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SENATE

JUDICIARY

by youth. Legality with regulation could. The Canadian Senate Report, submitted to this Committee separately, addresses this.

Again, given the very little time I have had to review and respond to the proponents' submissions, the remainder of my comments are necessarily truncated:

2) Potency

a) Increases in average THC potency of confiscated marijuana have been greatly exaggerated. (ElSohly, M. A., S. A. Ross, et al. (2000). "Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997." J Forensic Sci 45(1): 24-30 (abstract attached)).

The analysis of 35,312 cannabis preparations confiscated in the USA over a period of 18 years for delta-9-tetrahydrocannabinol (delta9-THC) and other major cannabinoids is reported. Samples were identified as cannabis, nashish, or hash oil. Cannabis samples were further subdivided into marijuana (loose material, kilobricks and buds), sinsemilla, Thai sticks and ditchweed. The data showed that more than 82% of all confiscated samples were in the marijuana category for every year except 1980 (61%) and 1981 (75%). The potency (concentration of delta9-THC) of marijuana samples rose from less than 1.5% in 1980 to approximately 3.3% in 1983 and 1984, then fluctuated around 3% till 1992. Since 1992, the potency of confiscated marijuana samples has continuously risen, going from 3.1% in 1992 to 4.2% in 1997. The average concentration of delta9-THC in all cannabis samples showed a gradual rise from 3% in 1991 to 4.47% in 1997. Hashish and hash oil, on the other hand, showed no specific potency trends. Other major cannabinoids [cannabidiol (CBD), cannabinol (CBN), and cannabichromene (CBC)] showed no significant change in their concentration over the years.

b) Moreover, no one has ever documented that increased potency means increased danger in cannabis. See attached article by Carlini. As already noted, people titrate their intake to achieve the desired effect. Also, as I stated earlier, higher potency marijuana is in fact almost certainly safer in terms of potential pulmonary risk since users smoke less.

c) Finally, it is important to recall that the concern the Alaskan Supreme Court expressed in the Ravin decision regarding higher potency cannabis was explicitly based upon three studies cited in the Court's decision, all from the early 1970s, in which it had been suggested that higher potency THC might cause DNA cellular damage, immune system damage, and reduced testosterone levels. All of these studies have been thoroughly discredited in the time since the Ravin decision, and no one, not even the proponents of this legislation, suggests today that these dangers are real. In other words, even if the marijuana available today does have slightly higher THC levels than in the 1970s, there is no reliable data to suggest that this increased potency results in any greater threat to public health such as to legitimize re-criminalizing adult possession of small amounts in the privacy of the home.

- 3) Marijuana use and crime: Documentation of cannabis metabolites in urine of criminals is meaningless in terms of cause and effect. It merely points to past use. Cannabis does not cause crime. *Psychological And Social Sequelae Of Cannabis And Other Illicit Drug Use By Young People: A Systematic Review Of Longitudinal, General Population Studies*. John Macleod, Rachel Oakes, Alex Copello, Ilana Crome, Matthias Egger, Mathew Hickman, Thomas Oppenkowski, Helen Stokes-Lampard, George Davey Smith, Published in The Lancet, May 15, 2004 (attached).
- 4) Driving: Most cannabis-only users drive cautiously, and the association is exaggerated by the proponents of this legislation. Please see attached chapter by Hadorn, and article by Movig.
- 5) Dependency: The proponents assertions in this regard are vastly over-stated. There is little evidence of any withdrawal syndrome (see Smith article attached).
- 6) Increased Numbers of Persons Seeking Treatment for Marijuana "Addiction": Most "treatment" for "marijuana addiction" is coerced by the courts, families or employers, and the "patient" will not graduate until they admit their problem. This is a travesty of both justice and statistics.

There is little documentation of medical need. (See attached DAIS report.)

7) Marijuana and Alcoholism: Cannabis actually may ameliorate alcoholism. NIDA never publicizes the two important studies that document that free access to cannabis lowers alcohol intake: (See the attached Chapter 25 from Bozarth (ed. 1987), *Assessing Drug Reinforcement*, reprinting Mello, N. K. and J. H. Mendelson (1978). "Marihuana, alcohol, and polydrug use: human self-administration studies." NIDA Res Monogr(20): 93-127 and Mello, N. K., J. H. Mendelson, et al. (1978). "Human polydrug use: marihuana and alcohol." J Pharmacol Exp Ther 207(3): 922-35.) More recent documentation is available by Mikuriya (2004, attached), and also data on cannabis helping cure cocaine addiction in Brazil. (Labigalini, E., Jr., L. R. Rodrigues, et al. (1999). "Therapeutic use of cannabis by crack addicts in Brazil." J Psychoactive Drugs 31(4): 451-5:

This study ensued from clinical observations based on spontaneous accounts by crack abusers undergoing their first psychiatric assessment, where they reported using cannabis in an attempt to ease their own withdrawal symptoms. Throughout a period of nine months, the researchers followed up on 25 male patients aged 16 to 28 who were strongly addicted to crack, as diagnosed through the Composite International Diagnostic Interview (CIDI), according

to CID-10 and DSM-IV diagnostic criteria. Most of the subjects (68%, or 17 individuals) ceased to use crack and reported that the use of cannabis had reduced their craving symptoms, and produced subjective and concrete changes in their behavior, helping them to overcome crack addiction. The authors discuss some psychological, pharmacological and cultural aspects of these findings.

Similar findings are also published from Jamaica (Dreher, attached).

8) **Marijuana and Pulmonary Risk:** I am not going to argue that smoke is completely innocuous, but the data submitted by the proponents of this bill is inaccurate, due to poor quality NIDA cannabis with stems and seeds. This is all documented in text and photos in the Chronic Use Study (attached). Also, never mentioned by the government is the development of alternatives to smoking marijuana that are becoming ever-more widely available, such as vaporizers (see Gieringer article, attached).

9) **Marijuana and Cardiac Risk:** Claims of cannabis producing heart attacks are exaggerated, as well. There is no epidemiological evidence of a real connection. (See Sidney, Beck et al. 1997; Sidney, "Cardiovascular consequences of marijuana use." J Clin Pharmacol 42(11 Suppl): 64S-70 2002, copies attached:

This review describes what is known about effects of marijuana and cannabinoids in relation to human

physiological and disease outcomes. The acute physiological effects of marijuana include a substantial dose-dependent increase in heart rate, generally associated with a mild increase in blood pressure. Orthostatic hypotension may occur acutely as a result of decreased vascular resistance. Smoking marijuana decreases exercise test duration in maximal exercise tests, increases the heart rate at submaximal levels of exercise. Tolerance develops to the acute effects of marijuana smoking and delta9-tetrahydrocannabinol (THC) over several days to a few weeks. The cardiovascular responses that occur in response to THC are mediated by the autonomic nervous system, with recent findings also demonstrating that the human cannabinoid receptor system plays a role in regulating the cardiovascular response. Although several mechanisms exist by which marijuana use might contribute to the development of chronic cardiovascular conditions or acutely trigger cardiovascular events, there are few data regarding marijuana/THC use and cardiovascular disease outcomes. A large cohort study showed no association of marijuana use with cardiovascular disease hospitalization or mortality. However, acute effects of marijuana use include a decrease of the time until the onset of chest pain in patients with angina pectoris; one study has shown that marijuana may trigger the onset of myocardial infarction. Patients who have coronary heart disease or are at high risk for the development of CHD should be cautioned about the potential hazards of marijuana use as a precipitant for clinical events. Research directions might include more studies of cardiovascular disease outcomes and relationships of marijuana with cardiovascular risk factors, studies of metabolic and physiologic effects of chronic marijuana use that may affect cardiovascular disease risk, increased understanding of the role of the cannabinoid receptor system in cardiovascular regulation, and studies to determine if there is a therapeutic role for cannabinoids in blood pressure control or for neuroprotection after stroke.

Sidney, S., J. E. Beck, et al. (1997). "Marijuana use and mortality." Am J Public Health 87(4): 585-90:

OBJECTIVES: The purpose of this study was to examine the relationship of marijuana use to mortality.

METHODS: The study population comprised 65,171 Kaiser Permanente Medical Care Program enrollees, aged 15 through 49 years, who completed questionnaires about smoking habits, including marijuana use, between 1979 and 1985. Mortality follow-up was conducted through 1991.

RESULTS: Compared with nonuse or experimentation (lifetime use six or fewer times), current marijuana use was not associated with a significantly increased risk of non-acquired immunodeficiency syndrome (AIDS) mortality in men (relative risk [RR] = 1.12, 95% confidence interval [CI] = 0.89, 1.39) or of total mortality in women (RR = 1.09, 95% CI = 0.80, 1.48). Current marijuana use was associated with increased risk of AIDS mortality in men (RR = 1.90, 95% CI = 1.33, 2.73), an association that probably was not causal but most likely represented uncontrolled confounding by male homosexual behavior. This interpretation was supported by the lack of association of marijuana use with AIDS mortality in men from a Kaiser Permanente AIDS database. Relative risks for ever use of marijuana were similar.

CONCLUSIONS: Marijuana use in a prepaid health care-based study cohort had little effect on non-AIDS mortality in men and on total mortality in women.

Additionally, recently published studies suggest that, in fact, cannabis may be cardioprotective. A new study by Steffens (attached) was published just this week, finding THC may help prevent atherosclerosis.

10) **Marijuana and Cognitive Effects:** The cognitive effects of cannabis have also been exaggerated by the proponents of this legislation. The two most comprehensive studies show no residual after brief abstinence: Pope, H. G., Jr. (2002). "Cannabis, cognition, and residual confounding." Jama 287(9): 1172-4; Pope, H. G., Jr., A. J.

Gruber, et al. (2001). "Neuropsychological performance in long-term cannabis users." Arch Gen Psychiatry 58(10): 909-15:

BACKGROUND: Although cannabis is the most widely used illicit drug in the United States, its long-term cognitive effects remain inadequately studied.

METHODS: We recruited individuals aged 30 to 55 years in 3 groups: (1) 63 current heavy users who had smoked cannabis at least 5000 times in their lives and who were smoking daily at study entry; (2) 45 former heavy users who had also smoked at least 5000 times but fewer than 12 times in the last 3 months; and (3) 72 control subjects who had smoked no more than 50 times in their lives. Subjects underwent a 28-day washout from cannabis use, monitored by observed urine samples. On days 0, 1, 7, and 28, we administered a neuropsychological test battery to assess general intellectual function, abstraction ability, sustained attention, verbal fluency, and ability to learn and recall new verbal and visuospatial information. Test results were analyzed by repeated-measures regression analysis, adjusting for potentially confounding variables.

RESULTS: At days 0, 1, and 7, current heavy users scored significantly below control subjects on recall of word lists, and this deficit was associated with users' urinary 11-nor-9-carboxy-Delta9-tetrahydrocannabinol concentrations at study entry. By day 28, however, there were virtually no significant differences among the groups on any of the test results, and no significant associations between cumulative lifetime cannabis use and test scores.

CONCLUSION: Some cognitive deficits appear detectable at least 7 days after heavy cannabis use but appear reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use.

The Chronic Use Study (previously attached) also deals with this in detail, with review of past studies in Jamaica, Costa Rica and Greece.

- 11) Marijuana and Sexual Assaults: The data on sexual assaults are grossly misleading. There is absolutely no evidence whatsoever of any causal link between marijuana use and engaging in violent sexual behavior.
- 12) Emergency Room "Mentions": The data on emergency room visits presented by the proponents of this legislation are also grossly misleading. These "mentions" have little or nothing to do with the true reasons for the hospital visits. There is absolutely no evidence whatsoever of a causal link between marijuana use and increased numbers of emergency room visits.\
- 13) Psychosis: As I've discussed in my foregoing written testimony, there is no reliable evidence of a causal link between marijuana use and psychosis. The recent studies that purport to find a link conflate correlation with causality, and are based on sample sizes too small to be statistically valid for extrapolation. Persuasive refutations of these claims are found in the Macleod article published in the May 15, 2004 Lancet (attached and already referenced under point 2 of this addendum and in the Iversen, and Shiffman articles (attached).
- 14) Cancer: The evidence is much greater that cannabis helps prevent and treat cancer and the deleterious side effects of chemotherapy, than that it causes harm: (see

Hall, Guzman, Musty and Rossi, and Maccarrone articles, all attached).

15) Marijuana and Prenatal Effects: These claims presented by the proponents of this legislation are also vastly exaggerated. Please see the Dreher article, attached and already referenced in point 7), above, and Russo (at end of article, attached).

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My name is Jack Cole. I retired as a Detective Lieutenant after a 26-year career with the New Jersey State Police. For fourteen of those years I worked as an undercover narcotics officer. My investigations spanned the spectrum of possible cases, from street drug users to international "billion-dollar" drug trafficking organizations.

I am also the executive director of LEAP or Law Enforcement Against Prohibition. LEAP was founded by five former cops to give voice to members of law enforcement who believe the war against drugs is not only a dismal failure but a terribly destructive policy. In the 2 ½ years of our existence we have grown to over 2,000 members and we are no longer just cops—now we are police, judges, prosecutors, prison wardens—we even have retired DEA officers who help make up our bureau of 85 speakers.

Passing bills that raise criminal penalties and assess harsher sentences for non-violent drug offenses is very poor public policy.

1. From 1975 to 1990, Alaska had 15 years of decriminalized adult use in the privacy of the home (based on the Alaska Supreme Court opinion in *Ravin*);
2. From 1990 to 2003 AK had a return to full de facto prohibition (based on an initiative that purported to recriminalize marijuana); and
3. From 2003 to now, marijuana in the home was decriminalized again (based on the Alaska Court of Appeals decision in November).
4. According to Alaska's own statistics overall use among children in grades 6 to 12 has **decreased** since 1975, while across the United States that rate has

increased (30 % for 12th graders, 65% for 10th graders, and 88% for 8th graders).

For 35 years, with a budget of over ½ trillion dollars, the United States has fought the war on drugs with ever harsher policies. We have arrested 1.6 million people for nonviolent drug offenses—fully half of the arrests were for marijuana violations. Two million two-hundred-thousand are in prison in the US, far more per capita than any country in the world. And what do we have to show for all those ruined lives and misspent money: Today drugs are cheaper, more potent and far easier to get than they were in the 1970 when I started buying them undercover. I believe that is the very essence of a failed public policy.

Nearly a thousand young people went to jail as a direct result of what I did as an undercover narcotics agent.

I can't say how many of those children would have gone on to become valuable citizens had I not intervened, but I'm sure the number would be huge.

Think of all the folks you know who used an illegal drug as a youngster, then put the drugs behind them and went on to live productive lives. Many are now members of our government. George Bush, Bill Clinton, Al Gore, Dan Quail, Newt Gingrich. The line is too long to enumerate but they all had two things in common, they all used illegal drugs, then quit, and when they arrived at a position of power they all got selective amnesia so now they say police should arrest young people and destroy their life prospects for doing exactly what they did.

We have a saying at LEAP: You can get over an addiction, but you will never get over a conviction. A conviction will follow you every day for the rest of your life—every time you apply for a job it is over your head like an ugly cloud.

There are many unintended consequences of the war on drugs. When you prohibit a drug, even the worst drug, you don't cause less people to imbibe. All you do is create an underground market that is instantly filled with criminals.

Worse, you create an artificially inflated value for that drug that can be up to 17,000 percent of the initial investment—making marijuana worth more than gold and heroin worth more than uranium. I would suggest that whole armies of police can not arrested our way out of drug problems when prohibition creates such obscene profit motives for prospective dealers. Every time I arrested a drug dealer I was simply creating a job opening.

For those of you who think that by backing this bill you are in the mainstream of public thinking, let me say that I believe that is not true: In the last year LEAP started attending national and international law enforcement conferences. We kept track of the opinions of the nearly 1,200 officials we spoke to on a one-to-one level. Even we were surprised to find that after we spoke with them, 6% wanted to continue the war on drugs, 14% were undecided, but a whopping 80% agreed with us that we must end prohibition. The most interesting thing about that 80% was only a very small number of them realized that any other law enforcement officer felt as they did. Peer pressure to not appear soft on drugs or soft on crime is so strong that they don't talk to each other about their beliefs.

Please, don't pass bills that tie up more police hours in projects that do nothing to lessen the incidence of death, disease, crime, and drug addiction—let police get back to protecting us from violent crime. We will all be much better off.

**Testimony to Senate Health and Social Services Committee
April 1, 2005**

My name is Bill Parker. I am a former member of the Alaska House of Representatives, and I retired from state service as Deputy Commissioner of Corrections. Today I speak for Alaskans for Marijuana Regulation and Control.

S.B.74 attempts to re-criminalize marijuana for adults in Alaska, in violation of the Alaska Constitution.

In 1975, in a landmark case known as **RAVIN**, the Alaska Supreme Court ruled the privacy clause of the Alaska Constitution protects possession of a small amount of marijuana by adult Alaskans in their own homes for their own use. In 1975, the Alaska Legislature changed the statutes to de-criminalize marijuana in Alaska.

Various attempts have been made in the 30 years since to attack this de-criminalization, both legally and politically.

An initiative in 1990 attempted to re-criminalize marijuana in Alaska, but initiatives change statutes, not the Constitution, and the initiative had no effect.

Many legal attempts have been made to test the constitutionality in the courts, all unsuccessful. The latest was last fall when the Alaska Supreme Court declined to take up the Appellate Court's latest ruling upholding **RAVIN**.

S.B.74 is another attempt to attack the constitutional issue in a legal and political manner.

If S.B.74 passes with these findings, they will be admissible in court, and the administration will have new arguments that marijuana is much more potent and dangerous than in 1975, so much so that it is almost a different substance.

That is why the findings section of this bill is important. The findings are flawed. Expert witnesses from Alaska and outside are going to explain those flaws today. They include:

They will discuss the complex medical and sociological issues that other government panels have studied at length.

- The Shafer Commission's report to President Nixon in 1972, "Marijuana: Signal of Misunderstanding."
- The National Research Council's 1982 report, "An Analysis of Marijuana Policy."
- The Institute of Medicine's 1999 report, "Marijuana and Medicine: Assessing the Scientific Base."
- The 2002 report of the British Advisory Council on the misuse of drugs, "The Classification of Cannabis."
- The House of Commons Home Affairs Committee 2002 study, "The Government's Drug Policy: Is It Working?"
- Jamaica's 2001 National Commission on Ganja came to the same conclusion: Marijuana is not so harmful that the penalties for possession need to be increased.

S.B.74 would take Alaska in the opposite and wrong direction.

The State's witnesses could not be called objective observers. Those directly involved in implementing an administration's policies cannot evaluate those policies impartially. Evaluators should be independent academics.

Many harms attributed to marijuana are actually caused by the prohibition of marijuana. Our policies are making things worse, as the statistics presented last week by the state's witnesses demonstrate.

Prohibition is failing, completely and spectacularly, and will only get worse until we have the courage to look honestly at where we are and how we got here.

The testimony today will show that the compressed time schedule alone for S.B.74 is inadequate to evaluate marijuana in Alaska. We have submitted, in writing, the findings of experts in their fields who determine marijuana to be relatively harmless compared to alcohol. Each finding must be examined individually as the other commissions and committees have done with scientific integrity.

Here is a quick review of the evidence you will hear today:

Experts will point out the differences between scientific research and pseudo-science, the confusion between correlation and causation.

The administration's assertions about increased potency of marijuana are inaccurate and misleading in several respects:

- There are serious questions about the actual potency of marijuana today and yesterday. There is no reliable way to measure potency.
- There is no proof that marijuana is more addictive or dangerous than previously.
- Basic logic would determine that more potent marijuana would result in people using less , because of the effect of autotitration.

The administration's treatment of statistics is misleading because most of their conclusions are court-ordered, not a clinical diagnosis of marijuana addiction or even a self-referral. Most had to choose between treatment or incarceration. Most chose treatment.

The rate of marijuana use among minors in Alaska is no higher today than it was in 1975. In fact, according to the government's own statistics, overall use in grades 6 to 12 in Alaska schools is lower now after 30 years of decriminalization.

Marijuana use by minors has not been shown to cause psychosis later in life.

Marijuana use does not induce violent behavior, rape, or child abuse.

The emergency room data used to show that marijuana is more dangerous today is not conclusive. Because the relationship to marijuana in patients is so widely construed as to be meaningless. And the administration has overstated and misinterpreted the evidence of marijuana's link to lung cancer, juvenile crime, and the possibility of addiction and dependence.

The weight of scientific evidence available today discredits the old 'gateway drug' theory.

There are laws already in place to prohibit driving while impaired by alcohol or marijuana. These laws will remain in effect.

S.B.74 would have a bad effect on medical marijuana patients by jeopardizing their ability to possess marijuana if adult use of marijuana in the home is criminalized.

If the administration's aim is to promote the public health and welfare, re-criminalizing personal, adult use of marijuana in the home won't do it. Re-criminalization will only feed the black market and increase the social costs that flow from it.

Science shows marijuana causes far less harm to the public health and welfare than alcohol or tobacco. And that's as true today as it was in 1975.

Shafer Commission, 1972

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

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

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

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

Institute of Medicine, 1999

“Marijuana and Medicine: Assessing the Science Base”

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

Report of the National Commission on Ganja, Jamaica, 2001

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

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

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

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

House of Commons Home Affairs Committee, 2002

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

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

Report of the Canadian Senate Special Committee on Illegal Drugs, 2002 “Cannabis: Position for Canadian Public Policy”

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

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

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

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

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

Index of Written Testimony

Alaska Senate HESS Committee

April 1, 2005

1. Lester Grinspoon, M.D., Associate Professor of Psychiatry Emeritus, Harvard Medical School, Curriculum Vitae, refer to list of Publications.
2. Kelly L. Drew, PH.D. Curriculum Vitae
3. Written Testimony of Kelly L. Drew, Associate Professor, Dept. Chemistry and Biochemistry, University of Alaska, Fairbanks
4. Written Testimony of Leslie Lars Iversen, PH.D., FRS, University of Oxford, England
5. Written Testimony of Mitch Earleywine, PH.D., Associate Professor of Psychology, University of Southern California
6. Written Testimony of Timothy Hinterberger, PH.D., Associate Professor, Biomedical Program, University of Alaska, Anchorage

Alaska Civil Liberties Union
Testimony of Michael W. Macleod-Ball, Executive Director
Senate HESS Committee
Senate Bill 74

The Alaska Civil Liberties Union opposes SB 74. It increases penalties for marijuana possession, thereby diverting enforcement resources from the investigation and prosecution of violent criminals to the investigation and prosecution of non-violent offenders of the possession laws. While we think that's not good policy, we oppose this bill primarily because it is designed specifically to restrict the uniquely Alaskan right to privacy.

SB 74 proposes, among other things, to increase penalties for marijuana ("MJ") possession. Under current law, if you have up to four ounces of MJ, for personal use in the home, the court rulings have said you can't be punished for that. Under the proposed law, if you possess an infinitesimal amount beyond that – you will be guilty of a Class C felony. If you pass this bill, that framework will be created – up to four ounces in the home – free....over four ounces – Class C felony – a crime on a par with incest or some classifications of statutory rape.

What's more – the law sets up yet another conflict with the state judiciary. The law creates penalties for possession of MJ under four ounces. One to four ounces will be a Class A misdemeanor and up to an ounce will be a Class B misdemeanor. When possession is in the home and non-commercial in nature – the enactment will be directly contrary to the court's interpretation of the scope of the privacy right set forth in the Alaska Constitution.

Alaskans adopted an express right of privacy and made it part of the state constitution in the 1970's. Shortly thereafter, the Alaska Supreme Court was called in to interpret that right of privacy in the Ravin case. In that case, the court was asked to decide whether the state had the right to bar possession of marijuana in the home – in other words, if someone had MJ in the home and if that MJ had no adverse impact on others, did the state have the right to go into that home without consent and arrest someone for simple possession.

After sifting through a great deal of evidence, the court decided that the Legislature had the authority to restrict marijuana possession in exercising its traditional public safety, health and welfare powers. However, it balanced that authority against the right of all Alaskans to a right of privacy – and set a somewhat higher standard for any law that might restrict the right of privacy. Some of the evidence the court weighed suggested that MJ was harmful and some suggested that MJ was not so harmful. The court said, in essence, that the degree of harm associated with MJ use was an important factor. If MJ was really harmful – proven to be addictive like heroin, proven to be associated with violent or aggressive behavior, for example – then there would be a sufficient rationale to justify restricting use and possession.

The normal standard to justify state action is a so-called 'rational basis' test. As long as there exists some rational basis for a law, the court presumes the law to be valid. However, where a fundamental right is restricted, the court has said that a higher standard must exist. It's not enough for there simply to be a rational basis between the law and the basis for the law. When a fundamental right exists, the relationship between the law's means and the law's ends must be close and substantial. And when a law narrows an individual's privacy right – a fundamental right is being restricted.

The court clearly said that possession and use of MJ is not a fundamental right. However, the right of privacy is fundamental and the personal possession and use of MJ in the home clearly restricts that fundamental right. The question for the court was whether the public safety purpose of the bill was so great as to justify the fundamental right restriction. The answer to that question depended in large part on the actual harm posed by MJ to society – separate and apart from the perceived harm. And so the court considered a wide range of evidence addressing the impact of MJ on society and individuals. The court considered the findings of a national commission appointed by President Nixon, as well as a wealth of scientific studies. The trial court had heard testimony from expert witnesses and considered written reports and books. In summary, the court chose not to say whether MJ is harmful or not – rather it said that the evidence was not overwhelming one way or the other. In light of the balanced nature of the evidence, the court determined that adequate justification did not exist for restricting the privacy right.

It's important to focus on the nature of the fundamental privacy right. The court considered the scope of the privacy right not in terms of marijuana usage – but rather in terms of those circumstances when an individual would have an expectation of privacy. In some senses the *Ravin* court's ruling was far broader than simply permitting use and possession of MJ in the home. It said that the constitutional right of privacy generally extended into one's private activities within the home – regardless of whether it's MJ use or some other activity.

“...the authority of the state to exert control over the individual extends only to activities of the individual which affect others or the public at large as it relates to matters of public health or safety, or to provide for the general welfare. We believe this to be a tenet of a free society. The state cannot impose its own notions of morality, propriety, or fashion on individuals when the public has no legitimate interest in the affairs of those individuals. The right of the individual to do as he pleases is not absolute, of course; it can be made to yield when it begins to infringe on the rights and welfare of others.”

The court said that alcohol was far more dangerous than MJ and that in light of conflicting studies, personal use and possession of MJ in the home fell within the privacy right.

Interestingly, it wasn't the Ravin court that came up with the four ounce limitation. Instead, that limit was determined by this Legislature. In the years following Ravin, this body adopted laws designed to bring state statutes into conformance with the court's ruling. Cases since then have generally deferred to the legislative four ounce threshold – though the high court has never said, to my knowledge, that four ounces is a magic number. Indeed, the court could easily say that there is no limit if the possession is entirely for private use – or it could say that four ounces is indeed the appropriate amount. We simply don't have guidance on that issue – except to the extent that the state's intermediate appeals court has blessed the framework.

The ACLU's policy is that criminalization of drug possession and use resolves nothing. It's the wrong way to prevent drug use and it's the wrong way to stop or reduce use. Even more important to the Alaska Civil Liberties Union is the goal of preserving our uniquely Alaskan right to privacy. It's generally conceded that the express right to privacy adopted by Alaskans in the 1970s and written into the state constitution is broader than the federal right to privacy inferred by federal courts from the Bill of Rights. It just so happens that my organization's drug policy goals and our basic mission of preserving and expanding individual civil liberties merge in the debate over this bill.

Because the restrictions of this bill impinge directly on a fundamental right embodied in the state constitution, it is incumbent on this legislature – and in particular on this committee – to determine the basis for the action. The court has already said that if the potential harm of MJ is not substantial – say, worse than the harm caused by alcohol or cigarettes, for example – an attempt to restrict purely private possession and purely private use in the home will unduly restrict the fundamental right to privacy in Alaska's constitution. In order to establish such substantial harm, this body must find, in effect, that there is no dispute about the harmful effects of marijuana. That means this committee must undertake a comprehensive review of the science in this area, much as the court did in Ravin, and conclude that there is no reliable science to support the relatively mild warnings about MJ that the Ravin court relied upon 30 years ago. Because of the wealth of evidence supporting the continued view of MJ as somewhat less dangerous than alcohol in most respects, it will simply be impossible for this committee to come to such a conclusion.

Even the studies put forward by the administration can be read in more than one way – and the administration's summary of some of these findings can at best be described as biased in favor of their interpretation of the facts. For example, one of the cited statistics asserted that 15% of rape suspects were under the influence of MJ. If you examine the actual report, though, you will see that 70% of the suspects were under the influence of alcohol – and there is no indication whether those that had used MJ had also used alcohol. Reading further into the report, you will see that the authors of the report were so concerned about the correlation between alcohol and this violent crime that they parsed out the alcohol subjects for further detail. And they ignored the MJ subjects – deeming that correlation too slight to be of further concern. But the administration did not highlight that context – arguably the more important conclusion of the study in question. Instead, they put the 15% figure out there by itself – hoping that no one would

pay attention to the narrative of the report itself. We have asked for a copy of the report to more fully examine whether other deceptive administration claims can be found – but our initial requests have been denied. Suffice to say, though, that this committee should not rely on the administration summaries of the evidence presented, because the conclusions are self-serving.

It's also important for this committee to recognize what concerns about MJ are relevant to this discussion. You have already heard about MJ as a huge cash crop – about huge increases in MJ discoveries in the state. You have heard about crime and driving issues. But your ability to legislate with respect to those issues is not restricted. The court rulings in this area have said quite clearly that there is nothing wrong with legislating against driving under the influence of MJ – or against commercial growing, selling, distributing. That's already the law of the land. And the court has said quite clearly that there is no right to possess and use MJ – it's the right of privacy that's sacrosanct. And since one's home is deemed to be one of the most private places – the bar is higher for the state to be allowed into the home to restrict behavior there. So the discussion about the negative impacts to society of marijuana as a cash crop or about driving issues or about breaking up large distribution rings is just not connected to the minor and private use in the home.

As a lawyer and representative of the Alaska Civil Liberties Union, it is not within my expertise to sit before you and testify about the degree of danger associated with minor and personal MJ possession and use. However, as a lawyer and ACLU representative, I can tell you that your evaluation of the science will have a significant bearing on whether this legislation is deemed legal or not. We see very serious problems with the findings as presented in the proposed bill. They are clearly one-sided and certainly not representative of weight of the scientific literature currently available. If left as they are, we believe the findings will be open to challenge as evidence of a prejudiced examination of the facts designed to improperly restrict the constitutionally protected right to privacy. Subsequent witnesses will present evidence that we believe will show the MJ is relatively harmless – certainly not any more harmful than the court determined in the 1970's.

In addition, I am presenting to the committee in written form a series of eight studies and articles – all of which will contradict the administration's position on the harmfulness of MJ. I will briefly summarize these studies at the end of my presentation – but in sum this committee will be hard pressed to state that the totality of the evidence weighs completely to one side or the other of this argument.

Therefore, I would urge the committee to adopt findings that are more balanced as to the issue of MJ's potential for harm. Each and every one of the findings addressing effects, impacts, or other characterizations of MJ are at least debatable and in their present state the findings are clearly biased. We believe a fair representation of the science will necessitate a complete revision of the findings. Alternatively, we would ask the committee to consider simply deleting the findings from the text of the bill.

We also strongly urge the committee to consider altering the penalties adopted in this bill. By this step the bill creates another class of felon – and turns the MJ user from being just that – a MJ user – into a criminal. The costs to the state and society are significant – in terms of prosecution and enforcement – and in terms of the impact on people in society. There is no evidence to suggest that the family of the individual who possesses over four ounces would benefit from the incarceration of the individual. In fact, quite the opposite is true. The burdens of single parenthood will befall the partners left behind – along with all the accompanying financial and emotional burdens associated with that state. The economic hardships will be borne by the wives, husbands, partners and children of those who are jailed – all for possessing a fraction of a gram more than the constitutionality protected amount of four ounces.

We can do better. We can focus on prevention and focus on it earlier. There are success stories with tobacco – and with drug use in other times and places. We can provide more and better outlets to help people stop drug use. It's unlikely that prison is the best place to learn to stop using drugs. In short, we believe this bill pursues the wrong policy – and its impact will be bad for Alaska families and a blow to individual privacy. Moreover, we believe that this bill will be subject to challenge – in the same manner as past attempts to legislate in this area – especially if the adoption of findings on this subject are one-sided and don't reflect the balance of science on this issue.

We urge you not to pass Senate Bill 74.

Thank you Mr. Chairman:

My name is Dr. Lester Grinspoon. I believe that you have copies of my curriculum vitae and two of my books: Marijuana Reconsidered (Harvard University press, 1971, 1977 and Marijuana, the Forbidden Medicine (Yale University press 1993, 1997). To be very brief, I am an associate professor of psychiatry, emeritus at the Harvard Medical School. Shortly after graduating from the Harvard Medical School in 1955, I joined the faculty and over the ensuing 45 years combined research and teaching with some clinical practice. In 1967, I had finished writing my part of a book on our seven-year study of schizophrenia. As the senior author I had to wait to finally put it together for what two junior co-authors estimated would be two to three months before they completed their parts. Because I was at that time very much concerned about the great danger young people were exposing themselves to as they recklessly ignored government warnings about its dangers, I decided to devote this unanticipated free time to studying marijuana in the Countway library with the object of producing a scientifically sound paper on the subject, one which I hoped to publish in a journal or periodical accessible to college-age people. Perhaps some would pay more attention to such a review than they apparently were to the material produced by the US Public Health Service. (A shortened version of the paper was published in Scientific American). As I delved into the medical, scientific and other literature I soon discovered, to my great surprise and

consternation, that, despite my training in medicine and science, I had been brainwashed like most other American citizens about the dangers of this drug. After I finished the book on schizophrenia, I began work on Marijuana Reconsidered which was published by Harvard University press in 1971, a second edition in 1977 and republished as a classic in 1997. Briefly, after documenting that most of what we believe about the dangers of cannabis were mythical, I concluded that marijuana was far less harmful than either alcohol or tobacco and that its greatest harmfulness arose from the way we as a society were dealing with it. (At that time we were arresting about 300,000 mostly young people on marijuana charges; today the figure is about 750,000.).

Let me say at the outset that marijuana is no more harmful today than it was in 1975 when I testified in the Raven case. Street marijuana is arguably more potent than it was at that time but this does not mean increased risk because both medicinal and recreational users very quickly learn how to titrate the dose to achieve the desired effect. A user who smokes (or vaporizes) marijuana has to inhale less of a more potent sample and, conversely, more of one that is less potent. It follows that to the extent that inhaling the smoke is considered a risk factor for pulmonary disease, the more potent sample provides a healthier choice. However, I should hasten to add that the pulmonary risk from smoking marijuana has been greatly exaggerated. There is not a single case of lung cancer or emphysema attributable to smoking marijuana to be found in the medical literature. I believe that the lungs of marijuana smokers are at greater

risk from the air of cities like Los Angeles or Houston (or any other city with poor air quality). However, for those, particularly in today's anti-smoking atmosphere, who wish to avoid smoke for any reason, there is now available a device called a vaporizer which holds the temperature of the marijuana to be consumed in a temperature window which vaporizes the cannabinoids at a temperature which is below the ignition point; thus no smoke.

I wish I had time to address the other 18 "Findings" because so many are erroneous and none is supported by documentation. Let me briefly consider another "Finding", the one that states... "marijuana use by children is associated with an increased risk of attempting suicide." I believe that the intention here is to suggest that because there is an association cannabis must be causal in this increment of risk. Psychiatry is becoming increasingly aware that children suffer from depression and some of them commit suicide. Like other children, some of the depressed children will use marijuana. In fact, because marijuana is an effective antidepressant, some of them may have discovered it as a self-medication. However, there is no credible evidence that I know of that establishes marijuana as a causal.

I am struck by the fact that so many of these "Findings" are the same claims of marijuana toxicity that have been made and discredited more than once in the history of this substance. For example, schizophrenics and patients suffering from other psychoses were thought to comprise a significant number of the

patients admitted to Indian Insane Asylums in the second half of the 19th-century and the use of ganja was thought to be causative. It was for this reason that the British organized the Indian Hemp Drug Commission Study which was published in 1894. The commission examined 800 doctors, superintendents of insane asylums, and so forth. In a 3000 page, seven volume report the commission concluded that "There is no evidence of any weight regarding mental and moral injuries from the moderate use of these drugs." This report put to rest the belief that cannabis led to schizophrenia and other psychoses for a while, but it has recurred periodically most recently during the last year or so. For example, a report from New Zealand with a study group of only 759 subjects, claims to have established that those who smoked marijuana three or more times by the age of 15 had a 10% higher chance of developing schizophrenia. Similarly, other studies from Great Britain and the Netherlands would predict greater numbers of schizophrenic patients. If these predictions were correct, given the number of young people who are or who have used cannabis, we would expect an increment in the incidence of schizophrenia. However, no such increment exists.

In "Finding" number two the assertion is made that "... [marihuana] has addictive properties similar to heroin and other similar illegal controlled substances..." Most of those who are sophisticated about cannabis would question whether the word addiction is even appropriate to this drug, and all would agree that the withdrawal syndrome seen with "heroin and other illegal controlled substances" are not observed upon cessation of marihuana use. The assertion made in "Finding"

number four, that marihuana use "... makes it more likely that the person will go on to use more potent illegal controlled substances..." is simply a restatement of what was known as the "stepping stone hypothesis"; a belief which has long since been thoroughly discredited.

As I participate in these hearings, I am reminded of those which preceded the passage of the Federal Marihuana Tax Act of 1937 the first of the draconian legislation aimed at marihuana. A reading of the hearings before the House Ways and Means Committee that preceded the passage of the legislation demonstrates quite clearly how little empirical data was found to support the Act. Indeed, the enactment reflected far more the mass hysteria surrounding the subject than any concrete evidence of the drug's harmfulness. The hearings were characterized by brevity and lack of information. Little expert medical, sociological, or of the scientific evidence was produced or listened to. I would urge this committee to acquaint itself with some of the excellent comprehensive special reports and commission reports which have been developed over the past half-century. They would include:

The La Guardia Report (1944)

The Wooten Report (1968)

The Shafer Report (1972)

The Le Dain Commission (1973)

Canadian Senate Special Committee on Illegal Drugs Report (2002)

I think that if this legislative body is as meticulous and comprehensive in collecting and assessing the data as these Commissions were, it will have a better chance of arriving at a sound judgment about whether the "harmfulness" of marihuana is sufficient to enact such a restrictive bill.

In conclusion, I must tell you that I have much more to say on this topic, but given the extremely short time allotted for these hearings, there is no way I can thoroughly respond to the erroneous findings proposed in this bill. It would take days, if not weeks, to carefully review each of the studies and reports submitted by the government in order to fully explain to you the fallacies and inaccuracies. In short, this committee cannot possibly hope to seriously consider in the amount of time allocated the relevant evidence necessary to reach conclusions about the public health effects of marijuana. I would urge the committee to postpone action on this legislation until such time as a full and fair review of all the evidence is achieved. If the legislature does adopt these findings, I would urge you to fully annotate those findings with specific references to specific evidence in the legislative record.



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My name is Robert Melamede, Ph.D. I am submitting the following testimony regarding Senate Bill NO. 74. I am the Chairman of the Biology Department at the University of Colorado in Colorado Springs. Additionally, I am an active scientist involved in cancer research and I am a founder of a new biotechnology company that is developing novel approaches to treat cancers. I am also the father of four and grandfather of two.

The stated purpose of Bill 74, "The purpose of this Act is to protect the health and safety of persons in this state, and to provide legislative findings concerning this Act regarding marijuana and its effects in this state" is a valuable pursuit for any state to embark on. Unfortunately, the findings stated in the bill are, for the most part, in direct contradiction to those that would have been arrived at had modern peer reviewed science determined the bill's findings.

Finding 1 is correct. Marijuana is the most commonly used illegal drug in the United States.

Finding 2 is largely incorrect. While marijuana has some adverse affects on health, its benefits far out weight its harm. Regarding Finding 8, while smoking anything is a respiratory irritant, there is no evidence that smoking marijuana causes lung cancer. Recent peer-reviewed scientific findings clearly demonstrate that the nicotine found in tobacco causes cancer by preventing genetically damaged cells from dieing **Cannabis does not contain nicotine, hence cells genetically damaged by the carcinogens in the smoke are insufficient to cause cancer in the absence of nicotine.** If the intent of Bill 74 is to protect the health of Alaskans it should be directed towards tobacco products that kill over 400,000 Americans yearly from respiratory and cardiovascular illnesses, including lung cancer.

In contrast to tobacco cannabis has many health benefits. Regarding Finding 7, the reason that the cannabinoid compounds exert multitudinous effects on the body is that they mimic the way our bodies function. **Current science shows that we all produce marijuana-like compounds that regulate all of our body systems (cardiovascular, neurological, immunological, respiratory, excretory, digestive, muscular-skeletal).** Age related biochemical imbalances in these systems lead to diseases such as autoimmune diseases (diabetes, arthritis, ALS, Crohn's, and multiple sclerosis), cardiovascular disease (heart attacks and strokes), neurological diseases (Alzheimer's, Parkinson's) and cancers. Again, modern science indicates that **cannabinoids that we produce or consume can delay the onset and reduce the severity of many of these illnesses.**

How can cannabis have so many positive health effects and yet be viewed as so dangerous? Again, the benefits come from how it mimics the way our bodies try to counter these illnesses by making marijuana-like compounds (endocannabinoids). The



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reason public policy has been contrary to the above scientific findings is due to the lag in widespread knowledge of these facts. For example, the Institute of Medicine report was released in 1998 and contained data that was a few years old. The bulk of the exploding level of research on cannabinoids has occurred since then. For example, the Institute report examined cannabis as an anti nausea agent potentially useful for cancer suffers. **We now know that cannabinoids kill a variety of cancer cells including those from breast, prostate, leukemia, lymphoma, glioma, and skin cancers.**

Regarding Finding 9, a recent article describes a new animal model for self-administration of marijuana (a measure of addictive behavior). The paper showed that a **monkey would self-administer THC only to a point and then would stop.** When extrapolated to equivalent human doses the study indicated that a **human would take a few drags and no more.**

The above experiment has important implications for current concerns regarding higher THC levels in current marijuana. Regardless of THC concentration, only a particular level of effect is desirable. Too much is avoided. Hence a logical conclusion is that the availability of strong cannabis means less would be consumed. It should be remembered that there is no achievable lethal dose of cannabis and consuming too much results in sleep.

Finding 10, regarding the increased number of individuals seeking treatment for cannabis use is a pathetic example of sacrificing the truth for an agenda. Persons arrested for marijuana possession are often given a choice between treatment or prison. Even with marijuana use, these persons are capable of making the logical decision in favor of treatment instead of incarceration.

The old Nahas studies referred to in Bill 74 do not reflect modern immunological knowledge. They were done with very high doses, beyond what anyone would use. His work has largely been discredited by the scientific community. The immune system has two arms to it, a pro-inflammatory TH1 response that is balanced by an anti-inflammatory Th2 response. Endocannabinoids, that we all produce, shift the immune response to TH2. Depending on circumstances this effect could be good or bad. We need a strong Th1 response to fight certain infections such as tuberculosis, Legionnaire's disease and leishmania infection. However, in a modern society most death occurs from age related diseases that are in fact exacerbated by an excessive TH1 response. Hence, as mentioned above, cannabis is good for autoimmune diseases such as diabetes, multiple sclerosis, arthritis and Crohn's disease, neurological diseases such as stroke and Alzheimer's disease, cardiovascular disease, as well as cancer. **THC has been show to directly kill a number of different cancer cells including breast, prostate, leukemia, lymphoma, glioma and skin cancer.**



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Cannabinoids regulate the biochemistry of our male and female reproductive systems. Excess consumption can impair sperm maturation and prevent the implantation of a fertilized egg into the uterine wall. These effects are not permanent and are readily reversed. In fact the uterus cannabinoid levels go down during ovulation to allow implantation but then are necessary for normal fetal development. **Keep in mind that cannabinoids are found in mother's breast milk where they are important for feeding and probably other functions such as sleep and stress relief in infants.**

Mother nature uses cannabinoids. Remember, every time every member of the legislature gets hungry, it is because they are giving themselves the munchies with the cannabinoids that they make. Every time they feel pain, the pain is less that it would be if they were not making cannabinoids to turn down the pain. When they are feeling relaxed and free of stress it is because cannabinoids that they make are helping them to feel better.

I have provided you with an article, Harm Reduction--The Cannabis Paradox. The article was peer reviewed and has been approved for publication in the Harm Reduction Journal. It contains references that verify the facts that I have testified to.

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Education:

Herbert H. Lehman College,	NYC	B.A.	1969	Anat/Phys.
Herbert H. Lehman College,	NYC	M.S.	1972	Molec/Biochem.
City University of New York,	NYC	Ph.D	1980	Molec/Biochem

Professional Experience

Chairman Biology Dept.	University of Colorado CS	9/01-present
Director	LCCRO Monoclonal Facility	1/93-2001
Assistant Research Professor	Univ. of Vermont	8/88-2001
Assistant Research Professor	N.Y. Medical College	1985-8/88
Research Associate	N.Y. Medical College	1978-1981
Graduate Fellow	Lehman College	1975-1978
Adjunct Lecturer	Lehman College	1970-1975
Part-time Lecturer	Bronx Comm. College	1970

Refereed Publications

1. Melamede, R. Harm Reduction-The Cannabis Paradox the Harm Reduction Journal. in press.
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1. Melamede, R. Cannabis and Tobacco: Different Carcinogenic Potentials submitted Harm Reduction Journal.

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Abstracts.

1. Susan Schweitzer, Steven Barton, Karen Newell, and Robert Melamede (2003), Colorado Policy Institute. Can Cannabinoids Protect Cells From the Harmful Effects of Excess Sugar Consumption?
2. Fields, Dana and Robert Melamede (2003), American Association for the Advancement of Science (AAAS). Entropomic Space.
3. Fields, Dana and Robert Melamede (2002), Butcher Symposium Open System Far From Equilibrium Thermodynamics Suggests the Need to Use Entropomic Space
4. Robert Melamede (2002) The Costs of Marijuana Prohibition Colorado Policy Institute.
5. Robert Melamede and Karen Newell (2002), Coleman Institute. Does the Endocannabinoid System Interact with UCP-2 to Protect or Kill Cells?
6. Robert Melamede and Karen Newell (2001), Coleman Institute. The Role of Endogenous Cannabinoids in Controlling the Life, Death and Differentiation of Nerve Cells.
7. Ivan A. Beshpalov, Andrei A. Purnal, Susan S. Wallace, and Robert J. Melamede* Engineering antibodies that bind thymine glycol in DNA, (2001) In The Twelfth

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2. Melamede, R. J. Indications for Cannabinoids: Autoimmune Diseases, in Cannabis und Cannabinoide. Pharmakologie, Toxikologie und Therapeutisches Potential. Huber-Verlag (Bern), January, 2001
3. Melamede Robert. Cannabis-whether like it or not. Chemistry and Industry. November 21, 2001 p.724
4. Lipton, Laura, and Robert Melamede. 'Organizational Learning: The Essential Journey.' In "The Process-Centered School: Sustaining a Renaissance Community," (1997) edited by Arthur L. Costa and Rosemarie M.
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Published Letters:

Journals

1. Robert Melamede (23 May 2003) British Medical Journal, A Science Based Evaluation of Cannabis and Cancer
<http://bmj.com/cgi/eletters/326/7396/942#31878>

Newspapers:

1. Science Needed Aldergrove Star (CN BC) 12 Aug 2004 Amendment Could Enable Patients to Avoid Opiates Gazette, The (Colorado Springs, CO) 19 Jun 2004
2. Medical Marijuana Allard Ignores Legalization Benefits Gazette, The (Colorado Springs, CO) Apr 2004
3. Marijuana Is A Miracle Rocky Mountain News (Denver, CO) 18 Dec 2003
4. Our Bodies Make, Use 'Pot'-Like Compounds Source: Rocky Mountain News (Denver, CO) 20 Jun 2003
5. Medical Marijuana Racine Journal Times, The (WI) 05 May 2003
6. Alternative Medicine? MARIJUANA CAN TREAT MANY DISEASES Source: Gazette, The (CO) 16 Apr 2003
7. Believe The Scientists And Patients Who Suffer Source: Ocean County Observer

- (NJ) 14 Apr 2003
8. Ignorant Doctors Boulder Weekly (CO) 6 Feb 2003
9. Heed The Science Denver Post (CO) Fri, 08 Nov 2002
10. Get Educated On The Benefits Of Marijuana Las Vegas City Life (NV) Thu, 31 Oct 2002
11. Mind-Alteration Daily Camera (CO) 27 Feb 2002
12. DEA's Crackdown Doesn't Make Scientific Sense Athens News, The (OH) 17 Jan 2002

Presentations at Professional Meetings and Seminars:

- 1985-1986 Beckman, Cetus, Dupont, LKB Pharmacia, Whitehead Institute
1993 Immune Response Corporation
1995 Wellness Council of Upper Peninsula
1995 Jefferson Cancer Center
1996 IDEXX Laboratories Inc.
1996 Alteon
1997 Morphosys (Germany)
1997 Pyrosequencing (Sweden)
1998 Pentose Pharmaceuticals
2000 University of Texas at Tylor
2001 Sigma Psi, University of Colorado
2003 Lecture for Pillar (education in retirement)
2003 Safe Access Now Hayden Ca
2003 Oakland Cannabis Buyers Club
2004 broadcast 90 minute lecture on KMUD Radio in Los Angeles.
2004 University of Virginia, The Third National Clinical Conference on Cannabis Therapeutics.
2005 National Organization for the Reform of Marijuana Laws. San Fransico.
2006 Invited to present at The Fourth National Clinical Conference on Cannabis Therapeutics.

Meeting Attended and Presented Abstracts

- American Association for the Advancement of Science 2003
Butcher Symposium 2002
Colorado Policy Studies 2002
Coleman Institute 2002
Coleman Institute 2001
Antibody Engineering Conference 2001

Grants and Research:

Principal Investigator

- Automated Process for Sequencing Nucleotides and Site-specific Mutagenesis, Whitehead Associates: Venture Capital Support
\$90,000 11/84-86
Development Grant to establish *in vitro* antibody technology at UVM.

Vermont Cancer Center	\$75,000	12/92-12/93
	\$45,000	1/94/-12-94
Development Grant A Novel Method for Determining Antigens that bind T-cells. Immune Response Corporation	\$30,000	1/94-12/94
NISSC - Modulation of Homeostatic Mechanisms to Reduce Biological Consequences of Radiation Exposure	\$10,000	6/03-12/03
Biologically Motivated Personalized Computation Forms for Wearable Computing. (with Dr. Semwal) NSF not funded	\$200,000	2/04

Co-Principle Investigator

An Immunological Approach to Study DNA Damage and Repair	DOE	\$780,000	3/1/97-11/30/98
Repair of DNA Damage Induced by Ionizing Radiation	NIH:	\$764,694	4/82-3/95
Research-based Computer-assisted Undergraduate Molecular Biology Labs.	NSF:	\$90,447	1/93-1/95

Patents and Disclosures

1. Automatable Process For Sequencing Nucleotides 9/5/89 USA Patent #4,863,849 (sold to PyroSequencing 1998)
2. Fluorometric Quantitation Mycoplasma Bromide USA Patent # 5,604,096, 2/18/97
3. A means of preserving organs and tissue for transplant, and for improving the success of transplantation (Disclosed 6/02)
4. Diagnostic And Therapeutic Treatments Related To Mitochondrial Disorders PCT. (application pending 5/13/03)
5. A method for treating a curing psoriasis (6/13/03,)

Gifts:

Monetary

Arranged \$40,000 Gift from Weinstein Family to Bioenergetics Institute (2004)

Equipment:

2004 ABI Automated DNA Sequencer (used)
 2003 BioTeK Fluorescent Plate Reader (used)
 2002 BioTek Spectrophotometric Plate Reader (used)
 2001 Visible Genetics Sequencers (2) (used)

Founder-Newellink Corporation License agreement with CU brings in \$180,000/yr for Dr. Newell's research, additionally, CU will receive royalties.

Students:

UCCS Students**Undergraduate**

Michael Collins – graduated, Darus Bechamie graduated, Rafael Vega graduated, Chris Stubbs-current, Jackie Hartley-current, Mike Port-current, Anna Strompolos,

Graduate Students

Steven Barton (left for med school),
Kathleen May (left for Newell lab and Osteopath school), Brad Storrs (graduated MBS), Maria McGee current, David Owens, Shady Eshak

Masters Committee William Richardson, Cecilly Dupree, Amber Havermaule
Darrah Evans, Brian Resnick, James Tillman

Local High School Students

Karen Jones and Kristen Wells-received first place in regional Science Fair (2004), went on to the internationals and each received \$45,000 scholarships for their cannabis and cancer project. In 2005 they place 4th in the regional science fair.

Courses:**Taught**

Biol 203 Microbiology, Fall 2001-current, fall and spring semesters
Biol 400 Endocannabinoids and Medical Marijuana, fall and spring semesters fall 2002-current.
Biol 401 spring 05

Guest Lecturer

Cell biology, Immunology, Advanced Immunology, Bioinformatics,
Computer Science

Professional Organizations

AAAS
Sigma Xi
ICRS (International Cannabinoid Research Society)
Vermont Cancer Center
NECSI (New England Complex System Institute)
University of Colorado Center for Computational Biology

Service on-Campus:

Chairman Biology Department (current)
Director of MBS Program (current)
NIH Institutional Review Committee (formerly Recombinant Research Committee, current)
Alternate member of IACUC (current)
Chairs Advisory Committee to the Dean
Budget and Planning Committee
Search Committee Dean of Education
Search Committee Exercise Science position

Search Committee Biochemistry Position (Biology Department)
Search Committee Biochemistry Position (Chemistry Department)

Service off-Campus

12/05 Board Member Sensible Colorado
10/18/04 Café Scientifique
9/18/04 Back to the Bluffs UCCS
8/21/04 Dean Becker Radio Show-Cultural Baggage KPFT Houston Texas
4/1/04 Million Marijuana March Acasia Park
12/9/03 PILLAR Institute for Learning in Retirement
11/03 Radio Interview Jim Dexter Show Utah KTKK
10/4/03 Fallfest presentation
10/23/02 FreeThinkers
10/12/02 Luncheon at BSCS with Bruce Alpert's President of National Academy
of Sciences
10/2/02 Radio Interview Colleen Brookes Show Denver WKBI
9/28/02 UCCS Fall Fest
9/15/02 Acasia Park Hemp Rally
9/2/02 Radio Interview Jim Dexter Show Utah KTKK
08/17/02 Denver HempFest
3/20/02 Member of TriBeta Society
01/15/02 Judged Black Forrest Peyton Middle School Science Fair

Abstract

Harm Reduction--The Cannabis Paradox

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This article examines harm reduction from a novel perspective. Its central thesis is that harm reduction is not only a social concept, but also a biological one. More specifically, evolution does not make moral distinctions in the selection process, but utilizes a cannabis-based approach to harm reduction in order to promote survival of the fittest. Evidence will be provided from peer-reviewed scientific literature that supports the hypothesis that humans, and all animals, make and use internally produced cannabis-like products (endocannabinoids) as part of the evolutionary harm reduction program. More specifically, endocannabinoids homeostatically regulate all body systems (cardiovascular, digestive, endocrine, excretory, immune, nervous, musculo-skeletal, reproductive). Therefore, the health of each individual is dependant on this system working.

Introduction

The concept of harm reduction is at the heart of conflicting international drug policies. The Dutch pioneered this approach. Today most European countries and Canada have embraced the idea that society benefits most when drug policy is designed to help people with drug problems to live better lives rather than to punish them. In contrast, the United States federal policy demands rigid zero tolerance with overwhelming emphasis on incarceration of offenders (the Drug War). Although, seemingly reasonable arguments can be made to support both sides of the dispute, the recent global trend towards harm reduction has resulted from the acknowledgement that drug use has been a part of all societies throughout history and the realization that repressive policies are expensive, ineffective, and often harmful.

A dramatic example of the benefits that can result from a harm reduction approach to drugs is seen with needle exchange programs. While prohibitionists argue that providing clean injection equipment promotes drug use, the facts do not support this contention. For example, the Australian needle exchange program is credited with keeping the HIV/AIDS infection rate very much lower than what is typically found globally (<http://www.chr.asn.au/about/harmreduction>). Commonly cited examples of the failed repressive policies championed by the United States are the now repealed alcohol prohibition and the current drug war. Crime, financial support for terrorism, disrespect for the law, and destruction of families, communities, and ecosystems can all be attributed to drug prohibition. Yet, the staggering cost of the drug war, driven by United States policy and taxpayers' money, amounts to many billions of dollars a year.

Cannabis is the third most commonly used drug in the world, following tobacco and alcohol. In the United States, much of the drug war is focused on marijuana (over 700,000 people arrested last year alone). Is there justification for this policy? The gateway theory states marijuana use leads to the use of other drugs, and drives the U.S. policy despite evidence that suggests alcohol and tobacco use may foster the gateway effect [1] [2]. In contrast, countries that support harm reduction focus their enforcement and social support efforts on "hard drugs." Consequently, many countries have effectively decriminalized marijuana. Holland, having the most liberalized drug laws, does not have more cannabis users (over age twelve) than do more repressive countries, and the per capita number of heroin users is also lower (http://www.minjust.nl:8080/a_beleid/thema/drugs/drugs.htm). The Dutch Ministry of Justice estimates that 0.16% of cannabis users are heroin users. This figure does not support cannabis being a gateway drug. Data from the 2000 National Household Survey on Drug Abuse (U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration) also shows that the vast majority of people who try cannabis do not go on to use hard drugs.

A little explored question is what does harm reduction specifically mean with respect to cannabis consumption? This article will address cannabis harm reduction from a biological perspective. Two directions will be examined: what are the biological effects

of cannabis use and what are the social effects that emerge from the biological foundation.

Like many substances that are put into the human body, there can be positive or negative consequences that result from cannabis consumption, depending on amount, frequency, quality, and probably most importantly, the idiosyncratic biochemistry of the user. Prohibitionists concentrate their efforts on the negative effects of cannabis use, while anti-prohibitionists tend to focus on the positive effects. If we assume that both sides have valid arguments, the issue to be resolved is one of balance between the negative and positive effects. Would a policy of tolerance, or prohibition, be more likely to reduce harm overall? Which policy would better serve society as a whole, as well as problematic drug users?

Biological science can be more objectively evaluated than social science. The central theme that will be presented in this article is that appropriate cannabis use reduces biological harm caused by biochemical imbalances, particularly those that increase in frequency with age. Proper cannabis use, as distinguished from misuse, may have significant positive health effects associated with the way cannabis mimics natural cannabinoids. In essence, it is proposed that the endocannabinoid system, selected by 600 million years of evolution, is a central mediator of biological harm reduction through its homeostatic activities. The social implications of cannabis use will be viewed as emerging from the biological platform. Herein lies the paradox of cannabis and harm reduction. Is appropriate use of cannabis better than no use?

The Controversy

Cannabis use can be divided into three categories, recreational, medical, and religious. The latter will not be examined in this article. Some, including those who favor or oppose cannabis use, presume recreational and medical use are the same. On the one side, it is often claimed that any cannabis use is justified by some underlying medical need. On the other side, cannabis use is presumed to have no medical value, with the implication that those who use it are simply "getting stoned." While the former claim may be too extreme, the latter defies current scientific understanding of the biological functions of the endocannabinoids. While many people are reluctant to approve recreational cannabis use, it appears that most people support medical use. The United States Federal Government denies that there is any valid medical use for cannabis, while the National Institute of Drug Abuse (NIDA) provides marijuana on a monthly basis to a few medical users through the compassionate Investigatory New Drug (IND) program of the Food and Drug Administration (FDA). Nevertheless, a number of states, through either legislative action or voter initiative, have approved the use of medical marijuana[3].

Current Federally Approved Medical Marijuana Uses

In order to better assess arguments for and against the medical use of marijuana, the scientific evidence for the health benefits of cannabis will be reviewed below. It should be noted that the federally supplied cannabis users have been receiving and using cannabis for 11 to 27 years with clinically demonstrated effectiveness in the treatment of glaucoma, chronic musculoskeletal pain, spasm and nausea, and spasticity of multiple

sclerosis [4]. Furthermore, there is no evidence that these patients have suffered any negative side effects of their cannabis use.

The Endocannabinoid System

Cannabis preparations have been used medically for thousands of years for illnesses such as epilepsy, migraine headaches, childbirth, and menstrual symptoms. However, it is only relatively recently that the active components have been identified and their mechanisms of action have begun to be understood. While delta-9-tetrahydrocannabinol (THC) was first synthesized by Mechoulam in 1967 [5], it was not until 1990 that the cannabinoid receptor was localized in the brain [6] and cloned [7]. Since then, discoveries in the field have proceeded at an ever-increasing pace. The discovery of cannabinoid receptors on cells naturally prompted the search for internal compounds (endogenous ligands) that would activate the receptors since it seemed unlikely that cannabis receptors had evolved so people could partake of cannabis. In 1992, anandamide was discovered [8]. This lipid metabolite was the first ligand of an ever-expanding class of molecules known as endocannabinoids (internal marijuana-like compounds) to be discovered.

Endocannabinoid synthesis, degradation, transport, and receptors together form the endocannabinoid system.

The broad therapeutic potential that can result from correctly manipulating the endocannabinoid system is just beginning to be realized [9][10]. In fact, major pharmaceutical companies, and university researchers all around the world are now engaged in the cannabinoid-related research [11]. Their efforts focus on learning how the endocannabinoid system functions, and on how to manipulate it in order to increase or decrease its activity, depending on the illness or condition under consideration. GW Pharmaceuticals in Britain has been developing and testing a plant extract-based product line that is in clinical trials in Britain and Canada [12]. The results thus far have been positive to the extent that Bayer AG has entered into a 25-million-dollar distribution agreement for GW's still unapproved product, Sativex. In contrast, Sanofi Research has developed an antagonist that will inhibit the ability of endocannabinoids to stimulate hunger and thus potentially be useful for weight control.

Evolution of Endocannabinoids

The cannabinoid system appears to be quite ancient [13][14], with some of its components dating back about 600 million years to when the first multicellular organisms appeared. The beginnings of the modern cannabinoid system are found in mollusks [15] and hydra [16]. As evolution proceeded, the role that the cannabinoid system played in animal life continuously increased. It is now known that this system maintains homeostasis within and across the organizational scales of all animals. Within a cell, cannabinoids control basic metabolic processes such as glucose metabolism [17]. Cannabinoids regulate intercellular communication, especially in the immune [18] and nervous systems [19]. In general, cannabinoids modulate and coordinate tissues, organ and body systems (including the cardiovascular [20], digestive [16], endocrine [21], excretory [22][23], immune [18], musculo-skeletal [24], nervous [19], reproductive [25], and respiratory [26] systems). The effects of cannabinoids on consciousness are not well

understood, but are well known, and underlie recreational cannabis use. These effects also have therapeutic possibilities [27].

Cannabinoids: Homeostatic Regulators

The homeostatic action of cannabinoids on so many physiological structures and processes is the basis for the hypothesis that the endocannabinoid system is nothing less than a naturally evolved harm reduction system. Endocannabinoids protect by fine-tuning and regulating dynamic biochemical steady states within the ranges required for healthy biological function. The endocannabinoid system itself appears to be up- or down-regulated as a function of need. As will be detailed later in this article, endocannabinoid levels naturally increase in the case of head injury and stroke [28], and the number of cannabinoid receptors increases in response to nerve injury and the associated pain [29]. In contrast, the number of cannabinoid receptors is reduced when tolerance to cannabinoids is induced [30].

Physical Characteristics of Living Systems

To illustrate the multidimensional biochemical balancing act performed by cannabinoids, a variety of endo- and exocannabinoid activities will be reviewed below. In order to appreciate these activities a brief introduction to cell biology may provide the context for this review. All life is dependant upon the maintenance of its dynamic organization through sufficient input of nutrients and removal of wastes. The more complicated an organism is, the more complex the coordination required to accomplish the essential tasks necessary to maintain this vital flow of inputs and outputs. Coordination requires communication. Cells communicate by thousands of different, but specific, receptors on cell surfaces that respond to thousands of different, but also specific, molecules (ligands) that bind to the receptors. A receptor that is bound to its activating ligand causes biochemical changes to occur in the cell. In response to such regulatory signals on the membrane, biochemical regulation within the cell occurs at the level of gene expression as well as at the level of enzyme action and other processes outside the nucleus. Ultimately these changes, through complex biochemical pathways, allow cells to divide, carry out specialized tasks, lie dormant, or die. Any of these cellular activities, when not properly coordinated, can result in illness. Two major categories of disease states are those that result from acute illness commonly caused by infections and those that are age-related. Historically, in the United States, the cause of death has transitioned from being pathogen-induced to age-related. Current scientific literature regarding cannabis indicates that its use is often bad for the former but good for the latter (see Immunology section below).

Cannabinoids and Brain Disorders

Since cannabis' action on the brain is most widely known due to its recreational use, the nervous system will serve as the starting point for examining cannabinoid activity as an example of a natural biological harm reduction system. Numerous disease states associated with the nervous system will be seen as potential targets for cannabinoid-based therapy [31]. The nervous system is composed of nerve and supporting cells. In addition to the role cannabinoids play in a healthy nervous system [32], the regulatory effects of cannabinoids in cases of stroke [28], Parkinson's disease [33], Huntington's disease [34],

amyotrophic lateral sclerosis (ALS) [35], Alzheimer's disease [36], glioma (a type of brain tumor), [37] multiple sclerosis [38], seizures[39], and pain [40][41] will be examined.

Cannabinoids and the Healthy Brain

In a healthy individual, cannabinoids play a direct role in neurotransmission of many nerve cell types. They exhibit the unusual property of retrograde transmission, in which the cannabinoid neurotransmitter diffuses backwards across the neural cleft to inhibit the presynaptic action potential [42]. This function essentially regulates the sensitivity of a nerve cell by acting as a feedback mechanism that prevents excessive activity. Some nerve cells die when they are excessively stimulated by excitatory neurotransmitters (excitotoxins) such as glutamate. Cannabinoids can reduce the level of stimulation and protect against this form of cell death [43][44]. In addition to their down-regulatory effect on neurotransmission, cannabinoids play other roles in reducing this type of cell death (biological harm reduction) by regulating the role of interleukin-1 (IL-1) and the IL-1 receptor antagonist (IL-1ra) [45]. For example, cannabinoids were shown to modulate the release of IL-1ra thereby protecting against IL-1 assisted cell death [46].

The role of cannabinoids in neurological health and disease goes beyond the prevention of cell death and regulates neuronal differentiation. Cannabinoid receptors are functionally coupled to the fibroblast growth factor receptor (FGF). The FGF receptor, when stimulated, activates lipid catabolism via diacylglycerol (DAG) lipase which causes the hydrolysis of DAG to produce 2-arachidonyl glycerol (2AG) [47]. 2AG is an endocannabinoid shown to be important for axon growth and guidance [48]. This function is critical for nerves to innervate their target effectors. The ability to control these fundamental neurological activities, in conjunction with the anti-inflammatory properties of cannabinoids, is likely to have important regenerative health benefits for people suffering from neurological damage as occurs with stroke or injury [28].

Multiple Sclerosis

Both animal and human studies provide strong evidence of the therapeutic potential of cannabinoids to provide relief from a number of neurological disease states [49]. The use of cannabinoids to treat people suffering from multiple sclerosis (MS) is an excellent example of the importance of "medical marijuana" as an agent of harm reduction.[50] MS is a neurodegenerative disease in which the immune system attacks components of the nervous system. The axons of many central nervous system (CNS) neurons are surrounded by a myelin sheath that acts much like an insulator around a wire. MS is associated with the degradation of the myelin sheath that leads to loss of axon function and cell death, thus producing the disease symptoms.

Cannabis-based therapies for the treatment of MS can provide symptomatic and true therapeutic relief. On the one hand, cannabinoids help to reduce spasticity in an animal model of MS (chronic relapsing experimental autoimmune encephalomyelitis (CREAE) [51]. However, the involvement of the cannabinoid system in the etiology of MS goes much deeper. MS is in reality an autoimmune disease. In order to appreciate why

cannabinoids can have an important role, beyond what has already been mentioned, in treating MS on a mechanistic level [52], a brief introduction to immunology is required.

Cannabinoids and the Immune System

The role of the immune system is simplistically thought of as protecting us from foreign attack. More inclusively, however, the immune system has the biological function of modulating the life, death, and differentiation of cells in order to protect us. The immune system accomplishes these tasks, in part, by balancing two mutually opposed pathways known, respectively, as the "Th1" and "Th2" response. The Th1 immune response is critical for fighting infections caused by specific infectious agents [53]. This function is inhibited by cannabinoids. Thus cannabinoids are important homeostatic modulators of the immune system. While often classified as immune inhibitors, cannabinoids actually promote the Th2 response while they inhibit the Th1 response. Therefore cannabinoids are immune system modulators. A specific cannabinoid receptor (Cb2) [54] is found on most cells of the immune system.

Th1 Immune Response

The Th1 pathway is proinflammatory and functions by inducing the defensive production of free radicals that are vital for fending off pathogens, especially intracellular pathogens, such as those that cause Legionnaire's disease, Leishmania, and tuberculosis.

Accordingly, the use of cannabis should be avoided when the Th1 arm of the immune system is needed to fight a particular disease. Although contagion as well as immune suppression may have been involved, a recent study supports this perspective, in that a cluster of new tuberculosis cases was traced to a shared water pipe [55]. Free radical production, inflammation and cell-mediated immunity are characteristic of the Th1 response. The targeting of infectious organisms, or infected cells, by a Th1 immune response results in healthy surrounding cells being exposed to free radicals. Much as if radiation had been applied, there is collateral damage that occurs with a targeted Th1 immune response.

Cannabinoids and Th1 Mediated Auto-Immune Diseases

In contrast to the Th1 immune response, the Th2 immune response promotes the humoral arm of the immune system. It turns down the Th1 response, is characterized by antibody production, and is typically anti-inflammatory. Ideally, the Th1 and Th2 pathways are functionally balanced to optimally meet the survival needs of an organism in its environment. In reality however, many autoimmune diseases, and other age related diseases, are characterized by an excessive Th1-driven immune response at the site of the tissue damage involved. Multiple sclerosis, arthritis, Crohn's disease, and diabetes are all diseases that fall into this category.

The therapeutic impact of cannabinoids on these diseases can be dramatic. For example, when rodents were given experimental autoimmune encephalomyelitis (EAE) as an MS animal model and were treated with cannabinoids, the results were profound [56]. In a study that involved both guinea pigs and rats, 98% of the EAE animals that were not treated with THC died. In contrast, greater than 95% of THC-treated animals survived. They had only mild symptoms with a delayed onset or no symptoms at all. The capacity

of cannabinoids to down-regulate a spectrum of auto-immune diseases should serve as a warning against the long term use of CBI inhibitors for weight control. Such drugs are currently in the regulatory pipeline [57] and one of the participants in the clinical trial unexpectedly developed multiple sclerosis [58].

Cannabinoid Actions-Biphasic Responses

The brief interludes into cell biology, neurology, and immunology provide a biological platform for considering how cannabinoids might impact a variety of other disease states. It is important to keep in mind that in its role as a general homeostatic modulator, too much or too little cannabinoid activity can be harmful. Cannabinoid levels or concentration ranges vary as a function of an organism's genetics, the cell types under consideration, and their health and environment. Care must be taken when evaluating the scientific literature on cannabinoids and their effects. Cannabinoids often exhibit biphasic responses [59]. Low doses of cannabinoids may stimulate the Th2 immunological response, whereas high doses may inhibit the Th2 response and shift the balance in favor of a Th1 response. From a harm reduction perspective, these observations demonstrate the critical importance of dose-dependent, disease-dependent, state-dependent, and individually tailored approaches to cannabis therapeutics [60].

The use of cannabinoids in the treatment of Parkinson's disease is an example of a condition where excessive or deficient cannabinoid activity may prove problematic. Parkinson's disease results from the loss of levo-dopamine (L-dopa) producing neurons. In an animal model of Parkinson's disease, L-dopa producing cells are killed with 6-hydroxydopamine. Rats so treated exhibit spontaneous glutamatergic activity that can be suppressed by exo- as well as endocannabinoids [61]. The standard treatment for Parkinson's disease involves L-dopa replacement therapy. Unfortunately, this treatment often results in dyskinesia (abnormal voluntary movements). Recent clinical trials have shown that cannabinoid treatment reduces the reuptake of gamma-aminobutyric acid (GABA) and relieves the L-dopa-induced dyskinesia [33], as well as L-dopa induced rotations in 6-hydroxydopamine-lesioned rats [62]. In contrast to the potential benefits of cannabinoid agonists just cited, using a different animal model, the cannabis antagonist SR141716A reduced reserpine-induced suppression of locomotion [63]. Thus, in this model locomotion was restored by inhibiting the endocannabinoid pathway.

Cannabinoids and Cancer

Possibly the greatest harm-reducing potential afforded by cannabinoids comes from their use by cancer patients. Cannabinoids possess numerous pharmacological properties that are often beneficial to cancer patients. Many people are aware of the anti-emetic and appetite stimulating effects of cannabinoids [64]. A systemic study designed to quantify the efficacy of cannabinoids as an anti-emetic agent examined data from 30 randomized controlled studies that were published between 1975 and 1997 and included 1366 patients who were administered non-smoked cannabis [65]. For patients requiring a medium level of control, cannabinoids were the preferred treatment (between 38% and 90%). This preference was lost for patients requiring a low or a high level of control. Sedation and euphoria were noted as beneficial side effects, whereas dizziness, dysphoria, hallucinations, and arterial hypotension were identified as harmful side effects.

The cancer cell killing [66] and pain relieving properties of cannabinoids are less well known to the general public. Cannabinoids may prove to be useful chemotherapeutic agents [67]. Numerous cancer types are killed in cell cultures and in animals by cannabinoids. For example, cannabinoids kill the cancer cells of various lymphoblastic malignancies such as leukemia and lymphoma [68], skin cancer [69], glioma [70], breast and prostate cancer [71], pheochromocytoma [72], thyroid cancer [73], and colorectal cancer [74]. Since 2002 THC has been used in a clinical trial in Spain for the treatment of glioma [75]. However, not all cancers are the same, and cannabinoid-induced biochemical modifications, while effective in killing the cells of some cancers, as indicated above, can have the opposite effect on the cells of other types of cancer. For example, recent work has shown that the synthetic cannabinoid, methandamide, can promote the growth of lung cancer cells by a receptor independent pathway that involves the up-regulation of COX2 [76]. Although much has been learned about the therapeutic value of cannabinoid agonists and antagonists in different situations, scientific understanding of how to appropriately modulate the endocannabinoid pathways remains preliminary, with much remaining to be learned.

Cannabinoids and Pain

One area of current research that has begun attracting public interest is the pain relieving potential of cannabinoids, for both cancer [77] and non-cancer patients [78]. Medicine based on cannabis extract has demonstrated positive effects for pain relief [79]. Recently, an intrinsic role for cannabinoids in pain circuitry was discovered: the endocannabinoid AEA was identified as the natural ligand for the vanilloid receptors [80]. Vanilloid receptors, which are ligand-gated cation channels, are primary targets for the treatment of pain [81]. The cannabinoids seem to function in a pathway parallel to the opioid pathway [82] and are thought to exert anti-nociceptive activity at the level of the spinal cord and the brain [83], although they can also act peripherally by inhibiting mast cell degranulation [84]. In recognition of the pain relieving properties of cannabinoids, England [11] and Canada [41] are using cannabis preparations to provide relief to citizens suffering from a variety of disorders. Human trials have established that co-administration of cannabinoids can dramatically lower opioid use and can provide pain relief for neurogenic symptoms where other treatments have failed [85]. Recently, the topical application of the synthetic cannabinoid WIN 55,212-2 significantly enhanced the antinociceptive activity of morphine, opening the door for possible cannabis-induced pain relief with reduced cognitive side effects [86]. The intrinsic role of endocannabinoids in modulating pain is further supported by the up-regulation of the CB1 receptor in rats following nerve damage [29]. Once again, nature has selected cannabinoids to reduce harm.

Smoking and Lung Cancer

Fundamental to any consideration of cannabis-based harm reduction, as a biological phenomenon or as a policy, is how to best administer the drug. Smoking cannabis preparations, in contrast to oral administration [87], has the benefit of rapid action that allows self-titration of the drug's activity [88][89]. Unfortunately, cannabis smoke contains numerous carcinogenic compounds [90]. In fact, cannabis smoke may contain more tars than tobacco smoke [91]. However, despite the fact that cannabis smoke does

produce cellular changes that are viewed as precancerous, a major epidemiological study does not find that cannabis smoking is associated with tobacco related cancers [92]. A number of recent studies provide a scientific foundation for the clear relationship between tobacco smoking and lung cancer, a relationship that does not hold true for cannabis smoke (manuscript submitted to HRJ). For example nicotine, acting via nicotine receptors, is critical in the development of tobacco related cancer by inhibiting the death of genetically damaged cells [93]. Tobacco also promotes the development of blood vessels needed to support tumor growth [94] whereas cannabis inhibits tumor vascularization in nonmelanoma skin cancer [69] and glioma [95]. Although conclusions derived from an oft-cited study examining the carcinogenic effects of cannabis, tobacco, and cannabis combined with tobacco claims to show a link between cannabis smoking and head and neck cancer [96]. But these results do not hold up under scrutiny. The study does support a link between tobacco use that is exacerbated by concurrent cannabis use and the development of head and neck cancer. However, the "cannabis use only" group was composed only of two subjects, undermining the statistical relevance of conclusions regarding this group.

Smoking Alternatives

Regardless of whether or not smoking cannabis can cause lung cancer, smoking anything containing partially oxidized hydrocarbons, carcinogens, and irritants a priori, is not healthy and will have negative health consequences. Fortunately, harm-reducing alternatives exist. While often touted as a problem, the availability of high THC cannabis with high levels of THC permits less cannabis to be smoked for therapeutic effects. Additionally, methods of vaporizing the active ingredients of cannabis have been shown to successfully remove most compounds of concern while efficiently delivering the desired ones [97]. These results contrast with a recent Australian study that found that the use of a water pipe, or bong, failed to reduce tars or carbon monoxide delivered to the smoker [98]. GW Pharmaceuticals is developing an oral spray that should prove to be an additional safe and effective alternative delivery system [12] and valuable to medical cannabis users. The company has also identified strains with defined ratios of various cannabinoids for which specific medicinal value will be determined.

Cannabinoids Affect Drug Metabolism

Another important cannabis and harm reduction topic that must be considered is that of how the use of cannabis impacts on the pharmacokinetics of other drugs [99]. A number of drugs are metabolized by the P450 family of isoenzymes, including numerous cannabinoids [100]. Even though cannabinoids stimulate the transcription of P450 (2A and 3C), they also directly inhibit the activity of this enzyme [101]. There are likely to be pros and cons associated with P450 inhibition. P450 activity activates procarcinogens in tobacco smoke to create active cancer-causing mutations [102]. Thus, the inhibition of these enzymes by cannabinoids may minimize some of the negative consequences of smoke inhalation. On the other hand, many pharmaceutical drugs are metabolized by these enzymes. The reduction of the rate of drug metabolism by cannabinoids with pharmacokinetic consequences has been shown for cocaine [103], barbiturates [104], opiates [105], alcohol, the antipsychotic haloperidol [106], and others [107].

Thus far, both endo- and exocannabinoids are seen to reduce harm in numerous circumstances. Cannabinoid-based therapies have been especially helpful for the treatment of a variety of neurological and immunological disorders. Yet, we have only scratched the surface of the scientific literature on cannabinoids and their biological effects. Nevertheless, it should be apparent that cannabinoids have enormous medical potential as we learn to manipulate the natural cannabinoid harm reduction system that has evolved in the animal kingdom.

A fundamental question that remains unanswered is how basic, complex biochemical phenomena, as touched on briefly in this article, collectively emerge as substantial contributors to health and behavior. In far-from-equilibrium, thermodynamic systems, such as living organisms, there are discontinuities between underlying molecular dynamics and associated emergent macroscopic phenomena [108]. In such systems, small changes (called "perturbations") can amplify with consequences for the organization of the whole system. The cannabinoids help to regulate an amazingly broad range of biochemical events. All of these effects have genetic foundations. As such, natural genetic/biochemical variation in a population can be expected to have significant effects on health and behavior. It should be expected that in a population distribution of cannabinoid levels and sensitivities, as a function of an individual's health/disease status, some individuals would naturally need to increase their cannabinoid activity while others would need theirs lowered. Although the focus of this paper has been to suggest the many circumstances in which higher cannabinoid activity would be beneficial, these circumstances will necessarily differ among individuals with different congenital cannabinoid levels and sensitivities. Therefore, reduced cannabinoid activity would be beneficial under some conditions. A prime example of potential harmful effects of excess cannabinoids is their effects on pregnancy where low levels are needed but high levels are harmful [109].

Behavioral Effects: Self-administration and Reward

The broad homeostatic activities of cannabinoids that have been developed in this article have been rooted in hard science. The extension of these ideas to the psychological and behavioral levels is intrinsically more speculative, but remains consistent with the literature. For years, researchers have looked into the possible addictive qualities of cannabis. The lack of significant reward behavior was indicated by the lack of self-administration in primates. Experiments examining preference in rats demonstrated that low doses of THC could induce place preference but that higher doses produced drug aversion [110], again demonstrating the homeostatic nature of cannabinoids. Self-administration is typical of most psychoactive drugs of abuse. Hence, one could conclude that marijuana has a low potential for abuse.

Some may question the conclusion that cannabis has a low abuse potential since an animal model using squirrel monkeys was recently developed in which self-administration behavior was maintained using THC [111]. Interestingly, and consistent with the notion that the cannabinoid system is a biological homeostatic harm reduction mechanism, the self-administration of THC ranges from 2 to 8 ug/kg and peaks at 4 ug/kg [112]. Thus, in this animal model a controlled dose is chosen. To further put these

experiments in perspective, the dose used must be examined more closely. A 1-gram joint of 10% THC content would contain 100 mg of THC. The self-administered dose schedule chosen by the animal of 4 ug/kg would correspond to 360 ug of THC (approximately 1/278 of the joint) for a 200-pound human. Similarly, in rats, the intravenous self-administration of the synthetic cannabinoid Win 55,212-2 also occurred in a biphasic manner, with a maximum response occurring at 12 ug/kg. [113] The self-regulated, controlled use of low drug doses is not characteristic of addictive drugs of abuse.

Additional cannabinoid involvement in reward behavior is suggested by the increased activity of dopaminergic neurons stimulated with psychoactive cannabinoids [114]. This pathway is shared by other major drugs of abuse including, morphine, ethanol, and nicotine [115]. However, the production of glucocorticoid hormones that are normally produced in response to stress [116], are suppressed by cannabinoids [117]. Are cannabinoids addictive, is pleasure addictive, or is a low stress state addictive?

Cannabinoids and Stress

Stress and reward are complicated components of addictive behavior. How does repeated use of THC influence these states? A recent study examines this question by measuring glucose utilization in different areas of the rat brain following repeated treatment with THC [118]. After 7 and 21 days of THC treatment, THC no longer resulted in reduced glucose utilization in many areas of the brain typically affected by a single THC dose (most cortical, thalamic, and basal ganglia regions). In contrast, glucose utilization in other areas of the brain remained unaltered (nucleus accumbens, mediodorsal thalamus, basolateral amygdala, portions of the hippocampus and median raphe). Thus while the effects of THC on body temperature and locomotor activity become resistant to repeated THC administration, those areas involved in many higher brain functions remain responsive to THC. This differential adaptation to THC administration is consistent with a low addictive potential. The best evidence that demonstrates the absence of an addictive response to cannabis use is the fact that most people who use it do not continue to use it, and stop using it without any effort.

The stress-relieving properties of cannabinoids are an important aspect of their pharmacological activity. An interesting mechanism by which cannabinoids may promote stress relief is through their effects on memory. Cannabinoids control the extinction of painful memories [119]. What a blessing for those suffering from debilitating or life threatening illnesses: cannabinoids may help them to forget their misfortune.

Independent of the direct addictive or non-addictive properties of cannabis, the cannabis-opioid connection will be examined in more detail. Both drug families function (not necessarily exclusively) through biochemical pathways that are regulated by specific receptor-ligand interactions. However, there appears to be, as yet not fully defined, crosstalk between these pathways [120]. For example, CB1 receptor knockout mice are non-responsive to CB1 cannabinoid activities and show reduced addictive effects of opiates [121]. Similarly, Lewis rats showed enhanced sensitivity to morphine self-administration after treatment with the synthetic cannabinoid CP55040 [122]. Examining the cannabis-opioid connection from the other direction, chronic morphine administration

results in some down-regulation of cannabinoid receptors along with a significant reduction in 2AG [123]. These results show both positive and negative feedback relationships between the endocannabinoid and opiate systems. They also suggest that cannabinoids might serve to reduce the symptoms of opiate withdrawal [124].

The possibility that cannabinoids could serve as an addiction interrupter was demonstrated in rats where the synthetic cannabinoid agonist Win 55-212,2 reduced intravenous self-administration of cocaine [125]. Similarly, recent studies indicate that THC may facilitate nicotine withdrawal in mice [126] and inhibit alcohol preference in a model of alcoholism [127]. The opposite indications, that blocking cannabinoid receptors could serve as an addiction interrupter has also been made [128].

Behavioral Complexity

Behavioral processes and their complexities set humans apart from other animals. Can we simply extrapolate from animal to human behavior? It is one thing to comparatively examine the molecular and cell biology of animals and extrapolate to humans. However, the behavioral repertoire of humans appears to be dramatically enhanced over other animals and is therefore more difficult to connect between the species. Evolutionary relationships show that the cannabinoid receptors are located in the more advanced areas of our brains. Again, any population is always a spread around the average value of any parameter. A subset of the human population will inevitably retain a more primitive behavioral repertoire. Is this subset more susceptible to addictive behavior or psychological problems that could result from cannabis consumption? Has the cannabinoid system been optimized for the regulation of more primitive behavior or, alternatively, is it better optimized for the behavioral flexibility required of modern humans? Indeed, is there any evidence that the cannabinoid system, like our cortical capacity, may enable even greater behavioral flexibility in the more complex societies and altered environments of the future?

Answers to these questions are suggested by the data of human cannabis consumption. Most people who use cannabis in their youth stop using it as their lives progress. Most do so as a natural part of their development. They do so without outside intervention or help. They do so without ever having become heroin users, schizophrenic, or motivationally compromised. These facts indicate that for the majority of people who try marijuana, it is not addictive, does not lead to heroin use, nor is it a trigger for the onset of psychological problems. However, due to the complexity of cannabinoid activities, it is likely that in a small percentage of the population, cannabis use may foster problems. The biology presented in this paper suggests that such individual differences should be expected. We must learn to identify individuals who would be negatively affected by cannabis use; they are the people that an intelligent drug policy would help to identify and assist. In contrast, our policy criminalizes the majority of users and further harms them, perhaps psychologically as well as medically, through its repercussions.

The use of cannabis—and any mind-altering drug—by young developing minds rightfully remains an area of focus and concern. For example, is there a relationship between cannabis use and schizophrenia? Schizophrenia is characterized by distortions of

reality, disturbances of language and thought processes, and social withdrawal. Certainly, aspects of cannabis intoxication parallel these symptoms. It is feared that cannabis can precipitate this state [129], especially in susceptible individuals [130]. It has been suggested that schizophrenics (or potential schizophrenics) fall into two categories with respect to cannabis use [131]. One group may find symptomatic relief in the use of cannabis, while the other may actually take the risk of inducing the onset of the disease. The complexities of this issue are illuminated by the unpredictable behavior of interacting complex systems such as the nervous and immune systems, as will be considered below.

In an important recent study, De Marchi et al [132], examined the endocannabinoid levels in healthy volunteers and compared them to that of schizophrenic patients, both before and after successful antipsychotic treatment. Patients suffering with acute disease had significantly higher anandamide levels in their blood than did the normal individuals or patients in clinical remission. Might these elevated cannabinoid levels be contributing to the disease symptoms, and what might be causing them? Cannabinoids act homeostatically across biological subsystems. A possible immune involvement in schizophrenia has long been suspected, and immunological parameters have been implicated in the disease. For example, there is an inverse correlation between schizophrenia and rheumatoid arthritis: an individual generally does not get both illnesses [133]. Interestingly, schizophrenia has been correlated with HLA type, *Toxoplasma gondii* infection, and exposure to cats [133]. *Toxoplasma gondii* infects brain neurons, and is best controlled with a strong pro-inflammatory immune response. Endocannabinoids modulate the pro-inflammatory TH1 response by up-regulating the anti-inflammatory Th2 response. Hence, it is likely that some individuals idiosyncratically respond to *Toxoplasma gondii* infections by producing excess endocannabinoids and suffering the associated abnormal mental state. Antipsychotic drugs have actually improved the outcome of infection with this parasite [134].

Conclusions

Evolution has selected the endocannabinoids to homeostatically regulate numerous biological phenomena that can be found in every organized system in the body, and to counteract biochemical imbalances that are characteristic of numerous damaged or diseased states, in particular those associated with aging. Starting from birth, cannabinoids are present in mother's milk [135], where they initiate the eating process. If the activity of endocannabinoids in the mouse milk is inhibited with a cannabinoid antagonist, the newborn mice die of starvation. As life proceeds, endocannabinoids continuously regulate appetite, body temperature, reproductive activity, and learning capacity. When a body is physically damaged, the endocannabinoids are called on to reduce inflammation, protect neurons [136], regulate cardiac rhythms [137] and protect the heart from oxygen deprivation [20]. In humans suffering from colorectal cancer, endocannabinoid levels are elevated in an effort to control the cancer [74]. They help relieve emotional suffering by reducing pain and facilitating movement beyond the fears of unpleasant memories [119].

While this review is far from complete, it attempts to provide a conceptual overview that supports the endocannabinoid system as being nature's method of harm reduction. There

is a pattern to all the cannabinoid-mediated activities described. Many of the biochemical imbalances that cannabinoids protect against are associated with aging. Aging itself is a system-wide movement towards chemical equilibrium (away from the highly regulated far-from-equilibrium state) and as such is an imbalance from which all living organisms suffer. In contrast, the harmful consequences of cannabis use, however exaggerated they often appear to be, are likely to represent significant potential risk for a minority of the population for whom reduced cannabinoid levels might promote mental stability, fertility or more regulated food consumption.

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STATEMENT REGARDING ALASKA SB 74 AND HB 96

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I am an Associate Professor in the Biomedical Program and the Department of Biological Sciences at the University of Alaska Anchorage. I have been the chair of the Nervous System course in the medical school curriculum of the WWAMI Program at UAA since 1992, with an affiliate appointment in the Department of Biological Structure at the University of Washington School of Medicine. I mention my University affiliations only to establish my credentials; my statements are not intended to represent the official positions of the University of Alaska or the University of Washington, their administrations, or their boards of regents.

Although I have not personally conducted research on the health effects of marijuana use, I am well acquainted with the current literature on this topic. More importantly, I do have first-hand experience in the process of scientific peer review, and I understand of how consensus is established among biomedical researchers.

It is important to remember that science is a continuously adjusting and self-correcting process. Therefore, the most recent consensus on any question reflects not only the most recent data, but it also incorporates all prior research and earlier consensus positions. My point is that the most recent reviews are generally the best, what may be called "state-of-the-art". The vast majority of evidence cited in support of SB 74 are older, preliminary studies, which have not been confirmed by other researchers. It ignores entire bodies of research showing little or no harm from marijuana. It is not good science.

One of the courses we teach to medical students in the University of Washington and the Alaska WWAMI program is about how to critically read and evaluate the medical literature. Besides emphasizing the most recent data, we emphasize that different sorts of papers carry different weight. A well-designed review of many experimental studies is more valuable than any single experimental study alone. When you look at the information cited in support of SB 74, it turns out that those papers are predominantly not review articles. My 1st-year medical students would easily be able to find their way to the latest, thoroughly reviewed literature on marijuana's health effects, such as the article by Dr. Iversen in the February 2005 issue of Current Opinions in Pharmacology that we have included in the written testimony for this hearing.

In the hierarchy of scientific consensus, the most authoritative conclusions are usually those from expert panels and commissions, since they conduct the most extensive review. A number of independent commissions, both in this country and abroad, have investigated the effects of marijuana. We don't have time today to discuss all of them, but one of the best known is the 1972 National Commission on Marijuana and Drug Abuse, appointed by President Richard Nixon. After reviewing the scientific evidence, they were "of the unanimous opinion that marijuana is not such a grave problem that individuals who smoke marijuana, and possess it for