

Dr. Fride Leaves Us

By Fred Gardner

Ester Fride, the Israeli scientist who showed that a newborn mammal cannot suckle and survive without a functional cannabinoid messaging system, died on New Year’s Day at the age of 56. The cause was lung cancer, diagnosed in July, 2008.

Ester was born in 1953, in Amsterdam. Her parents were Holocaust survivors, refugees from Germany. An ardent Zionist, she moved to Israel at age 19. Her family followed.

After getting a PhD in neurobiology from the medical school at Hebrew University of Jerusalem, Fride did research in the U.S. at Johns Hopkins and the National Institutes of Health on how prenatal stress affects the infant’s brain. In 1990 she returned to Israel and began work in the lab of Raphael Mechoulam, whose focus was on cannabinoids and their mechanism of action. Receptors activated by plant and synthetic cannabinoids had recently been identified — the CB1 receptor in the brain and central nervous system, the CB2 receptor in the immune system— and the search was on for the body’s endogenous (“endo-”) cannabinoids to which these receptors normally respond.

The Mechoulam lab identified one such compound, Arachidonyl Ethanolamide, which was dubbed “anandamide,” in 1992. Another, 2-Arachidonyl Glycerol (2-AG) was discovered in 1995. Fride took part in numerous studies with Mechoulam and was co-author on his landmark 1993 paper describing the pharmacological activity of anandamide. She was also involved in the identification of a third endocannabinoid, 2-Arachidonyl Glyceryl ether, which turned out to be of minor importance.

In 1998 Fride was co-author on a paper by Shimon Ben-Shabat and Mechoulam describing the “entourage effect” that results in 2-AG binding to the

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CB1 receptor more readily when certain other inactive molecules are nearby.

The studies for which Fride is best known were undertaken at the College of Judea and Samaria in Ariel, where the Departments of Behavioral Sciences and Molecular Biology gave her a lab of her own to direct in 2001. Knowing that cannabinoid receptors are present from the time of gestation and abound in the fetal brain, and that endocannabinoids



are present in milk, Fride hypothesized that the endocannabinoid system plays a key role in the nursing process.

She injected newborn mouse pups with an “antagonist” drug that binds to the CB1 receptor (preventing the endocannabinoids from doing so), and compared their development to a control group of pups. The controls gained weight normally, but the pups with blocked CB1 receptors failed to suckle (even though the mothers encouraged them with licking behavior) and starved to death within a week.

Fride *et al* determined that a baby’s 2-AG production spikes as it is being

pushed out into the world, and falls off about 24 hours after birth. This correlated with their finding that injecting the antagonist drug 24 hours after birth resulted in only 50% mortality. Injecting the antagonist on the fifth day of a mouse pup’s life had no effect (the pups having learned by then how to control their mouth muscles).

Fride also experimented with “knock-out” mice that had been bred to lack CB1 receptors and were unable to suckle at birth. When injected with THC promptly after birth, the knockout pups were able to suckle and developed normally.

“The medical implications of these novel developments are far-reaching,” Fride wrote in the *European Journal of Pharmacology* in 2004, “and suggest a promising future for cannabinoids in pediatric medicine for conditions including ‘non-organic failure-to-thrive’ and cystic fibrosis.”

Over the course of her career Fride was lead- or co-author on more than 40 papers. In recent years Fride did several studies involving Rimonabant, the CB1-antagonist drug that Sanofi-Aventis hoped to market for weight loss — the same drug that caused failure to thrive in her mouse pups. (Fride found that Rimonabant blocked the weight gain commonly caused by SSRI anti-depressants.) European regulators withdrew marketing approval after Rimonabant use was linked to an increased tendency to commit suicide.

Fride also took part in studies of a compound produced by the tree that is the source of Frankincense (*Boswellia serrata*). The compound — Incensole acetate, as in “incense” — was found to have anti-anxiety and anti-inflammatory properties.

Fride is survived by two children who are now young adults. A brother died of cystic fibrosis, a hereditary ill-

ness that claimed several other family members.

Future of the lab

Fride was supervising Shimon Rabi-chev’s research into the role of the endocannabinoid system in schizophrenia; Michal Schechter’s study of how the EC system affects maternal behavior and attachment; and Hodaya Dahan’s efforts to elucidate the mechanism by which the endocannabinoid system mediates suckling behavior (and how to induce appetite in cases of failure to thrive). Their findings must now be written up under the supervision of another scientist.

“She was the best teacher and a very democratic person,” says Dahan, who worked with Fride for seven years and will help the family produce a website in her honor when the traditional week of mourning is over.

Rosie and I rarely talk politics with the Israeli friends we’ve made at cannabinoid research conferences. We just express hopes for peace and leave it at that. But yesterday I asked Hodaya Dahan to fill me in — had Ester, who arrived in Israel as a 19-year-old Zionist, changed her outlook over the years? Hodaya said (over a grainy phone line in a Russian-Israeli-Bronx accent) that Ester was... “You have a word for it in America...”

I thought I heard her say “secular” and repeated, helpfully: “Secular! Of course — Ester was *secular*.”

“No,” said Hodaya, “Settler. She was *settler*.”

I’d known that “Judea and Samaria” was a term for the West Bank — “the occupied territories” — but I hadn’t thought of Dr. Fride’s running a lab there as a political act.

She was also an athlete, said Hodaya, a marathon runner. Which — like her incredible beauty — made her death at 56 seem even more unfair.

Medical Cannabis: The Situation in Israel

You would think that in Israel, home to so many leading cannabinoid researchers, patients who need cannabis for medical purposes would be able to get it.

The Health Ministry has authorized a reform group called Tikun Olam to cultivate and distribute on a small scale. “But only a few Israeli doctors know they can legally prescribe cannabis, and only a few patients know they can ask their doctor to prescribe it,” according to filmmaker Zach Klein. Which is why he made “*Medical Cannabis*,” an extremely informative and moving documentary.

Few Israelis even know that their scientists have been in the forefront. “Believe it or not,” says narrator Avria Gilad, referring to the discovery of THC and anandamide in Raphael Mechoulam’s lab, “it all began here in Israel...”

“The experiments conducted by Prof. Esther Fride prove conclusively how effective cannabis is in stimulating the appetite. She also discovered the importance of these substances in the development of infants... Prof. Shohami discovered that cannabis protects neurons in the brain... Prof. Itai Bab discovered that it promotes bone development... Prof. Ruti Galili proved that this plant has anti-inflammatory properties in cases of arthritis and diabetes and that it helps repair damage and promotes recovery after heart attacks.”

Gilad is an engaging narrator, never maudlin as he interviews sick people, and very brave (and polite) as he speaks truth to the authorities. He asks Dr. Yehuda Baruch, a hospital director who must approve every doctor’s letter of approval, “In Israel, how many people do you think need to, or should have a license to smoke?”

Baruch’s answer reveals a restrictive approach. “Most cancer patients in Israel get along very well without using cannabis. You give it to people for whom nothing else helps.” Then he modifies his response: “I’m not saying ‘nothing,’ but have tried at least two or three other types of treatment.”

Gilad: “You require that people try medications, some of which are very toxic and very damaging and very harsh before you give them permission to use something which is the least toxic, the most natural. Which means that politics plays a major part here...”

Baruch: “The answer is yes, because I’m worried that if my finger is too light on the trigger, this will be shut down completely. People are afraid of it. Marijuana has a bad reputation.”

Gilad: “Cannabis’ negative image comes from the authorities. The Israel Anti-Drug Authority has an annual campaign and has convinced the public that it’s nothing but a dangerous drug. Somehow they play down the fact that

it’s also a wonderful, valuable remedy. Perhaps out of ignorance or out of fear.”

Sound familiar?

Also familiar is the realization by combat veterans that cannabis helps relieve their pain and recurring nightmares. We meet Dudu ben Lulu manicuring the herb grown for Tikun Olam by a former biology teacher. (“Everyone leaves here a Vidal Sassoon,” she comments, Jewishly.)

A bomb concealed in a baby carriage cost Dudu lost his right leg above the knee and his left foot. He suffers from phantom pains. Gilad says, “Imagine not having a leg, yet your ankle hurts. *Your ankle actually hurts*. And there’s no ankle, nothing to grab. That must be really frustrating.”

“It really is,” Dudu says. “It’s terrible. It’s like a mosquito bothering you at night, in the dark. And when I smoke, the pain goes away.”

Another veteran, Ben, was shot point blank. He still sees “Everything we did, the whole series of events. I don’t know... how the hell my head stayed on my neck. Your system sends you back to the deathly panic and you can’t

forget, you can’t assimilate the memory among your regular memories... it becomes nearly impossible to live a normal life.”

Ben was prescribed pharmaceuticals that caused wooziness and depression. Only cannabis helps him forget and to get on with his life.

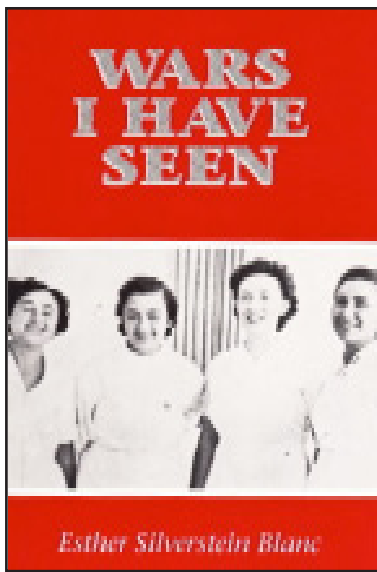
No matter where you stand politically, no matter what you think of the mission they were assigned, young people whose bodies and minds have been damaged by war deserve the best available treatment. For both phantom limb pain and PTSD, the best treatment is cannabis. This is as true at Walter Reed Army Hospital in Washington, D.C. as it is at the Abarbanel Psychiatric Hospital in Tel Aviv.

Medical Cannabis — the film, like the herb — is universally relevant.



“He is all of 31, and he’s only 17, He’s been a soldier for a thousand years...”
—Buffy St. Marie





Wars I Have Seen by Esther Silverstein Blanc, Volcano Press, 1996, 132 pages, \$12.95

Esther Blanc was trained as a nurse at the University of California San Francisco in the 1930s. She was politicized by the seamen and longshoremen she cared for at the Public Health Service Hospital. She was a nurse for the loyalists during the Spanish Civil War, then served in the Army in World War Two.

After a full career, she got a PhD in the history of science and taught at UCSF, where she witnessed “the triumph of the researchers over the clinicians” in the 1960s.

This book, a memoir of sorts, contains stories worthy of Chekhov and experience-based insights about health and healing.



A Program That Works!

Creating a Therapeutic Environment

By Esther Silverstein Blanc

We had fun being parents, and I think it was useful being real grown up. All those years of nursing and experience, developing my ideas about how you relate to people... I developed the idea that if you could create a therapeutic environment around yourself, you were the greatest beneficiary, because you lived in it. This worked on a psychiatric ward. It worked in any place I ever worked. It worked in the orphanage. It worked in my house, in my marriage, and in my life. And it's so simple. There are eight rules.

The first four have to do with how you deal with other people. You treat everyone you meet with respect and esteem and regard and normal affection. And if they don't respond to this, you don't want them in your life and so you don't gather them up. You avoid them.

The next one has to do with genuineness. You definitely have to be for real. You can't phony anything up. You have to say what you mean and mean what you say and keep your promises. This is tremendously important.

You really have to believe that all men are created equal.

The most important of all is egalitarianism. You really have to believe that all men are created equal. They may have deficiencies in some areas, and they're all different, and we all have different genes. But on the basis of race, creed, color or God knows what, you ain't got any right to look on anybody as lower than you or higher than you.

Next is empathy. In yourself you are empathetic, which is not the same as sympathetic. Sympathetic doesn't do anybody any good. But empathetic says “I'm going to do my best to feel as you feel, and I will act accordingly.”

The last one is desperately important, too. It says: the only kind of love you're allowed is non-possessive. You don't own anybody. This precludes jealousy from your life. Ethically, you don't have the right to be jealous.

You can embody all these principles if you work at it — because it takes work. Now if I disobey one I can feel the hair on the back of my neck rising and it says, “Esther, what are you doing?” You have to work at it and practice. It keeps you from saying nasty things. It keeps you from making people uncomfortable. It keeps you from all kinds of gross errors.

What happens when you practice these principles on a psychiatric ward is that you are a therapeutic tool. You have honed your surface to a purpose. And if you can teach everybody around you to do the same, then you will make a whole lot of people very comfortable. And once the patients are comfortable and they're relaxed in your presence, and they trust you, and you begin to get some insight into how terrible they feel all the time, and how confused and how distressed and how alone, you won't say anything that's wrong and you won't do anything that's wrong. This method keeps you from hurting other people. It keeps you looking at their insides instead of their outsides. And creating adequate responses from yourself which produce adequate responses from the patients.

This method also works very well in a family, because nobody's doing things to other people that they should not be doing. And you can teach people to do research by using it, too. I had one student who was a graduate student at UCSF. She did the most brilliant study of her patients at the Stockton State Hospital by putting on a patient's dress and sitting in a rocking chair on one of the wards and just shutting up and watching.



UCSF, 1967

At this time something very interesting happened. Dr. John Saunders lost his job as chancellor. There was a big fight, and as I understand what the fight was about, it was because he said that a medical school needed adequate clinicians, not just researchers. You weren't going to train good doctors without good other doctors. And therefore the clinicians had to have a prominent place. And the researchers had him fired. I may not have this exactly right, but I think that's about the way it was.

In order to make Dr. Saunders feel better — he was a member of the Royal College of Surgeons, and knew just about everything. He built the library from nothing. The great collections they have in the library now, which are worth millions, are all due to Dr. Saunders, who purchased them before the prices of books went up. I don't know how many people know that.

He was quite a fellow, and he was a brilliant, internationally known anatomist. He became chairman of the department of anatomy, and then chairman of the medical school, and then provost and then chancellor. Anyway, in order to make him feel better, because they must have felt disgraceful over what they did, they gave him a new department called the history of health sciences.... I used to see a lot of Dr. Saunders because he used to come down and have lunch with us everyday in the basement in the old medical school building with the clock on the tower.

—Esther Blanc

The Ballad of the Lab Mouse

You get seniority
by being paranoid
The lab was up to me
I chose Cannabinoids
Heard it's a fun house
where a little lab mouse
can par-tay

Pass that new compound
over to me, doc
Then I'll swim around
You can punch the clock
I ain't cynical
Life's a clinical trial
for mouse or man

I'll do anything
science might require
balance on your ring
or swing on your wire
And it gives me pleasure
to let you measure me
apres le work-out

Or I can play “Control”
knock down placebo
stand the heat or cold
As if I didn't know
Just to confuse 'em
and amuse ol'
Lucky, c'est moi

Mazes don't phase me
Till I get depressed
Or is it just ennui?
For that you never test
Real or synthetic,
speed or anesthetic
Try me on your

Calming CBDs
blue designer genes
White THC
Aromatic terpenes
Any delivery
system suits me
Je suis Lucky

But one thing I don't want
cause, man, I live to eat
No Rimonabant
Don't touch mon appetee
Just let me nibble your
cannabigerol.
Just let me nibble nibble nibble
your cannabigerol

just let me nibble nibble nibble
nibble nibble nibble nibble nibble...



“I remember quite clearly walking along the Avenida Reforma in Mexico City in the late fifties and seeing other shabbily dressed beatniks — sandals, peyote bags, Indian paraphernalia on our belts. Seldom did we speak to one another, rather our communication was unspoken and symbolic, each of us on our own special odyssey of discovery, reflective and open to the spirituality of the Mexican Indian, but at the same time wary. We knew we had found something, and we also knew that what we had found had to be discovered by each individual; it couldn't be transmitted by guidebook or conversation. Each of us who discovered the riches of rural Mexico, the humbleness, simplicity, human dignity, and warmth, realized that our discovery had to be protected, even from one another, for in our hearts we knew that what we had discovered was bound, eventually, to be lost, simply because of our discovery.”

—Jerry Kamstra, “Weed,” 1974

On Listening to Rick Steves

Let's roll a joint for Uncle Sam
Help him mellow out... of Afghanistan
Reduce his inflammation, help him be all he can
Let's roll a joint for Uncle Sam

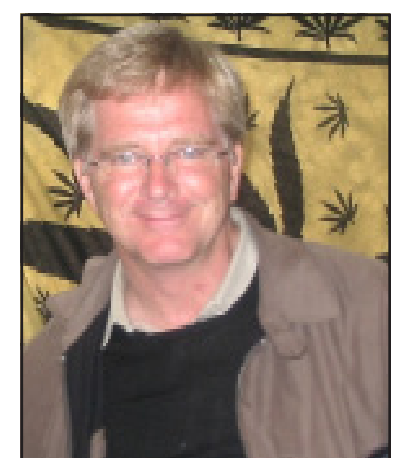
Notice how we pass the doob' around
Sharing don't have to bring you down
Peer-reviewed scientists have found
What goes around really comes around

Let's grow hemp for Uncle Sam
Make it organic and potent as we can
Support small farmers and a public option plan
Let's grow hemp for Uncle Sam

Let's help him see it don't make sense
To hit first and call it “defense.”

So, let's roll a joint for Uncle Sam
Reduce his stress, help him be all he can
And stop the next war in advance—
Hands off Iran!

Let's roll a joint for Uncle Sam



RICK STEVES for Secretary of State