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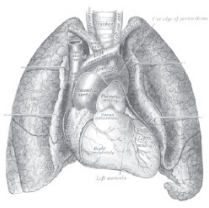
UCLA Lab Reports Surprising Results at ICRS Meeting

Smoking Cannabis Does Not Cause Cancer Of Lung or Upper Airways, Tashkin Finds; Data Suggest Possible Protective Effect

By Fred Gardner

Marijuana smoking —"even heavy longterm use"— does not cause cancer of the lung, upper airways, or esophagus, Donald Tashkin, MD, reported at this year's meeting of the International Cannabinoid Research Society.

Coming from Tashkin, this conclusion had extra significance for the assembled drug-company and university-based scientists (most of whom get funding from the U.S. National Institute on Drug Abuse). Over the years, Tashkin's lab at UCLA has produced irrefutable evidence of the damage that marijuana smoke wreaks on bronchial tissue.



With NIDA's support, Tashkin and colleagues have identified the potent carcinogens in marijuana smoke, biopsied and made photomicrographs of pre-malignant cells, and studied the molecular changes occurring within them.

It is Tashkin's research that the Drug Czar's office cites in ads linking marijuana to lung cancer.

It is Tashkin's research that the Drug Czar's office cites in ads linking marijuana to lung cancer. Tashkin himself has long believed in a causal relationship, despite a study in which Stephen Sidney, MD, examined the files of some 64,000 Kaiser patients and found that marijuana users did not develop lung cancer at a higher rate or die earlier than non-users.

Of five smaller studies on the question, only two —involving a total of about 300 patients— concluded that marijuana smoking causes lung cancer.

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Tashkin decided to settle the question by conducting a large, population-based, case-controlled study. "Our major hypothesis," he told the ICRS, "was that heavy, longterm use of marijuana will increase the risk of lung and upper-airways cancers."

The Los Angeles County Cancer Surveillance program provided Tashkin's team with the names of 1,209 L.A. residents aged 59 or younger with cancer (611 lung, 403 oral/pharyngeal, 90 laryngeal, 108 esophageal).

Interviewers collected extensive lifetime histories of marijuana, tobacco, alcohol and other drug use, and data on diet, occupational exposures, family history of cancer, and various "socio-demographic factors."

Exposure to marijuana was measured in "joint years"

Exposure to marijuana was measured in "joint years" —average number of joints per day *x* years that number smoked. Thus if a person had smoked two joints a day for 15 years they'd have consumed for 30 j-yrs.

Controls were found based on age, gender and neighborhood. Among them, 46% had never used marijuana, 31% had used for less than one joint year, 12% had used for 1-10 j-yrs, 5% had used 10-30 j-yrs, 2% had used for 30-60 j-yrs, and 3% had used for more than 60 j-yrs.

Tashkin controlled for tobacco use and calculated the relative risk of marijuana use resulting in lung and upper airways cancers. A relative risk ratio of .72 means that for every 100 non-users who get lung cancer, only 72 people who smoke get lung cancer. All the odds ratios in Tashkin's study turned out to be less than one!

Compared with subjects who had used less than one joint year, the estimated odds ratios for lung cancer were .78 for 1-10 j-yrs [according to the abstract book and .66 according to notes from the talk]; .74 for 10-30 j-yrs; .85 for 30-60 j-yrs; and 0.81 for more than 60 j-yrs.

The estimated odds ratios for oral/pharyngeal cancers were 0.92 for 1-10 j-yrs; 0.89 for 10-30 j-yrs; 0.81 for 30-60 j-yrs; and 1.0 for more than 60 j-yrs. "Similar, though less precise results were obtained for the other cancer sites," Tashkin reported. "We found absolutely no suggestion of a dose response."

The data on tobacco use, as expected, revealed "a very potent effect and a clear dose-response relationship —a 21-fold greater risk of developing lung cancer if you smoke more than two packs a day." Similarly high odds obtained for oral/pharyngeal cancer, laryngeal cancer and esophageal cancer. "So, in summary" Tashkin concluded, "we failed to observe a positive association of marijuana use and other potential confounders."

There was time for only one question, said the moderator, and San Francisco oncologist Donald Abrams, M.D., was already at the microphone: "You don't see any positive correlation, but in at least one category, it almost looked like there was a negative correlation, i.e., a protective effect. Could you comment on that?" (Abrams was referring to Tashkin's lung-cancer data for marijuana-only smokers, 1-10 j-yrs.)

"Yes," said Tashkin. "The odds ratios are less than one almost consistently, and in one category that relationship was significant, but I think that it would be difficult to extract from these data the conclusion that marijuana is protective against lung cancer. But that is not an unreasonable hypothesis."

At the Poster Session

Tongtong Wang explains her findings to Chris Breivogel. Wang and colleagues at McGill University searched medical literature databases for reports of adverse events attributed to cannabis between 1962 and 2004. Total incidence was suprisingly low: 141 articles describing 266 cases.

Abrams's Favorable Results

Abrams had results of his own to report at the ICRS meeting. He and his colleagues at San Francisco General Hospital had conducted a randomized, placebo-controlled study involving 50 patients with HIV-related peripheral neuropathy. Over the course of five days, patients recorded their pain levels in a diary after smoking either NIDA-supplied marijuana cigarettes or cigarettes from which the THC had been extracted. About 25% didn't know or guessed wrong as to whether they were smoking the placebos, which suggests that the blinding worked.

Abrams's results show marijuana providing pain relief comparable to Gabapentin, the most widely used treatment for a condition that afflicts some 30% of patients with HIV.

After Abrams's presentation, a questioner bemoaned the difficulty of "separating the high from the clinical benefits." Abrams responded: "I'm an oncologist as well as an AIDS doctor and I don't think that a drug that creates euphoria in patients with terminal diseases is having an adverse effect." His study was funded by the University of California's Center for Medicinal Cannabis Research.

Add ICRS Notes

The 15th annual meeting of the ICRS was held at the Clearwater, Florida, Hilton, June 24-27. Almost 300 scientists attended. R. Stephen Ellis, MD, of San Francisco, was the sole clinician from California. Medical student Sunil Aggarwal, Farmacy operator Mike Ommaha and therapist/cultivator Pat Humphrey audited the proceedings.

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—Donald Abrams, MD

Some of the younger European scientists expressed consternation over the recent U.S. Supreme Court ruling and the vote in Congress re-enforcing the cannabis prohibition. "How can they dispute that it has medical effect?" an investigator working in Germany asked us earnestly. She had come to give a talk on "the role of different neuronal populations in the pharmacological actions of delta-9 THC."

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For most ICRS members, the holy grail is a legal synthetic drug that exerts the medicinal effects of the prohibited herb. To this end they study the mechanism of action by which the body's own cannabinoids are assembled, function, and get broken down. A drug that encourages production or delays dissolution, they figure, might achieve the desired effect without being subject to "abuse."

News on the scientific front included the likely identification of a third cannabinoid receptor expressed in tissues

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ICRS Meeting *from page 1*

of the lung, brain, kidney, spleen and smaller branches of the mesenteric artery. Investigators from GlaxoSmith-Kline and AstraZeneca both reported finding the new receptor but had different versions of its pharmacology. It may have a role in regulating blood pressure.

Several talks and posters described the safety and efficacy of Sativex, G.W. Pharmaceuticals' plant extract containing high levels of THC and cannabidiol (CBD) formulated to spray in the mouth. See "Dr. X's Top Talks," on page 11.

G.W. director Geoffrey Guy seemed upbeat despite the slide his company's stock took this spring when UK regulators withheld permission to market Sati-vex pending another clinical trial. Canada recently granted approval for doctors to prescribe Sativex, and five sales reps from Bayer (to whom G.W. sold Canadian marketing rights) are promoting it to neurologists. Sativex was approved for treatment of neuropathic pain in multiple sclerosis, but can be prescribed for other purposes as doctors see fit.

Most of the work being done with CBD and CBN is done with materials provided by GW, and some two dozen papers and posters gave them acknowledgment. At last there is a realistic alternative to NIDA for the young researchers to look to for support (and plant cannabinoids to study). GW has contributed to a significant shift in attitude.

On numerous occasions during the meeting a NIDA-funded researcher would describe the negative effects of THC, and immediately a scientist with a British accent would be at the mike pointing out that such a high dose injected into the stomach of a rat had nothing to do with the human experience with cannabis. It must have happened five or six times. The Brits were always very diplomatic, but they functioned like a truth squad.

Roger Pertwee of the University of Aberdeen reported intriguing results from experiments using a cannabis strain bred by GW to be high in THCV (tetrohydrocannabivarin).

It turns out that THCV strongly antagonizes anandamide while hardly

THCV strongly antagonizes anandamide while hardly antagonizing THC!

antagonizing THC! It's as if the cannabis plant contains and makes available to the body a choice of drugs and the body uses those it needs to achieve a balanced state (homeostasis). If the body is producing endocannabinoids in excess, it can use the plant cannabinoid THCV to achieve homeostasis. If the endocannabinoid system needs a boost, the THC provides it (while the THCV shuts down the EC system, giving it a rest as it were). The key to relief, apparently, is not high cannabinoid levels but proper gradients.

"The endocannabinoid system is the supeme modulator. Its job is done once you're back to the norm."

Guy explained, "It's as if the plant contains a first-aid kit giving the body everything it needs to get bettter, and the body decides which components to employ... The endocannibnoid system begins to kick in in abnormality, in pathology. Perhaps it kicks in whether the pathology is an increase in something or a decrease in something. What it's trying to do is get whatever that abnormality is back to homeostasis.

"The antagonist may be working to restore function back to the center, and the agonist might be working to restore function back to the center, and once they've achieved the norm, they don't go any further. The endocannabinoid system is the supeme modulator. Its job is done once you're back to the norm. Most endocannabinoid modulators simply won't drive the physiology or biochemistry —whatever they're controlling— past the norm to a detrimental effect."

Rimonabant Comes Closer

Which might explain the apparent benignity of Rimonabant, a drug that works by blocking the CB1 receptor system. Rimonabant is being tested by Sanofi-Aventis for weight loss and smoking cessation. Originally known as SR-141716, it was developed in the early 1990s as an antagonist drug for use by researchers. At the 2004 ICRS meeting, Sanofi researchers described favorable results from clinical trials of Rimonabant as a diet drug. They informally predicted regulatory approval in Europe and the U.S. within a year. Some observers warned that blocking the CB1 receptor system could result in unforeseen longterm side effects and noted that at least one MS patient had experienced an exacerbation after taking Rimonabant. Although regulatory approval has not yet been granted, Sanofi reported good news at this meeting regarding side-effects: no more MS cases in a smoking-cessation study study involving more than 1,000 patients worldwide. "Both the 5mg and 20mg doses continued to show efficacy in the maintenance of abstinence from smoking," reported Gerard Le Fur. "The 20mg dose also demonstrated efficacy in the reduction of weight gain as well as significantly increasing the HDL-Cholesterol levels."

A Sanofi team also reported favorable results from studies using Rimonabant to treat various rodent models of "metabolic syndrome" —obesity-related high blood pressure, high insulin levels, excessive triglycerides and "bad" cholesterol and other problems increasing the risk of diabetes, heart attack and stroke. There is growing acceptance of the notion that the body can adjust to even a heavy blockade of the CB1 system. Perhaps when the CB1 receptor is blocked, the endocannabinoids are redirected to other targets. At times the layman is struck by how rudimentary the biochemists' understanding of the body's mechanism of action really is.

"We're on plateau one or two and the answer is on plateau 12. We could spend the next 30 years on receptors and still not fully understand them." —Geoffrey Guy

"We're on plateau one or two and the answer is on plateau 12," said Guy. " We could spend the next 30 years on receptors and still not fully understand them. When we talk about receptors and agonists and antagonists we should be talking in the same breath about functionality —real functionality, not models in non-pathological situations. We need an understanding of the clinical outcome."

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Cloning the Receptor

ALYNN HOWLETT

The existence of cannabinoid receptors in the brain —proteins on the outside of certain cells to which cannabinoids bind, triggering a cascade of molecular events within the cells— was established in 1988 by Alynn Howlett and William Devane at St. Louis University. Researchers were astonished to find that these receptors, now known as CB1 receptors, are at least 20 times more prevalent in the brain than opioid receptors.

A cell contains hundreds of thousands of protein molecules. The cell membrane is made of fat (lipid). If the cell were as big as a house, a protein would be as big as, say, a scissors or a doorknob.

A receptor is a protein on the surface of a cell that binds to something else. The something else is known as a "ligand" or an "agonist." Neurotransmitters, hormones, and drugs are smaller than proteins by a factor of 1:5 or 1:10 (they have many fewer atoms than a protein).

The neurotransmitter floats around in the bloodstream and hooks onto receptors that bind to it specifically. The receptor has contact with both the outside and the inside of the cell (like a doorknob that, being twisted on the outside, twists on the inside.) The receptor mediates between the outside signal and what happens inside the cell.

The job of DNA is to store the directions for how to make all the proteins in our cells. To clone a receptor means you've located and can copy the gene —the section of DNA— that encodes it.

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CB1 receptors are concentrated in the cerebellum and the basal ganglia (regions responsible for motor control, which may explain why marijuana reportedly eases muscle spasticity); in the hippocampus (storage of short-term memory); and in the limbic system (emotional control). Cannabinoids acting through the CB1 receptors seem to play a role in the processes of reward, cognition, and pain perception, as well as motor control.

Addiction and Learning

Gregory Gerdeman's poster described how behavior in rats associated with drug dependence — "amped-up running around the cage" after an injection of cocaine— diminished dramatically after five days on Rimonabant.

"I'm funded to look at mechanisms of drug reward and addiction," says Gerdeman. "I'm interested in how the cannabinoids interact with that. The pathways of drug reward interact with the pathways of motor function and are key to understanding psychomotor disorders like Parkinsons and, I believe, obsessive-compulsive disorder and Tourette's syndrome."

Gerdeman studies an area of the brain called the nucleus accumbens. His experiments try to determine:

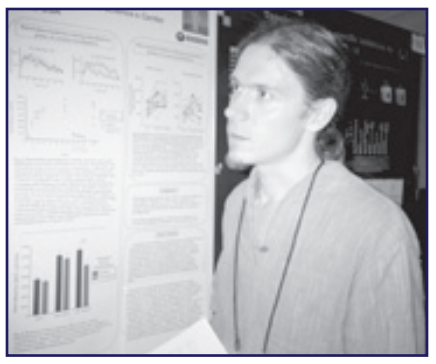
• By what mechanisms do neurons change their synaptic connection as habits are learned and unlearned?

• How, exactly is the endocannabinoid system involved?

• By what mechanism does the antagonist compound (Rimonabant) disrupt learning and memory at the cellular level?

Gerdeman, 31, is a naturalist, as interested in ocean life as he is in neurotransmission. He has a knack for clear exposition. With his long hair, soft spoken manner and democratic commitment to keeping the public (your correspondent) informed about advances in his field, I imagined that he might feel constrained, if not compromised, by reliance on funding from NIDA. I asked directly, "Did you do this work because of your interest in addiction or because you knew NIDA was interested in addiction? Did the fact that the money is there for this kind of research influence your study design?"

Gerdeman replied, "My interest is synaptic plasticity, which refers to brain mechanisms of cellular learning. These processes are involved in drug addiction, which I see as a strongly learned state of thinking and behavior. The cellular pathways we relate to 'learning' addiction are sensitized by addictive drugs and are clearly modulated by cannabinoids.



GREG GERDEMAN

I joined a lab as a postdoc and our funding structure is from NIDA and it is a grant based on studying the connection between cannabinoids and drug-abuse paradigms. That's what the experiments were proposed to do. So yes, focusing on addiction is where the funding is, and it's a major part of keeping my agreements about where I spend the money.

I think the therapeutic role of Rimonabant is interesting but what compels me is using the drug as a tool to investigate the function of endocan-nabinoids. It's interesting that Rimonabant may be effective to help curb a psychostimulant addiction, especially given the credible reports that some people use cannabis as a substitution therapy for addiction. That's something that I've had in mind as I've been doing the NIDA-funded work.

"If this neurocircuitry choreographed by endocannabinoids is playing a role in sustaining our habitual behavior, it is likely not a simple matter of the cannabinoid receptor being some kind of on-switch and when you turn it off you're blocking addiction. It's not anything so elementary like that. There are discrete neural circuits involved in our behaviors and how we define them to ourselves. When you start to influence that circuitry through manipulation of the cannabinoid system, it may open windows for rewiring the pathways related to your habitual behavior. Intention also feeds into this, and is very, very important. It's been long known that people have to have a motivation to quit drugs."

ICRS '05 *from previous page* —

Dr. X's Talks of Special Interest

Osteopathic Manipulation Boosts Endocannabinoid System

John McPartland of GW Pharmaceuticals reported that osteopathic manipulative treatment (OMT) works via the endocannabinoid system. McPartland and co-workers conducted a randomized, placebo-controlled study involving 31 patients of a New Zealand osteopath.

"Cannabimimetic effects" were measured by patients filling out a questionnaire before and after treatment defining levels of light-headedness, hunger, alterness, etc. Anandamide levels in the blood were also measured before and after treatments.

The "sham" manipulation mimicked a new technique called "biodynamic osteopathy in the cranial field." The sham practitioner sabotaged her own concentration and mental healing intention by silently reciting "backwards serial sevens" while she applied light manual contact to the patient's head.

Subjects receiving OMT indeed reported feeling cannabi-mimetic effects (more creativity, less coherence, for example) and their serum anandamide levels increased 168% over pre-treatment levels. Subjects receiving sham manipulation reported no changes in the questionnaire and there was no change in their serum anandamide levels.

McPartland et al noted that patients receiving OMT often experience an improved sense of well-being, sedation and euphoria —effects similar to those brought on by cannabis consumption. Previous studies indicated these psychotropic effects are not elicited by endorphins (as once had been assumed).

A recent study by Andrea Giuffrida, who contributed to the OMT study, showed that "runner's high" correlated with elevated anandamide and not endorphins. Patients receiving chiropractic, massage, acupuncture, and energy healing also experience parallel psychotropic effects. The authors conclude that the endocannabinoid system may be mediating a widespread but heretofore unrecognized therapeutic phenomenon.

The most interesting talks at the 2005 ICRS meeting were a mix of basic science and clinical science. The numbers are somewhat arbitrary —they were all amazing.

1. Krisztina Monory and colleagues at the Max Planck Institute in Germany unveiled dazzling expertise with the latest "conditional knockout" technology. Monory created a series of mutant mice and subjected them to behavioral tests.

With conditional knockouts, she dissected the involvement of different neuronal subpopulations colocalizing with cannabinoid 1 (CB1) receptors.

Provocatively, her results suggested that GABAergic forebrain interneurones are not required for the manifestation of typical symptoms produced by THC treatment, paving the way for a novel interpretation of cannabinoid pharmacology.

2. Patti Reggio has long researched the mechanisms by which THC, anandamide, and other cannabinoids bind to the CB1 receptor, the "key-in-lock" analogy. Her research indicated that the "lock" has more than one keyhole; THC and anandamide may share one binding site, and this differs from binding sites for WIN55 and other cannabinoids.

In fact, the binding site for THC may be a "side door," a part of the receptor that faces the lipid bilayer, rather than the extracellular portion of the receptor. Reggio identified two beta-branching amino acid residues on the receptor that specifically interact with THC (which she wonderfully called "groove residues," because of their chemical structure).

3. Many scientists have suspected the presence of a third cannabinoid receptor. Two research groups converged upon a molecular entity called "GPR55" as the long-sought "CB3" receptor. GPR55 was identified six years ago, but was labeled an "orphan receptor" because its endogenous ligand was unknown.

A team at GlaxoSmithKline went "ligand fishing" and discovered that GPR55 has affinity for anandamide, CP55,940, and SR141716A. Simultaneously, a team at AstraZeneca reported GPR55 is a G13-coupled receptor that activates the intracellular signaling mediator RhoA. GPR55 is expressed in the brain as well as mesenteric arteries, and regulates blood pressure.

4. The efficacy of THC at CB1 is modulated by other proteins. Chris Breivogel gave an update on beta-arrestin 2 (BA2), a protein implicated in the desensitization of CB1 and other G-protein-coupled receptors.

Experiments with mice suggested that BA2 shuts down CB1 signaling by THC, yet does not affect other cannabinoid ligands. Whether BA2 shuts down THC in humans remains to be seen; the BA2 gene is actively evolving, its sequence differs in humans, and the gene is undergoing positive selection.

Deborah Lewis presented research on CRIP (cannabinoid receptor interacting protein) 1a and 1b. CRIP1b may regulate the membrane localization of CB1. Intriguingly, CRIP 1b has only been identified in human and chimpanzee genomes, it may be unique to primates.

Several studies supported the notion that cannabis is more than simply THC.

5. Several studies supported the notion that cannabis is more than simply THC. This should be no surprise, given the number of people who consume medical cannabis yet cannot tolerate Marinol (pure THC).

Richard Musty and coworkers showed that anxiety induced by THC alone is mitigated by the addition of cannabichromene (CBC).

Ethan Russo showed that cannabidiol (CBD) acts at the 5HT1a receptor, a serotonin receptor targeted for the treatment of anxiety, depression, and pain.

Markus Leweke and colleagues at Köln conducted a randomized, placebo-controlled study involving 42 patients with acute schizophrenia. CBD significantly reduced psychopathological symptoms of acute psychosis, on par with Amisulpride (a new antipsychotic medicine not available in the U.S., said to be as effective as Clozapine).

CBD produced significantly less severe side effects than amisulpride.

CBD produced significantly less severe side effects than amisulpride. Stephan Wright and colleagues at GW Pharmaceuticals showed that a combination of CBD and THC was better than THC alone in the relief of refractory cancer pain, based upon a randomized clinical trial of 177 subjects.

6. In a similar "synergy" theme, Roger Pertwee and his team reported a unique characteristic of tetrahydrocannabivarin (THCV), a minor variant of THC (THC has a five carbon tail, THCV has a three carbon tail). THCV selectively antagonized the effects of anandamide, with little antagonism of THC. It's as if cannabis was formulated by a pharmaceutical company, and designed as a combination remedy that simultaneously gave our endogenous mechanism a rest (shutting down anandamide) and supplemented with an exogenous remedy (THC).

7. Donald Tashkin and colleagues at UCLA conducted a large, case-control study of marijuana smokers in Los Angeles. They determined that longterm heavy use of marijuana was not a risk for cancer of the lung, upper airwaves, or esophagus. This surprised Tashkin, whose lab previously demonstrated that marijuana smoke harbors potent carcinogens, and smoking damages airway tissues.

Tashkin's team interviewed over 1,200 L.A. patients with cancer, and compared them to an equal number of "controls" matched for age, gender, ethnicity, tobacco and alcohol use, diet, family history of cancer, and other socio-demographic factors. The relative risk of marijuana smoking, calculated as a statistical odds ratio, was < 1 (1 = the control group's chances of cancer). In contrast, heavy tobacco smokers had a 21-fold greater risk of cancer than control subjects.

Given the statistics, Donald Abrams posed a question from the floor, asking Tashkin to comment on the possibility that marijuana might provide a protective effect against lung cancer. Tashkin tried to back himself out of a corner, then concluded, "That is not an unreasonable hypothesis." The anti-inflammatory and anti-tumor effects of THC, terpenoids, and flavonoids in marijuana smoke may very well provide a protective effect against toxic L.A. air pollution!

8. Donald Abrams and colleagues at San Francisco General Hospital conducted a randomized, placebo-controlled study involving 50 patients with HIV-related peripheral neuropathy. Marijuana cigarettes supplied by NIDA provided pain relief comparable to Neurontin (gabapentin), the most widely used treatment for peripheral neuropathy. Given the poor worth of NIDA ganja, patient response to quality cannabis should be even better.

A questioner criticized the use of marijuana as medicine, brandishing the often-cited shibboleth, "you can't separate the high from the clinical benefits." Abrams deadpanned his reply, "I am an oncologist as well as a specialist in AIDS, and I don't think that a drug that creates euphoria in patients with terminal diseases is having an adverse effect."

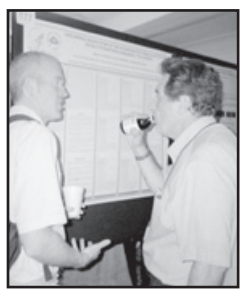
9. Ethan Russo of GW Pharmaceuticals showed that abrupt cessation of a medicinal cannabis extract was not associated with a withdrawal syndrome. A series of 25 patients with multiple sclerosis who took Sativex (50% THC and 50% CBD) for over one year experienced minor and transient disturbances of sleep and appetite when withdrawn from the drug.

Abstinence from Sativex was associated with re-emergence of MS-related symptoms, however. The study also showed that long-term treatment with Sativex did not result in dose escalation or tolerance.

Patients have never responded consistently to treatment. Every time a prescription is written (except for identical twins) what effectively begins is a clinical trial with n = 1.

—Alfred PJ Lake, MD

Goldberg's Monkeys Bat Last



Steven Goldberg (right) in conversation with **John McPartland**, maintains a colony of monkeys in Baltimore, Maryland that have been trained to self-administer THC (by injection).

Goldberg and Zuzana Justinova presented a poster on "The Abuse Potential of the Endocannbinoid Transport Inhibitor AM404: Self-Administration by Squirrel Monkeys." AM404 is one of the many compounds that corporate- and government-funded scientists have developed in hopes of achieving higher cannabinoid levels by means other than the illegal herb. Goldberg's monkeys liked AM404 enough to self-administer it, which means, in NIDA's terms, that AM404 is a drug with potential for abuse. After all their effort to create an alternative to smoked marijuana, the drug companies will have to run their products by Goldberg's monkeys!

The Goldberg-Justinova poster concluded "AM404 functioned as an effective reinforcer (comparable to THC, anadamide and cocaine under identical conditions) in non-human primates under a fixed-ratio schedule of drug injection. Our findings suggest that medications which promote the actions of endocannabinoids throughout the brain by inhibiting their membrane transport have a potential for abuse. It remains to be seen whether medications such as FAAH inhibitors, which augment CB1 signaling only in certain regions of the nervous system, would be self-administered in a similar manner."

Your correspondent had always heard that monkeys couldn't be trained to self-administer THC. When I asked Goldberg about this, he said other researchers had used "Old World monkeys," whereas he used squirrel monkeys from South America. But the real key to his success, he added, was the very low doses with which he rewarded the monkeys. This made sense —most of the primates I know prefer a slight alteration of mood to getting knocked-out-loaded. It also resonated with an ICRS talk on neuroprotection by Italian investigators who found that a synthetic cannabinoid was beneficial only at the lowest concentrations tested, and detrimental at high concentrations. When the name of the game is cannabinoids, less can be more.