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Anecdotal reports of benefit abound

Doctors stress need to document anti-cancer effects of Cannabis 'oil'

By Fred Gardner

Increasing numbers of people have been using Cannabis "oil" —plant extracts consisting of 50% or more THC and/or CBD— to treat conditions ranging from mild rashes to potentially fatal cancers.

Reports of success are circulating among medical Cannabis users and on the internet. They gain plausibility from a parallel stream of papers published in scientific journals establishing that cannabinoids have anti-tumor effects on the cellular level and in animals. *(See "The Anti-Cancer Potential of Cannabinoids," page 4.)*

The anti-cancer properties of cannabinoids were a recurring theme at this year's meeting of the International Cannabinoid Research Society, and also in a course for physicians presented Oct. 24 at the University of California San Francisco. One speaker, Jeffrey Hergenrather, MD, described a particularly dramatic case seen by a San Diego colleague: a 90% reduction in the size of an infant's brain tumor achieved over the course of a year by parents applying hemp oil to the baby's pacifier before naptime and bedtime. *(See illustration at right.)*

Aptly dubbed "MMJ13001A" on the UCSF website, the half-day course on cannabinoid medicine included talks by three researchers whose findings about cannabis and cancer have been under-reported, to put it mildly: Stephen Sidney, MD, director of research for Kaiser-Permanente in Northern California; UCLA pulmonologist Donald Tashkin, MD; and Donald Abrams, MD, Chief of Hematology-Oncology at San Francisco General Hospital.

Some 60 doctors received continuing medical education credits for attending the half-day course at UCSF's Laurel Heights auditorium, which was organized by the Canadian Consortium for the Investigation of Cannabinoids, with help from Abrams and the Society of Cannabis Clinicians, and reprised the next day in Santa Monica (MMJ13001B).

A very interested auditor at the UCSF session, Michelle Aldrich, had used cannabis oil as a treatment for lung cancer. Her first-person account of the experience starts on page 20 of this issue. Donald Abrams, who consulted on Aldrich's case, says, "The fact that Michelle didn't have cancer that could be located [after using the oil] is a bit unusual in someone who started treatment with an advanced stage. I don't usually see that in my patients. Did the cannabis oil make a difference? We don't know because we don't have a controlled study."

Abrams has met with a UCSF neurooncologist "to discuss whether or not we should do a clinical trial adding oil to chemo for patients with glioblastoma [a brain tumor that is usually fast-moving and fatal]. Manuel Guzman's studies have shown that cannabinoids have great potential in treating brain tumors."

Abrams has been assured by Dr. Mahmoud ElSohly that the lab at the University of Mississippi —where cannabis is grown under contract with the National Institute on Drug Abuse— can produce a uniform, highly concentrated extract for research purposes. "But whether or not NIDA will let me have it," Abrams says, "I don't know."

Abrams has jumped through bureaucratic hoops before. He has obtained all the necessary approvals and funding to conduct clinical trials involving cannabis, and published his findings in peer-reviewed journals. Because chemotherapy has a measurable benefit, he says, "There's no way we could get approval for a study that evaluates cannabis oil as a cure for brain tumors without giving patients temolozide [the standard treatment for glioma].

So what Abrams has in mind is "a study of the pharmacokinetic interaction between cannabis oil and temolozide." The participants would be patients undergoing treatment for glioblastoma. The doctors would measure the level of temolozide in their blood before and after adding cannabis oil to their regime. The primary objective would be to establish safety —to confirm that the large cannabinoid infusions were not intefering with the body's ability to process temolozide.

An ulterior objective would be to document examples of cannabis oil expediting or promoting tumor reduction. Such a 'signal' might justify a trial of cannabis oil on its own.

"A 'cure' in cancer means five years of disease-free survival," Abrams reminds us.

Abrams does not want to promote false hope. "I do integrative oncology," he says, "so I hear about 'miracle cures' all the time. I hear about about noni juice and graviola and many products. What's disturbing is to hear people talking about cannabis oil as a 'cure,' because a cure in cancer means five years of disease-free survival and people have not been using cannabis oil for five years.

"I think it does a disservice to the cannabis community to make claims that are not supportable. I may be seen as a nay-sayer but I'm not. I say 'Let's study it.'"

Doctors and Dispensaries

Doctors who see cannabis-using patients and dispensaries that provide their medicine are well positioned to advance research by collecting "observational data" that could justify clinical trials, says Abrams.

To do this properly, he advises, "You can't collect data on only the patients who respond well. You have to col-

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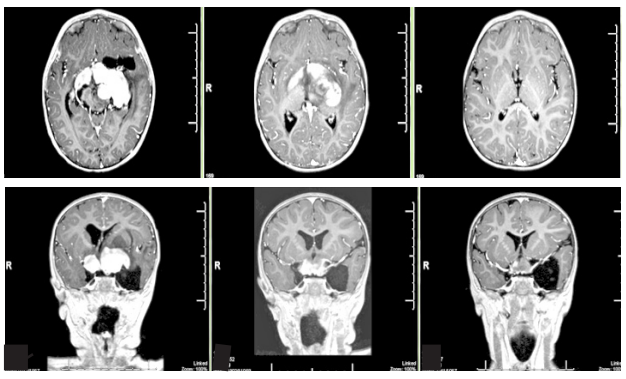

Magnetic Resonance Imaging scans display axial (top row) and ventral (bottom row) views that document the chronological regression of an optic pathway glioma (white area near center of skull) by approximately 90% over the course of nine months. Gliomas are known to be sensitive to cannabinoids. The sole treatment used to achieve these results was cannabis oil applied to the child's pacifier twice daily before nap and bedtime.

Hergenrather's presentation at MMJ13001A

SCC study of Crohn's patients: a template for clinical research?

"Cannabis in Primary Care" was the title of Dr. Jeffrey Hergenrather's presentation at the CME course accredited this fall by UCSF. The subtitle was "Issues for the Practicing Physician: IBD, patient screening and monitoring."

IBD —Irritable Bowel Disorders, which include Crohn's and Ulcerative Colitis— might seem relatively esoteric to include in an introductory talk about cannabis medicine. Hergenrather focused on it because his own study of IBD patients provides a model by which the effectiveness of the herb can be evaluated as a treatment for any given disorder. Cannabis medicine is an emerging field, and it provides an unprecedented opportunity for doctors to conduct meaningful research.

An efficient introduction to the body's cannabinoid signaling system had been provided by Mark Ware, MD, of the Alan Edwards Pain Management Unit, McGill University, so Hergenrather didn't have to define his terms as he discussed slides showing cannabinoid receptors throughout the bowel wall. Activating the CB1 receptor, he explained, down-regulates intestinal motility and intestinal secretions while decreasing inflammation, pain and the risk of tumors.

Activating the CB2 receptor decreases visceral pain and inflammation, and also down-regulates intestinal motility. "This has a huge effect on patients with Crohn's disease," said Hergenrather.

He traced the idea for his study to the initial meeting, called by Tod Mikuriya, MD in April 2000 of the group now known as the Society of Cannabis Clinicians. As the assembled handful of MDs compared notes, Hergenrather recalled, "We noticed right off that people were saying cannabis was working for Crohn's Disease."

With input from his patients Hergenrather developed a questionnaire which he shared with other SCC doctors so that their patients could be included in the study. In addition to demographic information and use patterns, patients are asked to report the level of certain signs and symptoms experienced when they are and when they are not using

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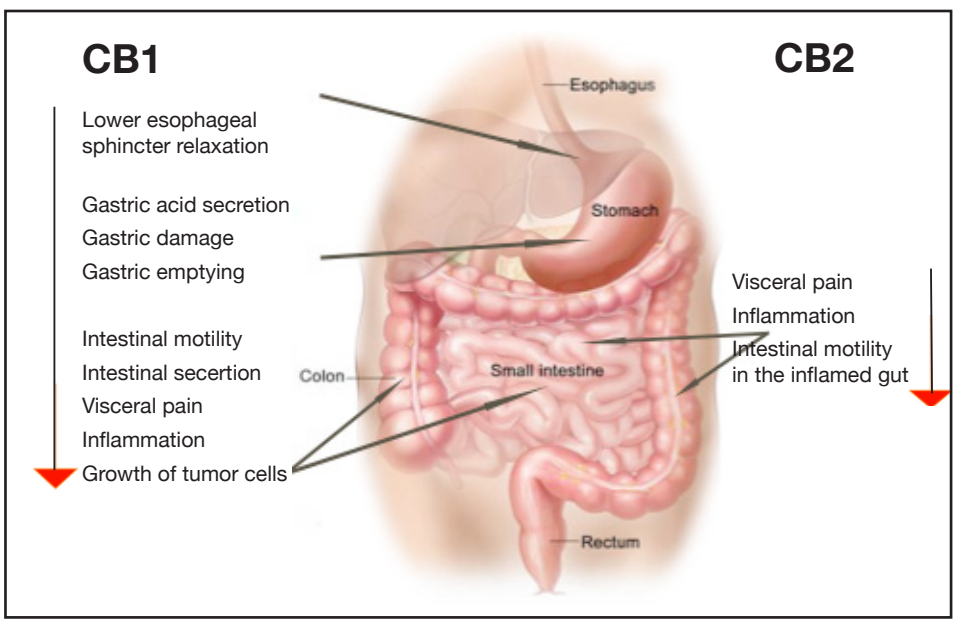


Cannabinoid receptors have been identified in the lower esophagus, stomach, small intestine, colon and rectum. They can be activated by cannabis-based medicine to alleviate many symptoms of Crohn's disease.

slide courtesy of Jeffrey Hergenrather, MD

Dosing Instructions

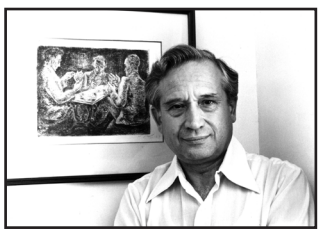
photo by Michael Aldrich

Michelle Aldrich (left) as Valerie Corral of WAMM writes out a dosing regimen for using cannabis oil as a treatment for lung cancer. Aldrich's remarkable first-person story starts on page 22.

Introducing a special section from *Smoke Signals,* the new "social history of marijuana" by Martin A. Lee

• The Riddle of THC

On August 28, 1964, the day Bob Dylan lit up and handed the Beatles their first joint in a New York City hotel room, Dr. Raphael Mechoulam was working intently in his laboratory at the Hebrew University in Jerusalem. The young Israeli chemist and his research partner, Yechiel Gaoni, would soon become the first scientists to fully isolate and synthesize delta-9-tetrahydrocannabinol, or THC, marijuana's principal psychoactive component.



Mechoulam's groundbreaking research was subsidized by the U.S. National Institutes for Health (NIH), which had suddenly become desirous of more objective information about the herb. As the use of marijuana soared among middle class youth, officialdom started to get anxious, especially when the sons and daughters of prominent politicians were caught smoking it.

Queried by members of Congress as to whether pot caused brain damage, the NIH scurried to gather basic scientific data. But hard science was difficult to come by in large part due to the stubborn refusal of the Federal Bureau of Narcotics to sanction laboratory research. For a long time, the illegality of cannabis acted as a deterrent to research in the United States.

From a scientific perspective, the riddle of THC was not easy to unravel. The small number of researchers who studied cannabis over the years found the herb difficult to work with because many of its 421 distinct compounds are "lipophilic" (soluble in fat but not in water), which means they can't be separated and scrutinized without sophisticated equipment. Scientists would eventually ascertain that at least 100 of these lipophilic compounds —known as "cannabinoids"— are unique to the marijuana plant. In addition to the cannabinoids, a term coined by Mechoulam, marijuana contains various alkaloids, flavonoids and terpenoids (essential aromatic oils).

The isolation and synthesis of THC would prove to be a highly significant event in the history of psychopharmacology. Mechoulam, then 34, announced his discovery in a letter to the editor of the Journal of the American Chemical Society on July 20, 1965. Although he didn't realize it at the time, Mechoulam had lit a slow-burning fuse that would detonate a revolution in medical science.

• The Brain and Marijuana

When American researchers at Johns Hopkins University identified receptor sites in the brain capable of binding with opiates in 1973, some scientists expected that the discovery of receptor sites for marijuana would soon follow. But these were difficult to pin down. Fifteen years would elapse before a government-funded study at the St. Louis University School of Medicine determined that the mammalian brain has receptor site —specialized protein molecules embedded in cell membranes— that respond pharmacologically to compounds in marijuana resin. Every cell membrane has lots of receptors for many types of messenger molecules, which influence the activity of the cell.

Initially identified by Professor Allyn Howlett and her graduate student William Devane, cannabinoid receptors turned out to be far more abundant in the brain than any other G-protein-coupled receptors.[1] Tagged radioactively, a potent THC analog synthesized by Pfizer ("CP55,940") enabled researchers to begin mapping the locations of cannabinoid receptors in the brain.

There are few cannabinoid receptors in the brain stem, the region that controls breathing and heartbeat —which is why no one has ever suffered a fatal overdose of marijuana.

These receptors were found to be concentrated in regions responsible for mental and physiological processes that are affected by marijuana —the hippocampus (memory), cerebral cortex (higher cognition), cerebellum (motor coordination) basal ganglia (movement), hypothalamus (appetite), the amygdala (emotions), and elsewhere. There are few cannabinoid receptors in the brain stem, the region that controls breathing and heartbeat —which is why no one has ever suffered a fatal overdose of marijuana.

On July 18, 1990, at a meeting of the National Academy of Science's Institute of Medicine, Lisa Matsuda announced that she and her colleagues at the National Institute of Mental Health (NIMH) had achieved a major breakthrough —they pinpointed the exact DNA sequence that encodes a THC-sensitive receptor in the rat's brain. People have the same receptor, which consists of 472 amino acids strung together in a crumpled chain that squiggles back and forth across the cell membrane seven times. Cannabinoid receptors function as subtle sensing devices, tiny vibrating scanners perpetually primed to pick up biochemical cues that flow through fluids surrounding each cell. Matsuda also disclosed that she had successfully cloned the marijuana receptor.

The cloning of the cannabis receptor was crucial. It opened the door for scientists to sculpt molecules —new drugs-that "fit" these receptors somewhat like keys in a slot. Some keys ("agonists") turned the receptor on; others ("antagonists") turned it off.[2] In addition to synthesizing cannabinoid receptor agonists and antagonists, scientists experimented with genetically engineered "knockout" mice that lacked this receptor. When administered to knockout mice, the THC had nowhere to bind and hence could not trigger any activity. This was further proof that THC works by activating cannabinoid receptors in the brain and central nervous system. Finally, after fifty centuries of medicinal usage, the scientific basis of cannabis therapeutics was coming into focus.

Researchers soon identified a second type of cannabinoid receptor, dubbed "CB-2," which is prevalent throughout the peripheral nervous system and the immune system. CB-2 receptors are also present in the gut, spleen, liver, heart, kidneys, bones, blood vessels, lymph cells, endocrine glands, and reproductive organs. THC stimulates the CB-2 receptor, but this does not result in the psychoactive high that pot is famous for (because CB-2 receptors are not concentrated in the brain); THC binding to CB-1, the central nervous system receptor, causes the high. The CB-1 receptor mediates psychoactivity. CB-2 regulates immune response. Marijuana is such a versatile substance because it acts everywhere, not just in the brain.

Just as the study of opium resulted in the discovery of endorphins, the brain's own morphinelike substance, so, too, marijuana research would lead to the discovery of a natural, internal THC-like compound, our "inner cannabis," so to speak. In 1992, Raphael Mechoulam, in collaboration with NIMH research fellow William Devane and Dr. Lumír Hanus, found a novel neurotransmitter, a naturally occurring endogenous (meaning "made internally") cannabinoid. This "endocannabinoid" attaches to the same mammalian brain cell receptors as THC. Mechoulam decided to call it "anandamide," deriving from the Sanskrit word for bliss. In 1995, his group discovered a second major endocannabinoid molecule, "2-AG" (2-arachidonoylglycerol), which binds to both CB-1 and CB-2 receptors.[3]

By tracing the metabolic pathways of THC, scientists had stumbled upon a hitherto unknown molecular signaling system that plays a crucial role in regulating a broad range of biological processes. This molecular signaling system modulates how we experience pain, stress, hunger, sleep, our circadian rhythms, our blood pressure, body temperature, bone density, fertility, intesti- nal fortitude, mood, metabolism, memory retention, and more.

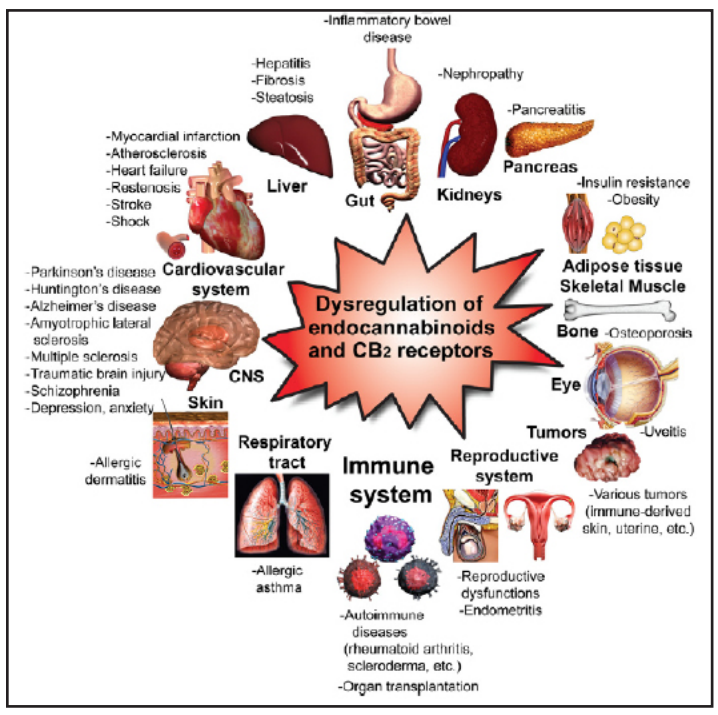
Scientists call it "the endocannabinoid system" —so named after the plant that led to its discovery. The name suggests that the plant came first, but in fact, as Dr. John McPartland explained, this ancient internal signal system started evolving more than 500 million years ago (long before cannabis appeared), when the most complex life-form was sponges. Endocannabinoids and their receptors are present in fish, reptiles, earthworms, leeches, amphibians, birds, and mammals —every animal except insects. Its long evolutionary history indicates that the endocannabinoid system must serve a very important and basic purpose in animal physiology.

Drug-company investigators paid close attention to cutting-edge developments in cannabinoid research, which few people outside the scientific community were privy to.† Endocannabinoids and their receptors emerged as a hot topic among scientists who shared their findings in highly technical peer-reviewed journals and at annual conclaves hosted by the International Cannabinoid Research Society (ICRS). Advances in the burgeoning field of cannabinoid studies would pave the way for new treatment strategies for various pathological conditions-cancer, diabetes, neuropathic pain, arthritis, osteoporosis, obesity, Alzheimer's, multiple sclerosis, and several odd diseases of unknown etiology that seemed to have as their common denominator an inflammatory or autoimmune dysfunction.

The discovery of the endocannabinoid system has breathtaking implications for nearly every area of medicine, including reproductive biology. Dr. Mauro Maccarrone at the University of Teramo, Italy, describes the endocannabinoid system as the "guardian angel" or "gatekeeper" of mammalian reproduction. Endocannabinoid signaling figures decisively throughout the reproductive process —from spermatogenesis to fertilization, ovuductal transport of the zygote, embryo implantation, and fetal development. Cannabinoid receptors proliferate in the placenta and facilitate neurochemical "cross-talk" between the embryo and the mother. A misfiring of the endocannabinoid system could result in serious problems, including ectopic pregnancy and miscarriage. Appropriate levels of endocannabinoids in maternal milk are critically important for the initiation of suckling in newborns. Infant colic has been attributed to a dearth of endocannabinoids.

Fride observed that knockout mice missing CB receptors resemble babies who suffer from "failure to thrive" syndrome.

Israeli scientist Ester Fride observed that knockout mice missing CB receptors resemble babies who suffer from "failure to thrive" syndrome. (Mice lacking CB receptors don't suckle and they die prematurely.) This is one of many enigmatic conditions that may arise because of a dysfunctional endocannabinoid system. Individuals have different congenital endocannabinoid levels and sensitivities. University of Washington neurologist Ethan Russo postulates that "clinical endocannabinoid deficiency" underlies migraines, fibromyalgia, irritable bowel disease, and a cluster of other degenerative conditions, which may respond favorably to cannabinoid therapies.[4]



Pathological conditions involving dysregulation of endocannabinoid-CB2 signaling were depicted in a paper by P. Pacher and R. Mechoulam, "Is lipid signaling through cannabinoid 2 receptors part of a protective system?" in Progress in Lipid Research, February 2011.

For Big Pharma, cannabinoid research became a tale of

continued on next page

Care and Feeding of the Endocannabinoid System

What we eat and drink, the drugs we use, treatments we receive, exercise, the stresses we respond to —many factors augment or diminish cannabinoid neurotransmission within our bodies.

By John M. McPartland, DO, MS

The endocannabinoid (eCB) system consists of an "alphabet soup" of acronyms for receptors, ligands (compounds that bind to receptors), and ligand-metabolizing enzymes.

Cannabinoid receptor type 1 (CB_1) is primarily located in the brain, spinal cord, and peripheral nerves. CB_1 is also expressed in reproductive tissues, and in several cell types involved in metabolism, such as adipocytes (fat cells) and hepatocytes (liver cells). Cannabinoid receptor 2 (CB_2) is principally associated with cells governing immune function.

Two ligands known as anandamide (AEA) and *sn*-2-arachidonoylglycerol (2-AG) activate both CB_1 and CB_2.

Anandamide is released by an enzyme called NAPE-PLD, and it is broken down by an enzyme called FAAH.

2-AG is primarily released by an enzyme named DAGLα, and it is primarily broken down by MAGL. Other enzymes may also metabolize AEA and 2-AG.

THC functions like anandamide and 2-AG by sliding into CB_1 and CB_2 and activating the receptors.

Tetrahydrocannabinol (THC) is a plant compound that mimics our endocannabinoids, much the same as opioids from poppies mimic our endorphins. That is to say, THC functions like anandamide and 2-AG by sliding into CB_1 and CB_2 and activating the receptors.

Rodents trained to discriminate anandamide from other substances will accept THC as a substitute, and rats trained to discriminate THC will accept anandamide. "Who mimics who?" is a question of chronology. The eCB system evolved 600 million years ago, whereas Cannabis and THC are johnnie-come-latelies that evolved perhaps 25 million years ago.

Hopes and Caveats

Can the eCB system be augmented to provide therapeutic benefit? That is the topic of today's talk.

Ethan Russo has proposed that migraine, fibromyalgia, irritable bowel syndrome, and related conditions represent "clinical eCB deficiency syndromes." Ester Fride speculated that the "failure to thrive" syndrome in infants may be caused by a dysfunctional eCB system. Paola Sarchielli posited eCB "system failure" as a basis of chronic migraine. Matthew Hill hypothesized that deficient eCB signaling contributes to depressive illnesses. Compensating for eCB deficincies might help patients with these conditions. Enhancing the eCB system may reduce symptoms caused by multiple sclerosis, chronic pain, epilepsy, and many other diseases.

John McPartland learned about medicinal plants from Euell Gibbons at boy scout camp. He rediscovered THC in New Jersey about eight years after Raphael Mechoulam discovered THC.

In this article McPartland summarizes the lecture he is presenting at the Patients Out Of Time *conference in Tucson. The lecture itself summarizes a forthcoming review article by McPartland and Vincenzo Di Marzo, which will cite references for all the studies described here.*

There are two important caveats: some diseases, such as visceral obesity and cirrhosis, are worsened by chronic overactivation of the eCB system. Vincenzo Di Marzo and others have shown that overactivation is driven by excessive levels of eCB ligands. In these diseases, *down*regulating the levels of eCB ligands would be beneficial.

CB_1 receptors desensitize and downregulate when faced with constant activation.

Secondly, generating a chronic, continual, high-level rise in anandamide and 2-AG would be counterproductive, even in people with eCB deficiency syndromes. This is because CB_1 receptors desensitize and downregulate when faced with constant activation. A desensitized receptor loses its responsiveness; intake of cannabinoids such as THC result in less receptor-mediated signal transduction.

A downregulated receptor is not functional—it does not bind ligand, has internalized away from the cell membrane, or no longer exists. These are not good things; they have been observed in rodent studies. *Acute* blockade of the MAGL enzyme elevates 2-AG levels and provides pain relief, but *chronic* blockade of MAGL erases this analgesia, because the sustained elevation of 2-AG causes desensitization of CB_1. This leads to downregulation of the eCB system.

Complementary and Alternative Medicine

This review focuses on therapeutic approaches classified as "complementary and alternative medicine" (CAM). The National Center for Complementary and Alternative Medicine (NCCAM) defines CAM as "a group of diverse medical and healthcare systems, practices, and products, that are not currently part of conventional medicine."

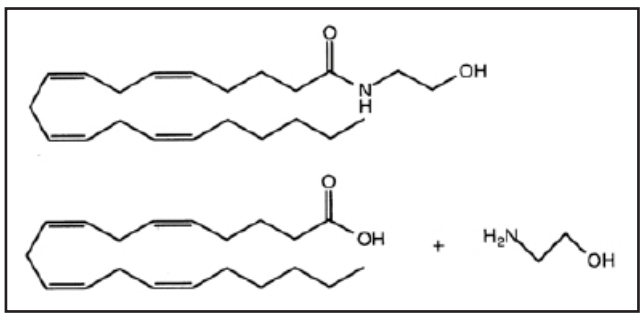
NCCAM categorizes CAM practices into three broad groups: "natural products" (dietary supplements and herbal remedies), "mind and body medicine" (meditation, yoga, and acupuncture), and "body-based practices" (massage, spinal manipulation). For the purposes of this review, we add "lifestyle modifications" (diet, weight control, exercise, and the use of psychoactive substances—ethanol, nicotine, caffeine, and cannabis).

We can enhance the eCB system by simply living a healthy lifestyle, beginning with aerobic exercise. Human studies show that running, biking, and hiking increase anandamide levels in the blood. The eCB system is primarily responsible for "runners high" (to a much larger degree than endorphins).

Rodent studies show that voluntary wheel running increases the expression of CB_1 in the brain. An interesting rat study by Hill and colleagues suggests that wheel running not only increases CB_1 expression, it also increases the sensitivity of CB_1 to activation by cannabinoids.

Diet is trickier. Overeating leads to obesity. Adipocytes produce excessive amounts of eCBs. The eCBs spill over into the blood, cross the blood-brain barrier, activate CB_1 in the brain, and cause the munchies.

The scenario becomes a feed-forward dysregulation of the eCB system. Our stereotype of the "happy fatman" gets erased after excessive amounts of eCBs cause CB_1 to desensitize and downregulate. It's not a happy or healthy picture—cardiovascular disease, diabetes, and systemic inflammation.



Anandamide (top figure) is a combination of arachidonic acid plus ethanolamine (bottom figures).

Caloric restriction (dieting, fasting) worsens the situation, at least initially: it leads to reduced eCB levels in the blood, and downregulated expression of CB_1 in the brain. Although some studies report conflicting results —and we need more research— a downregulated eCB system seems to fit the clinical picture of the "angry, depressed dieter."

But there is hope! A recent study of overweight women showed that dieting causes a decrease in CB_1 expression… but combining caloric restriction with aerobic exercise caused a net increase in CB_1 expression!

Trickier yet is the impact of polyunsaturated fatty acids (PUFAs) on the eCB system. The typical American diet contains excessive omega-6 PUFAs and lacks omega-3 PUFAs. Arachidonic acid is the archtypical omega-6. Some of its metabolites are bad actors —prostaglandins may cause pain and swelling, and leukotrienes may cause bronchoconstriction and asthma. But arachidonic acid is also required as a building block for endocannabinoids. *(See illustration at top right.)*

Many studies show that dietary supplementation with arachidonic acid increases serum levels of anandamide and 2-AG. There is a fine line here: we clearly need some arachidonic acid to biosynthesize eCBs. But excessive levels of AA may lead to excessive levels of anandamide and 2-AG, which eventually desensitize and downregulate CB_1 and CB_2.

The best-known omega-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Dietary supplementation with EPA and/or DHA increases the concentration of these compounds in tissues, cells, and plasma, and decreases the concentration of arachidonic acid.

Dietary supplementation with omega-3s decreases anandamide and 2-AG in tissues, cells, and plasma. Nevertheless, adequate levels of dietary omega-3s are required for proper functioning of the eCB system.

Mice supplemented with omega-3s, compared to mice on a control diet, express greater mRNA levels of CB_1 and CB_2. Another study with mice showed that omega-3 deficiency abolishes eCB-mediated neuronal functions. The omega-3 deficient diet led to CB_1 desensitization, because of a relative excess of arachidonic acid.

Omega-3 deficient mice did not respond to exogenous cannabinoids (in this case, the synthetic cannabinoid WIN55212-2; Δ^9-THC would have produced the same non-response). Omega-3 sufficient mice, however, showed normal cannabimimetic effects to WIN55212-2.

Human breast milk contains small amounts of anandamide, but the biological significance of this is not known. Mouse milk also contains anandamide. Ester Fride showed that when newborn mice have their CB_1 receptors blocked (with the synthetic antagonist rimonabant), the baby mice don't suckle at birth, and die.

Ester Fride showed that when newborn mice have their CB_1 receptors blocked (with the synthetic antagonist Rimonabant), the baby mice don't suckle at birth, and die.

"Probiotics" are microorganisms such as *Lactobacillus acidophilus* that confer health benefits upon humans. They occur in fermented foods, such as yogurt and kimchi.

Human intestinal cells exposed to *L. acidophilus* increase their expression of CB_2 mRNA. Mice fed *L. acidophilus* show less pain behavior following colonic distension than control mice, and this was reversed by a CB_2 antagonist. So probiotics likely protect us from irritable bowel syndrome and other gut problems by upregulating CB_2 receptors, whose activation decreases inflammation and visceral pain.

Several plants make compounds that selectively bind to CB_2 and modulate the immune system. But they have no affinity to CB_1 and do not elicit psychoactivity: Alkamides in Echinacea species bind to CB_2. Alkamides also inhibit anandamide breakdown. (E-)-**β**-caryophyllene in black pepper (and Cannabis) binds to CB_2, and its anti-inflammatory effects are reduced in CB_2 knockout mice.

Eating organic foods may promote eCB homeostasis. A range of pesticides, from nasty (chlorpyrifos and diazinon) to relatively benign (piperonyl butoxide, which is often added to pyrethrum) screw up the eCB system. Phthalates are plasticizers added to water bottles, tin cans, food packaging, and even the enteric coating of pharmaceutical pills. Among their nefarious qualities, phthalates block CB_1 as allosteric antagonists.

Acupuncture is a good thing. Electroacupuncture (EA) upregulates the expression of CB_2 in skin tissues. EA also increases anandamide levels in the skin, and the pain-reducing effects of EA are attenuated by CB_2 antagonists. EA also treats pain by reducing GABA levels in the spinal cord (periaqueductal gray area), which is reversed by CB_1 antagonists.

Osteopathic manipulative treatment (OMT) employs massage, myofascial release, and spinal manipulation. In one study, a single OMT session increased serum anandamide levels by 168% over pretreatment levels, with no changes in con-

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At the 2012 ICRS conference

Mechoulam's To-Do List for Researchers: CBD, the CB2 Receptor, and 'F-Triple-A's'

By O'Shaughnessy's News Service

Raphael Mechoulam, professor of Medicinal Chemistry and Natural Products at the Hebrew University of Jerusalem, began "reading on cannabis and planning some limited amount of work on it" in 1962.

The work turned out to be limitless.

Over the course of 50 years Mechoulam has made and participated in a remarkable series of Cannabis-related achievements. He and his colleagues isolated and elucidated the chemical structure of THC, CBD, and many other plant cannabinoids (a term Mechoulam himself coined). They did the same for the endogenous cannabinoids, anandamide and 2-AG. They figured out the steps by which these compounds are synthesized in the body and exert their effects by activating receptors. Their accomplishments —like all scientific advances— have extended the research agenda.

"Planning Research for the Next Half a Century" was the title of Mechoulam's talk at the International Cannabinoid Research Society meeting in Freiburg, Germany this summer.

If Mechoulam's speculation about the role of FAAAs can be substantiated, it will represent an advance in scientific understanding as significant as any he has contributed to in the past.

Mechoulam pointed to three areas of investigation likely to yield important medical discoveries: cannabidiol (CBD), the CB2 receptor system, and fatty acids bound to amino acids (FAAAs, pronounced "F-triple-A's"). FAAAs are signalling molecules abundant in the brain. They are found in clusters that include their precursor molecules and their derivatives. Anandamide and 2-AG are among the few FAAAs that have been studied to date.

If Mechoulam's speculation about the role played by FAAA clusters in the brain can be substantiated, it will represent an advance in scientific understanding as significant as any he has contributed to in the past.

• Cannabidiol

CBD is a non-psychoactive compound with no known adverse effects. It is a potent anti-inflammatory, a quality recognized by physicians in ancient Greece and Rome, Mechoulam said, where the available Cannabis was of the hemp type (with virtually no THC).

Mechoulam studied the anti-inflammatory effects of CBD in collaboration with his Hebrew University colleague Ruth Gallily, whose *in vitro* experiments showed that increasing doses of CBD cause cells cultured from the lining of arthritic joints to diminish production of pro-inflammatory compounds.

Experiments with mice by Gallily and Mark Feldmann of Imperial College, London, confirmed that CBD alleviates symptoms of rheumatoid arthritis such as swelling. They also confirmed that CBD has a biphasic effect — there is an optimal dose, below which and above which it is less potent.

"So I hope somebody will work with CBD or one of its derivatives as an anti-rheumatoid arthritis agent," said Mechoulam, hopefully.

Given that rheumatoid arthritis is an autoimmune disorder, Mechoulam decided to test the ability of CBD to counter the symptoms of diabetes type-1, another disease in which the immune system mistakes the body's own cells for pathogens. He described a study involving a strain of mice that develop diabetes type-1 at about 14 weeks. Treatment with CBD resulted in only 30 percent of the mice becoming diabetic (instead of 80-to-100 percent). Damage to the pancreas was reduced proportionally, with more than 70 percent of the hormone-producing islets remaining intact in the CBD-treated mice.

RAPHAEL MECHOULAM photo by Zach Klein

Unfortunately, Mechoulam said, clinical trials of this very promising treatment for diabetes type-1 cannot be conducted until funding becomes available.

"Chances are we'll see similar results with CBD in psoriasis and many other autoimmune diseases," he predicted, when the research can be carried out.

Elucidating the mechanisms by which CBD works is a big item on Mechoulam's to-do list. Although CBD has little binding affinity with the two known cannabinoid receptors, it confers a therapeutic effect through various receptor-independent channels and by directly activating or antagonizing several non-cannabinoid receptors.

Diabetes type-2 and obesity are characterized by chronic, low-grade inflammation. White blood cells build up in visceral adipose tissue (VAT), leading to insulin resistance and other problems. Citing several recent papers, Mechoulam suggested that CBD might play a protective role in diabetes type-2 via a receptor (PPAR-γ) that regulates fat-cell development.

• The CB2 receptor

We mammals have a sophisticated immune system that guards against foreign proteins and reduces damage they cause. "We must have an analogous system protecting against non-protein attack," Mechoulam stated.

The CB2 receptor may play a central role in such a protective system. "Endocannabinoids and endocannabinoid-like molecules acting through the CB2 receptor have been reported to affect a large number of pathological conditions," Mechoulam said.

Stimulation of CB2 "lowers pro-inflammatory cytokines [chemical messengers] of many different types," Mechoulam said. He was co-author on a paper by Pal Pacher reviewing the evidence that CB2 is a general protective agent. The paper listed numerous disorders in which the body's protective response involves CB2 activation. *(See illustration on next page.)* It took three slides to reproduce the list as Mechoulam spoke.

"We know that CB2 is involved in protection against inflammatory bowel disease and colitis... It protects against vascular inflammation. We see it skin disorders, bone disorders, myocardial infarctions. Decreasing inflammation in atherosclerosis. In stroke...

"I believe we should be looking very thoroughly at the mechanism of these diseases and the best way to affect those mechanisms," Mechoulam said. "There is quite a lot of work to do."

He cited three recently published papers indicating that the work is underway:

"A new cannabinoid 2 receptor agonist HU-910 attenuates oxidative stress, inflammation, and cell death associated with hepatic ischemia/reperfusion injury. Horvath *et al* 2012.

"Cannabinoid-2 receptor activation protects against infarct and oschemia-reperfusion heart injury. Wang *et al* 2012

"The action of the cannabinoid receptor type 2 reduces neutrophilic protease-mediated vulnerability in atherosclerotic plaques. Montecucco *et al* 2012."

A student of Mechoulam's developed a series of compounds that bind to the CB2 receptor (and slightly to the CB1 receptor.) They were found to improve functional recovery following brain injury. "As expected," Mechoulam said, "the CB2 receptor antagonist blocks this activity."

Unexpectedly, however, one of the new compounds, HU-914, blocks the damage but does not bind to the receptor. "The compound does not bind to the receptor and yet you can prevent its activity by the CB2 antagonist," Mechoulam repeated with emphasis.

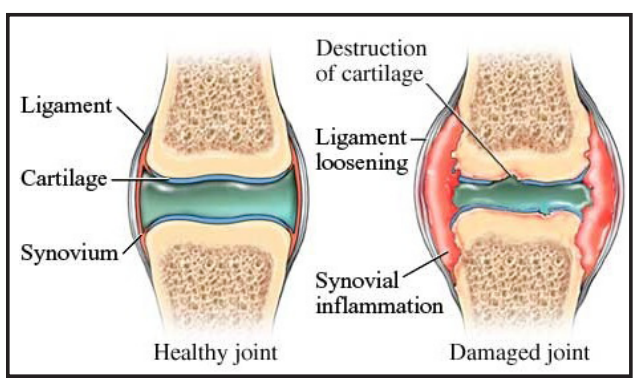
FAAAs are signaling molecules, abundant in the brain, that include the body's own endocannabinoids, anandamide and 2-AG.

• Fatty Acid Amino Acids

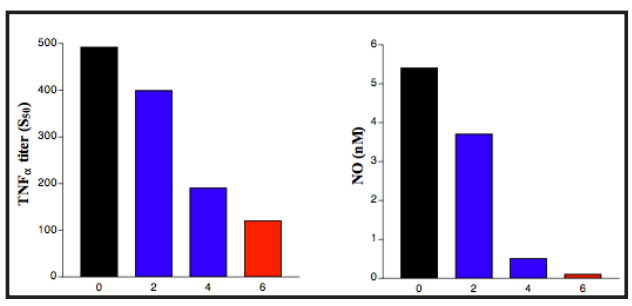
FAAAs are signaling molecules, abundant in the brain, that include the body's own endocannabinoids, anandamide and 2-AG. Very few of these compounds have been studied. Several are known to have therapeutic effects. For example:

Arachidonoyl Serine —AraS (prounced Arra-ess)— lowers vasoconstriction and brain trauma effects. Arachidonoyl glycine lowers pain. Oleamide is an endogenous sleep-inducing lipid. Oleoyl serine counters osteoporosis. Palmitoyl ethnaolamide (PEA) concentrations are enhanced after damage in a specific brain region.

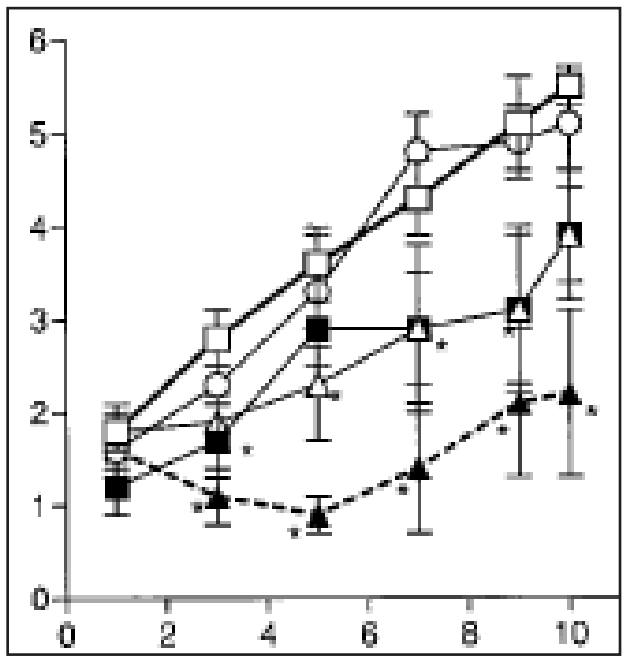
continued on next page



RHEUMATOID ARTHRITIS **involves inflammation of the synovium —the lining of the joint space.**



EFFECT OF CBD ON COMPOUNDS THAT PROMOTE INFLAMMATION **was measured by Mechoulam's colleague Ruth Gallily, working with a mouse model of Rheumatoid Arthritis. Graph at left shows decline in macrophage production of Tumor Necrosis Factor (TNF) in weeks following treatment with CBD. Graph at left shows decline in Nitrogen Oxide (NO).**



"BIPHASIC EFFECT" OF **CBD was demonstrated by experiment in which arthritic mice were given doses of zero (the controls, line marked by blank square); 2.5 milligrams per kilogram of body weight (line marked by octagon); 5mg/kg (darkened triangle); 10 mg/kg (blank triangle): and 20 mg/kg (darkened square). Vertical scale shows extent of swelling. Horizontal scale shows days after onset of arthritis. Clearly the optimal dose in this case was 5mg/kg..**

Smoke Signals Sampler *from previous page*

CAN had frequent run-ins with cops. But the hempsters knew their constitutional rights (they memorized the ACLU guidebook), and they always stood their ground politely but firmly when dealing with the police. Occasionally CAN convoys protested at state courthouses where judges were dispensing severe mandatory-minimum prison sentences to marijuana offenders. CAN's mainstay Monica Pratt would help launch Families Against Mandatory Minimums, a grassroots civil rights organization with the motto "let the punishment fit the crime."

In 1996, home-town hero Woody Harrelson, the famous actor, was arrested after he brazenly planted four hemp seeds in full view of the county sheriff's office in Lexington.

In the early 1990s, the Cannabis Action Network set up its national headquarters in Kentucky, a centrally situated and economically depressed state once known for its abundant hemp fields. The locals were receptive to CAN's message and welcomed their presence. Hard times had fallen upon farmers throughout the region, and many desperate families, lacking other sources of income, were cultivating marijuana to survive...

Hemp was a lightning rod for discontent in Kentucky. In 1996, home-town hero Woody Harrelson, the famous actor, was arrested after he brazenly planted four hemp seeds in full view of the county sheriff's office in Lexington. "Industrial hemp can help meet our fiber needs while also revitalizing our struggling rural economies," Harrelson told the press at the time of his arrest. He had long been outspoken against government policies that allowed the clear-cutting of old-growth forests while at the same time prohibiting the cultivation of hemp, which would lessen the need for timber. Thanks to Harrelson's celebrity status, his symbolic act of civil disobedience made national headlines. Later that year, the American Farm Bureau, the largest U.S. farming organization, urged federal and state authorities to reconsider the ban on growing hemp. The American Farm Bureau called hemp "one of the most promising crops in half a century . . . [It] could be the alternative crop farmers are looking for."

• The Seattle Hempfest

Cannabinoid compounds interact synergistically for maximum effect; so, too, with social-justice movements —they're far more potent in combination than as single-issue nedeavors.

The Seattle Hempfest grew out of a peace vigil opposing the 1991 Gulf War. Allen Ginsberg visited and sat with the vigil during the six months that it lasted. Shortly thereafter, Vivian McPeak and several co-horts organized the the inaugural Washington Hemp Expo, which drew 500 people. The keynote orator was Jack Herer, the bombastic hemp evangelist, who gave a barn-burner of a speech at this "humble gathering of stoners."

Renamed the Seattle Hempfest the following year, it was destined to become a major Northwest summer attraction, a flagship event of today's sprawling global cannabis culture. More than 20,000 people showed up in 1994, and the crowds kept increasing year after year, feted by the likes of Dennis Peron, Valerie Corral, Debby Goldsberry, and other activists who starred in the hemp movement.

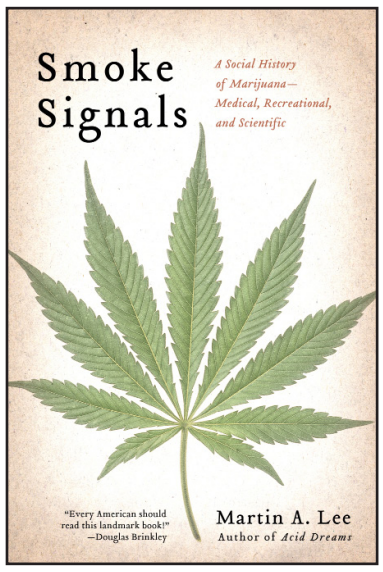
On the 10th anniversary of Hempfest in 2001, an estimated 150,000 attendees heard Woody Harrelson denounce America's "injustice system" and "the war on all natural, noncorporate drugs." In October of that year, the Drug Enforcement Administration tried to ban hemp food products, even though they packed about as much of a psychoactive punch as a potato. Emboldened by the authoritarian fervor that followed the 911 terrorist attacks, the narcs tried to pull a fast one. They thought they could get away with a sneak attack against a wide range of hemp food items, including nutrient-dense hempseed oil, one of the few, complete plant-based protein sources on the planet.

The DEA, citing THC concerns, pegged the hemp industry and medical marijuana as a smokescreen for folks who just want to smoke pot. But Uncle Sam's attempts to destroy hemp food commerce in America would falter largely due to the efforts of David Bronner, the young CEO of Dr. Bronner's Magic Soaps, who funded and coordinated the Hemp Industry Association's protracted litigation against the DEA. The industrial hempsters scored a major victory in February 2004 when the Ninth Circuit Court of Appeals rejected the DEA's hemp food ban on substantive grounds.

Hemp, the world's foremost agricultural crop in the 18th century, reemerged as the textile of choice among eco-conscious shoppers in 21st century America. New processing techniques made hemp cloth silky soft, but federal law stopped American farmers from growing the plant.

Vivian McPeak (left) on the Hempfest main stage, organizes a huge crew of volunteers who put on an amazingly peaceful, enjoyable, and informative mass gathering. Everything from booking the speakers to cleaning up the garbage gets done, miraculously, and there is no admission charge. Attendees from other cities and towns, accustomed to cold hostility from law enforcement, are pleasantly surprised by the respectful demeanor of the Seattle Police, and how few uniformed officers the brass assign to patrol the event. Traditionally held over a weekend, the 2012 Hempfest opened on a Friday, in hopes that the extra day would make for thinner crowds along the paths overlooking Elliott Bay. The strategy seems to have worked. Bravo to Vivian McPeak and all concerned!

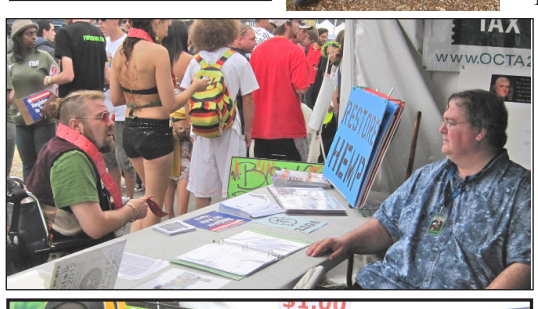
Author Martin Lee at the 2012 Hempfest. His wares included *Acid Dreams,* a book that middle-aged passersby smiled at knowingly and 20-somethings bought. Both are available at smokesignals.org.

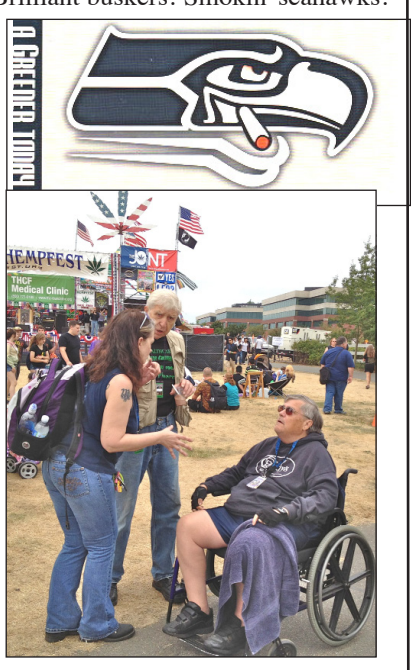


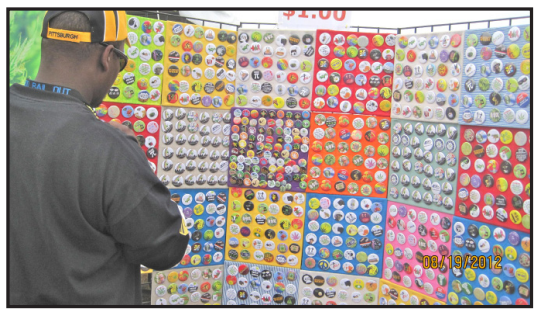
Add Scenes From the 'Fest

"Be there or be in DARE" —W.T.

Brilliant buskers! Smokin' seahawks!







Policing the area

Smileless in Seattle: from left, journalist Steve Elliot, political consultant Kari Bonier, NORML general counsel Keith Stroup, and ACLU attorney Alison Holcomb debated Washington's legalization measure, I-502, at the Hempfest Aug. 18, as a woman signed what was being said. Elliott and Bonier (the naysayers) protested a clause allowing police who have "reasonable suspicion" of impairment to order drivers to submit to a blood test, and a "per se" definition of impairment based on the amount of THC in a driver's blood (five nanograms per millileter, and zero for drivers under 21). Stroup, calling for a "yes" vote, said that the day after the election people across the U.S. and the world would read a headline proclaiming either "Pot Wins," or "Pot Loses," and that political momentum would shift accordingly.

Constance Gee *from previous page*

aspire during the ferocity of a drop attack.

"The rest of the day or night and sometimes both would be spent in bed drugged up on Valiium, Xanax, Zofran, Ativan, or Phenergan —whatever medication various physicians thought would ease the nausea and stop the vertigo."

Contance lost 17 pounds over the course of a few months. An old friend visited in March 2005. They went for a hike in a state park and Constance soon got sick to her stomach. Her friend "took a small round bonbon tin filled with marijuana and a little wooden pipe out of her backpack. She packed a small amount of the weed into the pipe and handed it to me. I took a couple of draws. The nausea melted away almost immediately. She repacked the pipe, took two hits herself, tapped out the ashes, and handed me the tin and pipe.

"'Keep this,' she smiled. 'It'll help.'

"'Sure does,' I agreed. The effects seemed miraculous. The nausea was gone."

Constance told her husband, whose responded, "I do not want to know about it!"

• "Hmmm.. He hadn't said, 'Don't do it'—although I probably would have ignored him anyway. He had said he didn't want to know about it.

She decided not to mention it again to her husband —but then did so several weeks later, en route to a luncheon in honor of Supreme Court Justice Sandra Day O'Connor.

"Other side effects of pot are truthfulness and talkativeness, a potentially dangerous combination," she observes.

Constance had been sick that morning, but she was determined to attend, so she took a few puffs. "Other side effects of pot are truthfulness and talkativeness, a potentially dangerous combination," she observes. Gordon "failed to perceive the humorous absurdity of the situation."

Among those to whom Constance revealed that she used marijuana to cope with nausea was a specialist at Johns Hopkins. "'You're not the first Meniere's patient to tell me that,' he said. 'I don't see how it would hurt, although I can't officially recommend it.'" Don't ask, don't tell...

Only one person Constance confided in didn't keep her secret —the Breaburn house manager, who informed a senior administrator who informed Vanderbilt's general counsel and several trustees. Constance was severely reprimanded and directed to receive treatment for her "behavior and drug use issues." She promised to never use marijuana again on university property.

• "I could not promise in all honesty to never use marijuana again. I knew I would resort to using it again for its palliative effects in the future if I experienced severe, long-lasting nausea. Also, I refused to rule out the possibility that at some point in my life I might just do it again for fun."

Desperate to find relief from her illness, Constance underwent a surgical procedure that destroyed her hearing and vestibular function in the affected ear.

Scapegoat

In September 2006 the *Wall St. Journal* ran a front-page story about whether the Vanderbilt board of trustees was exercising adequate financial oversight over the chancellor's spending. The broader topic was —supposedly— the extent to which universities were heeding the Sarbanes-Oxley legislation on the governance of publicly held companies. Vanderbilt was chosen as the focus because Gordon Gee was the highest paid and one of the best known university chieftains in the land. Or maybe he was chosen because an enemy on the Vanderbilt board —or some Brown alumnus— had influence with the *WSJ*. The decks of headlines and subheads read :

Golden Touch

Vanderbilt Reins in Lavish Spending
by Star Chancellor

———

As Schools Tighten Oversight
A $6 Million Renovation
Draws Trustees' Scrutiny

———

Marijuana at the Mansion

There was a line drawing of E. Gordon Gee's and his big bow-tie on the front page. In the story itself Gordon came out looking just fine. Yes, he may have spent $700,000 a year entertaining at the residence, but he raised more than a thousand times that amount. And if he spent $6 million on renovating Braeburn, "Mr. Gee has dramatically boosted the 133-year-old school's academic standing and overseen fund raising of more than $1 billion."

The trustees had been delighted with the revenue generated by the Gees' entertaining at the mansion. When they realized the *Journal* was going to ding them for failing to monitor expenditures, they diverted the reporters' attention to Constance's use of the infamous herb!

• "'The trustees' concern over their chancellor's expenditures,' the *Journal* sequed wobblingly, 'was aroused when they learned that Mrs. Gee was using marijuana at the mansion."

Constance Gee's use of marijuana to treat Meniere's Disease had absolutely nothing to do with the Vanderbilt trustees' failure to do their fiduciary duty.

Constance Gee's use of marijuana to treat Meniere's disease had absolutely nothing to do with the Vanderbilt trustees' failure to do their fiduciary duty. But it was turned into the lynchpin of the page-one piece by Joan Lublin and Daniel Golden, Pulitzer Prize winners who supposedly spent five-months researching it!

They wrote on behalf of their favored sources: "The marijuana incident troubled some trustees, who were bothered that Mr. Gee never told the full board about it, according to people familiar with the matter. To these trustees, the incident demonstrated that Mr. Gee needed to be more accountable to the board."

The article concluded, "In the fall of 2005, university employees discovered that Constance Gee, a tenured associate professor of public policy and education, kept marijuana at Breaburn and was using it there, according to people familiar with the matter. A few weeks later, several trustees and a senior university official confronted Mr. Gee in his office, telling the chancellor he shared responsbility for allowing marijuana on university property, the person familiar with the situation recalls.

"Trembling, the chancellor replied: 'I've been worried to death over this,' according to this person. Mr. Gee said his wife smoked marijuana to relieve an inner-ear ailment, this person says. The Gees declined to comment on the incident."

The word "*sativa*" means *useful*. Cannabis sativa certainly proved useful to the Vanderbilt administrators who wanted to point the reporters towards something other than their own malfeasance.

Constance had been directed by Vanderbilt lawyers to say "no comment" to the *Journal* reporters. In her book she comments:

• "An 'inner ear' ailment!' With two Pulitzer Prize-winning journalists doing five months of sleuthing, the word 'Meniere's' had not meen mentioned? Of course, a villainess with a genuinely serious disease might not seeem so villainous. Smoking pot on the pretext of a mere 'ailment' would better serve sensationalist innuendo."

"Braeburn," the original name of the residence built in 1914 and purchased by Vanderbilt University in 1960, was resurrected by Constance after she learned its history. She created stationery featuring an ink drawing of the building and explaining in fine type that the name is derived from the Scottish words for slope (brae) and brook (burn). She added, "The original owners, Miss Ida Hood and Miss Susan Heron, both being of Scottish descent, named their home appropriately because of its situation on a sloping hill leading to Richland Creek."

The day the *Journal* piece appeared Constance got a call on her cell phone from a reporter with the *Tennessean,* the Nashville daily. It came as a surprise because the number had hitherto been private. She replied "no comment," as ordered, but saw fit to add: '"The inner-ear ailment' reported in the *Journal* is Meniere's disease. If you want to find out more about it, go online to Washington University's Meniere's website."

Next day the *Tennessean* published a piece with a description of Meniere's disease, quotes from an ear specialist at Washington University, and a deceitful assertion that Constance had confirmed her marijuana use to the reporter.

• "Gordon marched into our bedroom brandishing the *Tennessean,* his face red and contorted: 'I told you not to talk to any reporters!'

"I related exactly how the reporter had contacted me and what I had said. He refused to believe me, yelling about my indiscretion and stupidity. I asked him whom he was going to believe, his wife or a reporter. I pointed out the numerous times he had been misinterpreted by the press.

"That observation gave him a moment's pause, during which I implored, 'Gordon, you saw how terribly ill I was. Would you have rather seen me lie on the floor and vomit, or have had me smoke a little pot for some occasional relief?'"

"He looked me in the eye and said, 'I would rather have seen you sick.'"

Five months later he said he wanted a divorce. She had seen how skillfully he fired others, and now she was being fired herself. Gordon handled the p.r. Vanderbilt's online student news service quoted a vapid admistration press release and added, "The split comes five months after a report in the *Wall St. Journal* addressed Constance Gee's use of marijuana in the chancellor's university-owned residence, Breaburn."

That article was supposed to be about the trustees' failure to do their job, but in memory the subject had become marijuana in the mansion. How handy for Vandy.

A Cameo Role for *O'Shaughnessy's*

The *Tennesseean* piece that identified Constance's ear ailment as Meniere's included information provided by otolaryngologist Timothy Hullar of Washington University School of Medicine ("one of two major centers of study on Meniere's"). Dr. Hullar said he had "never heard of anyone using medical marijuana to treat symptoms of Meniere's." He added, "There are a whole lot of other ways to treat it, lowering salt intake, take water pills, many other things. I can't imagine going to the extreme of marijuana."

Hullar's comment showed the extent of the knowledge gap between cannabis consultants and the rest of the medical profession.

Hullar's comment showed the extent of the knowledge gap between cannabis consultants and the rest of the medical profession. *O'Shaughnessy's Winter/Spring 2007* issue included an item about Constance Gee's medical/political ordeal, and quoted three California doctors who routinely approved the use of cannabis by Meniere's patients. Our item came to her attention and she quotes it in her memoir:

"Meniere's causes dizziness, dizziness causes nausea, cannabis relieves nausea," says David Bearman, MD. "I wouldn't be surprised if the symptoms caused Mrs. Gee to be a little depressed —and of course cannabis helps that, too."

Robert Sullivan, MD, corroborates: "I've issued many recommendations for Meneire's, as well as tinnitus [ringing in the ears]. It works well enough to make a significant improvement in patients' lives, i.e., symptoms not gone but much abated so they can function and carry on their daily activities, instead of sitting and suffering. It also aids sleep."

R. Stephen Ellis, MD, of San Francsico, has given some thought to how cannabis might help in the treatment of Meniere's. "Three possible mechanisms come to mind," he says. "Number one, the anti-anxiety effect of cannabis would be very useful to a Meniere's patient. These people are anxious as can be when they hit the ER. When they get an attack it's as if they are wired —that's why Ativan is one of the treatments, to bring them down. Two would be the anti-nausea effect. Duh! You're barfing and there's a drug that offers relief in 10 seconds. The third is slowing down the vertigo itself —the sensation of spinning caused by the inner ear problem. My patients say cannabis is as good as Antivert, which is the classic treatment, or Benadryl, which is used in certain situations. I recall reading that the auditory nerve does have CB1 receptors. I don't know about the cochlear structure itself."

In August 2010 Constance contacted Dr. Hullar and read him the quotes from Bearman, Sullivan and Ellis. "He was unmoved in his opinion," she relates in *Higher Education*. To date Hullar "had never had a patient tell him that he or she had used marijuana. He also did not know of any physicians who prescribed it for relief from Meniere's related nausea. 'It is not part of the standard repertoire,' he said."

It says something about Dr. Hullar that none of his Meniere's patients has revealed to him their use of marijuana. Not everyone is inhibited by prohibition from discussing marijuana use with their doctors. It depends on the two parties involved. Some individuals tend to be easily embarrassed, they fear disapproval; others are forthcoming. Some doctors signal that they are tolerant and open-minded, others signal rigid adherence to official dicta. Obviously, Hullar is among the latter.

Gordon Gee abruptly left Vanderbilt in 2007 (before the divorce was finalized) to return to the presidency of Ohio State. Constance resigned from the Vanderbilt faculty at the end of 2010. She moved to Massachusetts in October 2012, just in time to join the 63% of voters who approved. If that sounds like the epilogue of a movie... Susan Sarandon ought to option *Higher Education: Marijuana at the Mansion*.

Till then it's available in soft cover or as an ebook from Amazon, Barnes & Noble, and marijuanaatthemansion.com.