Raphael Mechoulam is ‘The Scientist’

By Fred Gardner

Many of us who get interested in cannabis as medicine get very interested and want to learn more about how it works. One of the first facts you pick up is that the chemical structure of THC was worked out and published in 1964 by Israeli pharmacologists Raphael Mechoulam and Yehezkel Gaoni.

Less well known is the sweep of Mechoulam’s career. He has been conducting and guiding cannabinoid research all these years, the central figure in a vibrant worldwide entourage.

Zach Klein’s beautifully filmed documentary *The Scientist* reviews Mechoulam’s role in discovering and elucidating the endocannabinoid system, and proposing clinical applications.

Klein, 46, is one of those people who get very interested in cannabis. His 2009 documentary *Prescribed Grass* told the story of Tikun Olam, Israel’s pioneering medical cannabis collective (a group Klein helped organize).

In *The Scientist* Klein plays the curious Everyman who questions Mechoulam about cannabis and how it works in the body. (Klein’s face is handsome and more expressive than Everybody’s.) The interviews are conducted in the pleasant Jerusalem apartment where Rapbi and Dahlia Mechoulam have lived since 1966, and in Mechoulam’s lab at Hebrew University, and in his car as the scientist drives to and from work, and at a meeting of the International Cannabinoid Research Society (a group Klein helped organize).

Klein occasionally carries a potted cannabis plant—a signature prop, like Charlie Chaplin’s cane.

Although Mechoulam’s manner is gentle and undemanding, he is making a strong plea in *The Scientist*: cannabis-based medicines should be made available to patients. He does not point an angry finger at any agency or entity that has impeded progress—he shrugs in bemused disappointment.

“Early Human Experiment” conducted by Mechoulam involved “a delicious cake” baked by his wife Dahlia with portions containing 10 milligrams of THC (and an unspeckled cake for control purposes). Five of the Mechoulams’ friends ingested THC in a social setting, and their responses were carefully observed. These responses ran the now familiar gamut ranging from pleasant social disinhibition to unpleasant anxiety. Illustrations by IvanArt.

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affected. In some cases we definitely see anxiety attacks. Most do not [experience anxiety]. Most just feel kind of a little bit disoriented. Just maybe a little bit sedated. Maybe a little bit open to discussion and socially open to whatever is being discussed.

Note Mechoulam’s use of “maybe” and “I believe.” He abjures strong assertions and tends towards understatement, as if his knowledge is provisional.

“It’s not just he discovered THC... but he continued to have such a vision for the next step and the next step and the next step.”

—Mahmoud ElSohlly

Promoting research
Klein filmed Mechoulam attending a meeting of the International Cannabinoid Research Society in Freiburg, Germany, in the summer of 2012. “I feel that Dahlia has to be next to me if I want to survive on a trip,” he comments over footage of them boarding a plane.

Among Mechoulam’s colleagues interviewed in The Scientist is Mahmoud ElSohlly, famous for growing the marijuana that the U.S. National Institute on Drug Abuse (NIDA) provides to researchers. ElSohlly tells Klein that Klein has never rested on his laurels, is always seeking to advance research. “I believe,” he tells Klein. “I was very well aware of the known drugs. We started giving them high doses of cannabidiol — 200 mg per day.

“We were happy to note that indeed they had no seizures while they were taking cannabidiol. And it was published. And nothing happened afterwards. So far, 34 years later, this is the only publication of CBD reducing epileptic seizures was report ed in the journal Pharmacology in 1980, but resulted in no follow-up research with an eye towards drug development.

ElSohlly says, “We are happy to note that indeed they had no seizures while they were taking cannabidiol. And it was published. And nothing happened afterwards. So far, 34 years later, this is the only publication of cannabidiol in humans against epilepsy.”

In 1988 the finding of a cannabinoid receptor in rat brain by Allyn Howlett and colleagues at the St. Louis University School of Medicine was characterized by Mechoulam as “a major, major discovery — the first indication that THC acts on a receptor.”

Undoubtedly, Mechoulam points out, “Receptors are made for compounds that we produce, not because there is a plant out there. So the next challenge for scientists was to find the body’s own endogenous cannabinoids. “In my lab there were three collaborators who contributed a lot in this research,” Mechoulam tells Klein, as he enters a room where two of those collaborators — Lumír Hanuš and Aviva Breuer — are still at the bench.

Hanuš explains that he came from Czechoslovakia 23 years ago “just for one year, and got a little bit overextended.” Al ly Howlett’s lab when the receptor was identified. At right (left). The receptor was first identified in humans are somewhat closely related. And probably pigs and humans are also somewhat closely related. We’re not sure that the pigs will be very happy to be related to humans, but that’s something else. So we wanted to work on pig brains and pig brains are not so easy to get in Jersey.” Hanuš recalls. “At the end it was very expensive.”

Devane explains how he would take a thin slice of the brain material “and put it over a silica sand column and separate a cannabinoid molecule (left) in the vicinity of the CB1 receptor pocket, into which it will fit.

Like most Bulgarian Jews, the Mechoulams emigrated to Israel after World War Two. After a stint as a land surveyor, Mechoulam spent three years in the army, which had been doing research on insecticides. He got his PhD degree from Hebrew University “on the topic of natural products related to biological problems.”

“After doing post-doctoral research at the Rockefeller Institute in Manhattan, Mechoulam took a position at the Weizmann Institute in Rehovot, which is where he and Gaoni isolated the compounds in hashish. Mechoulam joined the Hebrew University faculty in 1966.

Receptor and agonist
The Scientist is subtitled Are we missing something? — which is the last sentence in a book Mechoulam compiled, Cannabinoids as Therapeutic Agents (1986). Klein asks Mechoulam to explain what he had in mind. “Plant cannabinoids,” Mechoulam says, “had been evaluated in the test tube, they had been evaluated in animals and to a certain extent in human patients. But nothing was known at that time about the mechanism.”

“Receptors are made for compounds that we produce, not because there is a plant out there.”

“I believe.” He abjures strong assertions and tends towards understatement, as if his knowledge is provisional.

“Maybe” cannabis and other compounds in the vicinity of the receptor influence how it gets activated: the “entourage effect.”

—WILLIAM A. DEVANE proposed the name “anandaa”—the Sanskrit word for bliss— for the endogenous cannabinoid.

—LEON HANS (LEFT) joined the search for the endogenous cannabinoid(s) in 1991. At right is Esther Frade, who worked with Mechoulam.
In the beginning we wanted to do a double-blind study. Some of the children got the THC, some other children got only the olive oil. After a week she told me: ‘I’m not going ahead with that, I know exactly who is getting the THC, I know exactly who is not getting it.’

There was a complete separation. Those that didn’t get it continued to vomit. So she went ahead doing an open study. She gave THC — pure THC — under the tongue about 400 times [during the course of a child’s treatment]. And at the end we had complete — complete — block of vomiting, a complete block of nausea by a small amount of THC. We did not cause any psychoactivity, nothing.

So here we had a complete therapeutic effect and we published that, and again, essentially nothing happened. Finito, that was it. It’s still not being used in children.”

Klein repeats the conventional challenge: “And you think it’s a good idea to use it for children?”

Roger Pertwee, professor of Pharmacology at the University of Aberdeen, confirmed that anandamide produced by the body behaved like plant-produced THC.

few fractions and test them [radioactively tagged] for how they bound to the receptor. And I thought, ‘Oh, it won’t take long.’

But when Hanus’s year at the lab came to an end, the endogenous cannabinoid still hadn’t been isolated. “So we asked Professor Mechoulam to extend,” Hanus tells Klein.

Other scientists were seeking to identify the endogenous cannabinoid. Devane says Mechoulam “thought we might be scooped by some other lab.” But he kept Devane and Hanus on the project and in 1992 they isolated a small amount of compound they identified as arachidonoyl ethanolamide.

“I was only like a few droplets in the end of a little test tube,” Devane remembers.

The steps to confirm that the newly discovered compound did indeed have the properties that define a cannabinoid were carried out by University of Aberdeen pharmacologist Roger Pertwee.

Devane, who had studied Eastern philosophy, proposed that the newly identified cannabinoid should be named for the Sanskrit word for bliss, ananda. “Although some people do not agree with me,” Mechoulam tells Klein, “in Hebrew there are not too many names for happiness. For sorrow you can find a lot of names, but... are not too many names for happiness. For sorrow you can find a lot of names, but...”

Because the compound was an ethanol amide, and ananda fits nicely behind the Sanskrit root, the endogenous cannabinoid was dubbed “anandamide”—a name that says something about its effect and its chemical structure.

“Hashish for Children?”

Klein reminds Mechoulam, “In 1995 you had an idea of testing THC on children.”

It had long been known, Mechoulam responds, that cannabis reduces the nausea brought on by anti-cancer drugs. Children given these drugs “vomit and want to vomit — nausea — they’re really in a bad shape. And they cry all the time and their parents are in a bad shape. Luckily, most little children can be cured of the cancer. But the treatment is absolutely difficult.”

Manuel Guzmán: We know that cannabinoids can exert anti-tumor actions in animals. Not only in brain tumors but in many different types of tumors. We know that cannabinoids act not only by inducing cell death but by inducing cell death through that specific mechanism called apoptosis. We know that cannabinoids can tackle other processes of cancer cell growth, such as angiogenesis, metastasis, cell cycle etc.

We did a trial with nine volunteers that had a very malignant form of brain cancer, glioblastoma multiforme. And we observed some positive effects of cannabis on survival of the patients and also on tumor growth, based on magnetic resonance imaging and also based on the measurement of biomarkers of tumor progression.”

Mary About: For several years I was researching a motor neuron disease, Amyotrophic Lateral Sclerosis and was able to show that THC was actually protective in the mouse model of ALS. The mice that were given THC lived a little longer.

Aaron Lichtman: “We’re trying to discover how the world works. In our case, how cannabinoids work and how the brain works.”

Ally Hollett: “I’ve got a lot of research on how we know now that there are CB1 and CB2 receptors in those types of cells that either help degrade the bone or help rebuild the bone. In this day and age women are living beyond menopause and men well into old age. We’re going to think about how to preserve those bones so they can last another 40 years after menopause.

An entourage of investigators

In addition to directing research in his own lab, Mechoulam — all these years — has been disseminating ideas and encouraging worldwide. The Scientist includes a montage of ICRS investigators acknowledging Mechoulam’s guidance — a small cross-section of the many he has helped. It was Mechoulam who inspired Ethan Russo and Vincentino DiMaggio to think in terms of entourage effects — compounds acting in concert — instead of single molecules. It was Mechoulam who urged Itai Bab to explore the role of endogenous cannabinoids in bone, and Ester Frider to study their role in the birthing process and breastfeeding.

Mechoulam notes matter of factly that nowadays “a huge number of researchers are involved in investigating this system from many aspects... A very serious group of researchers has recently published a paper saying that the endocannabinoid system is involved in essentially all human diseases.”

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Mechoulam has no misgivings. “Well, I believe there are better ways to help those children that suffer. But I have no influence on oncologists.” He shrugs and smiles ruefully.

Cut to Ailyn Howlett re-enforcing the point, ardent: “If there is a cancer patient who’s got pain and that pain is not being controlled well by other types of drugs, they’re on cancer chemotherapy, they’re vomiting, I think it’s unethical to withhold a drug from them that can be very useful to help them in their pain management and in their ability to cope with their disease.”

Can cannabis cure cancer? Klein asks, “Can cannabis cure cancer?” Mechoulam answers: “We know that THC lowers the [nausea] effects of cancer treatment. But what we’re asking is ‘is it an anti-cancer drug?’ And the answer is, ‘I don’t know.’ And the reason for that is silly. “It has been tested in the test tube. THC has been tested, cannabidiol, crude canabi

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Rik Musty — an ICRS prime mover

By John McPhearland and Fred Gardner

The longtime executive director of the International Cannabinoid Research Society, Rik Musty, died July 26, at home in Waconqua, Minnesota, at the age of 72.

Rik was born in Minnesota, earned a BA from Carleton College in 1964, and a PhD in Psychology from McGill in 1968. He joined the University of Vermont faculty that year, and chaired the Department of Psychology from 1975 to 1987. He mentored 31 Masters and Doctoral students, and served on the committees of 20 additional theses and dissertations.

His cannabinoid research began in 1973, as a student at McGill with Alex Mazzei, working with Kannlin and Carltin. That fruitful collaboration continued through 2006, bolstered by sabbatical leaves to Brazil in 1991 and 2004. PubMed lists 25 publications. Musty also wrote a dozen book chapters — including two published in 1984 on the anti-anxiety effects of cannabidiol. Musty was a co-founder of the Cannabis Research Institute of New York, and founded the Cannabis Chemistry Group (Eur Neurol. 38:44-5) encouraged the development of a cannabis-based medicine for the treatment of multiple sclerosis and has been cited more than 200 times. In 1987, Rik, Greg Cheshier, and Paul Concorse chaired the Melbourne S

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Rik was a quiet-spoken man with wide interests. Few people know his political career. Rik teamed with Bernie Sanders in 1982, which propelled both of them into office — Rik as Burlington City Councilman for Ward 1, and Bernie as Mayor. Rik served for four years on the city council; no one in it to this day would say he was by any means a radical.

Mechoulam points to this as evidence that cannabis “seems to be helping the symp

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Mechoulam describes a study in which cannabis “seems to be helping the symp

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Heget to the center of the room and folded the chair. “We have to come to grips with the fact that we are facing something that we don’t understand. We don’t know why we have different personalities. We don’t know why we have different personal styles.”

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As scientists instead as intellectuals we should try always to be skeptical.