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 by UCSF, MMJ13001A and B. 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 cannabis: pain, appetite, nausea, vomiting, fatigue, stools per day ("a real number," Hergenrather remarked), depression, activity level, and weight in pounds.

Hergenrather is now tracking 38 patients —28 with Crohn's and 10 with ulcerative colitis. Twenty-two are employed full or part-time. Seventeen (43%) have had surgical interventions. "This will be an interesting number to follow over time." Hergenrather said, noting that 75% of Crohn's patients have surgery during their lifetimes, according to the Centers for Disease Control.

Hergenrather's results strongly suggest that herbal cannabis is beneficial in the treatment of Irritable Bowel Disorders.

Half of the patients in the SCC study had stopped the daily use of conventional pharmaceuticals to treat their IBD, except during flare-ups. The main limition on cannabis use were "social issues," including risk of discovery by an employer. Others limited use because it made them too sleepy or too spacey. Cost was another limitation.

Hergenrather's results strongly suggest that herbal cannabis is beneficial in the treatment of Irritable Bowel Disorders. Stools per days were reduced by a third, pain reduced by half, vomiting was down, appetite up. Overall, Hergenrather said, "patients' quality of life is improved significantly."

Issuing Cannabis Approvals

Hergenrather addressed various questions likely to concern MDs who had been taught nothing about cannabis in medical school but want to know what's really known about its safety and efficacy, and what kinds of interactions to expect when discussing cannabis use with patients.

"You're going to get asked a lot of questions about strains," Hergenrather advised, but there is no rigor to the nomenclature.

Sativas are said to provide a "head high." Users report feeling more "energetic, focused, alert, creative... Indica-dominant strains tend to promote sedation and 'couch

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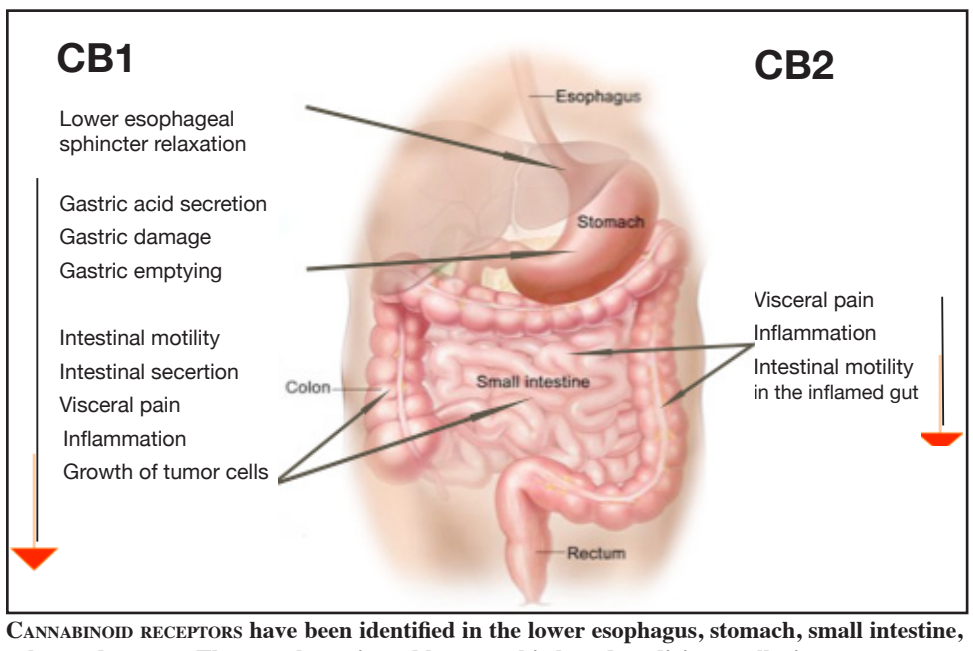

Cannabinoid receptors have been identified in the lower esophagus, stomach, small intestine, colon and rectum. They can be activated by cannabis-based medicine to alleviate many symptoms of Crohn's disease.

CME Course *from previous page*

Ware called the cannabinoids "synaptic circuit-breakers." The process by which they work is "retrograde signaling."

California audience that the era of cannabinoid therapeutics "isn't going to just be about medical cannabis."

Unlike neurotransmitters sent from Cell A across a synapse to impart a signal to Cell B, cannabinoids are made on the membranes of Cell B (the post-synaptic cell) and released across the synapse in the opposite direction to quell the firing of Cell A. Ware called the cannabinoids "synaptic circuit-breakers." The process by which they work is "retrograde signaling." *(See illustration at right).*

The body's own cannabinoid receptors, CB1 and CB2, were cloned in the late 1980s and '90s. CB1 and CB2 are G-protein coupled receptors. The expression of the CB1 receptor in numerous parts of the brain explains its wide-ranging effects. Although more prevalent than opioid receptors, CB1 is not present in the parts of the brain that control breathing —which is why overdosing isn't fatal.

The CB2 receptor is prevalent in the immune system and involved in modulating inflammation. Microglia and astrocytes —immune cells in the central nervous system— modulate neurological processes.

Ware described pain modulation as "a dynamic fluid process with input from the brain coming down the spinal cord." Endogenous cannabinoids diffuse back to the presynaptic neurons and suppress the firing of the (pain) signal. Two endogenous cannabinoids have been identified: anandamide (AEA) and 2-arachidonoyl glycerol (2-AG)

Exogenous cannabinoids receptors can augment the suppressive effect. Seizure disorders, Ware said, exemplify a condition in which the goal is to suppress the rate at which neurons are firing.

The cannabis plant is only one source of exogenous cannabinoids. Synthetic can-

Cannabinoids activate receptors other than CB1 and CB2, including serotonin receptors, and are viewed, increasingly, as part of a larger family of lipid compounds.

nabnoids such as Nabilone are being prescribed with increasing frequency.

Nor is providing exogenous cannabinoids the only way to augment cannabinoid tone. Compounds have been developed that block production of the enzymes that break down anandamide and 2-AG —FAAH (Fatty Acid Amide Hydrolase) and MAGL (glycerol lipase) respectively

"Studies are going on all the time," Ware said, with drug companies pursuing various strategies. Cannabinoids activate receptors other than CB1 and CB2, including serotonin receptors, and are viewed, increasingly, as part of a larger family of lipid compounds.

Ware described palmitoethanolamide (PEA) as "an endocannabinoid with potential CB1 activity" that is on the market in Italy as a dietary supplement. But developing pills that act like anandamide or 2-AG presents a daunting challenge to pharmacologists, he said. "These compounds are designed to be made locally [by cell membranes], to be active locally, and to disappear very quickly and be recycled."

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A Nursing Perspective

MaryLynn Mathre, RN, the final speaker, is co-founder with her husband, Al Byrne, of the reform group Patients Out of Time. Mathre and Byrne served as officers in the Navy during the Vietnam war, and have devoted themselves to helping veterans ever since. They had been active in NORML but split off in the mid-1990s to form their own group. Its core members included Irvin Rosenfeld, Elvy Musikka, George McMahon, and several other surviving patients from the "Compassionate" Investigational New Drug program established under Jimmy Carter and canceled by George H.W. Bush in 1992, just as AIDS patients who needed marijuana to counter wasting syndrome had begun applying in large numbers.

In addition to publicizing the existence of the federal IND program —which

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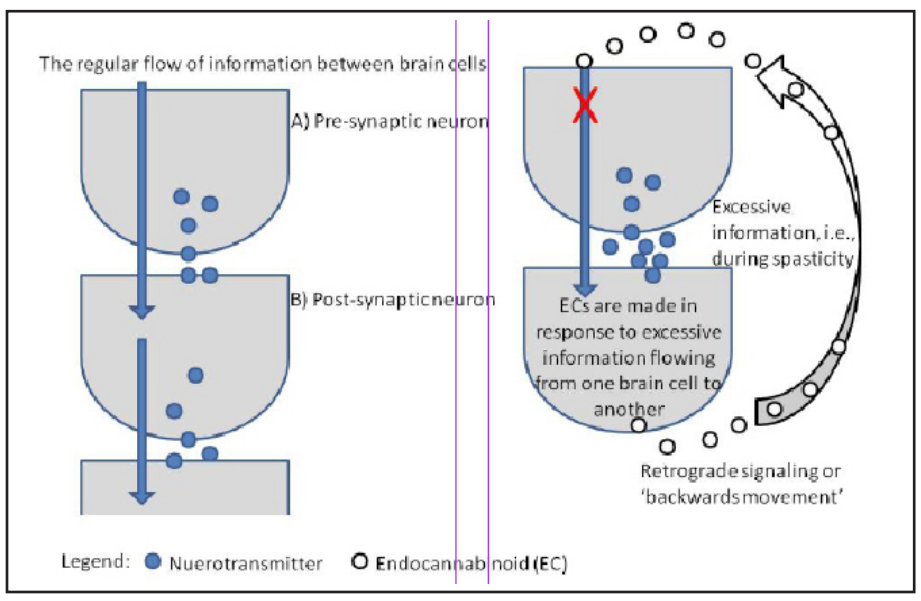
Retrograde Signaling (going against the flow)



Regular flow of information between brain cells involves neurotransmitters (serotonin, dopamine, et al), as illustrated above at left. Generally, a neurotransmitter travels from neuron *A* to neuron *B* or "presynaptic" to "postsynaptic." Neurotransmission by endocannabinoids, on the other hand, involves travel from *B* to *A*, or postsynaptic to presynaptic. This type of movement is called "retrograde signaling" to describe its "backward" direction —against the transmitter flow. In recent years the neurotransmitter nitric oxide (aptly abbreviated NO) has been found to have a similar "retrograde" method of signaling.

Research has shown that the activation of cannabinoid receptors can temporarily reduce the amount of a neurotransmitter released, or reduce the flow of information between neurons. This can be a helpful way to treat patients who have a disease or injury in which neurons are approaching excitotoxicity, a toxic state arising from overactivity that often results in the death of the brain cell. The mechanics of "going against the flow" underlies the protective effects of cannabinoids on brain cells. —*Jahan Marcu, PhD*

Hergenrather's Presentation *from previous page*

lock...' Names with 'Kush' or 'Afghan' tend to be Indica-dominant. Also those with colors in their names, purples, blues, grapes, blacks... 'Hazes' and 'Diesels' tend to be Sativas. There's so much crossing and hybridization that these generalizations fall apart," Hergenrather acknowledged.

Introducing CBD

Hergenrather described cannabidiol-rich cannabis as "the real star of the show." He explained that cannabis used recreationally might have a THC-to-CBD ratio of 50- or 100-to-1, but now strains were being used by patients that contain various cannabinoid ratios, including some that are predominantly CBD "so that you don't get stoned."

"CBD antagonizes THC and reduces tachycardia [rapid heartbeat]," Hergenrather said, allaying two fears in one sentence. It would be interesting to know how many of the doctors in attendance were hearing about THC's non-psychoactive cousin for the first time.

Acid and neutral cannabinoids

"In the green plant, THC is in the acid form, which is not psychoactive," Hergenrather explained. "When it's burned, vaporized, dried over a long period of time, or baked, you decarboxylate it. In the neutral form THC is psychoactive. But if you use the molecule in the green form you're going to be able to go way up on dose without going up on psychoactivity.

"Eventually terpenes will impart effect, but in general patients can go way up on dose when using green medicine. A patient can take a bud that would take a week to smoke and put it in a smoothie and do that two or three a times a day and not have any 'high' effect.

"You've got to do a hands-on evaluation. You've got to take the vital signs and write it down."

Nuts and Bolts for the Clinician

Hergenrather shared the SCC practice standards. "You've got to do a hands-on evaluation," he said for openers. "You've got to take the vital signs and write it down."

Patients should be advised about their needs. "Many people today do not have medical care. You've got to sit down and talk with them about their health —diabetes, hypertension, obesity. You need to make appropriate referrals.

"If you have a referral from another doctor, make a point of communicating with that doctor about your findings and observasions. On the other side, if your patient says 'I don't want my primary doctor to know about this, I'll take care of that on my own,' I think your responsibility is to your patient and not to the medical board or the treating physician."

"Let the patient know when you want to see them back and what you expect of them.

"Ask for lab work and imaging reports. And for anybody youthful, I want to see their grade cards. In general they do much better when they're using cannbis.

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"Be willing to testify. This has everything to do with proper record keeping.

"I would have documentation supporting the diagnosis that I'm treating in advance of seeing the patient for the first time.

"I like to quantify the use of cannabis and method of administration at every visit. It changes over time. After patients use it as vapor or topical forms, they're going to use a lot more cannabis.

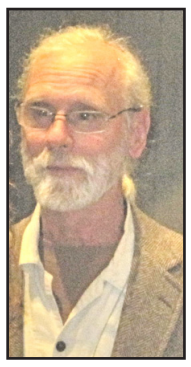
"We have to ask for a release of liability because patients are going to be out there driving. The release of liability spells out issues that the patient needs to sign and say 'Okay, this is on me and not on you.' Those forms are available at cannabisclinicians.org.

"The federal courts support the physician's right to have this relationship with the patient, including making a recommendation... This is not a permit to grow for profit. This is an approval to use cannabis for your own personal medical needs. It's important to make that clear to the patient. This is the extent of it: you can grow what you need for your own use."

Precautions

Hergenrather described cannabis use as "habit forming but not addictive."

Smoking can cause bronchitis, he said, echoing Tashkin.



HERGENRATHER

Hergenrather said he had seen five cases of cyclical vomiting syndrome caused by marijuana use.

He noted that ingestion of cannabinoids has not been found to adversely affect the liver's ability to metabolize clinically useful drugs —but the advent of megadoses via concentrated oils and raw buds and leaf might result in a different side-effect profile.

Hergenrather characterized the association of cannabis use with schizophrenia as "controversial," adding, "I found that the Keele study in England a few years ago really exonerated cannabis considerably. They followed 2.3% of the English population in clinics for 10 years; and over that period of time there was an 18-fold increase in cannabis use by their youth, while there was no increase in schizophrenia and psychosis in Great Britain."

In the audience were two midwives and another MD whom Hergenrather had worked with at the Farm, a large "intentional community" in Tennessee, where marijuana was used "with reverence" by almost everyone. Over the course of several years, Hergenrather said, "we, collectively, did not see any significant adverse effects associated with cannabis through gestation and nursing." Also, "It works better than anything for morning sickness." Nevertheless, he advised the doctors to "advise judicious use during pregnancy."

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"I've been encouraging patients to make the oil and put it directly on skin lesions," he said. "If I thought someone had a melanoma I would hustle them to the surgeon.But for just about any other kind of skin lesion, 'Put the cannabis oil on it and watch the results.'"

Hergenrather showed before and after slides of a patient with a keratosis on his cheek that had been there for 10 years. "A band-aid with cannabis oil for a month and it fell off," he reported. The growth has been gone for a year with no signs of recurrence, he said.

To treat skin lesions, Hergenrather recommended "the more concentrated the oil the better. An occlusive dressing works best, even a spot bandaid."

CME Course *from previous page*

comes as news to most Americans, and exposes federal hypocrisy on the subject of marijuana as medicine— Patients Out of Time organizes conferences every two years to update doctors, nurses and other healthcare providers about recent research and clinical findings. Since 2000 CME credits have been available to practitioners attending POT conferences.

MARYLYNN MATHRE

The Oct. 24-25 presentations in San Francisco and Santa Monica were right in sync with the Patients Out of Time mission, which Mathre summarized as "educating healthcare professionals and the public about therapeutic cannabis."

LARRY BROOKE (LEFT), the founder of General Hydro, chats with Alan Levinstone, MD, who came from Centreville, Virginia to attend the course at UCSF. A grant from Brooke enabled the Society of Cannabis Clinicians to underwrite the event.

In Santa Monica on Oct. 25, UC San Diego psychiatrist Igor Grant replaced Stephen Sidney and spoke on "The Neuropsychiatric Effects of Cannabis." Grant directs the University of California's Center for Medical Cannabis Research. The CMCR was created by state legislators led by John Vasconcellos in response to the passage of Prop 215. Annual allocations to the CMCR of $3 million for three years paid for nine studies involving cannabinoids, including Donald Abrams' pain study using herbal cannabis (described above).

Mark Ware had the air of a Broadway producer evaluating his show in Philadelphia. He knows he's got a blockbuster but is still tinkering with aspects of the production. Future bookings include Washington, D.C. February, 22, 2013, at the invitation of Americans for Safe Access.

For MaryLynn Mathre, participating in MMJ13001A and B was an extension of educational work she has been doing for decades. For Jeff Hergenrather and me it felt like fulfilling a last promise to Tod Mikuriya, MD, our friend, who founded the SCC with an eye towards enlightening the whole medical profession. ("Patients know much more about marijuana than doctors," he had observed.)

By coincidence, two of the speakers — Abrams and Sidney—showed pictures of old cannabis tincture bottles that Tod had emailed along with his congratulations after their studies were published.

MMJ1300 attendees were asked to fill out evaluation forms. They revealed that doctors from a wide range of specialties are interested in incorporating cannabis-based medicine in their practices:

"Emerg and Occ Med, ER (2), Family Practice (10), Family/Peds, Family/Tropical Medicine, General, Geriatrics, Geriatrics/GP, GP and Cannabis Consultant, HIV Medicine (2), Hospice & Palliative Care, Addiction medicine, Hospitalist, Infectious Diseases, Internal Medicine (6), Internal medicine/Anesthesia (pain), Neurology (2), Oncology (2) Opthalmology, Pain/PRM (2), Perinatal, Preventive Medicine, Psychiatry, Psychoanalysis, Public Health, Rheumatology, Addiction medicine, Alternative medicine (2), General practice/Emergency, Herbal medicine, Medical cannabis (2) Pain Management, Plastic Surgery."

Among those evaluating MMJ1300 were six nurses, two pharmacists, nine "allied health professionals," and 10 "industry representatives."

The course drew as many people from outside the medical field as it did from within. The organizers considered and rejected a suggestion that one dispensary and one tincture maker have booths at the event. Their goal is to reach MDs seeking an introduction to cannabis medicine from experts in the field —a mission of the utmost importance, nationally and internationally. They do not want to be perceived as Dr. Ware's Marching Pot Club Band.

The evaluation form asked the practitioners to list "three or more specific changes in patient care that you intend to make as a result of participating in this CME activity."

Evaluation comments:

TOD MIKURIYA, MD, with a Cannabis tincture manufactured by Parke, Davis. Drs. Sidney and Abrams showed slides of once-legal tinctures Mikuriya had sent them along with congratulations on the publication of their studies.

"Better advice to patients. Make caution in Cardiovascular patients. Better choice of appropriate patients. Better knowledge of pharmacology of cannabis.

"Increased understanding of novel formulations.

"Consider cannabis as adjunct to opioids.

"Consider more cannabis with anxiety and sleep. Consider for detox or withdrawal. Encourage use of oil for skin lesions.

"Reassure regarding use of cannabis with MS with other opioids.

"Stress the legitimacy of cannabis as medicine.

"I will encourage my patients suffering from poorly controlled Crohn's disease, chronic pain and some other conditions to see

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