other products.

Alaska Industry Potential

Industrial hemp agriculture in Alaska would probably be a specialty or "boutique" market, since large-scale production would put Alaska in direct competition with several countries that produce hemp currently. In particular, the European Union (EU) provides a subsidy with which Alaska would have difficulty competing. At present the EU subsidy is 350 Euros per hectare (personal communication, M Kraus: International Hemp Association, May 11, 2004). At current exchange rates, that amounts to \$165.20 per acre. In addition, there is a subsidy of 90 Euros per ton of short fiber, or about \$42.48. These subsidies are expected to continue. Land prices in Alaska are high due to government policies, and this also places Alaska at a competitive disadvantage in industrial hemp production.

Alaska would have to market hemp products in the same way it markets its berries, teas, honey, and other natural products. The uniqueness of Alaska itself can provide a novelty premium. It does not make sense for Alaska to try to compete by producing exactly the same product as larger scale, lower cost industries elsewhere in the U.S. or internationally.

A clever marketing approach would combine an Alaska mystique with the product. For example, lotions from hemp oil could be combined with natural Alaska products or fragrances. Alaska hemp fabrics could be designed with distinctive logos, or Alaska Native artwork or patterns. A small-scale production facility in the right location could generate tourist viewing dollars to augment production income.

An "Alaska Energy Bar" or "Alaska Nature Bar" may have appeal for the backpacker, fishing enthusiast, hiker, mountain biker, or kayaker market segment. It is well known that hempseed oil is a nutritious foodstuff. The Nutiva Corporation has been marketing hemp bars, shelled hempseed, and hemp protein powder for several years.⁴⁴ Again, niche markets with distinctive Alaska themes are the best avenue for Alaska hemp products.

A coffee-shop approach similar to that employed in Amsterdam (see below) would without question generate tourist activity in Alaska independent of the existing tourist trade. Marketing hemp products via such coffee shops would be a natural extension of the industry. Whether Alaska could produce hemp products itself or not, marketing hemp products in Alaska would be a natural outgrowth of a marijuana tourism industry.

Canada has a developing industrial hemp products market, and the Manitoba Agriculture and Rural Food Initiatives Department suggests oilseed as the most promising of these.⁴⁵ Professional studies have been undertaken both for the Pacific Northwest of the United States (Ehrensing 1998) and for Canadian conditions. These studies included "production budgets" with break-even analyses. The USDA (2002) also reviewed studies conducted in other areas of the U.S., much less similar in climate to Alaska.

⁴⁴ The U.S. DEA attempted to ban hemp foods in the U.S. beginning in 2001. The U.S. 9th District Court of Appeals struck down the ban in February of 2004.

⁴⁵ <http://www.gov.mb.ca/agriculture/crops/hemp/bko01s01.html#harvest>

One issue of some import in comparing these studies was the vastly higher per-acre costs found in the Ehrensing (1998) study. One reason for this is the dramatically higher land rent per acre in the U.S. Pacific Northwest as compared with Canada; in addition, the production costs followed a model based on corn as opposed to experimental results with hemp itself. The Canadian results followed several years of trial experiments with hemp and are also more recent. They suggest a much lower cost per acre.

It also makes a difference whether one is gearing operations primarily to produce fiber or grain (seed). One can market both, but one must primarily target one or the other to grow. Experimental work would have to be done under Alaska conditions to make a definitive statement about yields, but some work has already been done in other countries with similar conditions.

Siberian hemp strains have been studied in Finland, for example (Callaway and Laakkonen 1996). These varieties would be more appropriate for the northern latitudes of Alaska. Numerous sources indicate that some of the earliest hemp varieties were developed in southern Siberia. There is little doubt that the right varieties will grow in Alaska's climate. What remains to be determined is productivity per acre, and the relative advantages of seed vs. fiber production. Previous studies point to seed as the more valuable target market.

Tourism and Marijuana

Because there is an existing marijuana tourist industry in places such as Amsterdam and British Columbia, some recognition should be made of the tourist potential in Alaska. The more appropriate comparison would be with British Columbia, and Vancouver in particular. Although no formal studies have been done, the economic impact there is significant.⁴⁶ The mayor of Vancouver was quoted recently stating that, without the "pot" industry, British Columbia would be in a recession.⁴⁷

Formal studies of the economic impact of marijuana tourism in Canada are complicated by the fact that, under the law, marijuana is still technically illegal. But enforcement is curtailed so as to allow a "pot block" in cities such as Vancouver, with rates similar to those in Amsterdam, and tourists may "legally" smoke and purchase marijuana in these areas. Although it is significant economically, the "illegal but tolerated" status is not conducive to academic study. Thus, the full economic impact of "pot tourism" for cities such as Vancouver remains unknown.

In 2002, one article cited more than one million Euros (about \$1.2 million dollars at present exchange rates) in sales of "joints" per Amsterdam shop per year, with the government taking as much as 52% of revenues.⁴⁸ There are hundreds of coffee shops there. The same article cited a contribution of \$1.36 billion to the Dutch economy in 1995, the last time a study was conducted. That translates to about \$1.7 billion in 2004 dollars.

Alaska travel and tourism industry sales were estimated at \$2.4 billion in 2002 with employment at about 26,000⁴⁹. Every percentage increase in this industry represents about another \$24 million in sales. It is difficult to project a percentage figure for marijuana related tourism, but even a low percentage increase suggests between \$50 and \$100 million annually.

⁴⁶ See for example: "Vancouver tourism Gone to pot" *Peak*, 8(114) -- June 23, 2003. Accessed at: http://www.friendlystranger.com/info/recreational_03/tourism.htm

⁴⁷ "Vancouver Mayor Touts Pot Legalization CTV.ca Sunday, May 9, 2004.

http://www.ctv.ca/servlet/ArticleNews/story/CTVNews/1084109538512_57/?hub=Canada

⁴⁸ "Cannabis Trade Gets Dutch Economy High" *Taipei Times* Wednesday, Nov 13, 2002, p 12

⁴⁹ See http://www.dced.state.ak.us/oed/pub/TSA_Exec_Summary.pdf

In "hemp town" tourist blocks, ancillary businesses have emerged in a fashion somewhat analogous to a "Chinatown" setting. Such businesses may market hemp products, growing equipment, smoking accessories, books, and art, as well as souvenirs of the "zone": T-shirts, mugs, and all of the oddments dear to the touring collector. "Hip" performing arts venues may thrive. Perhaps it is wise to segment markets in this way, giving tourists who might be offended by this kind of industry the option to stay away. (It may be noted that Amsterdam employs a similar strategy to shield the unwary from its legal sex trade.)

Although detailed studies are lacking, it is safe to say that the potential for a tourism and "coffee shop" industry is an order of magnitude greater than the revenue potential from taxing resident marijuana use. It represents a significant opportunity for generating income and employment in the State of Alaska.

Appendix II: Summary of Alaska Marijuana Statutes and Case Law

Alaska Statutory Classifications and Penalties⁵⁰

<u>Possession</u>	<u>Classification</u>	<u>Incarceration</u>	<u>Fine</u>
Less than 8 oz.	Misdemeanor (Misconduct VI)	90 Days	\$1,000
Between 8 oz- 1lb.	Misdemeanor (Misconduct V)	1 Year	\$5,000
Over 1 lb. Or 25 plants	Felony (Misconduct IV)	5 Years	\$50,000
Any amount with "reckless disregard" within 500 ft. of school or youth recreation area.	Felony (Misconduct IV)	5 years	\$50,000
<u>Sale or Manufacture</u>			
Less than 1 oz.	Misdemeanor (Misconduct V)	1 Year	\$5,000
1 oz. or more	Felony (Misconduct IV)	5 years	\$50,000
Sale to under age 19	Felony (Misconduct III)	10 years	\$100,000
<u>Miscellaneous</u>			
Maintaining structure for keeping/delivering	Felony (Misconduct IV)	5 Years	\$50,000

⁵⁰ Source: Alaska Statutes

Judicial Notes

In *Ravin v. Alaska*,⁵¹ the Supreme Court of Alaska held that the constitutional right to privacy protects citizens in the possession of plants for personal use in the home:

The state has a legitimate concern with avoiding the spread of marijuana use to adolescents who may not be equipped with the maturity to handle the experience prudently, as well as a legitimate concern with the problem of driving under the influence of marijuana. Yet these interests are insufficient to justify intrusions into the rights of adults in the privacy of their own homes. Further, neither the federal or Alaska constitution affords protection for the buying or selling of marijuana, nor absolute protection for its use or possession in public. Possession at home of amounts of marijuana indicative of intent to sell rather than possession for personal use is likewise unprotected.

This decision left it to statute to determine quantities consistent with personal use vs. that for sale. Prior to 1990, the state legislature determined that amount to be four ounces.

As for the voter initiative of 1990 presumed to recriminalize marijuana possession for personal use, several cases have been heard by the Alaska courts. The Court of Appeals, in *Noy v State of Alaska*,⁵² held in August of 2003 that the voter initiative recriminalizing personal possession was unconstitutional, and that the law reverted to its previous constitutional (pre-1990) status of allowing up to four ounces. Since possession of 25 plants is defined as a felony under current Alaska law, and since that amount implies more than personal use, this standard remains unchanged by the *Noy* decision, as do other statutory provisions on weights over 4 ounces, cited above. The Alaska Supreme Court has refused to review the *Noy* decision. In *State of Alaska v. Crocker*, the Court of Appeals found that a presumption of innocent, lawful possession of marijuana in the home must exist in order not to subject Alaskans to intrusive government searches,, and that probable cause must be established that marijuana in someone's home falls outside the scope of *Ravin* before any search warrant is issued; furthermore, that probable cause is not established by a householder's electrical usage, nor by the odor of marijuana.

Medical Marijuana is permissible under Alaska Statute 11.71.090 and 17.37. Individuals must register under AS 17.37 as either patient or caregiver. The process of registration is tedious, costly, and invasive, especially given that it does not entitle patients or caregivers to a legal source of either seeds or plant cuttings. Oddly, this statute allows possession of only three oz. of marijuana, less than that allowed any adult according to pre-1990 law and today.

⁵¹ *Ravin v. State of Alaska* 537 P2d 494.

⁵² 2003 WL 22026345 (Alaska App.)

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Alaska State Legislature

Please enter into the record my testimony to the

Senate Health Education & Social Services
committee name

committee on

SB 74
bill/subject

, dated

4-1-05

- The Alaska Supreme Court has wrongly held Alaskan's constitutionally guaranteed right to privacy in one's home extends to adult possession of up to four ounces marijuana.
- Governor Murkowski needs to correct this problem.
- Under the new laws, possession of four ounces of marijuana should become a class C felony -- since it contributes to incest, child-pornography and all other crimes.
- The Alaska Public Defender Agency says that half of the 500 marijuana-related misdemeanors they handle a year would be felonies under the new law - GREAT. These new laws should rightly convict hundreds of drug abusers.
- If these new laws fill Alaska prisons with hundreds of drug abusers, it will be worth the cost.
- Marijuana's felony status will allow police to put these offenders away. Alaska has six times the national average of reported child sexual assaults and 2.4 times the national average of reported rapes. Controlling marijuana abuse will reduce these problems.
- I want my police getting all drug abusers off the street, including marijuana users.

Signed:

Doug Sonerkholm

Testifier

Representing (Optional)

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