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Citation for
The Alfred R. Lindesmith Award for Achievement
in the Field of Scholarship

Presented to Dr. Lester Grinspoon
1990

Dr. Lester Grinspoon of Harvard Medical School is the complete medical scholar. His research and writing have covered a broad spectrum but perhaps his most important work has been his pursuit of truth about the nature of certain illegal drugs. In the course of that work, like Alfred R. Lindesmith, he upset many powerful people, including some in the medical establishment, who viewed impartial research on feared drugs as tantamount to heresy. Yet, in the face of that criticism, Dr. Grinspoon has persisted in his heretical pursuit of truth.

Although his earlier medical education had convinced him that the drug was dangerous, upon reviewing all of the available scientific and clinical evidence, he found marijuana to be relatively benign and to have several helpful applications for human beings.

Dr. Grinspoon was one of the most important witnesses in the suit which won a ruling from the chief administrative law judge of the DEA that marijuana was one of the safest therapeutically active drugs known to the human race.

Lester Grinspoon represents all those scholars who report the results of their research truthfully, despite the political consequences of this unwelcomed honesty.

STATEMENT REGARDING S.B. 74 AND H.B. 96

MITCH EARLEYWINE, PH.D., Associate Professor of Psychology, University of Southern California; author, *Understanding Marijuana* (Oxford University Press, 2002)

Like the language in S.B. 74 and H.B. 96, many media reports suggest that cannabis (marijuana) has increased in potency quite dramatically in recent years. These reports have generated considerable debate, and in fact the magnitude of the increase is difficult to document and is most likely greatly exaggerated. In addition, the assur ption -- clearly implied in the bills' findings -- that increased marijuana potency translates into greater danger from the drug is untrue.

Reports of a stronger drug actually began over 30 years ago. By the middle of the 1980s, some authors suggested that marijuana's potency had increased by a factor of 100 (MacDonald, 1984). These claims clearly suffered from exaggeration or misinformation. Other arguments about increased potency arose from the University of Mississippi's Potency Monitoring Project, a program that reports the average THC content of cannabis taken in drug arrests. Estimates were extremely low in the 1970s, sometimes below 1%. But these figures are inherently suspect, because cannabis with this little THC has no impact on subjective experience -- that is, it does not produce a "high." The idea that a drug with no effects would increase dramatically in popularity over the years, as marijuana clearly did during the 1960s and 1970s, makes little sense. Thus, these estimates from the 1970s were probably inaccurate reflections of the amount of THC in marijuana available at the time.

Investigators hypothesize that the data from the Potency Monitoring Project underestimate the true amount of THC in marijuana from the 1970s. First, the estimates were based on very few samples of seized cannabis. In some years there were no more than 50 samples to analyze (PMP, 1974-1996). In addition, police may have stored the marijuana in hot lockers that allowed the THC to degrade rapidly (Mikuriya & Aldrich, 1988). Despite the small samples and poor storage, the average THC content in 1976 was 2% (ElSohly, Holley, & Turner, 1984).

An alternative source of potency information, an independent laboratory in California, analyzed many more samples than the Potency Monitoring Project. This laboratory found a large range in THC concentration. In 1973 this laboratory tested over 100 samples and found that marijuana had an average of THC content of 1.6 % (Ratcliffe, 1974). Later analyses ranged up to almost 8% THC (Perry, 1977). Thus, the idea that all, or even most, cannabis of the 1970s had less than 1% THC seems unlikely. Ratcliffe's (1974) estimate of an average potency level of 1.6% may be conservative but credible; the 1976 estimate of 2% may be closer to the truth. And clearly marijuana much stronger than 2% was available in the mid-1970s

Potency data from the 1980s through the middle of the 1990s suggest that THC content continued to vary dramatically from strain to strain and sample to sample. With improved storage techniques and much larger samples, the Potency Monitoring Project found THC concentrations varied from 2% to almost 4%. Average concentrations approached 4% THC in 1984, 1988, 1990, and 1991 (PMP, 1974-1994). Trends in the rest of the 1990s showed comparable THC content, with a peak around 4.5% THC in 1997. Other cannabinoids like cannabinol and cannabidiol have not increased in

concentration over the years (ElSohly, et al., 2000). Thus, claims of 1000% (Cohen, 1986) or 10,000% (MacDonald, 1984) increases in marijuana potency are clearly inaccurate. A threefold elevation from approximately 1.5% in the early 1970s to 4.5% in the late 1990s may be closer to the truth. A simple doubling from an average of 2% to an average of 4% also seems the most plausible.

Although many media reports warn that increased potency translates into greater danger, scientific data suggest otherwise. Recent alarms about increased mentions of marijuana in emergency rooms have received a great deal of attention, with many authors positing that stronger cannabis has created more emergency room visits. In fact, the data that allegedly support these allegations are extremely questionable. Emergency rooms have no estimates of the strength of the cannabis used by those who appear for treatment. The purported increase in reports of cannabis use in emergency rooms likely stem from improved assessments by emergency room personnel or a gradual decrease in the stigma associated with use of the plant, not from ill-effects caused by marijuana use. Previous work suggests that emergency room assessments of drug use were wildly inaccurate (Roberts, 1996). Because marijuana appears incapable of causing fatal overdoses, it is implausible that the reported increase in ER "mentions" of marijuana is due to life- or health-threatening reactions caused by cannabis.

Marijuana with greater amounts of THC is probably less hazardous than weaker cannabis. First of all, acute administration of the drug is essentially non-toxic. No one has ever died from THC poisoning. Smoking enough cannabis to ingest a lethal amount of THC may be physically impossible. Estimates of a fatal dose of any drug arise from some rather gruesome animal research. Different groups of animals receive large amounts of a

drug until a particular dosage kills 50% of them. Researchers refer to the dose that is lethal for 50% of the animals as the LD 50. Investigators then extrapolate from these data to estimate a lethal dose for humans. The LD 50 for THC is approximately 125 milligrams for every kilogram of body weight (Nahas, 1986). Thus, a 160 pound (approximately 73 kilogram) person would need 9,125 milligrams of THC to have a 50% chance of dying. A typical marijuana cigarette weighs one gram and contains roughly 20 milligrams of THC, suggesting that a lethal overdose would require smoking roughly 450 joints in a brief period . Furthermore, at least 50% of the THC is destroyed in the burning process or lost to sidestream smoke. Given this loss, 900 joints would be a more appropriate estimate of a fatal amount (Doweiko, 1999). The 900 joints would weigh roughly 2 pounds. Although experienced users tell many exaggerated tales about smoking large amounts of cannabis, this dosage exceeds 100 times the quantity typically consumed by the heaviest users.

Marijuana with larger percentages of THC actually has benefits. Stronger cannabis leads to smoking smaller amounts. Smoking smaller quantities could provide some protection against the health problems normally associated with inhaling smoke. Smokers may take smaller, shorter puffs when using more potent marijuana (Heishman, Stitzer, & Yingling, 1989). Smoking less may decrease the amount of tars and noxious gases inhaled, limiting the risk for mouth, throat, and lung damage (Matthias, et al., 1997). Obviously, avoiding smoke completely would eliminate these problems. Thus, eating or vaporizing cannabis products may have fewer negative consequences than smoking them.

For the reasons outlined above, I believe it is inappropriate to base penalties for marijuana-related offenses on purported dangers related to an increase in cannabis potency.

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STATE OF ALASKA, SENATE BILL No 74 "An Act making findings relating to marijuana use and possession;"

EXPERT WITNESS STATEMENT:

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Statement:

It is an honor and privilege to address the Alaskan State Senate about an issue that affects a large number of Alaskans and their families. Our purpose is to assess risks of marijuana use and ask if increased penalties are warranted based on these risks. First, I would like to introduce myself and testify to my expertise in the area of drug abuse and marijuana. I am a life-long Alaskan. I moved to Alaska with my family in 1976. I am an alumni of West Valley High School and UAF. I left Alaska in 1981 for graduate and post-doctoral training. I returned to Alaska in 1990 and have since been employed at UAF where I am currently an Associate Professor in the Department of Chemistry and Biochemistry. I have devoted my life to the study of the brain and how drugs and naturally occurring drug-like chemicals affect the brain. After receiving a bachelors of science degree in psychology at UAF, I did graduate work at Mount Sinai School of Medicine in New York, NY; and at Albany Medical College in Albany, New York. My Ph.D. training and research was in neuropharmacology. Pharmacology is the study of the theory and principles of drug action. Neuropharmacology is the study of the theory and principles of drug action on the brain. I was trained by Dr. Stanley Glick, an established neuropharmacologist who has studied drug addiction and abuse and pharmacotherapies for drug addiction for more than 4 decades. My Ph.D. thesis showed how learning is involved in drug addiction. Learned, drug seeking behavior, is now recognized as a primary target for treatment of addictions. I received 3 years of post-doctoral training at the Karolinska Institute in Stockholm, Sweden in the laboratory of Dr. Urban Ungerstedt, another preeminent neuropharmacologist who pioneered our understanding of dopamine, a neurotransmitter now known to lie at the heart of addiction, motivation and reward. I have published 33 peer reviewed papers and 5 book chapters regarding addiction and aspects of drugs and the brain. I was a leader in establishing a neuroscience program at UAF funded in 2000 by a $7.5 million grant from the National Institutes of Health. Most recently I am recognized as an expert on neuroprotection and neuroplasticity in hibernation, a phenomenon my laboratory studies as a model of tolerance to stroke and neurodegenerative disease such as Alzheimer's and Parkinson's disease. Here I comment on findings purported by the legislature to suggest that marijuana poses a threat to the

public health that justifies prohibiting its use and possession in the state of Alaska, even by adults in private.

FINDINGS.
The legislature finds that
(1) marijuana has been for many years and continues to be the most commonly used illegal controlled substance in the United States;

Estimates of the number of Alaskans who use marijuana emphasizes the numbers of Alaskans who will be affected by this legislation. In addition to users of marijuana, their families are affected by legal and health related consequences of marijuana use and highlights the importance of rational and informed discussion of these risks. As a wife, mother, and long-time Alaskan, I have witnessed devastating consequences of federal marijuana use and trafficking laws on families in the Fairbanks area. In my professional opinion as a neuropharmacologist, the health and social risks of marijuana do not in any way, justify the severity of consequences imposed by federal law. Indeed, legal risks far outweigh health and social risks associated with marijuana use.

(2) marijuana has many adverse health and social effects, and there is evidence that it has addictive properties similar to heroin and other similar illegal controlled substances;

Addiction, (operationally defined as drug seeking behavior), is a combined effect of drug reward and drug withdrawal. Reward, as well as desire to reduce unpleasant symptoms of withdrawal, increases frequency of drug seeking behavior. Human epidemiological data (i.e., statistical analysis of patterns of use) as well as animal data rank addictive properties of marijuana below tobacco, alcohol, cocaine and heroin. Regarding human use, evidence suggests that as few as 10% of individuals who experiment with marijuana become daily users (cf. McRae et al., 2003), and others (Anthony et al., 1994) report that dependence among users is highest for tobacco, followed by heroin, alcohol, cocaine and finally cannabis.

Drug	*Dependence* among users (%)*	
	Male	Female
Tobacco	33	31
Heroin	22	25
Alcohol	21	9
Cocaine	18	15
Cannabis	12	5

* Dependence is defined by DSM-III criteria, evaluated via a modified Composite International Diagnostic Interview. Adapted from Anthony et al., (1994).

Laboratory animal data is consistent with low addictive potential of cannabis where positive-reinforcing and dependence-producing actions of THC, the active ingredient in marijuana, have been difficult to demonstrate (reviewed by Tanda and

Goldberg, 2003). Three standard techniques known as, conditioned place preference, intracranial self-stimulation and self-administration are used to assess addictive potential. All three of these techniques have failed to show consistent, positive reinforcing effects of THC. While Tanda and Goldberg (2003) argue that 3 decades of negative findings regarding abuse potential of marijuana are due to suboptimal conditions of drug preparation and rates of intravenous administration, other drugs of abuse have not been difficult to optimize for animal studies.

The low addictive potential of cannabis may be due, in part, to the fact that abstinence seldom produces pronounced signs of withdrawal (Anthony et al., 1994; Tanda and Goldberg, 2003). THC is stored in fat tissue, due to its high fat solubility and then slowly released. This slow release likely prevents development of a pronounced withdrawal syndrome when cannabis use is abruptly stopped (Grotenhermen, 2003). Overall, given the difficulty in training animals to self-administer THC and the absence of pronounced withdrawal symptoms, the suggestion that marijuana has addictive properties similar to heroin and other illegal substances is not warranted.

Anthony et al, 1994, Experimental and Clinical Psychopharmacology, 2(3), 244-268.
Grotenhermen, 2003, Drug Disposition, 42(4), 327-360.
McRae et al., 2003, Journal of Substance Abuse Treatment, 24, 369-376.
Tanda and Goldberg, 2003, Psychopharmacology, 169(2),115-34.

(3) in addition to concerns about marijuana use generally, the legislature is particularly concerned with the rates of use of marijuana by young people and Alaska Natives, which exceed national averages; and,
(4) early exposure of children to marijuana increases the likelihood of lifelong health and social problems, and makes it much more likely that the person will go on to use more potent illegal controlled substances;

A model known as the "gateway theory" of adolescent drug use was first proposed in 1975 (Kandel, 1975). The gateway theory suggests that adolescents typically use tobacco or alcohol before progressing to illicit substances including marijuana. Later studies showed that cigarette or alcohol use predicts subsequent illicit drug use for females while alcohol use predicts progression to illicit drug use in males (reviewed in Helstrom et al., 2004). After cigarette and alcohol use, progression may continue to marijuana, however, the cause of this progression is unknown. The simplest explanation for the observed progression is that early access to and use of cannabis may reduce perceived barriers against the use of other illegal drugs and provide access through the illicit market to more addictive drugs of abuse such as heroin, cocaine and methamphetamine (Lynskey et al., 2003).

Kandel, 1975, Science, 190, 912-914
Lynskey et al., 2003, JAMA. 2003;289:427-433
Helstrom et al., 2004, Prevention Science,Vol 5(4), 267-277

As a mother I want my 14 year old daughter to know the difference between risks associated with marijuana and "harder" more addictive and life-threatening drugs such as cocaine, heroin, methamphetamine and the broad, poorly defined class of inhalants.

(5) a high percentage of adults arrested in this state for domestic violence test positive for marijuana at the time of arrest;

Marijuana intoxication reduces incidence of violence (Hoaken and Stewart, 2003) so a causal relationship is unlikely. Marijuana persists in fatty tissues and consequently plasma where the half-life for elimination varies between 20 to 57 hours (Grotenhermen, 2003). To interpret the relationship between positive tests for marijuana and arrests for domestic violence one would need to know, first, what analytical tests were used to detect THC or its metabolites and second, if these individuals also tested positive for alcohol.

Grotenhermen, 2003, Drug Disposition, 42(4), 327-360.
Hoeken and Stewart, 2003, Addictive Behaviors, 28, 1533-1554.

(7) marijuana consists of over four hundred different chemicals and can affect almost every organ and system in the body, including the lymph system, the heart, and the lungs; marijuana can disrupt memory, attention, judgment, and other cognitive functions and can impair motor coordination, time perception, and balance, especially in children;

Marijuana contains a large number of chemicals because it consists of the leaf and flowers of plants. Plants are complex mixtures of chemicals. Tobacco, for example is equally as complex, however, nicotine is the primary active ingredient in tobacco. Similarly, delta-9-tetrahydrocannabinol (THC) is the primary active ingredient in marijuana. THC is a chemical that affects the body by interacting with receptors. Receptors are specialized docking sites on cells and drugs bind to these receptors. Receptors that recognize THC are called cannabinoid receptors. There are two types of cannabinoid receptors, CB1 and CB2. Marijuana or THC will have effects where ever these receptors are located. Distribution of these receptors in the brain explains why marijuana intoxication is associated with effects on memory and motor function. Recently, it was found that activation of cannabinoid receptors on immune cells (microglia) in the brain prevents Alzheimer's disease pathology (Ramirez et al., 2005). Activation of CB1 receptors is also known to have therapeutic potential in Parkinson's disease and stroke.

Two other chemicals found in marijuana are cannabinol and cannabidiol. These compounds have some properties similar to THC, but cause less psychoactive effects. These chemicals do, however have beneficial effects because they, like THC, are antioxidants (Hampson et al., 2000). We consume complex mixtures of chemicals in the foods we eat everyday, and sometimes, worry that they may cause cancer or other adverse effects. Most evidence on marijuana, however, is pointing to positive effects. Like the complex mixture of chemicals in blueberries, red wine and chocolate, the mixture of chemicals in marijuana may have beneficial effects on health. Research is

focused on identifying the key beneficial components so that these may be isolated and developed as drugs. Most evidence suggests that THC, the ingredient that causes the high also causes positive effects elsewhere in the body through activation of CB1 receptors.

Ramirez et al., 2005, J. Neuroscience, 25(8), 1904-1913
Hampson et al., 2000, Ann N Y Acad Sci. 2000;899:274-82.

(8) marijuana smoke contains more carcinogenic hydrocarbons than tobacco smoke and a person who smokes several marijuana cigarettes a week may be taking in as many cancer-causing chemicals as someone who smokes a full pack of tobacco cigarettes every day;

The real health risks associated with chronic marijuana use may include chronic bronchitis, impaired lung function and increased risks of some types of cancers of the respiratory tract (Moore et al., 2005) . Prohibition may be the greatest barrier in identifying these real health risks because prohibition interferes with accurate reporting of marijuana use.

Moore et al., 2005, J Gen Intern Med.,20(1), 33-7

(9) the potency of marijuana in the 1960s and 1970s was very low compared to the potency in 2005; the average amount of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient, nationwide, was less than one percent in the 1960s and 1970s, but has increased steadily in the 1980s and especially the 1990s, and by 2003 was more than six times that level, at 6.4 percent; in addition, marijuana grown in this state is often more potent than national averages, and has been tested with THC levels of over 20 percent; marijuana of the potency generally available in 2005 is a strong hallucinogenic drug that can command hundreds of dollars per ounce on the illegal market; the increasing potency of marijuana corresponds to an increase in the number of persons seeking emergency medical care for marijuana-related incidents.

Increased potency does not mean that increased amounts are consumed. People (and animals) typically take less drug if the drug is more concentrated. This means that more potent marijuana will likely cause people to smoke less and this will decrease risk of respiratory complications. When research animals are enticed to self-administer THC (Justinova et al., 2003) the number of self-administered injections decreases as concentration is increased until animals stop taking the drug at all, presumably because the high concentrations produce unpleasant side-effects.

Justinova et al., 2003, Psychopharmacology, 169(2):135-40.

(11) Alaska consistently ranks in the top 10 states, and occasionally in the top five states, nationwide, in the amount of marijuana illegally grown indoors, and large amounts of marijuana grown in this state are sold throughout the state and exported to other parts of the

United States; the price of high-quality marijuana is hundreds of dollars per ounce and thousands of dollars per pound; testimony received by the legislature in 1999 and confirmed in 2005, shows that marijuana often sells for $500 or more per ounce;

The cost of marijuana seems irrelevant to the public health risks unless high costs are driving users to crime to pay for marijuana. In contrast to heroin, cocaine and methamphetamine abusers, no evidence exists to suggest that a significant proportion of marijuana users resort to crime to pay for the drug. This is consistent with a low addictive potential of marijuana.

(12) a large percentage of persons arrested in this state, including adults and juveniles who commit violent offenses, have marijuana in their system at the time of arrest;

Marijuana intoxication is known to decrease violent behaviors (Hoeken and Stewart, 2003) suggesting that other drugs, like alcohol, are involved (Parker, 2004)

Hoeken and Stewart, 2003, Addictive Behaviors, 28, 1533-1554.
Parker, 2004, J Psychoactive Drugs, Suppl 2,157-63.

(13) marijuana use by a parent has been, and will continue to be, a major contributing factor to children having easy access to and using marijuana;

Research shows that legal and financial hardship incurred on parents as a result of penalties for possessing marijuana may have as many detrimental consequences on families as increased risk of marijuana use by children (Robertson et al., 1996).

Roberson et al., 1996, Br J Gen Pract., 46(412), 671-4.

Summary and Conclusions:

In summary, evidence does not support the assertion that marijuana poses a threat to public health that justifies prohibiting its use and possession in this state, especially by adults in private. Issues regarding access to children warrant further investigation into the impact of access through illicit channels. As a mother, I want my daughter to know the difference between drugs such as methamphetamine and marijuana.

Final note: Given the growing presence of methamphetamine in Alaska, my personal and professional opinion is that it would be irresponsible to put time and money into persecuting marijuana users when resources are inadequate to respond to the growing threat of methamphetamine in our community. I hope you as legislatures can look beyond moral judgment of marijuana users and address real health risks associated with far more dangerous drugs.

CURRICULUM VITAE
Kelly L. Drew, Ph.D.

Personal:

Born:	September 19, 1959
Marital Status:	Married (1983), David N. Covey, Ph.D.
Children:	Amy J. Covey (1990)
Social Security No:	507-70-4178
Office Address:	Department of Chemistry and Biochemistry Institute of Arctic Biology Box 757000 Irving I, Rm 311 University of Alaska Fairbanks Fairbanks, AK 99775-7000
Fax:	907 474-6967
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Telephone:	907 474-7190
Home Address:	P.O. Box 84002 Fairbanks, AK 99708

Education:

1981	B.S. Psychology University of Alaska Fairbanks, Fairbanks, AK
1982-1984	Ph.D. Candidate, Pharmacology Mount Sinai School of Medicine New York, New York Advisor: Stanley D. Glick, M.D., Ph.D.
1984-1987	Ph.D. Pharmacology Albany Medical College Albany, New York Advisor: Stanley D. Glick, M.D., Ph.D.

Professional Training:

1987-1990	Post-doctoral Fellow Department of Pharmacology Karolinska Institute Stockholm, Sweden Advisor: Urban Ungerstedt, M.D., Ph.D.
1990 - 1993	Research Associate Institute of Arctic Biology University of Alaska Fairbanks, Fairbanks, AK

Professional Appointments:

1993 -1998	Research Assistant Professor

Institute of Arctic Biology
University of Alaska Fairbanks, Fairbanks, AK

1998 –July 2002 Assistant Professor
July 2002-present Associate Professor (Tenured)
Department of Chemistry and Biochemistry
Institute of Arctic Biology
University of Alaska Fairbanks, Fairbanks, AK

2001 – present Adjunct Assistant Professor
Department of Pathology
Case Western Reserve University

Teaching:

Honors/Awards/Fellowships:

2000-2001 Outstanding Advisor Award, UAF
2000 Laboratory Equipment for Chemistry 103 and 104: Basic Introductory Chemistry and Beginnings in Biochemistry ($8,400; funded by CSEM)
2000 Fellow, Educational Reform Institute, Oshkosh, Wisconsin
2001 Fellow, Summer Institute for the Teaching of Ethics, Snowmass, CO

Teaching Support:

Funded Research for Undergraduates

1998-1999 University of Alaska Fairbanks
Undergraduate Research (Bevin McNally – Neuroscience)
$5,000 (1998-1999)

1999 American Heart Association
Summer Intern (Margaret Krieg – Undergraduate – Chemistry)
$3,000 (Summer 1999)

2000 American Heart Association
Summer Intern (Allison Kelliher – Undergraduate - Indigenous Medicine)
$3,000 (Summer 2000

2001 American Heart Association
Summer Intern (Ryan Corrick – Undergraduate - Chemistry)
$3,000 (Summer 2001)

2003-2004 Alaska EPSCoR
Research for Undergraduates
Maegan Weltzin – (Undergraduate – Chemistry)
$10,000 (Spring and Summer 2003, Summer 2004)
Ben Warlick – (Undergraduate – Chemistry)
$5,000 (Spring 2003)

NIH Supplement for Underrepresented Minorities
(Ben Warlick – Undergraduate – Chemistry)
$60,000 (Fall 2003 – Fall 2005)
(Adrienne Orr – Postgraduate – Chemistry, BS)
$59,000 (Fall 2003 – Fall 2004)

2003-2004 Alaska BRIN

Research for Undergraduates
Maegan Weltzin – (Undergraduate – Chemistry)
$5000 (Summer 2004)
Johanna Fritsche –(Undergraduate – Anthropology)
$5000 (Summer 2004)

2004-2005 Alaska IBRE
Research for Undergraduates
Ben Warlick – (Undergraduate – Chemistry)
$2500 (Fall 2004)
Lonita Lohse –(Undergraduate – Chemistry)
$2500 (Fall 2004)

Teaching Experience and Certification:

Graduate:

1986-1987	Neuropharmacology/pharmacokinetics, Nurse Anesthetist Program, Albany Medical College
1991	Instructor, Pharmacology of Alcohol and Alcoholism, UAF, 3 credit hrs
2001	Basal Ganglia, WWAMI Medical School, Anchorage Alaska, guest lecturer
2001	Topics in Neurochemistry, UAF, 1 credit hr
2002	Stroke, WWAMI Medical School, Anchorage Alaska, guest lecturer

Undergraduate:

1998	Chemistry and Society (Chem F100X), UAF, 4 hrs
1997	Multiple Intelligences (ED F495), UAF, 3 credit hrs
1997-2003	Basic General Chemistry (Chem F103X), UAF, 4 credit hrs
1997-2005	Beginnings in Biochemistry, (Chem F104X) UAF, 4 credit hrs
2002	Biochemistry (Chem F451), UAF, 3 credit hrs
2003	Biochemistry Lab (Chem F456, 3 credit hrs)
2003	Neurochemistry (Chem 697, 3 credit hrs)
2005	General Chemistry (Chem F105X, UAF, 4 credit hrs

Certification:

1997	Alaska State Certification in Secondary Science Education (Chemistry)

Postdoctoral Fellows/Research Associate Mentored (Current Position):

1993-1998	Yong Hu, M.D. (Clinical Support Consultant, Solucient, LLC)
1998-1999	Peter Osborne, Ph.D. (Asahikawa Medical School, Hokkaido, Japan, Research Scientist)
1996-1998	Oivind Toein, Ph.D. (UAF, IAB, Research Associate)
2001-2004	YiLong Ma, Ph.D. (Received $670,000 R15 grant and promoted to Research Faculty Sept. 2004)
2001-2004	Brian Rasley, Ph.D. (Chemistry Instructor)
2004-present	Sherri Christian, Ph.D. (Research Associate, IAB)

Graduate Students Trained/Current Position:

1997-2001	Rafaella Stimmelmayr, Ph.D. Wildlife Biologist, Tanana Chiefs Conference, Alaska
1999-2001	Fang Zhou, MS, Technician, Johns Hopkins School of Medicine
2001-present	Austin Rosa, Masters Student, Research Assistant Alaska INBRE
2001-present	Huiwen Zhao, Ph.D. Student, Research Assistant Alaska EPSCoR
2001-present	Bongchu Chi, MS, Research Assistant NIH U54 NS4106

Graduate and Medical Student Rotations/Training:

1997	Kimberly Clapp, Ph.D. Student, Study of ultrastructure around microdialysis probe (Clapp-Lilly et al., 1999)

1997	Zachary Katz, M.S. student, Study of extracellular GABA in hibernating ground squirrels (Osborne et al., 1999)
1998-2000	Carol Stewart, D.V.M. Clotting times during hibernation

Graduate Student Committees:

1995-1997	Thesis Committee, Lars Ebbesson, Interdisciplinary Neuroscience, UAF (M.S.)
1996-1997	Thesis Committee, Philip Shelton, Psychology, UAF (M.S.)
1997-1999	Thesis Committee, Stephanie Dloniak, Biology, UAF (M.S.)
1996-1999	Thesis Committee, Kimberly Clapp, Biochemistry and Molecular Biology, UAF, (Ph.D.)
1997-1999	Thesis Committee, Nancy Matton, Biochemistry and Molecular Biology, UAA, (Ph.D.)
1995-2001	Thesis Committee, Michael Sullivan, M.D., Neuroscience, UAA, (Ph.D.)
1998-2001	Thesis Committee, Jo Simmonetti, Biochemistry and Molecular Biology, UAA, (Ph.D.)
1998-2001	Thesis Committee, Zhengyu Wei, Biochemistry and Molecular Biology, UAF, (Ph.D.)
1998-2001	Thesis Committee, Chance Riggins, Chemistry, UAF (M.S.)
1998-present	Thesis Committee, Chris Whittle, Chemistry, UAF, (Ph.D.)
1998-present	Thesis Committee, Carla Richardson, Biology and Wildlife, UAF, (M.S.)
2001-2001	Thesis Committee, Shawna Karpovich, Biology and Wildlife, (Ph.D.)
1997-2001	Thesis Committee (co-Chair), Rafaella Stimmelmayr, Biology and Wildlife UAF, (Ph.D.)
1999-2001	Thesis Committee (Chair) Fang Zhou, Biochemistry and Molecular Biology UAF, (M.S.)
2000-2002	Thesis Committee, Shelly Stewart, Biochemistry and Molecular Biology, UAF (M.S.)
2003	Thesis Committee, Shawna Karpovich, Biology and Wildlife, UAF (M.S.)
2001-present	Thesis Committee (Chair), Austin Ross, Biochemistry and Molecular Biol. UAF, (M.A.,Ph.D.)
2001-present	Thesis Committee (Chair), Huiwen Zhao, Biochem. and Molec. Biol. UAF, (Ph.D.)
2001-2003	Thesis Committee, Anna Godduhn, Interdisciplinary Environmental Science, UAF (M.S.)
2002-present	Thesis Committee, Sirisha Nerella, PhD in Engineering (PDE)
2002-present	Thesis Committee (Chair), Bongchu Chi, Chemistry, UAF (M.S.)
2002-present	Thesis Committee, Xioaming Zhao, Biochem. And Molec. Biol. UAF, (Ph.D.)
2003-present	Thesis Committee, Sarah Dirschel, Biochem. And Molec. Biol. UAA, (Ph.D.)
2003-present	Thesis Committee, Elvin Brown, Biochem. And Molec. Biol. UAA, (Ph.D.)
2003-present	Thesis Committee, Dana Green, Biology and Wildlife, UAF (Ph.D.)
2003-present	Thesis Committee, Kristian Swearingen, Biochem. And Molec. Biol. UAF, (M.S.)
2004-present	Thesis Committee, Asha Suryanarayanan, Biochem. And Molec. Biol. UAF, (Ph.D.)
2004-present	Thesis Committee, Prasad Joshi, Biochem. And Molec. Biol. UAF, (Ph.D.)

Undergraduate Students Trained (undergraduate research), current position:

1991-1995	Terri Fitka,* psychology
1995-1997	Zachary Katz, chemistry
1995-1996	Denise Newman*, psychology
1995-1996	Alex Dugaqua*, biology
1995-1997	Chena Bryan*, biology, Ph.D. Program in Neuroscience, Univ Hawaii
1995	Crystal Rublee, biology, BS, O.D. Program
1998	Maggie Kreig, chemistry, degree in progress
1995; 1998-1999	Nikoosh Carlo*, biology, Ph.D. Program in Neuroscience, UCSD
1998-1999	Bevin McNally, neuroscience (interdisciplinary), degree in progress
1998-present	Allison Kelliher*, indigenous medicine (interdisciplinary), MD program, WAMI
1999-2001	Ryan Corrick, chemistry, BS, MSTP University of Alabama
2000-2004	Lesa Hollen, BS biology
2001-present	Maegan Weltzin*, High School senior, BS chemistry degree in progress
2001-2002	Charles Peele*, chemistry, degree in progress
2002-2004	Adrienne Ore*, Ph.D. Program, Molecular Pharmacology, Stanford University
2002-2005	Lesa Hollen, MS, Interdisciplinary Program in Neuroscience Visualization, UAF
2002-present	Bongchu Chi, BS chemistry, MS program, Chemistry, UAF

2002-present	Ben Warlick*, BS chemistry, degree in progress
2004-present	Lonita Loshe*, BS chemistry, degree in progress
2004-present	Johanna Fritsche, BS anthropology, Technician, UAF CANHR

*under-represented minority students

Research:

Honors/Awards/Fellowships:

1982-1984	Predoctoral fellowship; PHS (#5T32-GM07163)
1984-1987	Trustee scholarship; Albany Medical College
1989-1990	Åke Wiberg Foundation Fellowship, Stockholm, Sweden
1987-1990	Visiting Scientist fellowship; Karolinska Institute

Research Support:

Postdoctoral ***($54,000)***:

1988 -1990	Individual National Research Service Award NS08240, Neurochemistry of postural Asymmetries Measured using *in vivo* Microdialysis

Principal Investigator:

1992-1993	National Science Foundation IBN 912-1-221, GABA and Dopamine Release in Coho Salmon Brain $40,000
1992 – 1995	National Institutes of Health A609483, GABA and Dopamine Release in Aged Rat Striatum, $100,000
1995 – 1998	American Heart Association, Natural Tolerance to Cerebral Ischemia and Hypothermia, $120,000
1998 – 2001	American Heart Association, Natural Tolerance to Cerebral Ischemia and Hypothermia, (Competitive Renewal) $145,000
2000- 2005	National Institutes of Health (NINDS, NIMH, NCRR), Alaskan Basic Neuroscience Program Project leader on "Mechanisms of Neuroprotection During Hibernation and Arousal", $1,500,000 for project ($7,500,000 for entire program)
2003-2004	National Institutes of Health (NINDS, NIMH, NCRR), Alaskan Basic Neuroscience Program, "Mechanisms of Neuroprotection During Hibernation and Arousal" Research Supplement for Underrepresented Minorities, $109,107
2003-2005	National Institutes of Health (NINDS, NIMH, NCRR), Alaskan Basic Neuroscience Program, "Mechanisms of Neuroprotection During Hibernation and Arousal" Research Supplement for Underrepresented Minorities, $60,198
2001-2004	Office of Naval Research, Central Nervous System Regulation of Metabolic Down Regulation During Hibernation: A Microdialysis Study using Capillary Electrophoresis with Laser Induced Fluorescence Detection, $300,000.
2002-2004	Office of Naval Research Supplement, Study of Metabolic and CNS Suppression during Hibernation Using Microdialysis and Capillary Electrophoresis with Laser-Induce Fluorescence Detection $27,416
2002-2004	Defense Advanced Research Projects Agency, Effects of Hibernation on Retention of Active Avoidance Tasks, $100,000

Co-Principle Investigator

2002-2004 CBD/Army Small Business Innovation Research (SBIR) program, Identification of Compounds to Induce Suspended Animation or Hypometabolism. PI: Karl Johe, Neuralstem Inc., Gaithersberg, MD, $119,419

2004-2006 National Institutes of health (NINDS) Brain 0_2 defense during hibernation and arousal. 1-R15-NS048873-01 (PI: Ma, UAF), $669,240

2005-2006 Research Supplement for Individuals with Disabilities to 1-R15-NS048873-01

Invited Seminars/Platform Presentations:

S1. Drew K.L., Origin of GABA sampled using microdialysis, Maryland Psychiatric Research Institute, May, 1992.
S2. Drew K.L., Hibernation: A model for studying the brain's tolerance to stroke. University of Alaska Anchorage, Biology Research and Graduate Seminar Series, Sept. 25, 1998
S3. Drew K.L., Rice M.E., Frerichs K.U. and Hallenbeck J.M., 1999, Stroke therapies from hibernating squirrels, Winter Conference on Brain Research, Snowmass, CO, Jan 23-30.
S4. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., 1999, Hibernation: a natural model of tolerance to brain trauma. Hibernation and Adaptations to the Cold, Estes Park, CO, May 20-22.
S5. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., Hibernation and Tolerance to Brain Trauma, 50th Arctic Science Conference, Science in the North: 50 Years of Change. Denali National Park and Preserve, Alaska, Sept. 19-22, 1999.
S6. Duffy L, Drew K, Kuhn T and Bult B, Neuroscience Research at the University of Alaska Fairbanks. May 5, 2000.
S7. Drew K.L., Neuroprotective correlates of hibernation. National Institute of Mental Health, August, 1999.
S8. Drew K.L., Hibernation, a natural model of neuroprotection, National Institute of Deafness and Other Communication Disorders, Sept. 23, 2000.
S9. Drew K.L. Hibernation: A model of neuroprotection, Institute of Pathology, Case Western Reserve University, April 16, 2001
S10. Drew K.L. Hibernation: Microdialysis in hibernating ground squirrels, Dept of Psychiatry, Case Western Reserve University, April 20,, 2001
S11. Drew K.L., Microdialysis, tissue trauma and glutamate in hibernating brains 9th Annual Meeting On In Vivo Methods For Monitoring Molecules In Neuroscience. Dublin, June 18, 2001.
S12. Drew K.L., Hibernation and Neuroprotection. Alaskan Summer Neuroscience Conference, Fairbanks, July 29, 2001
S13. Drew K.L. Antioxidant Protection in Hibernation. Workshop on comparative aspects of oxidative stress. La Paz, Mexico, October, 2001, Session Chair.
S14. Drew K.L. Neuroprotection in Hibernation. Life Science Seminar Series, Institute of Arctic Biology, University of Alaska Fairbanks, Dec. 9, 2001
S15. Drew K.L. Hypoxia Tolerance in Hibernation. The less you want the more you have. Winter Conference on Brain Research. Snowmass, CO, Jan 27, 2002
S16. Drew K.L. and Green T.K., Microdialysis: Theory, Application and Coupling to Capillary Electrophoresis with Laser-Induced Fluorescence Detection, Center for Nanosensor technology, University of Alaska Fairbanks, Feb 7, 2002.
S17. Drew K.L. Memory, Learning and Hibernation, PI meeting for Continuous Assisted Performance Program, Defense Advanced Research Projects Agency (DARPA). New Orleans, March 25, 2002.
S18. Drew K.L. Hibernation a Natural Model of Neuroprotection. Alaska Summer Neuroscience Conference. Fairbanks, Alaska, July 14-15, 2002.
S19. Drew K.L., Neuroprotection in Hibernating Arctic Ground Squirrels (Spermophilus parryii): Metabolic Suppression. Advanced Technology Applications for Combat Casualty Care (ATACCC). St. Pete Beach, Florida, Sept. 9-11, 2002
S20. Drew K.L., Learning and Memory in Hibernation. PI meeting for Continuous Assisted Performance Program, Defense Advanced Research Projects Agency (DARPA). Honolulu, Hawaii. Sept 22-26, 2002.

S21. Drew K.L. Neuroprotection in Hibernation. Pacific Biomedical Research Center, University of Hawaii, Sept 27, 2002.
S22. Drew K.L., Neuroprotection in Hibernation: Is it Clinically Relevant? University of Miami, Neurology Grand Rounds. October 31, 2002.
S23. Drew K.L., Neuroprotection in Hibernation: A comparative Perspective. University of Miami School of Marine Biology. October 31, 2002
S24. Drew K.L. JNK activation during arousal from hibernation: a pivotal pathway of regeneration. University of Nebraska Omaha Center for Neurovirology and Neurodegenerative Disorders. August 21, 2003
S25. Drew K.L. Novel therapeutics from hibernating brain? Neuralstem Inc. Gaithersburg, MD. August 23, 2003.
S26. Drew K.L. Hypoxia Tolerance in Mammalian Heterotherms. Journal of Experimental Biology Discussion Meeting, Defenses Against Brain Hypoxia: Molecule to Organism, Organised by R.G. Boutilier and P.L. Lutz, September 13th – September 17th 2003, Cicalino, Italy
S27. Drew K.L. Living without in Hibernation. Winter Conference on Brain Research. Copper Mountain, Colorado, Jan 29, 2004.
S28. Drew K.L. Neuroprotection in Hibernation. Life in the Cold. Vancouver, Canada to Seward, Alaska, July 31, 2004.
S29. Kelly Drew and Roger Edberg "Visualizing Chemistry: Tools for the ARSC Discovery Lab", Fairbanks, Alaska, Dec 7, 2004
S30. Drew K.L. Cellular stress and MAPK modulation in Hibernation. Workshop on comparative aspects of oxidative stress. La Paz, Mexico, February 15-19, 2005. Session Chair

Publications:

Full-Length Papers:

P1. K.L., Lyon, M., Tietler, M. and Glick, S.D., 1986. Asymmetry in D-2 binding in female rat striata. Brain Res. 363:192-195.
P2. Drew, K.L. and Glick, S.D. 1987. Classical conditioning of amphetamine-induced lateralized and nonlateralized activity in rats. Psychopharmacology. 92:52-57.
P3. Glick, S.D., Shapiro, R.M., Drew, K.L., Hinds, P.A. and Carlson, J.N. 1986. Differences in spontaneous and amphetamine-induced rotational behavior, and in sensitization to amphetamine, among Sprague-Dawley derived rats obtained from different sources. Physiol. Behav. 38:67-70
P4. Drew, K.L. and Glick, S.D. 1988. Characterization of the associative nature of sensitization to amphetamine-induced circling behavior and of the environment dependent placebo-like response. Psychopharmacology. 95:482-487.
P5. Drew, K.L. and Glick, S.D. 1988. Environment dependent sensitization to amphetamine-induced circling behavior. Pharmacology Biochemistry and Behavior 31:705-708.
P6. O'Connor, W.T., Drew, K.L. and Ungerstedt, U. 1989. Differences in dopamine release and metabolism in rat striatal subregions following acute clozapine using in vivo microdialysis. Neurosci. Lett. 98:211-216.
P7. Drew, K.L., O'Connor, W.T., Kehr, J. and Ungerstedt, U. 1989. Characterization of γ-aminobutyric acid and dopamine overflow following acute implantation of a microdialysis probe. Life Sci. 45(14):1307-1317.
P8. Drew, K.L. and Glick, S.D., 1990. Role of D-1 and D-2 receptor stimulation in sensitization to amphetamine-induced circling behavior and in expression and extinction of the Pavlovian conditioned response. Psychopharmacology. 101:465-471.
P9. Drew, K.L., O'Connor, W.T., Kehr, J. and Ungerstedt, U. 1990. Regional specific effects of clozapine and haloperidol on GABA and dopamine release in rat basal ganglia. Eur. J. Pharm 187(3):385-397.
P10. Osborne, P.G., O'Connor, W.T., Drew, K.L. and Ungerstedt, U. 1990. An in vivo microdialysis characterization of extracellular dopamine and GABA in dorsolateral striatum of awake freely moving and halothane anesthetized rats. J. Neurosci. Methods. 34:99-105.
P11. Drew, K.L. and Ungerstedt, U. 1991. Pergolide presynaptically inhibits calcium-stimulated release of γ-aminobutyric acid from rat dorsolateral striatum. J. Neurochem. 57:1927-1930.

P12. O'Connor, W.T., Drew, K.L. and Ungerstedt, U., 1995, Differential cholinergic regulation of dopamine release in the dorsal and ventral neostriatum of the rat. An in vivo microdialysis study. J. Neurosci., 15(12):8353-8361.
P13. Drew, K.L., Fitka T. and Hu, Y. and Ungerstedt, U. 1997, Non-exocytotic γ-aminobutyric acid efflux in rat striatum inhibits gnawing. Life Sciences, 61(16):1593-1601.
P14. Clapp-Lilly K.L., Roberts R.C., Duffy L.K., Irons K.P., Hu Y., Drew K.L., 1999, An Ultrastructural analysis of tissue surrounding a microdialysis probe. J. Neurosci. Methods, 90(2), 129-142.
P15. Drew, K.L., Osborne, P.G., Frerichs, K.U., Hu, Y., Koren, R.E. Hallenbeck J.M. and Rice, M.E., 1999, Ascorbate and glutathione regulation in hibernating ground squirrels. Brain Research, 851(1-2), 1-8.
P16. Osborne, P.G., Hu, Y., Covey D.N., Barnes, B.M., Katz, Z., and Drew, K.L., 1999, Determination of striatal extracellular γ-aminobutyric acid in non-hibernating and hibernating arctic ground squirrels using quantitative microdialysis. Brain Research, 839, 1-8.
P17. Tolen, O., Drew K.L. Chao, M.L., and Rice M.E., 2001, Ascorbate dynamics and oxygen consumption during arousal from hibernation in Arctic ground squirrels. American Journal of Physiology, 281, R572-R583
P18. Zhou, F., Zhu X., Castellani R.J., Stimmelmayr R., Perry G., Smith M.A. and Drew K.L., 2001, Hibernation, a Model of Neuroprotection. American Journal of Pathology, 158, 2145-2151.
P19. Smith MA, Drew KL, Nunomura A, Takeda A, Hirai K, Zhu X, Atwood CS, Raina AK, Rottkamp CA, Sayre LM, Friedland RP, Perry G. Amyloid-β, tau alterations and mitochondrial dysfunction in Alzheimer disease: the chickens or the eggs? Neurochem Int. 2002, 40(6), 527-531.
P20. Drew, K.L., Rice, M.E., Kuhn T.B. and Smith M.A., 2001, Neuroprotective adaptations in hibernation: therapeutic implications for ischemia-reperfusion, traumatic brain injury and neurodegenerative diseases. Free Radical Biology and Medicine. 31(5), 563-573
P21. Drew K. L, Tølen Ø., Rivera P., M. Smith M. A., Perry G. and Rice M. E., 2002, Role of the Antioxidant Ascorbate in Hibernation and Warming from Hibernation. Comparative Physiology and Biochemistry, 133(4):483-92.
P22. Zhou F, Braddock J F, Hu Y, Zhu X, Castellani RJ, Smith MA and Drew KL., 2002, Microbial Origin of Glutamate, Hibernation and Tissue Trauma: An in vivo Microdialysis Study .J. Neuroscience Methods, 119(2), 121-128
P23. Perry G, Taddeo M, Nunomura A, Zhu X, Zenteno-Savin T, Drew KL, Shimohama S, Avila J, Castellani RJ, Smith MA., 2002, Comparative Biology And Pathology Of Oxidative Stress In Alzheimer And Other Neurodegenerative Diseases: Beyond Damage And Response. Comparative Physiology and Biochemistry, 133(4):507-13.
P24. Rice ME, Forman RE, Chen BT, Avshalumov MV, and Drew KL, 2002, Brain antioxidant regulation in mammals and anoxia-tolerant reptiles: balanced for neuroprotection and neuromodulation. Comparative Physiology and Biochemistry, 133(4):515-25.
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P29. Ma YL, Rice ME, Chao ML, Rivera PM, Zhao HW, Ross AP, Zhu X, Smith MA, Drew KL, 2004, Ascorbate Distribution during Hibernation is Independent of Ascorbate Redox State. Free Radical Biology and Medicine, 37(4):511-20.
P30. Drew KL, Pehek EA, Rasley BT, Ma YL, Green TK (2004) Sampling Glutamate and GABA with Microdialysis: Suggestions on how to get the Dialysis Membrane Closer to the Synapse. J. Neuroscience Methods, 140 (1-2): 127-131.
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P1. Ma YL, Zhu X, Rivera PM, Tolen O, Barnes BM, LaManna JC, Smith MA, Drew KL Cellular and physiological stress in hibernation and arousal, In preparation for Am. J. Physiol.,
P2. Weltzin MM, Zhao HW, Bucci D, Drew KL, Arousal from hibernation: a natural model of adult cognitive enhancement. in preparation for J. Neurosci.
P3. Drew KL, Warlick BP, Chi BC, Taylor BE, Harris MB, Green TK, Central Nervous System Control of Hibernation, invited review for J. Neurochem.
P4. Ross, AP, Christian, SL, and KL Drew, Intrinsic Tissue Tolerance in Arctic Ground Squirrel Hippocampal Slices, in preparation for submission for J Neurosci.
P5. Zhao H, Castillo MR, Christian SL, Bult-Ito A, Drew KL. Distribution of NMDA Receptors in the Arctic Ground Squirrel. In preparation for J. Comparative Neurobiology.
P6. Zhao H, Ross AP, Christian SL, Buchholz JN, Drew KL. NMDA Receptor Function in Hibernating Arctic Ground Squirrels. In preparation.

Book Chapters/Book Reviews/Letters to Editor:

C1. Shapiro, R.M., Drew, K.L. and Glick, S.D. 1988, Brain asymmetry, animal. In: Encyclopedia of Neuroscience. Birkhauser Boston, Inc., Cambridge, Mass.
C2. O'Connor, W.T., Drew, K.L., Carlsson, H. and Ungerstedt, U., 1992, Neostigmine enhances haloperidol-induced increases in acetylcholine release from rat striatal subregions: An in vivo microdialysis study. Current Separations. 10(3):115-116,
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C4. Drew KL, Zhou F, Zhu X, Castellani RJ, Smith MA (2004) Protection from traumatic brain injury during hibernation. Life in the cold. BM Barnes (Ed).
C5. Hermes-Lima M, Ramos-Vasconcelos GR, Cardoso LA, Orr AL, Rivera PM, Drew KL (2004), Animal adaptability to oxidative stress – gastropod estivation and mammalian hibernation. Life in the Cold, BM Barnes (Ed).

Book Chapters Submitted or in Preparation

C1. Ross A. and Drew, K.L., Clinical profiles of hibernating and euthermic arctic ground squirrels. In preparation

Abstracts

A1. Drew, K.L., Lyon, R.A., Tietler, M. and Glick, S.D. Right>left asymmetry in D-2 binding in female rat striatum. Neurosci. Abstr. 1985. 11:870.
A2. Drew, K.L. and Glick, S.D. Classical conditioning of amphetamine-induced rotation in unlesioned rats. Neurosci. Abstr. 1986. 12:1535.
A3. Drew, K.L. and Glick, S.D. Environment dependent sensitization to amphetamine-induced circling behavior in unlesioned female rats. Neurosci. Abstr. 1987.
A4. Baird, J.L., Glick, S.D., Carlson, J.N. and Drew, K.L. Epinephrine in rat corpus striatum: In vivo microdialysis and HPLC analysis. Neurosci. Abstr. 1987.
A5. Glick, S.D. Carlson, J.N., Baird, J.L. and Drew, K.L. Asymmetry in striatal dopamine release and metabolism: Bilateral in vivo dialysis in normal rats. Neurosci. Abstr. 1987.
A6. Drew, K.L., O'Connor W.T., Kehr, J. and Ungerstedt, U. GABA overflow in rat globus pallidus following neuroleptic and apomorphine administration measured by in vivo microdialysis. Neurosci. Abstr. 1988.

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A20. Clapp K.L., Roberts R.C., Duffy L.K., Hu Y., Irons K. and Drew K.L., 1998, Ultrastructural analysis of microdialysis-induced trauma in rat brain. American Society for Neurochemistry, March 1998.

A21. Hu Y., Osborne P.G., Stimmelmayr R. and Drew K.L., 1998, Hibernation: A model of tolerance to brain trauma. Society for Neurosi. Abstr., 676.13.

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A23. Drew K.L., Rice M.E., Frerichs K.U. and Hallenbeck J.M., 1999. Stroke therapies from hibernating squirrels, Winter Conference on Brain Research, Snowmass, CO, Jan 23-30.

A24. Drew K.L., Clapp-Lilly K.L, Roberts R.C., Duffy L.K., Irons K.P., and Hu Y., 1999, An Ultrastructural Analysis of Tissue Surrounding a Microdialysis Probe. 8th International Conference on In Vivo Methods: "Monitoring Molecules in Neuroscience." Stony Brook, NY, June 19-23.

A25. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., 1999. Hibernation: a natural model of tolerance to brain trauma. Hibernation and Adaptations to the Cold, Estes Park, CO, May 20-22.

A26. Drew K.L., Osborne P.G., Hu Y., Stimmelmayr R., Barnes B.M., 1999, Hibernation and Tolerance to Brain Trauma, 50th Arctic Science Conference, Science in the North: 50 Years of Change. Denali National Park and Preserve, Alaska, Sept. 19-22.

A27. Tøien, Ø. Rice, M.E. Barnes, B. M. and Drew, K.L. 1999, Plasma ascorbate and oxygen consumption during rewarming from hibernation in arctic ground squirrels. Society for Neurosi. Abstr., 736.21

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A33. Drew K.L., Rivera, P.M. Ross A.P. Corrick R. M., Toien Ø. Zhu X. Chao M.L. Smith M.A. Rice M.E., Antioxidant effects of ascorbate during rewarming from hibernation in arctic ground squirrels. Society for Neurosi. Abstr. San Diego, CA, Nov. 2001

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A35. Drew KL, Ma Y, Rivera P, Cozad K, Toien O, Arterial Blood Gases During Hibernation in the Arctic Ground Squirrel, Stroke - Molecular, Cellular, Pharmacological and Development of New Therapeutics, March 9 - March 14, 2002, Taos, New Mexico.

A36. Ross A and Drew KL, Neuroprotection during Hypoxia in the Arctic Ground Squirrel Molecular, Cellular, Pharmacological and Development of New Therapeutics, March 9 - March 14, 2002, Taos, New Mexico.

A37. Richardson C, Drew KL, Kuhn TB, Decreased Rise in Free Intracellular Ca^{2+} in Synaptosomes and Slices from Hibernating Arctic Ground Squirrels. 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A38. Cozad K, Ma Y, Rivera PM, Zhao H, Drew KL, Mechanisms of Hypoxia Tolerance Compared with Hibernation 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A39. Drew KL, Ma Y, Rivera PM, Cozad K, Toien O, Zhu X, Smith MA. Exit from Torpor: A Natural Model of Tolerance to Reperfusion 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A40. Rivera PM, Zhu X, Smith MA, Rice ME, Drew KL. Study of Oxidative Stress in CA-1 Region of Hippocampus during Euthermia, Torpor and Arousal from Torpor in Arctic Ground Squirrels (*Spermophilus parryii*) 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A41. Ross A, Drew KL NMDA Tolerance in Organotypic Hippocampal Slices : A Hibernating Versus Non – Hibernating Species 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A42. Zhao H, Weltzin M, Drew KL, Effects of Hibernation on Retention of an Active Avoidance Task 2nd Annual Conference of Specialized Programs in Neuroscience, May 15-17, 2002, San Antonio, Texas

A43. Cozad K, Ma Y, Rivera PM, Zhao H, Drew KL, Mechanisms of Hypoxia Tolerance Compared with Hibernation. Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

A44. Drew KL, Ma Y, Rivera PM, Cozad K, Toien O, Zhu X, Smith MA. Hibernation: A Natural Model of Tolerance to Reperfusion Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

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A47. Zhao H, Weltzin M, Drew KL, Effects of Hibernation on Retention of an Active Avoidance Task. Alaskan Summer Neuroscience Conference, July 14-15, 2002, Fairbanks, AK

A48. Ma Y, Rivera P, Kelliher A, Smith MA, Zhu X, Rice ME, Drew KL. Fate of Ascorbate During Hibernation in Arctic Ground Squirrels. Society for Neuroscience, November 2-7, 2002, Orlando, Florida.

A49. Zhao H, Weltzin M, Bucci D, Drew KL. Effects of Hibernation on Retention of an Active Avoidance Task. Society for Neuroscience, November 2-7, 2002, Orlando, Florida.

A50. Drew KL, Ma Y, Rivera P, Cozad K, Tolen O, Zhu X, LaManna J, Smith MA. Arousal from Hibernation: A Natural model of Tolerance to Reperfusion. Society for Neuroscience, November 2-7, 2002, Orlando, Florida.

A51. Rivera P.M. Ma Y.L. Zhu X. Ross A, Castellani R, Smith MA, Rice ME and Drew KL (2003) Study of oxidative stress in CA1 neurons and liver during euthermia, torpor and arousal from torpor in arctic ground squirrels (spermophilus parryii) 3rd Annual Conference of Specialized Programs in Neuroscience, May 28-30, 2002, Honolulu, Hawaii

A52. Green TK, McGill CG, Swearingen KE, Rasley BT, Drew KL, Characterization of Side Products from NDA/NaCN on-column derivatization of amino acid neurotransmitters. Proceedings of the 10th International Conference on In Vivo Methods, J. Kehr, K. Fuxe, U. Ungerstedt, T. Svensscn, eds. Karolinska Institute, 2003, p 478.

A53. Rasley BT, Drew KL, Dick E, Swearingen KE, Green TK, In Vivo Monitoring of Glutamate in Hibernating Ground Squirrels: Construction of an On-line Microdialsysis/Capillary Electmphoresis/Laser-induced Fluorescence Instrument. Proceedings of the 10th International Conference on In Vivo Methods, J. Kehr, K. Fuxe, U. Ungerstedt, T. Svensson, eds. Karolinska Institute Stockholm 2003, p 481.

A54. Drew KL, Pehek EA, Rasley BT, Ma Y, Green TK, Sampling Glutamate and GABA with Microdialysis: How to get the Membrane Closer to the Synapse? Proceedings of the 10th International Conference on In Vivo Methods, J. Kehr, K. Fuxe, U. Ungerstedt, T. Svensson, eds. Karolinska Institute Stockholm 2003,

A55. Zhao, H, Castillo MR, Bult-Ito, A, Drew KL, Distribution of NMDA receptors in Arctic ground squirrels. Society for Neuroscience, November 7-13, 2003, New Orleans, LA

A56. Ma YL, Rivera P, Wu SF, Drew KL, Enhanced plasma ascorbate stability in hibernation. Society for Neuroscience, November 7-13, 2003, New Orleans, LA

A57. Weltzin MM, Bucci DJ, Zhao H, Drew KL (2003) Hibernation, Learning and Memory, Cell Biology of the Neuron, November 7, 2003, New Orleans, LA.

A58. Zhao HW, Ross AP, Buchholz JN, Drew KL, Intracellular [Ca2+] in Cultured Hippocampal Slices of Hibernating Arctic Ground Squirrel. American Society for Neurochemistry, New York, NY, August 2004

A59. Ross, AP, Christian, SL, Zhao, HW, and KL Drew, Excitotoxic Tolerance in Hippocampal Slices from a Hibernating Species, Society For Neuroscience 34th Annual Meeting, San Diego, CA, Oct.23-27, 2004

A60. Ma YL, Cozad KD, Rivera PM, Zhao, HW, Drew KL (2004) Differences in hypoxia tolerance between AGS and rats. Society for Neurosci

A61. Dave KR, Prado R, Raval AP, Drew KL, Perez-Pinzon MA (2004) Remarkable ischemic tolerance by the Arctic ground squirrel against cardiac arrest during euthermia. Society for Neurosci.

A62. Ross AP, Drew KL (2004) Neuroprotection from excitotoxic insult in hippocampal slices from a hibernating species, arctic ground squirrel. 10th International Symposium on Pharmacology of Cerebral Ischemia Marburg, Germany, July 25-28, 2004

A63. Zhao H, Ross AP, Buchholz JN, Drew KL. (2004) Intracellular [Ca2+] in Cultured Hippocampal Slices of Hibernating Arctic Ground Squirrel Society For Neuroscience 34th Annual Meeting, Oct. 22-26, 2004, San Diego, CA.

Patents:

Ma Y and Drew KL, Adapter between microdialysis guide cannula and microsensors. Provisional Patent, United States Patent Office, filed Aug. 16, 2002 – Not pursued

Service:

Committee Appointments and Service:

University:

1995-1996 Appointed member, Research Advisory Committee

2001-2002	Appointed member, Institutional Review Board
2001-2003	Appointed duty, Center for Nanosensor Technology, Seminar Coordinator
2001-2003	Volunteer, Alaska Basic Neuroscience Program Summer Seminar Series Coordinator
2002-present	Appointed, Research Advisory Committee, Institute of Arctic Biology
2003-present	Appointed, BICS-Central Animal Facility Project Committee
2004-present	Appointed, Institutional Animal Care and Use Committee
2005-present	Appointed, Emergency Services Program Review Committee
2005-present	Appointed, Interdisciplinary Studies Program (INDS) Steering Committee

Departmental:

1999-2000	Appointed member, Search Committee (Assist. Professor, Organic Chemist)
2000-2001	Appointed member, Search Committee (Laboratory Coordinator)
2000-2001	Appointed member, Search Committee (Veterinary Technician)
2001-2002	Appointed member, Search Committee (Director, Alaskan Basic Neuroscience Program)
2001-2002	Appointed member, Search Committees (Assistant Professor, Cell/Molecular Neuroscientist)
2001-2002	Appointed member, Search Committee (Assistant Professor, Analytical Chemists)
2003	Appointed Chair, Search Committee (Assistant Professor, Molecular Physiologist)

Regional/National/International:

(i) Conferences:

Organizer, Stroke therapies from hibernating squirrels, Winter Conference on Brain Research, Snowmass, CO, Jan., 1998.

International Organizing Committee, Monitoring Molecules in Neuroscience, Conway Institute of Biomolecular and Biomedical Research, June 16-19 2001, University College Dublin, Ireland.

Organizer, Alaskan Summer Neuroscience Conference, Fairbanks, Alaska, July 29, 2001, Fairbanks, Alaska

Organizer, Hypoxia tolerance; the less you want, the more you have, Winter Conference on Brain Research, Snowmass, CO, Jan., 2002

International Organizing Committee, Monitoring Molecules in Neuroscience, June 2003, Karolinska Institute, Stockholm, Sweden.

Organizer, Alaskan Summer Neuroscience Conference, Fairbanks, Alaska, July 14-15, 2002, Fairbanks, Alaska

Organizing Committee, Living in the Cold, July 2004, Vancouver, BC

Organizer, Living without in Hibernation. Winter Conference on Brain Research. Copper Mountain, Colorado, Jan 29, 2004.

(ii) Societies/Agencies:

American Heart Association, Alaska Affiliate, Research Committee, Anchorage, Alaska, 1995- 1998
American Heart Association, Northwest Affiliate, Research Committee, Seattle, Washington, 1998 – present
American Heart Association, Northwest Affiliate, Summer Science Fellowship Task Force, 1999 – present
American Heart Association, National, Peer Review Steering Committee, 2000-present
National Institute of Deafness and Communication Disorders, Partnership Program Committee, 1994 – present
National Science Foundation, Ad-hoc reviewer, June, 2002

National Institutes of Health, Neurological Sciences and Disorders B Study Section, *Ad Hoc* Member, June, 2002

(iii) Grant:
Paid-Consultant, NIH Grant (1P50 NS34116), Ascorbate and glutathione in CNS injury, (Chesler, M., PI; Rice M.E., leader project 3), 1997-1998.

(iv) Corporations:
Paid-Consultant, Santa Fe Science & Technology, Inc., Santa Fe, New Mexico, 2000- present.

Community Service:

1990-present	Expert Witness, neuropharmacology of drugs of abuse (Ritalin, alcohol, cocaine, amphetamine, benzodiazepines etc.)
1997-present	Science Potpouri, College of Science, Engineering and Mathematics, UAF
1999-present	Science Education, Wood River Elementary School, "Dr. Science"
2003	Chilled Brains, Lathrop High School
2004	Pharmacology of drugs of abuse, Fairbanks North Star School District 1 day in-service
2004	Pharmacology of drugs of abuse, North Pole Alternative High School
2004	Job Shadow for Ana Davis, high school student
2004	Channel 11 interview concerning questions on Ballot Measure 2
2005	Invited testimony for public hearing on Alaska SB 74 and HB 96
2005	Chilled Brains, UAF Museum Lecture Series

Society Memberships:

1985-present	Society for Neuroscience
2001-2002	President, local chapter Society for Neuroscience
1995-present	American Association for the Advancement of Science
1998-present	American Chemical Society
1998-present	American Society for Neurochemsitry
2000-present	International Society for Neurochemistry
2000-present	Oxygen Society
2000-present	American Heart Association Stroke Council
2000-present	International Society of Cerebral Blood Flow and Metabolism

Granting Agencies:

American Heart Association, External Reviewer, 1997
Baker Fund Awards Committee, External Reviewer, 2002
NIH, Neurological Sciences and Disorders-B, 2002
DOD (ARO), External Reviewer, 2004
Maryland Industrial Partnerships, University of Maryland, External Reviewer, 2004
NIH, Biological Rhythms and Sleep [BRS], 2005

Ad Hoc Journal Reviewer:
Journal of Neuroscience, Journal of Neurochemistry, Brain Research, Journal of Neuroscience Methods, Life Sciences, Psychopharmacology, Redox Report, Cellular and Molecular Biology, Journal of Experimental Biology, American Journal of Physiology, Hippocampus, Journal of Cerebral Blood Flow and Metabolism, Neurobiology of Aging, Journal of Physiology

Textbook Reviewer
Horton et al., Principles of Biochemistry, 4th edition, Chapters 11-14. Prentice Hall, Upper Saddle River, NJ

References:

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My name is Jim Welch and for all of you except Fred Dyson I am a faceless name. Fred Dyson knows me and I hope because of that, he at least will listen to me. For almost 20 years now I have had MS. MS is a disease which short-circuits nerve pathways. So it can affect anything that depends upon nerve messages getting through, whether it be the functioning of a limb or an organ, or sensation, be it numbness or pain. There is no cure for it, so as things deteriorate doctors try to treat symptoms. One of the problems with this however, is that many of the drugs have side effects as least as prominent as the effects.

Over the years I've tried many prescription drugs for many different reasons, usually with very limited success and often with unpleasant side effects. In 1998 I was active in the campaign to pass the initiative legalizing medical marijuana. I found that for two or three years marijuana was the only thing that allowed me to get through most nights without racking muscle spasms or headaches that would not allow me to sleep and still allow me to function the next day.

I applaud what the Legislature has tried to do with crystal meth. That's a drug which I think everyone can agree has no redeeming qualities. But further demonizing marijuana is engaging in the wrong battle. Comparing marijuana to heroin is like comparing aspirin to morphine. Saying that the marijuana today is stronger than it was in the 70s and therefore dangerous is like saying Alleve is stronger than Tylenol, that you only have to take one pill instead of two.

To me that seems a good thing because it means you have to put less smoke into your lungs. I've never smoked tobacco and if I never had to put any more smoke in my lungs or take another drug in my life it would be fine with me.

This is not the 40s era of "Reefer Madness" or even the Nancy Reagan 80s of "just say no." This is the 21st century and in the last election 44% of Alaskans voted to legalize marijuana. You may have the power of the majority to make criminal penalties more severe, but it is a slap in the face to a very large portion of the Alaskan populace who believe that marijuana is okay and who just a few years before voted by a substantial majority to legalize the use of medical marijuana.

I don't know why the Governor has chosen to make marijuana the bad boy of his drug campaign. It doesn't make any sense to me. I know it's not addictive. I smoked marijuana several times a week for three years. When it was no longer effective I stopped. I experienced no withdrawal, no craving, no side effects, no problem.

Unlike tobacco or alcohol no one has ever died from marijuana. I would argue that at worst it's innocuous and at best it has some significant medical benefits.

As for its connection to violent criminals, anyone who has ever used marijuana knows the effects last only a few hours, whereas it can be detected as having been used up to 30 days ago. That's like blaming a DWI on a beer someone drank a month before.

In the last World Cup soccer matches in Portugal, Security checked the persons and all bags being brought into the stadium. Any alcohol was immediately seized, but any marijuana that fans were bringing into the game was not even confiscated. That tells you what kind of behavior the people in charge of security thought resulted from people using marijuana. They worried about the notoriously rowdy soccer fans, but not the ones using marijuana.

I have no illusion or intention to make you proponents of legalizing marijuana. That's not even the issue before you. I do ask you however, to recognize the folly of harsher criminalization penalties. It means putting more nonviolent offenders in jail, devoting more time and money resources of our police to what amounts to a low-priority use of their time. I ask you to put your anti-drug energies against something like crystal meth. Fighting marijuana is the wrong battle in any war on drugs. You have bigger issues to deal with.

Written Testimony – Senate Bill 74

For the Alaska Senate Health, Education and Social Services Committee

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Summary of Written Testimony

1. Teasing Apart....

"The relationship between frequent marijuana use and violence (and vice versa) was spurious; it was no longer significant when common risk factors such as race/ethnicity and hard drug use were controlled for."

2. Effects of Varying Marijuana Potency....

"Tar delivery is reduced relative to THC content in a minority of subjects, and this reduction appears to be due to a reduced intake of smake and/or a reduced tar yield from the stronger marijuana preparation."

3. The Limited Relevance of Drug Policy....

"...no evidence to support claims that criminalization reduces use or that decriminalization increases use."

4. Long-Term Effects....

"There is little evidence . . . that long-term cannabis use causes permanent cognitive impairment...."

5. The Good and Bad Effects....

"[THC] does not constitute a substantial risk to public health and its abuse is rare if at all."

6. The Health and Psychological Effects....

"...on current patterns of use, alcohol and tobacco are much more damaging to public health in developed societies than cannabis, which makes no known contribution to deaths and a minor contribution to morbidity."

7. An Overview of Cannabis Potency....

"Statements in the popular media that the potency of cannabis has increased by ten times or more in recent decades are not supported by the limited data that are available from either the USA or Europe."

8. Psychological and Social Sequelae....

"Available evidence does not strongly support an important causal relation between cannabis use by young people and psychosocial harm...."

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1.

TEASING APART...

"Teasing Apart the Developmental Associations Between Alcohol and Marijuana Use and Violence"

Evelyn H. Wei, Rolf Loeber, and Helene Raskin White
National Institute of Drug Abuse
Grant #MH050778

Teasing Apart the Developmental Associations Between Alcohol and Marijuana Use and Violence

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This study explored the longitudinal associations of alcohol and marijuana use and violence over ages 11-20 in the youngest sample of males from the Pittsburgh Youth Study (N = 503). We examined trends in alcohol and marijuana use and violence, how they covaried both concurrently and over time, and whether frequent substance use predicted violence and vice versa in multivariate models controlling for common risk factors. The analyses focused on frequent alcohol or marijuana users, those who scored in the highest 25% of frequency. Throughout adolescence, substance use was more prevalent than violence. Most substance users did not engage in violence, and the proportion of substance users who engaged in violence was smaller than the proportion of violent offenders who were also substance users. Concurrently, frequent use of alcohol and marijuana were both significantly associated with violence. Longitudinal associations between frequent drinking and violence were weak, whereas longitudinal associations between frequent marijuana use and violence were more consistent. However, the relationship between frequent marijuana use and violence (and vice versa) was spurious; it was no longer significant when common risk factors such as race/ethnicity and hard drug use were controlled for. We conclude that the marijuana-violence relationship is due to selection effects whereby these behaviors tend to co-occur in certain individuals, not because one behavior causes the other; rather, both are influenced by shared risk factors and/or an underlying tendency toward deviance.

Keywords: *alcohol; marijuana; violence; developmental associations*

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A substantial body of literature has addressed the link between substance use and violence. The substance use–violence relationship has been addressed by two angles of research: Acute or pharmacological effects have been examined in survey and laboratory studies, and longer term, developmental effects have been addressed by longitudinal survey studies. These studies have shown differences in the effects of alcohol and marijuana on violent behavior. Several key issues remain, such as developmental trends between substance use and violence throughout the adolescent period, and concurrent and predictive associations, especially when appropriate statistical controls are introduced.

Numerous studies have shown an association between alcohol use and violence (see reviews by Boles & Miotto, 2003; Chermack & Giancola, 1997; Miczek et al., 1994; White, 1997a). However, the evidence concerning the association between marijuana use and violence is much more ambiguous and controversial. Federal documentation on the Internet (Center for Substance Abuse and Prevention, 2003) cites as one of "ten good reasons to focus on marijuana use" that "violence and other crime have been attributed directly to marijuana use." In the year 2000, marijuana was the most popular drug used by juvenile male detainees; across nine sites nationwide, 42% to 55% of detainees tested positive for marijuana (U.S. Department of Justice, 2003).

Acute and Concurrent Associations

There is a consensus that most users of alcohol do not commit violence but that heavy or frequent alcohol use lowers the threshold for the manifestation of violence, especially among aggressive individuals. This consensus is supported by experimental laboratory studies, longitudinal survey studies, and reviews of the literature (Chermack & Giancola, 1997; Ito, Miller, & Pollock, 1996; Parker & Auerhahn, 1998; White, 1997a).

On the other hand, most studies do not support an acute or direct association between marijuana use and violence (Boles & Miotto, 2003; Dembo et al., 1991; Friedman, 1998; Miczek et al., 1994; Reiss & Roth, 1993; White, 1997a). Laboratory research has demonstrated that alcohol and marijuana have opposite psychopharmacological associations vis-à-vis aggression (Miczek et al., 1994). Survey data also fail to find that marijuana use psychopharmacologically induces violence (Boles & Miotto, 2003; Goldstein, 1985). According to Reiss and Roth (1993), "In general, scientific reviews have concluded that violent behavior is either decreased or unaffected by marijuana use" (pp. 1165-1167).

Most studies have examined the acute effects of substance use on violence among adults. In one survey study of adolescent males from the Pittsburgh

Youth Study (PYS). White, Tice, Loeber, and Stouthamer-Loeber (2002) found that offenses against persons were committed more often than general theft while under the influence of alcohol. In addition, aggressive acts were more often related to self-reported acute alcohol use than to marijuana use. Offenses committed under the influence were more prevalent among heavier alcohol and drug users, more serious offenders, more impulsive youth, and youth with more deviant peers. White and Hansell (1998) also found that acute use of alcohol compared to marijuana was more strongly associated with fighting, especially in late adolescence and early adulthood.

Most research on substance use and violence among adolescents has focused on the developmental associations rather than acute associations. Whereas studies of acute effects clarify the association between doses of substance use and immediate aggressive behavior, developmental studies help to clarify the temporal associations and to delineate longer term effects (Huang, White, Kosterman, Catalano, & Hawkins, 2000, p. 80). Rather than assuming a pharmacological association, much of the developmental research is based on the assumption that substance use and aggression are problem behaviors that co-occur during adolescence and that both types of problem behaviors are dependent on a similar set of common risk factors (White & Labouvie, 1994).

There are several plausible ways by which alcohol, and possibly marijuana use, can be developmentally implicated in violence. For example, (a) substance use may lead to violence; (b) violence may lead to substance use; (c) causation may be reciprocal (i.e., one causes the other and vice versa); (d) violence and substance use may be seen as aspects of general dispositions to deviance (i.e., they may be alternative manifestations of the same concept); and (e) substance use and violence may be seen as independent forms of deviance that share common precursors, resulting in a spurious relationship (Kaplan & Damphousse, 1995, pp. 189-191; see also White, 1997a, 1997b).

Developmental Associations and Direction of Effects

Studies examining developmental relationships in adolescence have generally found that early aggressive behavior predicts later substance use and that increases in substance use are related to increases in violent offending (Elliott, Huizinga, & Menard, 1989; White, 1997a, 1997b). The linkage between frequent alcohol use and violence has also been confirmed in longitudinal studies (e.g., Elliott et al., 1989; White, Loeber, Stouthamer-Loeber, & Farrington, 1999). Frequent alcohol use has been shown to predict violence, even when controlling for marijuana use and for other shared risk factors (White et al., 1999).

Using a sample of predominantly White, middle- and working-class adolescent males, White, Brick, and Hansell (1993) found that while controlling for concurrent associations and stability of behaviors over time, aggression in early adolescence (age 12) predicted increases in later alcohol use (age 15), but alcohol use did not predict increases in aggression. White and Hansell (1998) repeated these analyses after following their sample into young adulthood (ages 25-31) and did not find an association between early aggression and later substance use nor between early alcohol use and later aggression. They did find that marijuana use in adolescence (ages 12-18) was negatively related to later aggressive behavior (ages 15-21) and that marijuana use in later adolescence (ages 18-24) was positively related to aggression in young adulthood (ages 25-31). Cross-sectional correlations were much stronger between alcohol and aggression than between marijuana and aggression. In this latter study, aggression was measured by a single indicator of minor aggressive behavior.

In a study of a high-risk Seattle sample, Huang and colleagues (2000) found that the concurrent associations between alcohol use and aggression decreased with age from midadolescence (age 14) into late adolescence (age 18). In terms of cross-lagged associations, aggressive behavior at age 15 predicted increases in alcohol use at age 16, and alcohol use at age 16 predicted increases in aggressive behavior at age 18. However, when common risk factors were controlled for, only the association between alcohol use and later aggressive behavior remained significant. This study focused on aggression as measured by throwing objects, picking fights, and hitting to hurt, as opposed to more serious criminal acts of violence.

Similarly, White et al. (1999) also examined the cross-lagged associations between substance use and violence using data from the oldest cohort in the PYS from ages 13 to 18. The authors found reciprocal associations between alcohol and violence. These associations held even after risk factors that have been associated with both sets of behaviors were controlled for, thus ruling out a purely spurious relationship. White and colleagues found that the concurrent associations were stronger for marijuana and violence than for alcohol and violence, but the longitudinal associations were opposite. Nevertheless, marijuana use in early adolescence (at age 13) was a strong predictor of later violent behavior. However, although changes in marijuana use predicted changes in violence, the association was no longer significant once the effects of prior alcohol use and violence were partialled out. This finding is important, because frequent marijuana users also consume alcohol, and the pure effect of each substance on violence can best be investigated by means of partial correlations in which the effect of one substance on violence is examined while holding constant the effect of the other substance.

In summary, the relationship between substance use and violence appears to be a complicated one. Findings have not been consistent across studies and tend to differ depending on the substance that is examined and the sample that is used. Use of different age ranges and outcome measures (minor aggression versus violence) also contributes to the inconsistency in findings. In addition, previous studies have pointed to the importance of investigating developmental associations between substance and violence while partialling out the effects of co-occurring substance use.

These issues are addressed in this study, which is a replication and extension of prior developmental research in the Pittsburgh Youth Study on substance use and violence in the oldest sample from ages 13 to 18 (White et al., 1999). In this article, we use the youngest sample of the PYS to examine the concurrent and longitudinal associations between alcohol and marijuana use and violence over a 10-year period from ages 11 to 20 years. This study addresses the following questions:

1. What are the developmental trends of substance use and violence throughout adolescence in terms of the prevalence and frequency of each behavior?
2. What are the concurrent and longitudinal associations between frequent substance use and violence?
3. What is the direction of effect between substance use and violence when controlling for shared risk factors?

It is important to replicate findings across different samples. This study extends the earlier study with the older sample (White et al., 1999) in several ways. First, the earlier study was based on a shorter window of time (from ages 13 to 18 compared with 11 to 20). Second, those findings were for a sample that reached adolescence during the peak of the violence epidemic in Pittsburgh (Fabio, Loeber, & Farrington, 2003), whereas this sample is less violent but more involved in illegal drug use (White, Stouthamer-Loeber, Loeber, & Farrington, 2001). Finally, in this study we control for two important demographic factors that are related to violence and substance use (i.e., neighborhood context and race/ethnicity), which were not included in the earlier study.

Nevertheless, we anticipate replicating earlier associations between alcohol and violence. Second, we hypothesize that frequent marijuana use will predict violence and that violence will predict frequent marijuana use. However, we also predict that once statistical controls for confounding factors are taken into account, the association between frequent marijuana use and violence will appear to be spurious, whereas the association between frequent alcohol use and violence will remain.

METHOD

Data were collected as part of the PYS, a longitudinal study of the development of delinquency, substance use, and mental health problems among inner-city adolescent males (Loeber, Farrington, Stouthamer-Loeber, & Van Kammen, 1998). In 1987, three samples of boys were randomly drawn from the first, fourth, and seventh grades of public schools. Of the 3,436 randomly selected, 85% of the boys and their caretakers (93% of whom were biological mothers) consented to participate in a screening assessment. From each sample, the top 30% (about 250 from each grade) of boys with the highest rates of antisocial behavior were selected, along with an equal number randomly selected from the remaining 70%. This resulted in three samples of about 500 boys each. The present analyses focus on the youngest cohort (N = 503), those who were in the first grade when the study began.

At the first assessment, participants in the youngest sample were an average of 7 years old. Slightly more than half (56.3%) of the sample was African American, and almost half (41.4%) was Caucasian, reflecting the racial composition of Pittsburgh public schools when the study began. The population of other ethnic/racial minority groups in Pittsburgh is very low. About 40% of the boys lived with a single parent, and about 40% of the caretakers received public assistance. Further details about the study design and participants can be found in Loeber et al. (1998).

The first 8 assessments were conducted semiannually, and the next 10 were conducted annually. Information was collected from the boys and their caretakers and teachers until age 17 and then from interviews with the boys only. These analyses use data from ages 11 to 20. Data from the semiannual assessments were combined to reflect behaviors occurring in the past year. Data from ages 7 through 10 were not used, because few boys were using substances at these ages, and measures at the younger ages (ages 7-10) used categorical rather than continuous scales. At the last data collection phase (age 20), the participation rate was 82%, and the overall average follow-up rate was 92%, reflecting very low attrition.

Violence Measures

Violence was measured annually by the Self-Reported Delinquency scale (Loeber et al., 1998) and included the past year frequency (number of times) of gang fighting, strong-arming, attacking someone with a weapon or intent to seriously hurt or kill, and rape or forced sex.

Substance Use Measures

Self-reported frequency (number of times in the past year) of alcohol, marijuana, and hard drug use was assessed annually by the Substance Use Scale (Loeber et al., 1998). Hard drugs included hallucinogens, cocaine, crack, heroin, PCP, and nonmedical use of tranquilizers, barbiturates, codeine, amphetamines, and other prescription medications. The lifetime prevalence of hard drug use from ages 11 to 20 was too low ($n = 73$) to include hard drug use as an outcome measure. Therefore, the analysis focuses on the relationship of alcohol and marijuana use with violence. Hard drug use is controlled for in some of the analyses.

The frequency of alcohol consumption was the sum of the number of times participants drank beer, wine, or hard liquor and did not count trying a few sips or drinking with the permission of adults during special occasions/religious services.

Common Risk Factors

Based on findings of previous studies examining substance use and violence (Huang et al., 2000; White et al., 1999), several risk factors common to both substance use and violence were selected as covariates. Because many distributions were skewed, and to ease interpretability, risk factors were dichotomized at the top 25%. These risk factors included the *lifetime frequency of hard drug use*, assessed annually by self-report, and the *frequency of self-reported property crime* (theft, fraud, and vandalism), assessed at age 11. Other child factors were *low academic achievement*, assessed by the primary caretaker and teacher when the boy was age 7, and *depressed mood* and *hyperactivity/impulsivity/inattention problems* (from the Child Behavior Checklist; Achenbach & Edelbrock, 1979, 1983; Edelbrock & Achenbach, 1984), assessed by caretaker and teacher when the boy was age 7. Family risk factors were based on reports by caretakers and participants and included *poor communication with caretaker*, measured at age 11, and *poor supervision*, measured at age 7. In addition, we controlled for *caretaker perception of bad neighborhood*, assessed by the primary caretaker at the first interview (when the boy was age 7). This variable measured caretakers' perceptions of factors such as crime, unemployment, racial conflict, vandalism, and so on in their neighborhood. We also controlled for African American ethnicity because the prevalence of violence is much higher among African Americans (Reiss & Roth, 1993). However, we do not assert that race or ethnicity per se is a risk factor. Rather, we treat African American race/ethnicity as a *marker*

of environmental, socioeconomic, or psychosocial risk, for which we wish to control in investigating the substance use–violence relationship.

Analyses

Prevalence and frequency of substance use and violence over time were used to examine trends in the behaviors. For all analyses, frequent substance use was a dichotomous variable defined as being in the highest 25% of frequency. Concurrent associations between substance use and violence were tested with 2×2 contingency tables, and odds ratios are reported.

In examining longitudinal associations of frequent alcohol use and later violence, prior violence and frequent marijuana use were controlled for. Similarly, analysis of the relationship between frequent marijuana use and later violence controlled for prior violence as well as prior frequent alcohol use. Reverse associations were also tested (i.e., the relationship between violence in one year and frequent alcohol or marijuana use in the next, controlling for prior frequent alcohol and marijuana use). Logistic regression analyses were conducted and adjusted odds ratios are reported.

Longitudinal associations were examined first by cross-lagged (year-to-year) associations from ages 11 to 20. Then, several waves of data were aggregated into two time periods covering ages 11 to 14 and 15 to 20. Based on a cutoff point of the top 25% of alcohol use frequency, frequent users during the first time period drank a total of four or more times between ages 11 and 14, and frequent users during the second time period drank a total of 181 or more times between ages 15 and 20. Any use of marijuana between ages 11 and 14 classified participants as frequent users in the first time period, and for the second time period, the cutoff point was using a total of 300 or more times over ages 15 to 20. In terms of violence, participants who ever engaged in *any* violence were considered, and this applied to both time periods. To reduce false negative classification, participants who were not classified in the top 25% in terms of frequency *and* who missed three or more of the 10 assessments were excluded. Logistic regression analyses were repeated as described above.

Finally, to determine whether longitudinal associations between substance use and violence are spurious, common risk factors were added to the logistic regression models. First, univariate associations between the selected risk factors with frequent alcohol use, frequent marijuana use, and violence were tested, and tests for multicollinearity were conducted. Risk factors that were associated at the $p < .10$ level with both frequent alcohol use and violence, or with both frequent marijuana use and violence (or all three outcomes), and

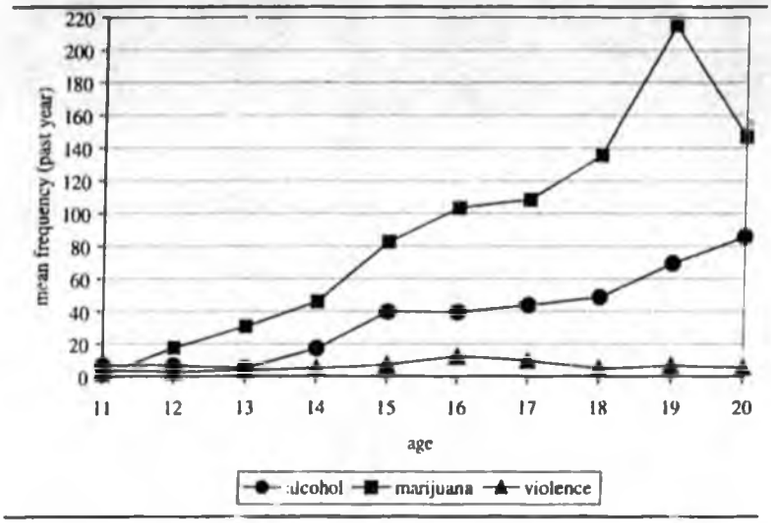

Figure 1 Mean Frequencies of Substance Use and Violence by Age Among Active Users/Offenders

were not highly collinear were selected as covariates. Predictors were entered simultaneously into logistic regression models.

RESULTS

In the youngest sample of the PYS, the lifetime prevalence of alcohol use by age 20 was 84%. The percentage of participants who had ever used marijuana by age 20 was 61.8%. Slightly more than a third (35.4%) had ever engaged in violence by age 20.

Figure 1 shows the mean frequency of alcohol consumption, marijuana use, and violence among active users/offenders by age. Among those who used alcohol, the frequency of consumption increased sharply between ages 13 and 15 and again after age 18. From age 12 on, marijuana use was more frequent among marijuana smokers than the frequency of alcohol use among drinkers, and the difference increased with age through age 19. Starting at age 15, marijuana users reported an average frequency reflecting use as often as once per week or more (i.e., frequencies > 52 times in past year), peaking at age 19. The frequency of violent behavior followed a typical age-crime curve, peaking at around age 16 (at about one time per month) and then declining (Farrington, 1986). Frequencies of substance use were substantially higher than frequencies of violence at all age levels.

TABLE 1
Associations Between Use and Frequent Use of Alcohol and Marijuana and Violence (ages 11-20)

	N	%
Ever used alcohol:	417	84.8
Also engaged in violence	162	38.8
Ever used alcohol frequently:	329	37.1
Also engaged in violence	154	46.8
Ever used marijuana:	417	61.8
Also engaged in violence	162	48.7
Ever used marijuana frequently:	329	51.4
Also engaged in violence	154	54.0
Ever engaged in violence:	174	35.4
Also ever used alcohol	162	93.1
Also ever used alcohol frequently	154	88.5
Also ever used marijuana	162	85.1
Also ever used marijuana frequently	154	78.2

Next, we examined the overall associations between the prevalence of substance use and violence. Table 1 shows the overall associations between *any* substance use and violence and between *frequent* substance use and violence. Of the 84.8% of participants who had ever used alcohol between ages 11 and 20, 38.8% had engaged in violence. Turning to frequent users, of the 67.1% of participants who had ever consumed alcohol frequently (had ever been in the top 25% frequency), 46.8% had engaged in violence.

Of the 61.8% of participants who had ever used marijuana, less than half (48.7%) had engaged in violence. Of the 51.4% of participants who had ever used marijuana frequently (had ever been in the top 25% frequency), slightly more than half (54.0%) had engaged in violence between ages 11 and 20. In contrast, of the 35.4% of participants who had ever engaged in violence, 93.1% had ever used alcohol, 88.5% had ever used alcohol frequently, 85.1% had ever smoked marijuana, and 78.2% had ever smoked marijuana frequently. Thus, throughout the adolescent period, the proportion of substance users who engaged in violence was lower than the proportion of violent individuals who used substances.

Table 2 shows the percentages and odds ratios of the concurrent associations of frequent alcohol and marijuana use with any violence for each age from 11 to 20. At every age, the percentage of violent individuals who used alcohol frequently was greater than the percentage of frequent drinkers who engaged in violence. This was also true for marijuana use starting at age 14; the percentage of violent individuals who used marijuana frequently exceeded the percentage of frequent marijuana smokers who engaged in violence. All associations were in the positive direction (i.e., all odds ratios were

TABLE 2
Concurrent Associations Between Frequent Alcohol and Marijuana Use and Violence by Age

		Frequent Alcohol Use & Violence				*Frequent Marijuana Use & Violence*			
Age	*Total* N	n	*% Violence With Alcohol*	*% Alcohol With Violence*	*Odds Ratio*	n	*% Violence With Marijuana*	*% Marijuana With Violence*	*Odds Ratio*
11	464	11	26.19	18.97	2.83**	0	.00	.00	—
12	475	22	45.83	29.33	5.97***	5	10.42	83.33	—
13	469	17	44.74	16.50	3.25***	10	26.32	34.48	7.74***
14	464	37	71.15	27.41	7.93***	26	50.00	39.39	9.30***
15	452	34	62.96	27.42	5.84***	31	57.41	31.00	6.43***
16	445	26	61.90	22.03	5.49***	26	61.90	22.61	5.73***
17	436	18	54.55	16.07	3.95***	21	63.64	19.27	6.26***
18	434	12	57.14	11.01	4.34**	16	76.19	14.68	11.01***
19	419	10	58.82	9.52	4.62**	11	64.71	10.48	6.01***
20	414	6	50.00	5.50	2.90	9	75.00	8.65	9.70***

NOTE: — = 1+ cell with $n < 5$.
** $p < .01$. *** $p < .001$.

greater than one). For example, at age 18, frequent marijuana users were 11 times more likely than nonfrequent users to also engage in violence (OR = 11.01), whereas frequent drinkers were 4 times as likely as nonfrequent drinkers to also engage in violence (OR = 4.34).

Table 3 summarizes the longitudinal associations between frequent alcohol and marijuana use and violence. Cross-lagged associations are presented first to address whether substance use in one year was associated with violence in the next year. For example, at age 11, frequent alcohol use was associated with violence at age 12, while controlling for violence and marijuana use at age 11 ($OR_{adj} = 2.68$). However, after age 11, there was no significant association between frequent alcohol use in one year and violence in the following year. Frequent use of marijuana was associated with violence in the following year (controlling for prior year violence and alcohol use) for five of the eight annual comparisons ($OR_{adj} = 2.67\text{-}3.83$).

We also addressed whether violence increased substance use in the following year. In terms of violence predicting frequent drinking in the following year, those who were violent at age 14 were more than twice as likely as those who were not violent to be frequent drinkers at age 15 ($OR_{adj} = 2.38$). However, violence during late adolescence, at age 19, was significantly associated with a *lower* likelihood of frequent drinking at age 20 ($OR_{adj} = .22$). Violence was significantly associated with frequent marijuana use in two of the nine comparisons ($OR_{adj} = 4.96$ from ages 13 to 14 and $OR_{adj} = 5.50$ from ages 17

TABLE 3
Longitudinal Associations Between Frequent Alcohol and Marijuana Use and Violence

	Adjusted Odds Ratios			
Prediction From Age to Age	*Alcohol → Violence*[a]	*Marijuana → Violence*[b]	*Violence → Alcohol*[c]	*Violence → Marijuana*[d]
11 → 12 (*N* = 461)	2.68*	n/a	1.36	2.23
12 → 13 (*N* = 465)	1.07	.00	1.69	2.22
13 → 14 (*N* = 456)	1.31	3.11*	1.83	4.96***
14 → 15 (*N* = 443)	1.79	3.07**	2.38*	1.71
15 → 16 (*N* = 432)	.79	3.36**	1.56	1.03
16 → 17 (*N* = 426)	.93	2.67*	1.67	1.31
17 → 18 (*N* = 413)	1.41	2.58	1.35	5.50***
18 → 19 (*N* = 407)	1.44	3.83*	.42	.65
19 → 20 (*N* = 394)	.61	1.31	.22*	.89
Ages 11-14 → 15-20 (*N* = 417)				
No risk factors	1.79	2.34*	1.36	1.90*
Risk factors included[e]	1.97*	1.91	1.70	1.67

a. Controlling for prior year violence and marijuana.
b. Controlling for prior year violence and alcohol.
c. Controlling for prior year alcohol and marijuana.
d. Controlling for prior year marijuana and alcohol.
e. Common risk factors = hard drug use, property crime (theft, fraud, and vandalism), low academic achievement, poor communication with caretaker, caretaker perception of bad neighborhood, and African American ethnicity.
* $p < .05$. ** $p < .01$. *** $p < .001$.

to 18). Thus, frequent marijuana use appears to predict violent behavior over time, especially during midadolescence, whereas frequent alcohol use only predicts later violence at the youngest age. In addition, violence does not appear to be a consistent predictor of frequent alcohol or marijuana use.

Next, data were aggregated into two time periods (ages 11-14 and 15-20) and the total frequency of each behavior was dichotomized to isolate the top 25%. The results are shown on the second to last line of Table 3. For these analyses, we only included boys for whom we also had complete data on risk factors so we could compare, for the same individuals, this model to the final model that includes the risk factors ($N = 417$). If we had not restricted the sample to participants for whom we had complete data on risk factors, the sample on the first model would have been 431. The results for this model ($N = 417$) were the same as for the sample of 431. Males who drank frequently were not significantly more likely to be violent later. However, those who used marijuana frequently between ages 11 and 14 were significantly more likely than nonusers and nonfrequent users to engage in violence later

($OR_{adj} = 2.34$, $p = .012$), and this was independent of prior violence or frequent use of alcohol. As frequent drinking did not increase the likelihood of violence, early violent behavior was not associated with later frequent drinking, when controlling for prior frequent alcohol or marijuana use. In terms of marijuana–violence relationships, a reciprocal association was found; early violence was significantly associated with later frequent use of marijuana, when controlling for prior frequent marijuana or alcohol use ($OR_{adj} = 1.90$, $p = .028$).

To determine whether the above relationships were spurious, common risk factors were added to the model. Following a univariate screening, the following risk factors were controlled for: lifetime hard drug use, frequency of self-reported property crime (theft, fraud, and vandalism), low academic achievement, poor communication with caretaker, caretaker perception of bad neighborhood, and African American race/ethnicity. The last line of Table 3 shows the results of the logistic regression analyses while controlling for common risk factors ($N = 417$). The prediction of alcohol to violence was not statistically significant until common risk factors were taken into account, indicating a suppressor effect ($OR_{adj} = 1.97$, $p = .033$; without the risk factors, it was $OR_{adj} = 1.79$, $p = .052$). Post-hoc analyses indicated that a disproportionate lower prevalence of frequent drinking and higher prevalence of violence among African Americans suppressed the effect of alcohol on violence. In converse, when common risk factors were considered, the prediction of marijuana use to violence was no longer statistically significant ($OR_{adj} = 1.91$, $p = .068$); this finding suggests that the association was spurious. Turning to the reverse associations, violence was still not associated with later frequent alcohol use. The prediction from early violence to later marijuana use was no longer statistically significant when common risk factors were included ($OR_{adj} = 1.67$, $p = .107$), again suggesting that the association was spurious. Common risk factors that predicted both violence and frequent marijuana use in the multivariate models were African American ethnicity ($OR_{adj} = 1.98$, $p = .043$ for violence; $OR_{adj} = 2.04$, $p = .029$ for marijuana) and lifetime hard drug use ($OR_{adj} = 2.28$, $p = .034$ for violence; $OR_{adj} = 5.25$, $p < .001$ for marijuana).

DISCUSSION

From ages 11 to 20, substance use was more prevalent and frequent than violence. Substance use continued to increase throughout late adolescence, whereas violence followed a typical age-crime curve, increasing to around age 16 and then decreasing. Frequent alcohol and marijuana use were both concurrently associated with violence. Overall, odds ratios showed that the longitudinal relationship with violence was stronger for marijuana use than

alcohol use, and the relationship between marijuana use and violence was bidirectional; earlier violence was also related to later marijuana use but not alcohol use. However, the association between marijuana use and later violence was spurious; it was mediated by common risk factors. Participants who were African American or hard drug users were more likely to engage in violence and also were more likely to become frequent marijuana users.

With regard to the associations between early frequent marijuana use and later violence, our conclusions are similar to those of White et al. (1999), in that what we are seeing is a selection effect. In other words, marijuana use is more atypical during early adolescence and becomes more normative with age, and the subset of males who begin marijuana use at younger ages are at elevated risk for several serious outcomes, including poly drug use, violence, and property offending. It is likely that this subgroup of males is inherently more deviant, engaging in multiple problem behaviors at earlier ages, choosing deviant peers, and being more likely to manifest their individual propensity for aggression and antisocial behavior later on. Our findings reinforce the benefits of primary prevention efforts that address multiple risk factors early on, as well as early intervention with high risk or aggressive males.

Because the proportion of violent individuals who used marijuana frequently was larger than the proportion of frequent marijuana users engaging in violence, and because the prediction of violence from earlier frequent marijuana use was mediated by common risk factors, our results do not indicate that early frequent marijuana use causes later violence. Rather, we conclude that frequent marijuana use and violence co-occur because they share common risk factors (e.g., race/ethnicity, hard drug use). It is important to keep in mind that marijuana has been used for centuries and is the most widely used illicit drug today and that the majority of marijuana users do not engage in violence (Boles & Miotto, 2003). Our findings indicate that intervention with young violent offenders to prevent or treat substance use problems may be more practical than targeting marijuana users for violence prevention.

Selection effects may also explain why we did not find a longitudinal association between frequent drinking and violence. Alcohol is a legal drug, and drinking is more commonly accepted by society than marijuana use, which is illicit. Thus, alcohol is seen as normative, whereas marijuana use and violence are not normative and are more likely to cluster in individuals with more deviant tendencies. Obviously, these findings apply to an inner-city adolescent sample and do not necessarily apply to frequent or heavy drinking and violence among adults.

Our findings differed somewhat from those for the older sample in terms of alcohol and violence relationships (White et al., 1999). In that study, White and colleagues found that the longitudinal associations between alcohol and

violence were slightly stronger than those between marijuana use and violence except in very early adolescence. The longitudinal associations between alcohol and violence remained significant when marijuana use as well as other risk factors were controlled. One reason that the findings from this study differed from the previous study may relate to cohort or period effects. The older sample experienced more violence and was in middle to late adolescence in 1993 during the peak of the violence epidemic in Pittsburgh, whereas the youngest sample was just entering adolescence (Fabio et al., 2003). The oldest sample came of age during the lowest rates of drug use in the early 1990s. In contrast to the oldest sample, the youngest sample is more involved in substance use and less involved in violence (White et al., 2001).

Differing results may also be due to the different age ranges used in the longitudinal analyses. The previous study examined behaviors at age 13 predicting behaviors at ages 14 to 18. This study examined behaviors at ages 11 to 14 predicting behaviors at ages 15 to 20. It is likely that developmental processes and temporal windows that fluctuate throughout adolescence shape the substance use–violence nexus. In the earlier study, race/ethnicity and hard drug use were not controlled for. In this study, both these factors were strongly related to violence and frequent marijuana use. Being African American was significantly related to engaging in violence as well as frequent marijuana use. We surmise that contextual effects may drive cultural differences in the associations between substance use and violence. We know that inner-city neighborhoods with a high minority concentration are plagued by violence. At the same time, a subculture of young African American males is using marijuana as their "drug of choice" instead of alcohol (Golub & Johnson, 2001). Thus, at the individual level, it may be hard drug rather than marijuana use that is the important predictor of violence.

Some limitations of the study should be considered. This study focused on a group of adolescents from one city. Therefore, the findings may not be generalizable to other areas of the country. Furthermore, we only included males in the study. Future research should also examine females. Our measure of violence can also be seen as a limitation. Because we focused on those who ever engaged in violence, those who may have committed violence only once are included with those who committed multiple acts of violence. It may be that associations between substance use and violence differ according to the degree or frequency of violent behavior, possibly in a dose-response fashion.

The strengths of this study stem from it being a community-based, longitudinal study with high follow-up rates and regular assessments with no gaps. Substance use and violence were measured prospectively, minimizing recall bias. The data are highly complete and collected at multiple waves, and infor-

mation about risk factors was gathered from multiple informants. Recent analyses of this dataset do not indicate selective attrition: Follow-up rates did not significantly differ according to initial high-risk status, race/ethnicity, socioeconomic status (SES), or baseline levels of alcohol, marijuana, or hard drug use. Further, substance use was based on frequency counts (rather than use/no use) and focused on the most frequent users.

The developmental relationships between substance use and violence are quite complex and are moderated by a host of individual (biological and psychosocial) and environmental factors. The nature of the substance use–violence relationship changes over the life course, and it is likely that the range and influence of risk factors also vary over time. It is also important to consider differences between bingeing, or acute episodic substance use, as opposed to patterns of chronic use. The developmental relationships between substance use and violence are further complicated by the fact that the prevalence and influence of risk factors also vary throughout development. In this study and the previous study, risk factors were measured at one point in time. It is possible that studies using time-varying covariates (e.g., changing levels of parental supervision or neighborhood quality) or more proximal risk factors (e.g., weapon carrying) would offer different findings as well.

Future research should explore the notion of alcohol consumption being more normative among Caucasian participants, in comparison to marijuana use being more normative among African American participants. Differential expectancies of the effects of alcohol or marijuana on violent behavior should also be considered. It is likely that different subcultures may adopt varying expectancies of the effects of substance use intoxication on aggressive behavior. Research on criminal careers can benefit from research about the persistence of violence, in terms of how substance use patterns are associated with chronic offending, desistance, and recidivism. Separate analysis by race/ethnicity can aid the development of culturally specific prevention and intervention programs for multiproblem youth. Finally, research should continue to identify factors that mediate or moderate the associations between substance use and violence.

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"Effects of Varying Marijuana Potency on Deposition of Tar and Delta-9 TCH in the Lung During Smoking"

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Effects of Varying Marijuana Potency on Deposition of Tar and Δ^9-THC in the Lung During Smoking

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MATTHIAS, P., D. P. TASHKIN, J. A. MARQUES-MAGALLANES, J. N. WILKINS AND M. S. SIMMONS. *Effects of varying marijuana potency on deposition of tar and Δ^9-THC in the lung during smoking.* PHARMACOL BIOCHEM BEHAV **58**(4) 1145–1150, 1997.—To determine whether smoking more, compared to less, potent marijuana (MJ) cigarettes to a desired level of intoxication ("high") reduces pulmonary exposure to noxious smoke components, in 10 habitual smokers of MJ, we measured respiratory delivery and deposition of tar and Δ^9-tetrahydrocannabinol (THC), carboxyhemoglobin (COHb) boost, smoking topography, including cumulative puff volume (CPV) and breathholding time, change in heart rate (ΔHR) and "high" during ad lib smoking of 0, 1.77, and 3.95% MJ cigarettes on 3 separate days. At each session, subjects had access to only a single MJ cigarette. On average, smoking topography and COHb boost did not differ across the different strengths of MJ, while THC delivery, as well as HR, were significantly greater ($p < 0.01$) and tar deposition significantly less ($p < 0.03$) for 3.95% than 1.77% MJ. Although individual adaptations in smoking topography for 3.95% compared to 1.77% MJ were highly variable, three subjects with the lowest 3.95% MJ:1.77% MJ ratios for CPV also displayed the lowest 3.95% MJ:1.77% MJ ratios for tar deposition. In vitro studies using a standardized smoking technique revealed a mean 25% lower tar yield from 3.95% than 1.77% MJ ($p < 0.05$), but no difference between 1.77% and 0% marijuana. Under the conditions of this study, we conclude that tar delivery is reduced relative to THC content in a minority of subjects, and this reduction appears to be due to a reduced intake of smoke (decreased CPV) and/or a reduced tar yield from the stronger MJ preparation. © 1997 Elsevier Science Inc.

Marijuana Δ^9-tetrahydrocannabinol (THC) Smoking topography Tar yield Tar deposition Lung Carboxyhemoglobin boost "High"

WE have previously shown that compared to tobacco smoking, marijuana smoking results in an approximately fourfold greater deposition of tar in the lung and a four- to fivefold larger boost of carboxyhemoglobin (COHb) in the blood when equivalent quantities of the two substances are smoked (12,16). These differential effects appeared to be mainly due to less filtration of marijuana than tobacco cigarettes, resulting in a relatively greater tar yield from marijuana (13), and the longer breathholding time following inhalation of the smoke of marijuana than that of tobacco, resulting in a greater fractional retention in the lung of the inhaled tar and a greater absorption of carbon monoxide (13,16). These findings suggest that, at least for equivalent weights of plant material smoked, marijuana joints might have a greater potential than tobacco cigarettes for adverse health effects related to the carcinogenicity and respiratory irritant effects of components in tar (6) and the reduced myocardial oxygen delivery (1) and reduced maternal and fetal tissue oxygenation caused (8) by an elevated COHb.

It has been hypothesized that the health hazards from toxic components in marijuana smoke could be reduced if habitual marijuana users smoked higher potency marijuana (4). This hypothesis assumes the following: 1) that smokers are able to "titrate" the amount of THC absorbed during marijuana smok-

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ing in a manner that will result in decreasing their cumulative puff volume of inhaled smoke when smoking a more potent compared to a less potent preparation, to achieve a given desired level of intoxication; and 2) that the yield of tar relative to Δ^9-tetrahydrocannabinol (THC) from marijuana preparations of different potency always decreases as the THC concentration of the preparation increases. To test this hypothesis and these assumptions, we evaluated the effects of varying THC concentrations in marijuana cigarettes (0, 1.77, and 3.95%) on the deposition of tar in the lung, carboxyhemoglobin boost, and subjective and physiological measures reflecting the bioavailability of THC in ten habitual smokers of marijuana.

METHODS

Subjects

We studied 10 male habitual marijuana smokers [mean age (± SD), 23.2 ± 2.3 years], who smoked an average of 12.7 ± 11.5 joints/week and reported a cumulative lifetime smoking history of 27.2 ± 46.5 joint-years (number of marijuana joints per day times the number of years of marijuana smoking). All were in good general health and had normal values for routine pulmonary function tests. None reported intravenous drug abuse or smoking illicit substances other than marijuana. Three were current tobacco cigarette smokers (14.0 ± 13.9 cigarettes/day) and four were ever-smokers of tobacco with a cumulative lifetime smoking history of 3.6 ± 1.1 pack-years (number of packs of cigarettes per day times the number of years of tobacco smoking). The study was approved by the UCLA Human Subject Protection Committee and the California Research Advisory Panel. All subjects signed an approved informed consent form prior to their participation in the study.

Study Protocol and Procedures

Each subject was studied on 3 separate days approximately 1 week apart after refraining from smoking tobacco for ≥1 h and marijuana for ≥6 h. During each study session, subjects smoked a marijuana cigarette (85 mm length × 25 mm circumference) containing either 0.000 ± 0.002% THC (mean weight 833 mg; range 808–864 mg), 1.77 ± 0.01% THC (mean weight 832 mg; range 789–924 mg) or 3.95% THC (mean weight 734 mg, range 687–774 mg), according to a crossover design. The order of assignment of the three different strengths of marijuana to each subject was randomized and subjects were masked to the assignment. All marijuana cigarettes were prepared from Mississippi-grown Mexican marijuana and were supplied by the National Institute on Drug Abuse; the 0% THC preparation was prepared by ethanol extraction. Marijuana cigarettes were stored at 4°C to minimize chemical degradation and were maintained in a humidifier at 60% humidity and 21°C for 24 h before the study to reduce harshness.

Subjects were asked to smoke each marijuana cigarette ad lib but were specifically instructed to stop smoking once they had achieved their desired level of intoxication ("high"). Peripheral venous blood was withdrawn anaerobically immediately before and 2 min after each cigarette was smoked for measurement of the percentage of COHb saturation using a CO-oximeter (Model 282, Instrument Laboratory, Lexington, MA). Immediately prior to smoking at 2, 5, 15, 30, and 45 min after smoking, heart rate was measured electrocardiographically and subjects were asked to rate their level of intoxication on a scale of 0 to 10, with 10 representing the greatest "high" they had ever achieved.

Smoking topographic measures were determined, as previously described (16). Briefly, the volume and number of puffs and the interpuff interval were measured using a 00 Fleisch pneumotachygraph (resistance 0.0068 cm H_2O; linear from 5 to 100 ml/s) connected through a differential pressure transducer (Model 282 MP54-3, Validyne, Northridge, CA) (range ± 2 cm H_2O) to a 12-channel oscilloscopic recorder with a differential integrator-computer and a rapid infrared writer attachment (Honeywell Simultrace Recorder, Model VR-12, White Plains, NY). The pneumotachygraph was connected through 1-cm diameter Tygon tubing (length 70 cm) to the distal end of a glass cylinder (diameter 5 cm; length 12 cm) that contained two 1-cm diameter ventilation ports and was sealed at its proximal end by a rubber stopper. The marijuana cigarette was held in a small plastic holder inserted through the rubber stopper. During a puff, the ventilation ports were occluded by rubber stoppers so that the entire volume of air drawn through the cigarette could be measured by the pneumotachygraph. Between puffs, the ventilation ports were uncovered to prevent extinction of the cigarette or accumulation of carbon monoxide. The volume of smoke and air inhaled into the lungs ("inhaled volume") in association with each puff was measured using inductive plethysmography (Respitrace-Plus, NonInvasive Monitoring Systems, Miami Beach, FL). During calibration maneuvers, inhaled volumes calculated from inductive plethysmography agreed with measurements obtained by spirometry within ±10%. The amount of time the inhaled smoke was retained in the lungs ("breathholding time") was calculated as the interval between the times corresponding to one-third of the maximum inhaled volume and two-thirds of the maximum volume exhaled following breathholding.

The amount of inhaled insoluble smoke particulates (tar) was measured by a previously described proportional smoke-trapping device (10) that was connected to the plastic cigarette holder at the proximal end of the puff-volume measuring apparatus (1). From the plastic cigarette holder, mainstream smoke was diverted into two parallel pathways, one containing one capillary tube and a Cambridge filter pad ("high-resistance" pathway) and the other containing seven parallel capillary tubes ("low-resistance" pathway). The filter pad trapped the smoke that passed through the high-resistance pathway. The tar (including THC) trapped by the filter was extracted with methanol. The tar content (total insoluble particulate matter) was analyzed by means of a spectrophotometer (wavelength 400 nm). THC concentrations were determined by injecting dilutions of the methanol wash into a Waters high performance liquid-chromatograph outfitted with a diode array detector according to modifications of ElSohly et al. (2). Ion pair technology was employed using a Beckman ultrasphere C18 column, a water:acetonitrile mobile phase of 15:85, and isocratic flow of 2 ml/min. Ultraviolet detection was performed at 220 nm with standards obtained from Alltech, Inc. (San Jose, CA). Because a constant fraction of the tar (approximately 12.5%) was retained in the filter over a wide range of puff volumes and flow rates, the actual quantity of inhaled tar, as well as inhaled THC, could be calculated by multiplying the amount of particulates and THC trapped in the Cambridge filter pad in the high-resistance pathway by the term ([1 ÷ 0.125] − 1), or 7 (10). At the end of the period of breathholding after each puff, subjects exhaled the smoke into a megaphone device, the distal end of which (4.5-cm diameter) was fitted with another Cambridge filter pad attached to a vacuum system (5,16) to trap the exhaled particulates. Following methanol extraction, the latter were also quantitated by spectrophotometry and the ex-

haled THC by HPLC (3) as detailed earlier. The amount of tar or THC retained (deposited) in the lung was calculated by subtracting the amount of exhaled from the amount of inhaled tar or THC.

The amount of tar delivered to the lung from different strengths of marijuana cigarettes is dependent not only on smoking technique but also on the actual tar yield of the cigarettes, which could vary with the potency of the preparation. We, therefore, measured the amount of tar in mainstream smoke generated from five 0%, five 1.77%, and five 3.95% marijuana cigarettes under standardized smoking conditions using a syringe with a 50-ml puff volume, 2-second duration and 30-s interpuff interval to uniform butt lengths of 25 mm. All the tar in the mainstream smoke was captured in a Cambridge filter interposed between the syringe and the cigarette and measured spectrophotometrically after methanol elution, as described above.

DATA ANALYSIS

For each subject, topographic measurements (puff volume, interpuff interval, inhaled volume, breathholding time) were averaged for each cigarette smoked. These mean values, as well as the number of puffs, cumulative puff volume (the product of the mean puff volume and the number of puffs for each cigarette), butt length, and the amounts of inhaled and retained tar and THC were averaged for all 10 subjects for each potency of marijuana smoked. COHb "boost," peak changes in heart rate from baseline and peak subjective ratings of degree of intoxication after smoking each strength of marijuana were also averaged for all subjects. In addition, for each subject, each measurement variable was expressed as a ratio of that variable determined in relation to smoking 3.95% marijuana to that determined for 1.77% marijuana; these ratios served as indicators of the relative pattern for each subject of smoking active marijuana of two different strengths. The Hotelling's T^2 test, a multivariate test for within-subject differences in repeated measures models, was used to determine the significance of differences in smoking patterns, delivery, and deposition of particulates and THC, and the "boost" in COHb and change in heart rate among the different strengths of marijuana cigarettes (9). Multiple comparisons were then performed using paired t-tests, where appropriate. Because the subject's levels of "high" were based on an ordinal scale, these data were analyzed for differences between the THC concentrations using Friedman's nonparametric two-way analysis of variance (7). Differences for all tests were considered significant for p values <0.05. Statistical analyses were performed using SAS (11) and BMDP (2) software.

RESULTS

Smoking topography, pulmonary deposition of tar and THC, COHb boost, and psychophysiologic responses to smoking all showed similarly wide variability across subjects for each strength of marijuana. The extent of this variability is illustrated for cumulative puff volume, breathholding time, tar deposition, and THC retention in Fig. 1, which shows the individual values for these variables for each type of marijuana preparation smoked.

Mean values (±SE) for cumulative puff volume (CPV), inhaled volume (Vol_I), breathholding time, butt length, amount of tar and THC retained in the lung, COHb boost, peak change in heart rate, and peak level of intoxication for each potency of marijuana smoked are shown in Table 1. As expected, both "active" marijuana preparations (1.77% and 3.95% THC) delivered significantly more THC, $F(2, 8) = 51.7$, $p < 0.001$; Hotelling's T^2, to the lung and resulted in a significantly greater change (increase) in heart rate, $F(2, 8) = 24.0$, $p < 0.001$; Hotelling's T^2, than the "inactive" (0% THC) preparation, although neither active preparation elicited a significantly greater "high" than "inactive" marijuana ($p = 0.12$; Freedman nonparametric two-way ANOVA). No differences in any of the measured smoking topographic variables [cumulative puff volume; average puff volume, number of puffs, or interpuff interval (data not shown); inhaled volume; breathholding time; butt length], nor in COHb boost, were noted across the different potencies of marijuana. On the other hand, despite the lack of any mean difference in smoking pattern for the different strengths of marijuana, the average amount of tar delivered to and retained in the lung from the most potent preparation (3.95% THC) was significantly lower than that from both the 0% THC and 1.77% THC preparations ($p < 0.03$). Moreover, the THC delivered to and retained in the lung from 3.95% marijuana was significantly greater than that deposited in the lung from 1.77% marijuana ($p < 0.001$); this difference is reflected in the significantly greater heart rate increase ($p < 0.01$) following the more potent "active" preparation.

The mean percent of inhaled (delivered) tar that was not exhaled and was thus deposited in the respiratory tract was comparable across the different strengths of marijuana (80.7 ± 2.1%, 86.9 ± 3.2%, and 83.6 ± 2.4% for the 0, 1.77, and 3.95% preparations, respectively). Likewise, the average percent of inhaled (delivered) THC that was retained in the lung was similar for the 0, 1.77, and 3.95% potencies (74.1 ± 5.0%, 83.6 ± 3.8%, and 76.5 ± 4.5%, respectively). Consequently, the differences between the amounts of tar (or THC) delivered to the lung between any two strengths of marijuana were similar to the differences between the amounts of tar (or THC) de-

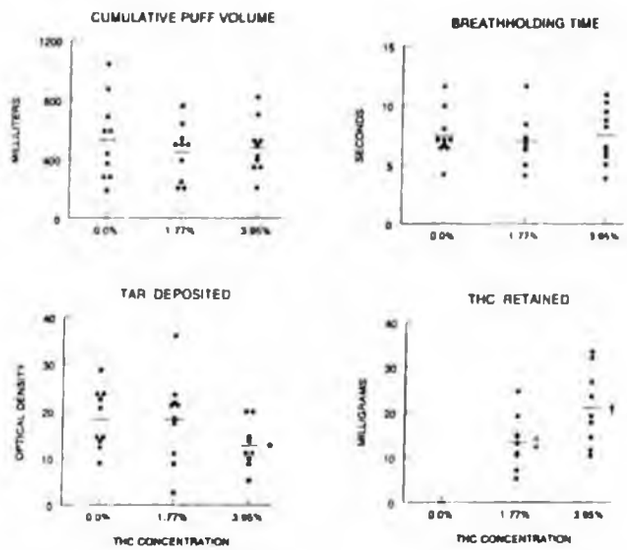

FIG. 1 Individual values for cumulative puff volume (ml) and breathholding time (s) and for amount of tar [optical density (O.D.) units] and amount of THC (mg) deposited in the respiratory tract for 0.0, 1.77, and 3.95% marijuana. Horizontal lines represent mean values. *$p < 0.03$ (compared with 1.77% and 0% THC); †$p < 0.01$ (compared with 1.77% and 0% THC); ‡$p < 0.001$ (compared with 0% THC).

TABLE 1

MEAN VALUES (±SE) FOR SMOKING TOPOGRAPHY, TAR, AND THC DEPOSITION IN THE LUNG, BLOOD CARBOXYHEMOGLOBIN BOOST, AND PSYCHOPHYSIOLOGIC RESPONSES TO THC DETERMINED DURING AND AFTER SMOKING MARIJUANA CIGARETTES OF DIFFERENT THC CONCENTRATION

	TAR O.D.	THC mg	BHT sec	CPV ml	Vol_t liters	Butt length mm	COHb %	High (0–10)	ΔHR min^{-1}
0% THC	18.9	0.1	7.5	534	2.52	16.7	2.6	3.0	6.2
	(2.1)	(0.0)	(0.6)	(87)	(0.28)	(4.3)	(0.5)	(0.7)	(1.6)
1.77% THC	19.9	13.4*	7.0	447	2.17	19.3	2.0	4.3	30.2*
	(2.6)	(2.0)	(0.6)	(5.9)	(0.33)	(4.7)	(0.4)	(0.7)	(3.8)
3.95% THC	13.6†‖	21.0*‡	7.5	479	2.11	19.0	2.0	6.0	39.0*‡
	(1.5)	(2.8)	(0.7)	(57)	(0.20)	(7.2§	(0.3)	(0.6)	(4.3)

Definition of abbreviations: Tar = respiratory tar deposition; O.D. = optical density units; THC = respiratory retention of Δ^9-tetrahydrocannabinol; BHT = breathholding time; CPV = cumulative puff volume; Vol_t = inhaled volume of smoke and air; COHb = carboxyhemoglobin saturation; ΔHR = change in heart rate from pre-smoking baseline.

*Significantly different from 0% THC; $p < 0.001$.

†Significantly different from 0% THC; $p < 0.02$.

‡Significantly different from 1.77% THC; $p < 0.01$.

§Significantly different from 1.77% THC; $p < 0.03$.

posited (retained) in the lung between the same two potencies of marijuana.

The ratio of values for the variables shown in Table 1 for 3.95% marijuana to those for 1.77% marijuana were calculated for each subject and averaged across all subjects. The distributions of the individual values for most of these ratios across the 10 subjects are illustrated in Fig. 2. Deviations of these ratios from 1.0 would imply a difference between the more and less potent "active" marijuana preparation with respect to smoking technique, delivery of smoke contents to the lung or the physiological effects of such delivery. The broad range of these ratios, which straddled 1.0 for all variables except the amount of THC delivered to and retained in the lung, reflects the large degree of variability across subjects in differential smoking technique and in subjective and physiological responses to THC between the two strengths of marijuana (Fig. 2). On average, ratios of values for smoking pattern, including cumulative puff volume, breathholding time, and inhaled volume, were close to 1.0. On the other hand, ratios for THC deposition, change in heart rate and "high" were always or mostly above 1.0, while ratios for tar deposition were mostly less than 1.0.

The individual tar yields determined using a standardized, syringe-simulated smoking technique for each of the five cigarettes of each strength that were tested are shown in Fig. 3.

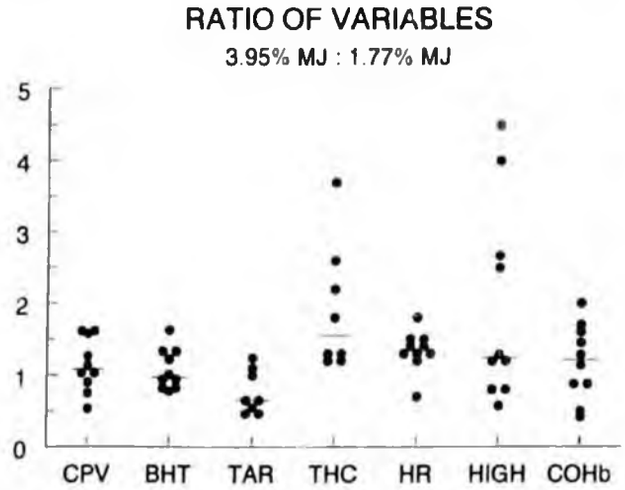

FIG. 2. Individual ratios of values for cumulative puff volume (CPV), breathholding time (BHT), respiratory tar deposition (TAR), respiratory retention of THC (THC), heart rate increase over presmoking baseline (HR), level of intoxication (HIGH) and carboxyhemoglobin boost (COHb) determined for 3.95% marijuana to those determined for 1.77% marijuana (3.95% MJ:1.77% MJ).

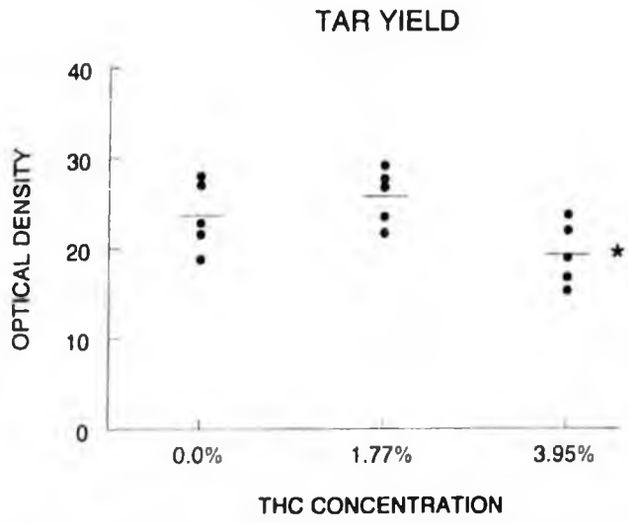

FIG. 3. Individual values for amount of tar (O.D.) in mainstream smoke generated from five 0.0%, five 1.77% and five 3.95% marijuana cigarettes using a syringe with a 50-ml puff volume, 2-s duration and 30-s interpuff interval to butt lengths of 25 mm. Horizontal lines represent mean values. *$p < 0.05$ (compared with 1.77% and 0% THC).

The average tar yield from the 3.95% marijuana cigarette was 19.3 ± 1.6 (SEM) optical density (O.D.) units, which was significantly lower ($p < 0.05$) than the tar yields from both the 1.77% preparation (25.2 ± 1.4 O.D.) and the 0% preparation (23.5 ± 1.6 O.D.).

DISCUSSION

The major findings from this study are that, in a small number of healthy, habitual marijuana smokers asked to smoke different strengths of marijuana to a desired level of intoxication, the amount of tar delivered to and deposited in the lung from the most potent marijuana preparation tested was significantly reduced compared to that of less potent preparations, despite the lack of demonstrable overall differences in smoking topography, including cumulative puff volume, across the different strengths of marijuana (Table 1). In contrast, no difference in COHb boost was observed between more and less potent marijuana cigarettes, while THC delivery and lung retention were significantly greater for 3.95% than 1.77% marijuana, as reflected in a significantly greater heart rate increase ($p < 0.01$) following the 3.95% than the 1.77% preparation (Table 1).

Differences in THC delivery and the related physiological responses to smoking marijuana of different strengths were found despite instructions to the subjects to smoke only to their desired level of intoxication. Possible reasons for the observed differences in THC delivery are 1) that subjects were generally unable to "titrate" THC delivery to achieve a uniform "high" from the 1.77 and 3.95% marijuana cigarettes; or 2) that their desired level of intoxication was greater than that which could be achieved with the weaker of the two active marijuana preparations under the conditions of the experiment, in which they were constrained to smoking only a single marijuana cigarette. In favor of the former possibility is that maximum levels of intoxication were not attained in the majority of subjects (7 of 10) until at least 5 min, and in some subjects (4 of 10) as long as 15 min, after completion of smoking, thus compromising their ability to self-titrate intake of smoke (and thus THC) based on levels of "high" perceived during active smoking. On the other hand, it is still possible that adjustments could be made during smoking with the expectation of delayed peak "highs" based on previous experience. The alternative possibility, namely that the single 1.77% preparation was insufficient, even if consumed to the maximum extent tolerable, to produce the desired level of intoxication, appears inconsistent with the finding that mean butt lengths of the smoked 1.77% and 3.95% marijuana cigarettes were nearly identical (19.3 mm and 19.0 mm, respectively). On the other hand, in 3 of the 10 subjects, butt lengths of the 1.77% marijuana cigarette were substantially shorter than those of the 3.95% preparation and, in 2 additional subjects, both preparations were nearly completely consumed (butt lengths 2–4 mm). Therefore, the possibility remains that in this subset of subjects the weaker of the two active preparations was insufficient to yield the desired level of intoxication, even when smoked to a relatively short butt length, in the absence of access to more than one marijuana cigarette.

The observation that the amount of tar deposited in the lung tended to be reduced for 3.95% marijuana compared to 1.77% marijuana (Table 1 and Fig. 1) is difficult to explain solely on the basis of differences in smoking topography, because smoking topography, including the variables that have been found to correlate best with the amount of tar delivered to and retained in the lung (cumulative puff volume and breathholding time) (13) were, on average, nearly identical for both the higher and lower strengths of active marijuana. Smoking marijuana down to a longer butt length would be expected to decrease tar delivery partly due to the increased filtration through the longer shaft of the cigarette (14); because average butt lengths were similar for the two active strengths of marijuana that were studied, however, this factor could not have accounted for the generally lower tar delivery from the more potent cigarette. On the other hand, considerable interindividual variability was observed in the 3.75:1.77% marijuana ratios both for tar delivery and deposition and for cumulative puff volume and breathholding time (Fig. 2). For the most part, those subjects who exhibited lower cumulative puff volumes when they smoked 3.95% marijuana than 1.77% marijuana also deposited lower amounts of tar in their lungs when they smoked the more potent preparation. A similar relationship between breathholding time and respiratory tar delivery for the two active strengths of marijuana was not observed. These observations suggest that, at least in some subjects, the reduced tar delivery to the lung from the higher potency marijuana preparation might be accounted for, at least in part, by adjustments in smoking technique that result in a lower cumulative puff volume.

Reduced tar delivery from more potent marijuana cigarettes could also occur if the actual tar yield from stronger preparations were reduced relative to that from the same quantity of weaker preparations, when smoking technique was standardized. To evaluate this possibility, we measured the amount of tar in mainstream smoke generated from the different strengths of marijuana cigarettes using a standardized in vitro smoking technique. As shown in Fig. 3, the average tar yield from the 3.95% marijuana cigarette was significantly lower ($p < 0.05$) than the tar yields from both the 1.77% and the 0% preparations. Consequently, a reduced tar yield from stronger preparations of marijuana might contribute, at least partly, to less delivery of tar to the lung. On the other hand, no difference was noted between the tar yields of the 0 and 1.77% preparations, so that a linear relationship between the potency of a marijuana cigarette and its tar yield was not apparent over the entire range of potencies (0.00–3.95% THC) of the preparations that we tested. Data from a recent preliminary Australian study on the relative yields of condensed particulate matter (tar) and THC from different samples of seized marijuana ranging in potency from 0.57 to 13.0 % (mean 3.42%; median 1.8%) (Hall, W., National Drug and Alcohol Research Centre, Kensington, Australia; Personal Communication) show a weak relationship between THC content and tar yield for preparations with THC concentrations ≤2.5% and inconsistently lower tar yields for the few preparations tested with THC concentrations >5%. Consequently, had we been able to evaluate the influence of smoking marijuana cigarettes with THC concentrations >5%, we might have found greater reductions in respiratory tar delivery than we demonstrated in the present study for 3.95% compared to 1.77% marijuana.

Mainstream smoke from marijuana or tobacco is a highly concentrated aerosol of liquid particles that is formed by complex chemical reactions, including hydrogenation, pyrolysis, oxidation, decarboxylation, dehydration, chemical condensation, distillation, and sublimation (15). The smoke aerosol is composed of a large variety of organic and inorganic chemicals dispersed in a gaseous medium of nitrogen, oxygen, hydrogen, carbon dioxide, carbon monoxide, and a number of volatile and semivolatile organic chemicals. The tar phase consists of total particulate matter minus water and contains a

number of constituents, including tumor initiators, carcinogens, and cocarcinogens that contribute to the health hazards of smoking. Several factors influence the tar yields of tobacco cigarettes (15) that might also be relevant to marijuana. These include plant genetics and growth conditions that affect chemical composition and physical properties of the leaf, moisture content, the curing and fermentation process, burning temperature, the quality of the cigarette paper (e.g., porosity), and the presence or absence of a filter. Which of these factors may be responsible for the apparently lower tar yield from more potent preparations of marijuana is unclear.

The mean percentage of inhaled tar deposited in the lung in the present study from marijuana cigarettes of different potency (80.7–86.9%) is similar to that previously reported from our laboratory from 0.00 and 1.24% marijuana cigarettes (84.4–86.1%) and higher than that deposited from tobacco cigarettes (64.0%) (16). The greater percentage deposition of inhaled tar from marijuana than tobacco cigarettes is attributable to the longer breathholding time characteristic of marijuana smoking compared to tobacco smoking (13,16). The similarity in mean breathholding times observed in the present study during the smoking of marijuana cigarettes of different strengths (Table 1) is consistent with the comparability in mean percentage of delivered tar that was deposited in the lung across the different potencies of marijuana.

In summary, in a small number of habitual marijuana users studied during the smoking of single marijuana cigarettes of varying potency up to a maximum THC concentration of 3.95%, adjustments of smoking topography to the different strengths of marijuana were highly variable between subjects. Under the conditions of the experiment (limited maximum potency of marijuana and a limit of a single cigarette), smokers generally appeared unable to titrate THC delivery to achieve a uniform "high," so that the level of intoxication and heart rate were often more increased after smoking cigarettes of higher than lower potency. Tar delivery from 3.95% marijuana was reduced relative to that from 1.77% marijuana in 3 of 10 subjects, and the reduction in tar delivery appeared to be related to reduced intake of smoke (lower cumulative puff volume) in these few subjects, as well as to the reduced tar yield during combustion of the stronger marijuana preparation. COHb boost was not affected by the potency of the marijuana smoked. We conclude that, compared to lower potency marijuana cigarettes, stronger preparations appear to lead to a modest reduction in exposure of the lung to tar in some smokers but not to carbon monoxide. We did not assess the influence of varying THC content on the respiratory delivery of volatile constituents other than carbon monoxide in the gas phase of marijuana smoke, some of which are known to be biologically hazardous. Although it is possible that relatively reduced exposure to carcinogenic components in the tar phase of marijuana from smoking cigarettes with a higher THC content might reduce the carcinogenic risk of marijuana smoking, the true health implications of these findings are as yet unclear.

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"The Limited Relevance of Drug Policy: Cannabis in Amsterdam and San Francisco"

Craig Reinarman, Peter Cohen, and Hendrien Kaal
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The Limited Relevance of Drug Policy: Cannabis in Amsterdam and in San Francisco

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Objectives. We tested the premise that punishment for cannabis use deters use and thereby benefits public health.

Methods. We compared representative samples of experienced cannabis users in similar cities with opposing cannabis policies—Amsterdam, the Netherlands (decriminalization), and San Francisco, Calif (criminalization). We compared age at onset, regular and maximum use, frequency and quantity of use over time, intensity and duration of intoxication, career use patterns, and other drug use.

Results. With the exception of higher drug use in San Francisco, we found strong similarities across both cities. We found no evidence to support claims that criminalization reduces use or that decriminalization increases use.

Conclusions. Drug policies may have less impact on cannabis use than is currently thought. (*Am J Public Health.* 2004;94:836–842)

There is a trend among Western democracies toward liberalization of cannabis laws. (Cannabis includes both marijuana and hashish.) In 1976, the Netherlands adopted de facto decriminalization. Under Dutch law, possession remains a crime, but the national policy of the Ministry of Justice is to not enforce that law. After 1980, a system of "coffee shops" evolved in which the purchase of small quantities of cannabis by adults was informally tolerated and was then formally permitted in shops that were licensed.[1–3] During the 1990s, Switzerland, Germany, Spain, Belgium, and Italy shifted their drug policies in the Dutch direction. Portugal decriminalized cannabis in 2001, and England similarly reclassified cannabis in 2004. Canada and New Zealand are currently considering cannabis decriminalization. These shifts constitute the first steps away from the dominant drug policy paradigm advocated by the United States, which is punishment-based prohibition.[4–6]

Moving in the opposite direction, the United States has stiffened criminal penalties for drug offenses and has increased arrests for cannabis offenses. Since 1996, voters in 8 states and the District of Columbia have passed medical-marijuana initiatives, but the federal government has resisted implementation. In 2001, 723 627 people were arrested for marijuana offenses.[7] In 2002, the Drug Enforcement Administration began raiding medical-marijuana organizations,[8] and the White House Office of National Drug Control Policy launched a campaign against marijuana.[9,10]

Such policies are designed to deter use. The core empirical claim made by criminalization proponents is that, absent the threat of punishment, the prevalence, frequency, and quantity of cannabis use will increase and will threaten public health.[11–16] The question of whether deterring use enhances public health was beyond the scope of our study, but we did examine the proposition that drug policies affect user behavior and deter use. It is possible that the causal arrow points the other way—that user behavior affects laws and policies, which has been the case with alcohol policies in some countries.[17] However, the Marijuana Tax Act of 1937, which first criminalized cannabis, predated widespread cannabis use in the United States and had clear political origins.[18–21] In the Netherlands, de facto decriminalization of cannabis was first forged in the late 1960s, when use was spreading among the youth counterculture. But Dutch policymakers decided that cannabis use was unlikely to lead to deeper deviance and that criminalization could lead to greater harm to users than the drug itself.[3] In neither country, then, was user behavior the effective cause of laws or policies.

The presumed effects of cannabis policies have been explored by those who are critical of criminalization in the United States[22] and by those who are skeptical of Dutch decriminalization.[23] However, until now there have been no rigorously comparative studies of user behavior designed to assess whether criminalization constrains use or whether decriminalization increases it. Our study compared the career use patterns of representative samples of experienced cannabis users in 2 cities with many similarities but with different drug-control regimes—Amsterdam, the Netherlands (decriminalization), and San Francisco, Calif (criminalization).

San Francisco was selected as the US comparison city not because it is representative of the United States but because it is the US city most comparable to Amsterdam. Both cities are large, highly urbanized port cities with diverse populations of slightly more than 700 000. They are financial and entertainment hubs for larger regional conurbations, and they have long been perceived within their home countries as cosmopolitan, politically liberal, and culturally tolerant.

Law enforcement officials in San Francisco are not as zealous about enforcing marijuana laws as law enforcement officials are in most other US cities. Nonetheless, San Francisco is embedded in the drug policy context of criminalization, which is a markedly different drug policy context than that of Amsterdam. Buying and selling cannabis are permitted in Amsterdam in 288 licensed "coffee shops,"[24] and public use is permitted, whereas in San Francisco, buying, selling, and public use of marijuana remain criminal offenses. In Amsterdam, there is neither proactive nor reactive policing of use or low-level sales, although police do enforce regulations against coffee shops' advertising, selling to minors, and creating public nuisances.

In San Francisco, there is strong proactive and reactive policing of sales, and there is moderate reactive policing of use.

These differences in drug policy context are palpable to users. San Francisco students are suspended from schools and are placed in treatment for marijuana use. San Francisco users risk citations, fines, and arrests if they are detected buying, possessing, or using marijuana. In Amsterdam, users face none of these risks. The use and sale of other illicit drugs sometimes used by cannabis users is proactively policed in San Francisco. In Amsterdam, police occasionally engage in reactive policing of complaints about open use or sale of other drugs, but they do not proactively patrol in search of these offenses.

METHODS

We required not merely a random sample of cannabis users but a random sample of users who had enough experience (defined as at least 25 episodes of use during their lifetimes) to answer questions about career use patterns. In Amsterdam, recruitment of users began as part of a drug-use prevalence survey of the general population. This survey was administered to a random sample that was obtained from Amsterdam's Municipal Population Registry. The overall response rate was 50.2%, which yielded a sample of 4364.[25] (The response rate was slightly below the 55% response rate of a 1990 iteration of the survey. Sampling details and an extensive response/nonresponse study can be found in Sandwijk et al.[24] or at http://www.cedro-uva.org/lib.) Comparisons of responders with nonresponders and with known city demographic data indicated no need for weighting. All respondents who reported having used cannabis at least 25 times (n=535; 12.3%) were asked to participate in an in-depth interview about their cannabis use. Of these 535 experienced users, 216 (40.5%) were interviewed in 1996.[26]

This modest response rate necessitated a check of representativeness. We compared the 216 users who responded with the 319 who did not on 12 demographic and drug-use prevalence variables. Respondents had slightly higher levels of formal education and slightly higher past-year prevalence of cannabis use,[26,27] but otherwise, they showed no differences compared with nonrespondents and thus were reasonably representative of experienced cannabis users in the general population. Homeless and institutionalized persons were not interviewed for either survey.

Beginning in 1997, the Amsterdam survey of experienced cannabis users was replicated in San Francisco, where there is no population registry. To remain consistent with Amsterdam, we first drew an area probability sample by randomly selecting census tracts, blocks, buildings, households, and adults within households. We administered a brief prevalence survey containing demographic and drug-use prevalence questions. Unlike the Amsterdam prevalence survey, which was an extensive study in its own right, the brief prevalence survey in San Francisco was principally designed to generate a random representative sample of experienced cannabis users.

The overall response rate of the San Francisco prevalence survey was 52.7%, which yielded a sample of 891.[28] Of these respondents, 349 reported that they had used cannabis 25 or more times (39.2% of the population sample and 3 times the prevalence found in the Amsterdam sample) and were asked to participate in the in-depth interview; 266 (76.2%) respondents were ultimately interviewed in depth about their career use patterns. As a check on their representativeness, respondents were compared with nonrespondents on 10 demographic and drug-use prevalence variables. No statistically significant differences were found.

The Dutch questionnaire was translated for use in San Francisco. Non-English-speaking Asian Americans were excluded because of the prohibitive costs of translating instruments and training interviewers in the many Chinese and other Asian languages found in San Francisco. This exclusion was not consequential, because national prevalence studies show that illicit drug use among Asian Americans is the lowest of any ethnic group.[29] Also, non-English speakers are mostly elderly and are thus least likely to be cannabis users. However, the instruments were translated into Spanish, and bilingual interviewers conducted interviews when necessary. Homeless and institutionalized persons were not interviewed.

RESULTS

Age at Onset, First Regular Use, and Maximum Use

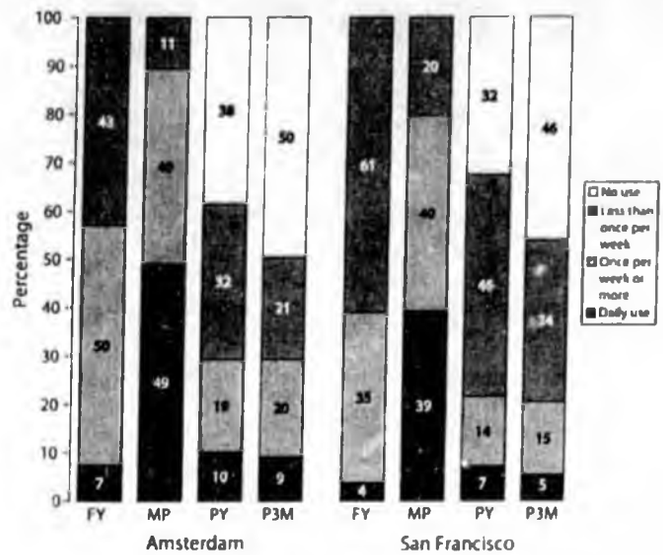
The mean age at onset of cannabis use was nearly identical in both cities: 16.95 years in Amsterdam and 16.43 years in San Francisco. The mean age at which respondents commenced regular use (≥once per month) also was nearly identical: 19.11 years in Amsterdam and 18.81 years in San Francisco. The mean age at which respondents in both cities began their periods of maximum use was about 2 years after they began regular use: 21.46 years in Amsterdam and 21.98 years in San Francisco. Clear majorities in both cities reported periods of maximum use of 3 years or less.

Cannabis Use Patterns Over Time

We asked about the frequency and the quantity of use and the intensity and the duration of intoxication. To assess how these dimensions of use may have changed over time, we asked about each for 4 periods: first year of regular use (≥once per month), maximum-use period, past year (12 months before the interview), and past 3 months (3 months before the interview).

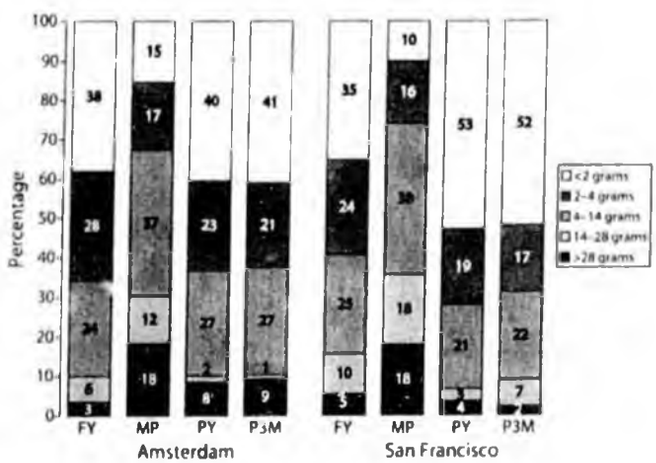
Frequency of use. Figure 1 shows the frequency of reported marijuana use for these 4 periods; the overall pattern is similar across both cities. During first year of regular use, strong majorities reported use of cannabis once per week or less, whereas small percentages reported daily use. Frequency increased during the period of maximum use but declined sharply thereafter. Amsterdam respondents reported more frequent use than did San Francisco respondents during their first year of regular use ($t=4.019$; $df=479$; $P=.000$) and during their period of maximum use ($t=2.979$; $df=479$; $P=.003$). When the maximum-use period was compared with the past year, daily use declined from 49% to 10% in Amsterdam and from 39% to 7% in San Francisco. This decline was even greater for the past 3 months.

The basic trajectory of frequency of use across careers was parallel in both cities. Most users reported a maximum-use period of 2 to 3 years, after which the vast majority sharply reduced their frequency of use or stopped al-



Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = past year; P3M = past 3 months.
[a]All respondents.

FIGURE 1—Frequency of cannabis use for 4 periods, by city (%).[a]



Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = last year; P3M = past 3 months.
[a]Respondents who still used at time of survey, for past year and past 3 months.

FIGURE 2—Average quantity of cannabis used per month (%).[a]

together. Roughly three fourths of the respondents in each city reported that they had used cannabis less than once per week or not at all in the year before the interview.

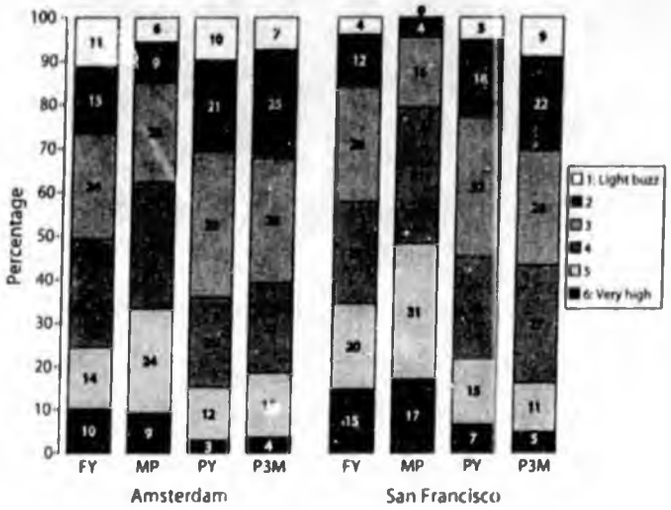
Quantity of use. Figure 2 shows that in the first year of regular use, few respondents in either city consumed large quantities of cannabis. Only 3% in Amsterdam and 5% in San Francisco used 28 grams (approximately 1 ounce) during an average month. Amsterdam respondents used significantly smaller quantities than did San Francisco respondents during this period. When the 2 smallest categories were combined, two thirds in Amsterdam (66%) and slightly less in San Francisco (59%) were found to have consumed 4 or fewer grams per month during their first year of regular use. More than one third used less than 2 grams per month during their first year of regular use—38% in Amsterdam and 35% in San Francisco.

Quantities consumed during maximum-use periods were larger and very similar across the cities. About two thirds of respondents consumed an average of 14 or fewer grams per month—69% in Amsterdam and 64% in San Francisco. Less than 1 in 5 respondents in each city (18%) consumed an average of 28 grams per month or more during their maximum-use periods.

During the year before the interview, consumption among those who still used cannabis declined sharply. Clear majorities used 4 or fewer grams per month, although this proportion was smaller in Amsterdam (63%) than in San Francisco (72%) ($t = 2.207$; $df = 297$; $P = .028$). About 1 in 3 respondents in each city reported no use. Overall, the patterns were parallel in both cities; quantities used increased from first regular use through maximum use but then quantities used declined steadily or use ceased altogether over the course of the respondents' careers.

Intensity of intoxication. Respondents were asked to estimate "how high or how stoned you generally got" when they consumed cannabis. Some recalled this occurence with greater consistency than did others, but all of them were able to make basic ordinal distinctions between more- and less-intense highs. To increase reliability of respondents' estimates, we displayed a 6-point scale ranging from "light buzz" (1) to "very high" (6) and asked them to select the number that best summarized their highs during each period.

Figure 3 shows that respondents in both cities generally increased the intensity of their highs during periods of maximum use but moderated their highs thereafter (past-year and past-month figures exclude those who had quit). Amsterdam respondents were significantly more likely than San Francisco respondents to report milder intoxication during the first year of regular use and during maximum-use periods: mean scores for the first year were 3.5 in Amsterdam and 3.9 in San



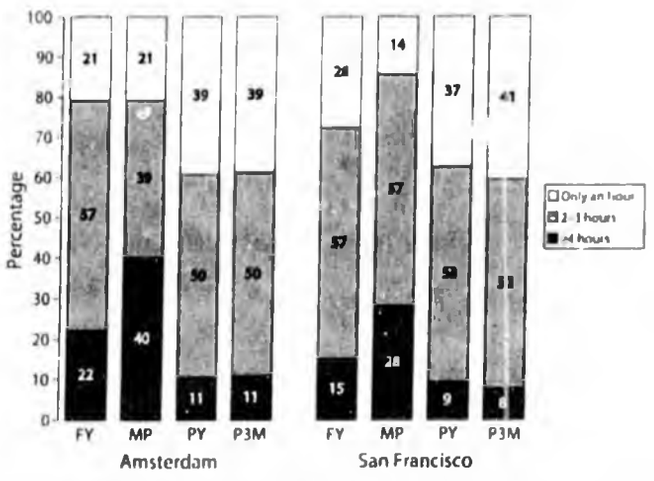
Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = past year; P3M = past 3 months.
[a]Respondents who still used at time of survey, for past year and past 3 months.

FIGURE 3—Intensity of intoxication during typical occasion of cannabis use (%).[a]

Francisco ($t = -3.180$; $df = 476$; $P = .002$), and these scores rose for maximum-use periods to 3.9 and 4.4, respectively ($t = -4.932$, $df = 413$; $P = .000$).

The same pattern was found for the more recent periods, although the mean scores declined. The proportion of respondents who chose 6 (very high) remained small and was between 3% and 7% in both cities. For highs experienced during the past year, Amsterdam respondents were again more likely to report milder intoxication ($t = -2.233$; $df = 310$; $P = .026$). For the past-3-month periods, majorities in both cities reported milder highs of 1 to 3 on the 6-point scale. In short, respondents in both cities reported less intoxication with use over the course of their careers.

Duration of intoxication. We also asked "about how long" respondents were high during a typical occasion of cannabis use. Reported durations were correlated with frequency and with quantity but were not a function of frequency and quantity alone. Here, too, we found a tendency toward moderation over the course of users' careers in both cities. Figure 4 shows that Amsterdam respondents reported highs of somewhat longer duration than reported by respondents in San Francisco during the first year of regular use ($t = 2.329$; $df = 476$; $P = .020$). (One reviewer noted a divergence between San Francisco respondents, who reported more intense highs during 3 of the 4 periods, and Amsterdam respondents, who reported highs of longer duration during 1 period. Because we found no reason to suspect that either sample played up or played down their responses to any of the questions, this divergence may indicate culture-specific consumption styles or cultural grammars of intoxication.[30,31]) However, during the other 3 time periods there were no significant differences: in each city, a clear majority of users regulated their ingestion so that highs lasted 2 to 3 hours or less. Substantial minorities in each city reported being high for 4 or more hours during maximum-use periods, but these proportions dropped sharply after those periods. Of those who used cannabis during the 3 months before the interview, 89% in Amsterdam and 93% in San Francisco reported being high for 2 to 3 hours or less.



Note. FY = first year of regular use (≥ once per month); MP = maximum-use period; PY = past year; P3M = past 3 months.
[a]Respondents who still used at time of survey, for past year and past 3 months.

FIGURE 4—Duration of high during a typical occasion of cannabis use (%).[a]

Overall Career Use Patterns

We also asked respondents to characterize their overall career use patterns. We presented a typology of trajectories[12] and asked them to identify the 1 that "best describes" their cannabis use over time (Table 1).

Two career use patterns were dominant in both cities. Pattern 4—gradual increased use followed by sustained decline—was the most common (49.4% of the combined sample). The second most common was Pattern 6—wide variation over time (24.4% of the combined sample). Patterns 1, 2, 3, and 5 were each selected by only 6% to 8% of the com-

TABLE 1—Trajectories of Overall Career Use

Pattern	Amsterdam, No. (%)	San Francisco, No. (%)
1: declining	17 (7.9)	18 (6.8)
2: escalating	13 (6.0)	17 (6.4)
3: stable	24 (11.1)	5 (1.9)
4: increase/decline	104 (48.1)	133 (50.4)
5: intermittent	7 (3.2)	25 (9.5)
6: variable	51 (23.6)	66 (25.0)
Total	216 (100.0)	264 (100.0)

Note. $\chi^2 = 24.047$; $df = 5$; $P = .000$. Pattern names listed as shown to respondents.

TABLE 2—Prevalence of Other Illicit Drug Use, Lifetime and During the Past 3 Months

	Amsterdam ($n = 216$)		San Francisco ($n = 264$)		Significance $\chi 2$	
	LTP	P3MP	LTP	P3MP	LTP	P3MP
Cocaine	48.1	9.3	73.2	7.5	*	NS
Crack	3.7	0.5	18.1	1.1	*	*
Amphetamines	37.5	1.9	60.4	4.5	*	NS
Ecstasy	25.5	9.3	40.0	6.4	*	NS
Opiates	21.8	0.5	35.5	2.7	*	*

Note. LTP = lifetime period; P3MP = past 3 months; NS = not significant.
*Too few cases in cells to compute statistical test.
*$P < .001$.

bined sample. Pattern 3—stable use from the beginning onward—was selected significantly more often by Amsterdam respondents (11.1%) than by San Francisco respondents (1.9%), whereas Pattern 5—intermittent use (many starts and stops over time)—was selected significantly more often by San Francisco respondents (9.5%) than by Amsterdam respondents (3.2%).

These findings are consistent with findings on frequency and quantity of use and intensity and duration of intoxication, and they have important public health implications. Claims that cannabis produces addiction or dependence[13–15] lead one to expect that many experienced users would report Pattern 2—escalation of use over time. But this pattern was reported by only 6% in both cities, which means that 94% of respondents had overall career use patterns that did not entail escalation across careers.

Other Illicit Drug Use

Another important question about the effects of drug policies concerns the use of other illicit drugs. The "separation of markets," in which lawfully regulated cannabis distribution reduces the likelihood that people seeking cannabis will be drawn into deviant subcultures where "hard drugs" also are sold is one public health objective of Dutch decriminalization.[1–3] The reduction of cannabis use and thereby the reduction of the extent to which it serves as a "gateway" to "harder" drugs is one public health objective of US criminalization.[11,12,14,16]

Users who had ingested cannabis 25 times or more during their lifetimes were far more prevalent in San Francisco than in Amsterdam, and the same was true for users of other illicit drugs. Table 2 shows a significantly lower lifetime prevalence of other illicit drug use in Amsterdam than in San Francisco. During the 3 months before the interview, prevalence of crack and opiate use also were significantly higher in San Francisco, but cocaine, amphetamine, and ecstasy use were not significantly different. Thus, rates of discontinuation—the decline from lifetime prevalence to prevalence during the past 3 months—were somewhat higher in San Francisco for cocaine, amphetamine, and ecstasy; however, rates of discontinuation were high (64%–98%) for all drugs in both cities.

DISCUSSION

Proponents of criminalization attribute to their preferred drug-control regime a special power to affect user behavior. Our findings cast doubt on such attributions. Despite widespread lawful availability of cannabis in Amsterdam, there were no differences between the 2 cities in age at onset of use, age at first regular use, or age at the start of maximum use. Either availability in San Francisco is equivalent to that in Amsterdam despite policy differences, or availability per se does not strongly influence onset or other career phases.

We also found consistent similarities in patterns of career use across the different policy contexts. Although a few significant differences were found in some dimensions of use during some career phases, the basic trajectory was the same in both cities on all dimensions of use: increasing use until a limited period of maximum use, followed by a sustained decrease in use over time or by cessation. It is significant, from a public health perspective, that clear majorities of experienced users in both cities never used daily or used large amounts even during their peak periods, and that use declined after those peak periods. Furthermore, both samples reported similar steady declines in degree and duration of intoxication. Only 6% in each city reported escalation of use over time.

We expected differences in drug policies to affect the duration of cannabis-use careers and the rates of cessation. Criminalization is designed to decrease availability, discourage use, and provide incentives to quit. Decriminalization is said to increase availability, encourage use, and provide disincentives to quit. Thus, we expected longer careers and fewer quitters in Amsterdam, but our findings did not support these expectations. Cannabis careers ranged from 1 to 38 years, and 95% of respondents in both cities reported careers of 3 years or longer. The mean career length was slightly greater in San Francisco (15 years) than in Amsterdam (12 years), but this finding was mostly because of the somewhat higher mean age in the San Francisco sample (34 years vs 31 years). Similarly, nearly identical proportions of respondents in each city had quit by the time they were interviewed—33.8% in Amsterdam and 34.3% in San Francisco.

If drug policies are a potent influence on user behavior, there should not be such

strong similarities across such different drug control regimes. Our findings do not support claims that criminalization reduces cannabis use and that decriminalization increases cannabis use. Moreover, Dutch decriminalization does not appear to be associated with greater use of other illicit drugs relative to drug use in San Francisco, nor does criminalization in San Francisco appear to be associated with less use of other illicit drugs relative to their use in Amsterdam. Indeed, to judge from the lifetime prevalence of other illicit drug use, the reverse may be the case.

Our study has limitations and should be replicated in other cities over longer periods. While our findings share the limitations of all self-report studies (e.g., vague or selective memory, over- or understatements of fact), we attempted to minimize these limitations by means of carefully worded questions, extensive pretesting, and use of multiple measures. The questionnaire is available under *questionnaire* at http://www.cedro-uva.org/lib/cohen.canasd.html. Our comparable samples and measures helped isolate the effects of drug policies, but "all else" is not necessarily "equal." Cultural and social conditions in the United States are different from in the Netherlands; therefore, cannabis use might increase if the United States were to adopt a Dutch approach. Further studies that examine prevalence before and after policy shifts would be illuminating, although previous studies of the impact of marijuana decriminalization among 11 US states during the 1970s found no increases.[33–36]

One hypothesis for future research is that with a widely used drug like cannabis, the informal social controls that users develop as part of their culture[30,31,37–39] have more powerful regulatory effects on their behavior than do formal social controls such as drug policies. This possibility emerged from responses to questions about the circumstances respondents found appropriate for cannabis use. In both cities, relaxation was the most common purpose of use, and majorities from both cities reported that they typically used cannabis with friends and at social gatherings. Majorities in both cities most often mentioned work or study as situations in which use was inappropriate. In both cities, 69% reported negative emotional states as unsuitable for cannabis use, and 80% reported having advised novices about the virtues of moderation.

CONCLUSIONS

These data suggest that most experienced users organize their use according to their own subcultural etiquette—norms and rules about when, where, why, with whom, and how to use—and less to laws or policies. When experienced users abide by such etiquette, they appear to regulate their cannabis use so as to minimize the risk that it will interfere with normal social functioning. This pattern suggests that if formal drug policies are based on the folk (informal) drug policies users themselves already practice, drug policies may achieve greater relevance. ■

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Contributors

C. Reinarman assisted in conceiving the study and analyzing the data. H.L. Kaal composed the figures and the tables that form the core of the data analysis. P.D.A. Cohen proposed the study, led its conceptualization, designed and supervised the data analysis, and assisted with writing the article.

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Human Participant Protection

This protocol was approved by all relevant institutional review boards and funding agencies.

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"Long-term effects of exposure to cannabis"

Leslie Iversen

Current Opinion in Pharmacology, 2005, 5:69-72

ELSEVIER

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 is 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 down-grading 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 1969 and 1970 suggested that those who had used cannabis >50 times before the age of 18 years had a 6.7-fold increased risk of developing schizophrenia in later life [7]. A review of this and four other longitudinal cohort studies also concluded that early cannabis use might be a causal factor for schizophrenia-like illness in later life [8••]. However, the interpretation of such studies is fraught with many difficulties, as reviewed by Macleod *et al.* [9••]. These authors highlighted that proof of a causal relationship is subject to many confounding factors. When known confounding factors were applied to the Swedish army data, for example, the odds ratio was reduced from 6.7 to 3.1 [7]. This, in turn, suggests that other residual unidentified confounding factors are also likely to exist. The published studies show that the existence of 'prodromal' symptoms of psychosis clearly increased the risk of subsequent psychiatric illness in cannabis users [8••]. This factor was adequately controlled for in only one of the five published longitudinal studies [10]. In this New Zealand cohort, even when those exhibiting prodromal symptoms of psychosis were eliminated, those who started cannabis use by age 15 years (but not those who started later) showed a fourfold increase in the risk of developing schizophrenia-like illness by age 26 years. However, the number of subjects involved was small (there were 26 15-year old cannabis users, of whom three developed mental illness) so the statistical power of this study was limited. Degenhardt *et al.* [11] sought to test the hypothesis of a causal relationship between cannabis use and schizophrenia by a careful examination of the incidence of schizophrenia in Australia during the past 30 years. Although the prevalence of cannabis use had increased markedly during this period, there was no evidence of a significant increase in the incidence of schizophrenia. The question of whether cannabis use can precipitate psychiatric illness in a vulnerable minority of previously well people remains unanswered. One could equally argue that a tendency to psychotic illness might increase the likelihood of early cannabis use [9••]. It is possible that cannabis may precipitate schizophrenic illness earlier in vulnerable people who exhibit 'schizophreniform' tendencies. Such a conclusion is supported by the results of a study of 122 newly admitted schizophrenia patients in the Netherlands, which showed a strong association between cannabis use and the age of onset of the first psychotic episode in men, with users experiencing their first psychotic episode 6.9 years earlier than non-users [12].

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

Psychosocial sequelae of cannabis use

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

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

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