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 Cannabis,” page 4.)

The anti-cancer properties of cannabinoids were a recurring theme at this year’s meeting of the International Cannabis 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.)

Anecdotally, “MMJ3001 A” 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 canna-bis oil make a difference? We don’t know because we didn’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.”

Hergenrather’s study of glioblastoma (white area near center of skull) shows the chorological regression of an optic pathway glioma (white area near center of skull) by approximately 96% 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.

To do this properly, he advises, “You can’t collect data on only the patients who respond well. You have to collect data on all patients who use the prepared medicine.”

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 slides 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 MarkWare, 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 Todd Shedlin, 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 cannabis oil to their regime. The primary objective would be to establish safety—-to confirm that the large cannabinoid infusions were not interfering with the body’s ability to process temozolamide.

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 to hear is 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 dispensers 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 collect data on all the patients who respond well, and also the ones who don’t.”

Hergenrather’s presentation at MMJ13001A continued on page 14

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Doctors and Dispensaries continued on page 14

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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 intensely 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 ground-breaking research was subsidized by the U.S. National Institutes for Health (NIH), which had suddenly become desirous of more objective information about the herb. Mechoulam’s team’s findings were sorely needed 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 scourred to gather basic scientific data. But historians agree, this was 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 by any known solvent and then subjected to various tests.

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 receptors for morphine and its relatives 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 sites — special 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 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.

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.

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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 squeezes back and forth across the cell membrane seven times. Cannabinoid receptors function as gates that allow ions and signaling molecules into or out of cells. They have a set of 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.

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 in the laboratory, THC had no effect on breathing 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 therapies 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. However, this does not result in the sensation of euphoria. 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 cannabinoids,” so to speak. In 1992, Raphael Mechoulam, in collaboration with NIMH research fellow William Devane and Dr. Lumir 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-arachidonoylgllycerol), which binds to both CB-1 and CB-2 receptors.

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 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-forms — our precursors — emerged. 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 “air findings in highly technical peer reviewed journals and at regular conclaves devoted to cannabinoid research, convened 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 old diseases of unknown etiology that seemed to have as their common denominator an inflammatory or autoimmune dysfunction.

The discovery of the endocannabinoid system has breaking research implications for nearly every area of medicine, including reproductive biology. Dr. Marco Campanella 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, ovudtural 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 Medulhous, “a fragile signaling through cannabinoid 2 receptors part of a protective system?” in Progress in Lipid Research, February 2011.

For Big Pharma, cannabinoid research could be seen as a tale of 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.

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Care and Feeding of the Endocannabinoid System

What we eat and drink, the drugs we use, treatments we receive, 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 acneform receptors, ligands (compounds that bind to receptors), and ligand-metabolizing enzymes.

Cannabinoid receptor type 1 (CB1) is primarily located in the brain, spinal cord, and peripheral nerves. CB2 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 (CB2) is principally associated with cells governing immune function.

Two ligands known as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) activate both CB1 and CB2.

Anandamide is released by an enzyme called NAF-PLD, and is broken down by an enzyme called FAAH. 2-AG is primarily released by an enzyme called DAGLs, 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 CB1 and CB2, and activating the receptors.

Tetrahydrocannabinol (THC) is a plant compound that mimics our endocannabinoids, much the same as opioids from poppies mimic endogenous opioids. Thus, THC functions like anandamide and 2-AG by sliding into CB1 and CB2, 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 relatively recent additions.

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

In this article McPartland summarizes the lecture he is presenting at the Patients Out Of Time conference in Tuscum. The lecture itself summarizes a forthcoming review article by McPartland and Vinzence 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 overexpression by chronic overactivation of eCB ligands. In these diseases, downregulating the levels of eCB ligands would be beneficial.

CB1 receptors desensitize and downregulate when faced with constant activation.

Secondly, genetically chronic, chronically high levels in anandamide and 2-AG would be counterproductive, even in people with eCB deficiency syndromes. This is because CB1 receptors desensitize and downregulate when faced with constant activation. A desensitized receptor loses its responsiveness; intake of cannabinoids such as THC results 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 CB1. 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-body interventions” (diet, weight control, exercise, and the use of psychoactive substances—ethanol, nicotine, caffeine, and tobacco), 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 tobacco).

We can enhance the eCB system by simply living a healthy lifestyle, beginning with aerobic exercise. Human studies show that aerobic exercise, and climbing 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 CB1 in the brain. An interesting rat study by Hall and colleagues suggests that wheel running not only increases CB1 expression, it also increases the sensitivity of CB1 to anandamide.

Diets are trickier. Overeating leads to obesity. Adipocytes produce excessive amounts of eCBs. The eCBs spill over into the blood, cross the blood-brain barrier, activate CB1 in the brain, and cause the munchies.

The scenario becomes a feed-forward dysregulation of the eCB system. Our stereotype of the “happiest fatman” gets even happier as further excessive amounts of eCBs cause CB1 to desensitize and downregulate. The “munchies” picture—cardiovascular disease, diabetes, and systemic inflammation.

Caloric restriction (dieting, fasting) worsens the situation, at least initially: it leads to reduced CB1 levels in the blood, and downregulated expression of CB1 in the brain. Although some studies report conflicting results—and we need more research—a downregulated eCB system may explain the clinical picture of the “anorectic dieter.”

But there is hope! A recent study of pyrorethrin women showed that dieting causes a decrease in CB1 expression... but combining caloric restriction with aerobic exercise caused a net increase in CB1 expression! Trickier yet is the impact of polyunsaturated fatty acids (PUFAs) on the eCB system. The typical American diet contains excessive omega-3 PUFAs and lacks omega-3 PUFAs. Arachidonic acid is the archetypical 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 supplement with arachidonic or eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Dietary supplement 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.

Rats and mice supplemented with omega-3, compared to mice on a control diet, express greater mRNA levels of CB1. An other study with mice showed that omega-3 deficiency abolishes eCB-mediated neuronal functions. The omega-3 deficient diet led to CB1 desensitization, because of a relative excess of arachidonic acid.

Omega-3 deficient mice did not respond to exogenous cannabinoids (in this case, delta-9-tetrahydrocannabinol, THC). A difference in diet—THC would have produced the same non-response). Omega 3-deficient mice, however, showed normal cannabinimimetic 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 Frid showed that when newborn mice have their CB1 receptors blocked (with the synthetic antagonist rimonabant), the baby mice don’t suckle at birth, and die.

Acupuncture is a good thing. Electro-acupuncture (EA) upregulates the expression of CB1 in skin tissues. EA also increases anandamide levels in the skin, and the pain-reducing effects of EA are attenuated by CB1 antagonists. EA also treats pain by reducing GABA levels in the spinal cord (periaqueductal gray area), which is reversed by CB1 antagonists.

Stress is a good thing. Electro-acupuncture upregulates the expression of CB1 in skin tissues. EA also increases anandamide levels in the skin, and the pain-reducing effects of EA are attenuated by CB1 antagonists. EA also treats pain by reducing GABA levels in the spinal cord (periaqueductal gray area), which is reversed by CB1 antagonists.

Opioids and cannabinoids are microproteins such as Lactobacillus acidophilus that confer health benefits upon humans. They occur in fermented foods, such as yogurt and kimchi.

Human intestinal cells expressed to L. acidophilus increase their expression of CB1, RNA. Mice fed L. acidophilus show less pain behavior following cold stress control, as fewer 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 relatively recent additions.

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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: cannabinoid (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 FAAAs 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 Galilly, 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 Galilly 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 derivates 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.

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 endocannbinoid-like molecules acting through the CB2 receptor have been reported to affect a large number of pathological conditions,” Mechoulam said.

Stimulation of CBD “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...”

“Medical science is 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 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) (pronounced Aar-ess)—lowers vasosconstriction and brain trauma effects. Arachidonoyl glycine lowers pain. Oleamide is an endogenous sleep-inducing lipid. Oleinol serine counters otopoiesis. Palmitoyl ethnaolamide (PEA) concentrations are enhanced after damage in a specific brain region.

Mechoulam’s To-Do List for Researchers: CBD, the CB2 Receptor, and ‘F-Triple-A’s’ continued on next page
Smoke Signals Sampler from previous pages...

CAN had frequent run-ins with cops. But the hempters 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 convos 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 lighting 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 endeavors.

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, Debbi Goldsberry, and other 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 DEA, citing THC concerns, pegged the hemp industry and medical marijuana as a

VIVIAN MCEAK (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!

Add Scenes From the ‘Fest

“Be there or be in DARKE” —W.T.

Brilliant buskers! Smokin’ seahawks!
Constance Gee from previous page

aspire during the ferocity of a drop attack. “The rest of the day or night and some- times weeks could be spent in bed drog- ing up on Valium, Xanax, Zofran, Ativan, or Phenergan — whatever medication various physi- cians might advocate would ease the nausea and stop the vertigo.”

Constance lost 17 pounds over the course of a few months. An old friend visited in March 2000, and they went for a hike in a state park and Constance soon got sick to her stomach. Her friend “took a small round brown tin filled with marijuana and a lit- tle 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 puffs as we walked and felt much better immediately. She repacked the pipe, took two bites herself, tapped out the ashes, and handed me the tin and pipe.”

“Keep this,” she smiled. “I’ll help.”

“Sure does,” I agreed. The effects seemed miraculous. The nausea was gone.” Constance told her husband, whose re- sponse, “I don’t know about wanting it!”

• “Hmm.. He hadn’t said, “Don’t do it” — although I probably would have ig- nored him. Rob Sullivan 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. “Other side effects of pot are truthfulness and talkativeness, a potentially dangerous combination,” she observes. Or “to perceive the humorous absurdity of the situation.”

Among those to whom Constance re- vealed 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 rec- ommend it.”

‘Don’t ask, don’t tell...”

• “And I had shared responsibility for allowing mariju- ana 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- one using medical marijuana to treat symp- toms of Meniere’s。” He added, “There are a whole lot of other ways to treat it, low- er dosage of 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 counseling counselors and the rest of the medical profession.

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 ren- ovating Bruebne, “Mr. Gee has dramati- cally boosted the 133-year-old school’s ac- ademic standing and overseen fund raising of more than $1 billion.”

The trustees had been delighted with the revenue generated by the Gee’s entertain- ing. The mansion was then the center of attention. “The Journal was going to ding them for failing to monitor expenditures, they diverted the reporters’ attention to Constance’s use of the home.”

• “The trustees’ concern over their chancellor’s expenditures,” the Journal sequed wobbly, “was aroused when they learned that Gee was using marijua- na at the mansion.”

Constance Gee’s use of mari- juana to treat Meniere’s Disease absolutely had 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. Constance Gee, a tenured associate profes- sor of public policy and education, kept marijuana at Bruebne and was using it there, according to people familiar with the matter. A few weeks later, several trustees and a senior university official confronted Constance, but according to those tees, the incident demon- strated that Constance 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 profes- sor of public policy and education, kept marijuana at Bruebne and was using it there, according to people familiar with the matter. A few weeks later, several trustees and a senior university official confronted Constance, but according to those tees, the incident demon- strated that Constance needed to be more accountable to the board.”

Constance’s ear ailment as Meniere’s in- volved vertigo, or a spinning sensation, or Benadryl, which is used in certain ear problems. My patients say cannabis is as good as Antivert, which is the classic treat- ment, or Benadryl, which is used in certain ear problems. My patients say cannabis is as good as Antivert, which is the classic treat-

“Meniere’s”

Meniere’s disease had absolutely nothing to do with the Vanderbilt trustees’ failure to do their fiduciary duty.

Hullar’s comment showed the extent of the knowledge gap between counseling counselors and the rest of the medical profession. O’Shaughnessy’s Winter/Spring 2007 issue included an article about Constance Gee’s medical/political ordeal, and quoted three academic counselors who routinely pro-ved 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.”

MD, corroborates: “I issued many recommendations for Meniere’s, as well as tinnitus [ringing in the ears]. It works well enough to make a significant improvement in many cases, i.e... symptoms not gone but much abated so they can function and carry on their daily activities, instead of sitting and suffering. It’s a real benefit.”

R. Stephen Ellis, MD, of San Francisco, has given some thought to how cannabis might help in the treatment of Meniere’s disease. “Three possible mechanisms come to mind,” he says. “Number one, the anti- anxiety ef- fect of cannabis would be very useful to a Meniere’s patient. Their anxiety is usually as serious as when they hit the ETR. When they get an attack it’s as if they are wired that — why are I’ovin is one of the treatments, to bring that under control. Two, 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 treat- ment, or Benadryl, which is used in certain ear problems. I read auditory that the aesthetic nerve does have CB1 receptors. I don’t know what the cochlear structure looks like, i.e., symptoms not gone but much abated so they can function and carry on their daily activities, instead of sitting and suffering. It’s a real benefit.”

In August 2005 Constance contacted Dr. Hullar and read him the quotes from Bear- man, Sullivan and Ellis. “He was unmoved by the quotation and contended the re- portation. 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 described it in the treatment of Meniere’s related nausea. It is not part of the standard repertoire,” he said.

There’s something about Dr. Hullar that none of his Meniere’s patients has revealed to him of their use of marijuana. Not everyone is inhibited by prohibition from discussing their condition or symptoms on the two parties involved. Some individu- als tend to be easily embarrassed, they fear disapproval; others are forthcoming. Some doctors have not regarded they are tolerant and open-minded, others signal strong adherence to official dicta. Obviously, Hullar is among the former.

Gordon Gee abruptly left Vanderbilt in 2007 (before the divorce was finalized) to return to the presidency of Ohio State University. Constance resigned as chancellor of the University of Tennessee in November 2010. She moved to Massachusetts in December 2010, just in time to join the 63% of voters who approved. If that’s not a testimonial to virtue... Susan Sarandon sought to option Higher Education: Marijuana at the Mansion....

Till then it’s available in softcover as an eBook from Amazon, Barnes & Noble, and marijuanamemilation.com

Another side effects of pot are truthfulness and talkativeness, a potentially dangerous combina- tion,” she observes.