By Fred Gardner

I had been working for the District Attorney of San Francisco — Terence Hallinan, the only DA in California who had supported the medical marijuana initiative enacted by voters in '96 — and this ICRS meeting was my second introduction to the science side of the story.

In recent years ICRS researchers have determined that cannabinoids modulate the activity of virtually every messenger system in the brain — GABA, dopamine, acetylcholine, the endorphins, prolactin, glutamate, serotonin… This may explain why cannabis has an impact on so many medical conditions.

The biggest news at Asilomar: there is growing evidence that anandamide works as a “retrograde messenger,” causing the other receptors to slow down when they’re firing too intensely.

Endogenous cannabinoids may or may not rely on a “transportor” molecule to enter cells they activate (instead of going through the membrane by passive diffusion). Existence of a transporter would provide a strategy for drug companies: block the action of the transporter and keep anandamide in the synapse, firing away at the cell (instead of diffusing out of it).

Several labs are honing in on which specific amino acids in the receptor are critical for selectively binding cannabinoids.

Therapeutic Potential

Among the findings reported:

- Rats, when stressed, increase their production of anandamide, according to Andrea Hofman. The implication is that it serves to reduce stress.
- Anandamide may operate the growth of colorectal cancers in rats, reported Vincenzo Di Marzo.
- Anandamide induces sleep. Cecilia Hillard reported that the general anesthetic propofol works by inducing a 10-15 fold increase in anandamide and 2-AG. When people wake up from propofol, they tend to have nice dreams and may be euphoric. “One physiological role of the endocannabinoids is in the induction of natural sleep,” Hillard suggested.
- Anandamide binds to both the cannabinoid and the vanilloid receptors. The vanilloid receptor is activated by capsaicin (which has a vanilloid active group). Can one receptor signal “pain” when activated by capsaicin and “analgiesia” when activated by anandamide? A push-pull mechanism?
- Giovanni Marsicano reported that “extinction of aversive memories is controlled by the endogenous cannabinoid system.” His group found that the cannabinoid receptor is necessary for synaptic plasticity in the amygdala, a part of the brain where memory of pain and fear resides.
- Several papers and posters focused on cannabidiol (CBD), the non-psychoactive component of the plant that has supposedly been bred out of the high THC strains available in California. CBD reportedly has anti-convulsant, neuroprotective, and anti-inflammatory effects.

GW Pharmaceuticals

The final day of the conference — devoted to “therapeutic potential” — featured keep promises by GW Pharmaceuticals, the British company founded in 1998 by Geoffrey W. Guy, MD. Guy is a pharmaceutical entrepreneur in his late 40s whose interest in cannabis was piqued when he attended a meeting in London of multiple sclerosis patients demanding access to legal medicine. (The patients had been inspired by the passage of Prop 215 in California.)

Guy then obtained licenses from the Home Office to grow cannabis at a secure 20,000-square-foot glasshouse complex, and purchased the seed strains collected and refined over the years by two American expatriates — Robert Clarke and David Watson — who had relocated to Amsterdam and founded a company called HortaPharm. Talk about a “brain drain…”

At the 1999 ICRS meeting in Acapulco, Guy had laid out his long-range plan. GW would grow plants under controlled conditions in which various cannabinoids of interest (THC, CBD, and several others) were predominant. Then they would blend uniform, pharmaceutical-grade extracts containing cannabinoids and ratios to provide them for investigators to use in clinical trials. This has been done and two English physicians were able to report promising results at the Asilomar meeting.

Alphonse Nocutt and colleagues at the James Paget Hospital in Great Yarmouth used GW’s extracts — formulated for spraying under the tongue — in clinical trials involving 29 chronic pain patients. Initially patients were given a 1:1 mix of THC and CBD for two weeks. The 27 who reported benefits then received, over the next eight weeks, one-week treatments with high-THC, high-CBD, placebo, and 1:1 THC/CBD extracts. The order in which patients used the various extracts was unknown to either them or the doctors.

This method, in which each patient is his/her own control, is called an “N=1” trial.

Patients were assessed weekly. This method, in which each patient is his/her own control, is called an “N=1” trial.

Nocutt reported that 24 of the 27 patients showed consistent benefit:

- “Improvements in pain, sleep, depression, activity and general health were the most important… All of the 24 patients who showed benefit had started a long-term safety extension of the study.”
- P.J. Robson and his group at the Oxford University Department of Psychiatry tested GW’s plant extracts on 24 patients with multiple sclerosis and spinal cord injuries whose pain, spasticity, and other symptoms did not respond to standard treatments. After two weeks on the THC:CBD 1:1 mix, patients were given the three extracts and placebo in two-week blocks. Four patients dropped out due to adverse effects.

“Unequivocal alleviation of at least one target symptom (pain, spasticity, muscle spasm, bladder-relaxation symptoms, tremor) was seen in all of the remaining 20 patients. Both THC and CBD significantly improved pain and stimulated appetite, while THC:CBD 1:1 significantly improved sleep. Intoxication occurred most frequently after THC. Larger scale studies are warranted in a variety of neurological conditions.”

The GW contingent included John McPartland, co-author of a textbook on pests of the cannabis plant, who debunked the assumption that homo sapiens evolved CB receptors that bind to cannabis compounds. By measuring dissimilarities between genes that express cannabinoid receptors in various animals, McPartland estimated that cannabinoid receptors have been evolving for “at least 600 million years.” Fossil records don’t pinpoint the epoch when the cannabis plant appeared, but the fossils of related plants should provide a rough estimate.

The closest relatives are Cannabis probably plants in the family Urticaeae (nettles), based on their morphology, chemistry, gene structure, and the fact that seven obligate parasites of Cannabis are shared by hosts in the Urticaeae. The fossil record of the Urticaeae goes back 34 million years, so cannabis is a relatively young plant species.

McPartland concludes, "CB receptors evolved long before cannabis." The plant developed compounds that bind to CB receptors, a very successful evolutionary strategy that has resulted in its cultivation everywhere on the planet.

Geoffrey Guy and his partner Brian Whittle co-authored a poster suggesting that cannabinoids might treat motion sickness effectively. They worked with the Japanese House Munk Show (rats don’t vomit). Animals given CBD and THC extracts and placebo were placed in cages that could be mechanically shaken to induce nausea. The CBD extract was found to significantly delay the onset of an "emetic episode," and to reduce the number of emetic episodes observed.

As GW expands its operations, the company is also beginning to influence the research agenda. Most ICRS members still rely on grants and research materials provided by NIDA — the National Institute on Drug Abuse, a U.S. government agency whose stated interest is to prove the harmfulness of marijuana. At every ICRS meeting there’s an enticing talk by NIDA bureaucrat — this year it was Hari S. Singh — listing all the hard-to-get substances that only the government can supply. But with GW beginning to offer support and pharmaceutical-grade drugs that can be worked with legally, the picture is changing. A number of speakers thanked GW for providing their substrates.

"...Single-handedly forcing the research away from the super-TTH: synthetics and back into natural cannabinoids," McPartland exulted.

Three California doctors who have recommended cannabis for thousands of patients — Tod Mikuriya, David Bearman and R. Stephen Ellis — followed the proceedings with interest. Mikuriya presented two posters: one listing 147 conditions for which cannabis reportedly provides relief; and one reviewing cases of patients who have attempted to substitute cannabis for alcohol.

It was clear at Asilomar that the passage of Prop 215, ironically, led to more research in Europe than in the U.S., where the forces of reaction simply dely the will of the people when they think the people are being disobedient.

In California, six and a half years after Prop 215 became law, the individuals most willing and able to explore the medical potential of cannabis are on the defensive, their funds and energy tied up in courtroom fights.

O’Shaughnessy’s Summer 2003 — 21 —

Notes from the 2002 ICRS Meeting at Asilomar