

“Therapeutic Potential” In Spotlight At Cannabinoid Researchers' Meeting

By Fred Gardner

The 13th annual meeting of the International Cannabinoid Research Society was held in late June 2003 in Cornwall, Ontario — a rustbelt city on the St. Lawrence Seaway about halfway between Toronto and Montreal — at a labyrinthine conference center built and then sold off by the Canadian Navy.

The ICRS is made up mainly of university-connected scientists, many of whom receive support from the U.S. National Institute on Drug Abuse. ICRC members also include drug-company researchers and a small number of physicians, including several from the California Cannabis Research Medical Group (two of whom made it to Cornwall).

Abbott, Allergan, AstraZeneca, Cayman Chemical, Johnson & Johnson, Eli Lilly, Merck, Pfizer, Schering Plough and Solvay (makers of Marinol, synthetic THC in sesame oil) were among the drug companies represented at this year's meeting. “None of them are presenting data,” a university researcher observed, “They're all just here to keep an eye on one another and stay abreast of the science.”

Also in attendance were reps from Sanofi-Synthelabo (a giant French company hoping to market a drug that blocks the appetite-inducing effects of the body's own cannabinoids); GW Pharmaceuticals (the British firm awaiting government approval to market a cannabis-plant extract in alliance with Bayer); and Elsohly Laboratories (a company owned by America's only legal grower, Mahmoud Elsohly, who has devised a test that can distinguish between traces of Marinol and natural cannabis in the urine. Elsohly also has patented a novel THC delivery system, the suppository. “And he is the friendliest gentleman you'd ever want to meet,” said a Californian who knows somebody who is doing time thanks to the Elsohly test.)

There are three types of cannabinoids — herbal, synthetic, and endogenous. First to be characterized, in the 1930s and '40s, were active ingredients of the cannabis plant, hence the name. Some 68 natural plant cannabinoids have been described to date.

Since the 1970s synthetic compounds have been developed by various labs to exert effects like those of the plant cannabinoids (synthetic agonists) and to block such effects (synthetic antagonists). In the 1990s several chemicals in the body were identified as acting similarly, and dubbed “endocannabinoids” (short for “endogenous cannabinoids”).

Drugs that cancel the effects of cannabinoids — like Sanofi's diet pill — are

called cannabinoid “antagonists.”

Receptors activated by cannabinoids are highly concentrated in the cerebellum and the basal ganglia (areas of the brain responsible for motor control, which may help explain why marijuana eases muscle spasticity in disorders like multiple sclerosis), the hippocampus (responsible for storage of short-term memory), and the amygdala, which is part of the limbic system (emotional control, memory of fear, memory of pain). These receptors are now known as “CB 1” receptors.

A second cannabinoid receptor was initially detected in spleen cells, white blood cells, and other tissues associated with the immune system. The discovery of this second receptor type — called the CB2 receptor — suggested a product-development strategy for the drug companies: create a molecule that, by activating only the CB2 receptor, won't induce the nasty side-effect known as “euphoria.”

Any alternative to direct activation of the CB1 receptor is considered promising by the drug companies.

The first endogenous cannabinoid, arachidonyl ethanolamine (AEA), was identified by Raphael Mechoulam and William Devane of Hebrew University. They named it “anandamide” after the Sanskrit word for “bliss.” The discovery of anandamide and then another endocannabinoid, 2-AG, suggested a different commercial drug-development strategy: find the molecules that break down anandamide and 2-AG within the cell and create drugs to block their effect, allowing the endocannabinoids to linger. (This might sound unnecessarily complicated, but any alternative to direct activation of the CB1 receptor is considered promising by the drug companies.)

ICRS meetings adhere to a standard scientific-meeting format. Over the course of three-and-a-half days researchers presented 67 papers. Each had 15 minutes to describe their team's work (aided by computer-generated graphics). Another 86 studies were recounted on posters tacked to partitions in a large gymnasium. Each day there was a two-hour session at which investigators stood by their posters to answer questions.

The first day and a half of talks — and a proportional number of posters — were devoted to studies elucidating the chemical mechanisms by which cannabinoid compounds exert their effects in the body



ITAI BAB, GEOFFREY GUY AND RAPHAEL MECHOULAM talk shop at the 2003 meeting of the International Cannabinoid Research Society in Cornwall, Ontario.

and get broken down. Several groups presented evidence that there is a lot more to the basic cannabinoid signaling system than two receptors and two endogenous cannabinoids. (For example, Breivogel has found that the brains of mice lacking CB1 receptors still respond to stimulation by endogenous and synthetic cannabinoids. Kunos et al have found a receptor in epithelial tissue that is neither CB1 or CB2...

“Any blockbuster talks?” we were asked when we got back. Time will have to tell. Dramatic announcements are rare in any field of science; most studies contribute a finite bit of information that might or might not result in significant applications or new understandings — “cannabinoids modulate neuronal firing in the rat baso-lateral amygdala,” for example.

A talk by Itai Bab of Hebrew University seemed unambiguously significant to the layman (me): “Endocannabinoids stimulate bone formation,” according to Bab, “and possibly inhibit bone resorption directly by activating osteoblastic and osteoclastic CB2 receptors.” (Osteoblasts are bone-forming cells, osteoclasts are bone-removing cells.) What do the Bab Lab's findings — based on work with mice — imply for the homo sapien cannabis user? “Stoned heads equal stone bones,” said Bab, making a little joke.

Irv Rosenfeld, the Florida stockbroker who is one of seven patients receiving U.S. government-issued cannabis, was told about Bab's results. Rosenfeld

has a rare disorder characterized by tumor formation at the ends of his bones. “My doctors warned me to expect thinning of the bones,” he said. “They told me it was a certainty, but it hasn't happened. Maybe now we know why.”

The real news at the 2003 ICRC meeting was a subtle-but-pervasive shift in focus from the harmful to the helpful potential of cannabinoids. Adverse effects are still being studied, of course — Sarafian, Tashkin and colleagues at UCLA's David Geffen School of Medicine (sic) have pictures of blistered lung epithelial tissue that could make the joint-smokingest reprobate invest in a vaporizer. But we heard no dire warnings about addiction, permanently impaired brain structures, etc. There was no pitch from the director of NIDA urging ICRC members to renew their efforts to prove the harmful effects of cannabis. (Alan Leshner sent such a motivational message to the assembled scientists in 1998.) The new head of NIDA, Nora Volkow, who happens to be Leon Trotsky's great-granddaughter, has done some work in the cannabinoid field, and is said to understand its potential.

Another indicator of the political winds shifting: Peter Fried, an Ottawa-based professor who has conducted a 25-year, NIDA-funded study of the children of women who smoked marijuana while pregnant, has apparently given up trying to prove “cognitive dysfunction.” Fried was always straining because much of his data actually suggested that marijuana smoking had a positive

continued on next page

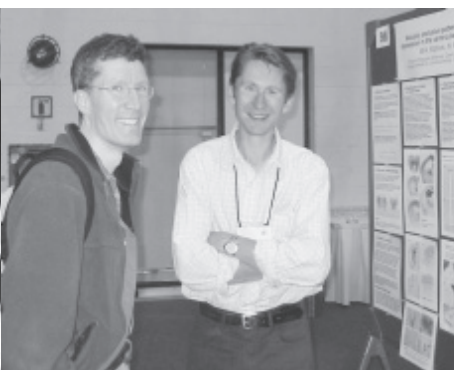
Comparing Notes in Cornwall



Roger Pertwee and Thomas Klein



Mauro Maccarone and Ester Fride



Ken Mackie and Maurice Elphick



Vincenzo di Marzo, Alexandros Makryannis

ICRS Report *from previous page*

impact, cognitively and socially. Fried's latest study compared the cognitive abilities of heavy users, quitters, and non-users among the kids (now adolescents and young adults). He reports that heavy use impairs cognition (slightly), but quitting restores it fully in a matter of months. In fact, the quitters wind up scoring better than the non-users!



ALISON MYRDEN

Fried's tone has changed over the years. When we first heard him in 1998, the subtext was "Danger! Beware! Marijuana use is associated with concealed pitfalls..." This time the subtext was: "So nu?"

The charming professor and other stars of the NIDA constellation — people who had spent a good part of their careers funding or carrying out the decades-long, inevitably futile search for adverse effects — have repositioned themselves as the leading pioneers of that most promising new field, the hope of suffering humanity, cannabis therapeutics!

The glad tidings were not confined to the last-day set of talks on "Therapeutic Potential." Indeed, therapeutic benefit has been so firmly established in recent years — thanks in part to California physicians and patients, and thanks, also, to G.W. Pharmaceuticals — that even the arcane molecular-level research seemed humanized and ennobled.

And the promising, positive findings just keep coming in:

- "...2-AG may regulate sperm functions in male and female reproductive tracts... human sperm may produce and degrade AEA to modulate their own swimming behavior via cannabinoid receptors." —Burkman *et al*

- "Blockade of the cannabinoid receptor in one-day-old mouse pups prevented milk intake and resulted in death within days of birth. The endocann-

binoid receptor system plays a critical role in milk ingestion and survival of the newborn." —Fride, *et al*

- "...These results provide a neural basis for previous studies that showed potent suppression of the abnormal pain responses of nerve-injured rats." —Liu and Walker

- "...This work could imply that combination treatment for pain, using cannabinoids jointly with opioids, may be more effective than opioids alone while utilizing lower doses and attenuating side effects." —Cichewitz *et al*

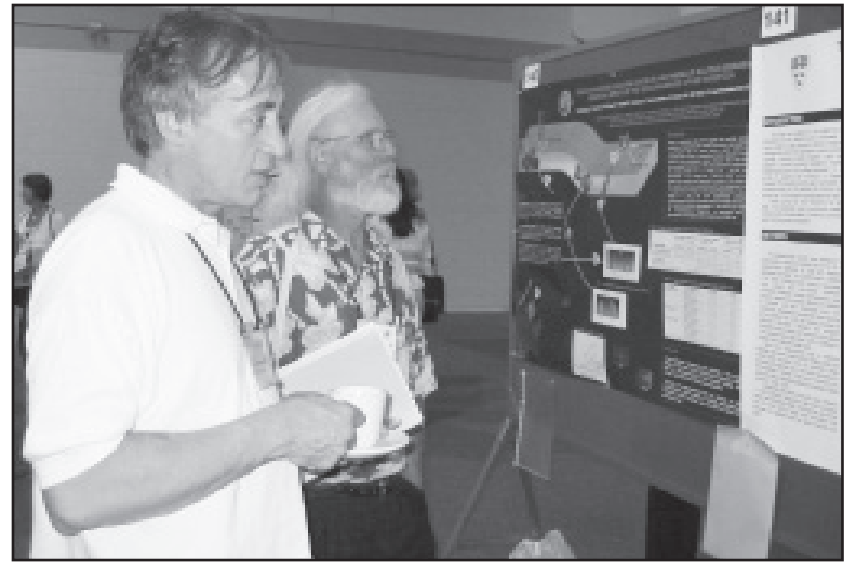
- "... Delaying the loss of CB1 receptors, either by environmental stimulation or pharmacologically, may be beneficial in delaying disease progression in Huntington's Disease patients." —Glass *et al*

- "This work may help to understand the mechanism of cannabinoid anti-tumoral action, and provides a novel pharmacological target for cannabinoid-based anti-tumoral therapies." —Blazquez *et al*

- "The endocannabinoids and 2AG inhibit cancer cell proliferation by acting at cannabinoid receptors. Endocannabinoid levels are enhanced in some tumors, possibly to counteract cancer cell proliferation via cannabinoid receptors. Inhibitors of endocannabinoid inactivation, by enhancing this endogenous tumor suppressing tone, may provide useful, non-psychoactive agents against cancer growth." —Di Marzo *et al*

- "... CBD (cannabidiol) acts to produce a significant antitumor activity inducing apoptosis [programmed cell death] ... the present results further confirm the possible application of cannabinoid compounds as antineoplastic agents." [neoplastic refers to unregulated growth] —Massi *et al*

- "... Our results indicate that THC



CALIFORNIA CLINICIANS R. Stephen Ellis and Jeff Hergenrather at the ICRS poster session, keeping abreast of the science on which cannabis therapeutics is based.

may reduce the progressive degeneration of... neurons occurring in Parkinson's Disease... The fact that the same neuroprotective effects were elicited by cannabidiol, a cannabinoid with negligible affinity for the CB1 receptors, suggests that both cannabinoids protect... neurons from death because of their antioxidant (and CB1 receptor-independent) properties." —Fernandez-Ruiz *et al*

- "Activity of the CB1 receptor has anticonvulsant effects in animal models of seizure and epilepsy... The results of this study provide evidence that, in the hippocampus, plasticity of the endogenous cannabinoid system occurs in response to epilepsy." —Wallace, *et al*

- "...The endogenous cannabinoid system plays a fundamental role in the physiological protection against excitotoxicity by dampening neuronal excitability and activating protective molecular cascades." —Monory *et al*

- "...There is rapidly emerging evidence that the cannabinoid receptor system has the potential to reduce both excitotoxic and oxidative cell damage... Here we report that treatment with D9-THC was effective if administered either before or after onset of signs in the ALS mouse model... To our knowledge, this is the first time a compound has been shown to be effective in this model

when administered after onset of disease signs... This profound anti-oxidant effect was not blocked by the CB1 receptor antagonist... suggesting the anti-oxidant effect was not receptor mediated. Additionally, D9-THC is anti-excitotoxic in vitro. These cellular mechanisms may underlie the presumed neuroprotective effect in ALS. As D9-THC is well tolerated, it and other cannabinoids may prove to be novel therapeutic targets for the treatment of ALS." —Abood *et al*.

Probably the most influential report of all was a brief statement made by Alison Myrden, a radiant Canadian woman, weakened at 37 by multiple sclerosis, who attend the closing sessions of the conference at the invitation of Ethan Russo, MD. During a question period Myrden walked to the mike and explained her situation. She had brought her mother, whom she pointed out. She said her mother (a retired surgical nurse) had been skeptical about the medicinal validity of cannabis, but had been convinced by what she'd heard from the scientists. Alison expressed thanks for the basic research done to date, and her hope that it would pay off before too long. It was short and simple, but it helped people in the room reconnect to their mission and their ideals.

Copyright 2004, 2012 by Fred Gardner. All rights reserved. Address reprint requests to editor@beyondthc.com