

Science and Politics at Rhode Island Conference

Patients Out of Time Welcome Disabled Vets

By O'Shaughnessy's News Service

Patients Out of Time is a pro-cannabis reform group led by Al Byrne, a retired Naval officer, and MaryLynn Mathre, a Vietnam era nurse. Byrne survived two catastrophic events in which others died and over the years he's had to deal with post-traumatic stress. He calls it PTS not PTSD. He says, "It's not a disorder, it's a rational response to what you've seen."

Byrne is a big, lanky man who played outfield for Notre Dame before he went off to war. He has spent years counseling vets in Appalachia for the Department of Veterans Affairs Agent Orange Class Assistance Program. MaryLynn Mathre, who goes by ML, is an addictions consultant. Her publications include "Cannabis and Harm Reduction: A Nursing Perspective," in the *Journal of Cannabis Therapeutics*. They are married and based in Virginia.

Byrne and Mathre had been active in NORML but split off in 1994. (Everyone's faction fights seem inconsequential and avoidable except one's own.) In 1995 they formed their own group, with participation from Irvin Rosenfeld, Elvy Musikka, George McMahon, and other surviving patients from the federal Investigational New Drug program. Neurologist Denis Petro was also involved from the start.

Since 2000 Patients Out of Time has organized a conference every two years to update doctors, nurses and other healthcare providers — none of whom heard a word during their education and training about the medical uses of cannabis or the body's endogenous cannabinoid signaling system— about recent research and clinical findings. The University of California at San Francisco and the Rhode Island Nurses Association provided continuing education credits to MDs and nurses attending this year's conference, which was held at the Crowne Plaza hotel in Warwick, RI, April 16-17.

Twelve nurses and more than 30 doctors registered for credit. Byrne estimates there were another 40 "allied professionals such as social workers." Total attendance was more than 225. Whereas recent POT conferences have been West-Coast-centric, this one drew participants from Colorado, New Mexico, Michigan, Montana, Maine, Massachusetts, New Jersey, and of course, Rhode Island.

All the talks will be online at medicalcannabis.com as soon as Ervin Dargan and his first-rate crew process their footage.

The conference to attend

For a doctor new to the field or a patient looking to stay abreast of scientific and clinical developments, Patients Out



RAPHAEL MECHOULAM opened the Patients Out of Time conference with an overview of cannabinoid therapeutics.

of Time is *the* conference to attend (in person or online). Many ICRS talks are too pharmacological; reports of clinical findings are rare. NORML meetings are too political, there's no science to speak of. But Patients Out of Time is just right in terms of understandability and emphasis on the medical side of the story, while giving the political side its due.

Raphael Mechoulam, the Israeli pharmacologist who, with colleagues, worked out the stereospecifics of the CBD and THC molecules in the 1960s, opened the 2010 conference with a detailed summary of what he and his colleagues have learned to date. (*"The Discovery of the Endocannabinoid System,"* pages 5-6 of this issue, covers some of the same ground.)

Mechoulam's partial list of physiological symptoms and conditions affected by endocannabinoids included anxiety, appetite, blood pressure, bone formation, cerebral blood flow, the digestive system, emesis and nausea, the immune system, inflammation, memory, mood, movement, neuroprotection, pain, reproduction, and stress.

Brain regions in which cannabinoid receptors are abundant include the basal ganglia (movement control), cerebellum (coordination), hippocampus (learning and memory, stress); cerebral cortex (higher cognitive function); intrabulbar anterior commissure (the link between cerebral hemispheres); and the nucleus accumbens (reward pathway).

Mechoulam reviewed the cannabinoids' wide range of therapeutic applications and then, in a second talk, focused on "an unexpected trio," Head Trauma, Osteoporosis, and Alzheimer's.

Head injuries trigger both destructive and protective responses — the production of compounds that lead to neuronal death and the production of the endocannabinoid 2-AG, which protects neurons. 2-AG is known to work through the CB1 receptor. Synthetic cannabinoids that work predominantly through the CB2 receptor also reduce damage resulting from stroke and head injury in animal models.

In discussing osteoporosis,

Mechoulam emphasized the health-giving benefits of oleoyl serine, a fatty acid predominant in olive oil. He cited a paper that concluded, "The positive association between bone mineral density and monounsaturated fat, which in the Greek diet is derived mostly from olive oil, is fairly strong, statistically significant."

Plant cannabinoids have been shown by Israeli researchers to promote the heal-

* *in the U.S.*

For a doctor new to the field or a patient looking to keep up with scientific and clinical developments, Patients Out of Time is the conference to attend (online at medicalcannabis.com, if not in person).*

ing of bone fractures. Mechoulam suggested, "Patients could benefit using preparations consisting of THC and CBD that may shorten the post-fracture immobilization period."

In Alzheimer's, amyloid plaques form in the brain, resulting in neuron loss. Studies with mice show that 2-AG levels rise after plaques are induced, and CB2 expression is increased in microglial cells (which dispose of neuronal debris). Mechoulam reported that in a 2009 study by Tolon *et al*, "A CB2 agonist caused beta-amyloid removal from human frozen tissue sections. The selective CB2 antagonist SR144528 prevented the plaque removal."

CBD may be protective in prion disorders such as scrapie and mad cow disease.

There is evidence suggesting that CBD could be protective against prion disorders such as scrapie (in sheep), bovine spongiform encephalopathy (mad cow disease), and Creutzfeldt-Jakob disease. Alzheimer's itself seems to be a prion disorder involving misfolded proteins. Mechoulam cited an under-publicized study by Dirikoc *et al* (2007) showing that in a mouse model of scrapie, injection of CBD limited the accumulation of prions, blocked neurotoxic effects, and led to increased survival time!

It is often the case in cannabinoid research that a promising result of potentially great significance does not get followed up on. Mechoulam cites a study conducted in the 1980s in Brazil showing that CBD prevented epileptic seizures. "I don't know why more work hasn't been done on this," he adds with a shrug.

The Synergistic Shotgun

John McPartland characterized THC (isolated, synthesized, and marketed as Marinol) as a medically useful "silver bullet," in contrast to herbal cannabis, an even more useful "synergistic shotgun." Various compounds in the plant augment the therapeutic activity of THC and mitigate its side effects. Foremost among these is CBD, which is "a silver bullet on its own," McPartland noted.

There seems to be conflicting data on whether CBD potentiates or negates

the effects of THC. On the one hand, the presence of CBD may enable more THC to cross the blood-brain barrier. On the other hand, CBD blocks THC from binding to the CB1 receptor.

CBD-Rich Strains in California

The coming availability of CBD-rich cannabis at California dispensaries was discussed by Steve DeAngelo, director of Oakland's Harborside Health Center. DeAngelo said that when he and a partner launched Harborside in the fall of 2004, they contacted numerous analytic chemistry labs in hopes of having their cannabis tested for mold and cannabinoid content. No lab was willing to take their money. In 2008 DeAngelo backed the entrepreneurs who started Steep Hill lab. Now, in a typical week, Harborside will send 60-70 samples — buds from the pounds supplied to the collective by growers — for testing.

Steep Hill outsources the mold testing to a lab that cultures and grows out the spores present on the sample buds. The type of mold and its concentration get reported back to Steep Hill, then to Harborside, then to the grower. DeAngelo says Harborside has had to withhold about two percent of the cannabis it purchases because of unacceptable levels of aspergillus. "Too many immunocompromised patients out there," he says. "We'd rather be safe than sorry."

Growers whose cannabis contains unacceptable levels of mold are advised to consult the "Clean Green" certification program and adopt better production and curing methods.

DeAngelo reported that three of eight CBD-rich strains identified by the lab are being grown out for distribution by Harborside and Project CBD. (Two more CBD-rich strains were identified this spring. *See story on page 1.*) DeAngelo said Harborside is committed to helping the Society of Cannabis Clinicians collect data on the efficacy of high CBD strains, and described the "preliminary effort at data collection" taking place at his dispensary.

Pendular Nystagmus

Multiple sclerosis can result in numerous visual problems. Some two to four percent of MS patients are afflicted by Pendular Nystagmus, a condition in

continued on next page



ORGANIZERS AL BYRNE AND MARYLYNN MATHRE CONFERRED AS MELANIE DREHER (silhouetted at left) addressed the Patients Out of Time conference.



HEATHER BRADSHAW discussed the role of cannabinoids in chronic pelvic pain. Anandamide is precursor to a compound called N-arachidonoyl glycine (NAGly) that may facilitate uterine contractions and reverse uterine inflammation. But NAGly may promote the growth of endometrial tissue outside the uterus — a process that has been blocked in the lab by pre-treatment with CBD.



GREGORY GERDEMAN (LEFT) reviewed the research on cannabinoids and the neurobiology of habit formation and addiction. Cannabinoids, unlike opioids and cocaine, do not represent a reward to mice. Cannabis dependence is "rare and atypical" in humans. "This is likely due to the inherently different mode of endocannabinoid action in the neural circuitry of reward compared to catecholamines, glutamate, or opioids," Gerdeman concluded.

At right: JOHN MCPARTLAND.

Patients Out of Time from previous page

which the eyeballs oscillate involuntarily. According to neurologist Denis Petro, smoked cannabis is the treatment of choice for Pendular Nystagmus. He showed a slide listing 13 drugs, from acetazolamide to valproate, that have been used without much success.

Petro recounted his own observation of several patients whose symptoms were controlled by smoking cannabis. He also cited a paper in *Neurology* (Schon et al, 1999) describing “the dramatic suppression of acquired pendular nystagmus in a patient with MS after smoking cannabis resin but not after taking nabilone tablets or orally administered capsules containing cannabis oil.”

Petro excoriated the FDA for sup-



DENIS PETRO

porting the DEA’s definition of cannabis as a Schedule I drug with “no currently accepted medical use.” He expressed embarrassment as a physician and as a citizen that the government would blatantly deny physical reality.

“In the Matter of Lyle Craker”

Among those frustrated by the federal marijuana prohibition is Lyle Craker, a botany professor at the University of Massachusetts Amherst, who recounted his Kafkaesque dealings with the federal government.

Craker applied in 2001 for a DEA license to grow cannabis for research purposes. Both U.S. senators from Massachusetts supported his application, but he got the runaround for eight years. At a hearing before an administrative law judge, Mahmoud ElSohly, the only federally licensed grower, testified in defense of the monopoly the University of Mississippi has been granted for decades, claiming that the cannabis he produces at Ol’ Miss meets the foreseeable needs of all U.S. researchers.

The judge determined that Craker/UMass should get a license. DEA Administrator Karen Tandy then overruled the judge’s recommendation, and Craker appealed. In the last week of George W. Bush’s reign, Acting DEA Administrator Michele Leonhart (the second-in-command who had taken over when Tandy resigned in the summer of ‘08) rejected Craker’s application.

A motion to reconsider kept *In the Matter of Lyle Craker* alive until Barack Obama could pick his own DEA Administrator. Earlier this year Attorney General Eric Holder announced the Democrats’ choice: Michele Leonhart.



LYLE CRAKER

The Situation in New Mexico



WILLIAM JOHNSON

Psychiatrist William Johnson, MD, is on the physicians advisory committee created by New Mexico’s medical cannabis law, which was passed by the legislature in spring 2007.

The law initially authorized cannabis use for seven conditions: cancer, glaucoma, multiple sclerosis, spasticity due to spinal-chord injury, epilepsy, HIV, and admission to hospice care. The physicians committee recommended adding nine more — including PTSD — that were approved by New Mexico’s secretary of health and added to the list.

PTSD soon became the leading condition for which people use cannabis legally in New Mexico. “We still run into the problem of VA physicians being unable to certify patients for PTSD because they’re federal employees,” said Johnson. “So those patients come to me or to another psychiatric practitioner to get their recommendations.”

Severe chronic pain was added to the list with a stipulation that the patient had to get a second approval by a pain specialist. “This has made it very difficult for patients with disabling conditions, who tend to be poor,” to legally use cannabis for pain, Johnson observed.

The secretary rejected the recommendation that Bipolar Disorder be added to the list, and is still weighing whether to add behavioral disturbances associated with autism, Alzheimer’s, and severe-to-moderate mental retardation.

Bryan Krumm, a psychiatric nurse practitioner, worked for 10 years to push through the New Mexico law. He decried its short list of applicable conditions, the restrictions on producers (95 plants total), and the small number of authorized producers (five as of April).

“Our biggest problem is that marijuana remains on Schedule I,” said Krumm. Medical research is being impeded. “We now have 14 states that have accepted the medical use of marijuana. Not one of those states has stood up to the federal government to stop their interference.”



STEVE DEANGELO AND REINALDO TAKAHASHI. Takahashi employs a model of PTSD in which rodents are trained to associate a stimulus with a painful event. He compared the effects of diazepam (as in Valium, a commonly prescribed treatment for nightmares), CBD, and AM404, an experimental drug that slows the breakdown of anandamide. CBD and AM404 measurably limited the formation of adverse memories and reduced fear responses, and were found to work via the CB1 receptor. Takahashi concluded, “the phytocannabinoid CBD could be an interesting pharmacological tool to reduce the anxiogenic effects of stress and promote the extinction of fear memories.”

When Issues Converge

As the Great Playwright would have it, the state chapter of Disabled American Veterans was meeting at the Crowne Plaza at the same time as Patients Out of Time.

DAV had a registration table set up in the lobby. There was a vet selling raffle tickets. We bought 12 for \$10 and gave him some back issues of *O’Shaughnessy’s*. We said that if we won, instead of the prize, we wanted our groups to hold a joint session. The vet selling tickets said he was all for it (lowering his voice and looking towards a man down the line) but didn’t think the commander would be.



MICHAEL KRAWITZ

Over the next two days we got to meet some of the DAV members and it turns out that, just like during the war, almost all the GIs smoke pot when it’s available, while the brass (supposedly) look down on it. That’s how it was back in “the day,” and that’s how it is to this day! The men who were GIs and NCOs in Vietnam seemed as deferential — maybe more deferential — now than they were when they were young. At least that was so for this small sample

of DAV members.

We made friends and smoked with two of them (one of whom had his own stash). On the afternoon of the second day, ML Mathre went running through the halls of the Crowne Plaza as Mike Krawitz started a talk about the Veterans Administration line on medical marijuana. (See story on page 58.) She came back with three DAV members in tow. Six more soon followed. Briefly, we had broken out of the single-issue trap!

One of our new friends confided that he hopes to be elected DAV state commander so he’s keeping his pro-cannabis politics hidden. MaryLynn said, “It’s your organization, the majority are for it, why not make access to medical marijuana your demand as a candidate? Disabled Veterans of America should have a strong pro-cannabis position.” The vet just repeated, “I’ve worked for this for a long time...”

The disconnect is obvious: a majority of the rank-and-file are pro-cannabis but the candidate is afraid to reveal his pro-cannabis outlook. What causes the disconnect?

Fear — a vague, pervasive, unending fear of the brass. And hope — the lingering hope of making it in some small way within a system run by the brass.



Another informative meeting:

THE INTERNATIONAL ASSOCIATION FOR CANNABIS AS MEDICINE

The IACM, founded in 2000, meets every other year in Germany. Some highlights from the 2009 meeting in Cologne:

- Manuel Guzman and colleagues at Complutense University in Madrid have determined the mechanism by which THC induces glioma cells to self-destruct.
- Donald Abrams reported on a study involving chronic pain patients at San Francisco General Hospital who had been using morphine and oxycodone. When vaporized cannabis was added to their regimen, “Most reported further relief.”
- Andreas Zimmer of the University of Bonn reported that beta-caryophyllene, a non-psychoactive terpenoid present in cannabis, modulates inflammatory and immune responses by activating CB2 receptors. Beta-caryophyllene is also found in avocado, lemon, oregano, cinnamon, clove, rosemary, thyme, sage, and black pepper.

• A team led by Rudolf Brenneisen at the University of Berne questioned the wisdom of the World Anti-Doping Agency testing athletes’ urine for THC-COOH, a long-lasting metabolite of THC. Its presence “does not allow a conclusion concerning the time of consumption or the impact on the physical performance,” according to Brenneisen. Testing for

pharmacologically active THC or THC-OH (11-hydroxy-THC) would make more sense.

- Michelle Sexton, with the Stella lab at the University of Washington, has been studying the role of the endocannabinoid system in MS. Would higher cannabinoid levels result in monocytes entering the brain more readily? Would the effect be to reduce neuroinflammation?

• Ethan Russo described his visit to the Yanghai Tombs in Western China, where excavation of a grave had revealed “a large cache of cannabis, superbly preserved.” It had been buried with a shaman some 2,500 years ago.



MICHELLE SEXTON



RAPHAEL MECHOULAM AND DEBORAH MALKA at the IACM meeting in Cologne, October 2009.