In the summer of 1999 I was finishing my 13th year as managing editor of Synapse, the UC San Francisco weekly. The paper was staffed and produced mainly by medical students, nursing students from the school of pharmacology, nursing and dentistry. In July I was-busy taking notes on medical school, and one of the stories I planned was about cannabinoids.

I used vacation time in June to ‘99 to attend the International Cannabinoid Research Society meeting in Acapulco, and the meeting provided a perfect hook for a Synapse story! UCSF pharmacologist Lester Bornheim presented a paper on cannabinoids — giving me a local angle and a platform to start preaching the gospel of CBD in the US of A.

The following piece ran in the July 1999 issue of Synapse, accompanied by photos of Bornheim in his lab at UC, Bornheim confronting with Geoffrey Gray at the ICRS meeting; and Hambert of the National Institutes of Health, who had established that CBD has neuroprotectant properties. I If one can find those pix in my “files,” I’ll post them. I’m kicking myself for operating with the mentality of a leafleter, not thinking beyond getting a good graphic or two for use in a black-and-white tabloid. I could have been a collecter.

F.G.

THC’s uncelebrated cousin

By Fred Gardner

When the International Cannabinoid Research Society held its annual meeting last month in Acapulco, UCSF’s Lester Bornheim, a postdoc in the lab of neuroscientist George W. Gray taking careful notes. Since the mid-1980s Bornheim, a researcher in the Department of Cellular and Molecular Pharmacology, has been studying the metabolism of cannabidiol (CBD). This compound in the cannabis plant, unlike THC, its celebrated relative, does not result in a “high” when inhaled or ingested. THC is frequently described as the “active ingredient” in cannabis, but this is a misnomer. THC is the predominant compound in cannabis plants that have been bred for fiber i.e., hemp. CBD has shown potential as an anticonvulsant — an antiepileptic in humans — in studies dating back 20 years. It is a nonpsychotomimetic compound that exerts a fleeting effect. The first cannabinoid was identified in the early 1940s by a University of Michigan chemistry researcher with the plant, a vote was taken to change the C-word to “Cannabinoid,” and still is a vote today.

The first CBI antagonist, WIN 55,212--22. The existence of cannabinoids was published in the 1970s by a University of California, San Francisco, chemist. "Virtually every drug that has been investigated in brain at concentrations 170 times greater than anandamide. It now appears to be responsible for most CB1 receptor-mediated effects. Some researchers feel that, because AEA and 2-AG have relatively weak affinities for the cannabinoid receptor, the most important endogenous cannabinoid agonist yet to be discovered.

In 1993 Munro et al found a second cannabinoid receptor (CB2) in spleen cells, white blood cells, and other tissues associated with the immune system. Both cannabinoid receptors are seven-transmembrane domain proteins coupled to G-proteins inhibiting adenyl cyclase. The CB1 receptor has also been discovered in various brain areas, but the CB2 receptor was recently found in the spleen and lymph nodes.

The following piece ran in the July 1999 issue of Synapse, accompanied by photos of Bornheim in his lab at UC, Bornheim confronting with Geoffrey Gray at the ICRS meeting; and Hambert of the National Institutes of Health, who had established that CBD has neuroprotectant properties. I If one can find those pix in my “files,” I’ll post them. I’m kicking myself for operating with the mentality of a leafleter, not thinking beyond getting a good graphic or two for use in a black-and-white tabloid. I could have been a collecter.

F.G.

The following piece ran in the July 1999 issue of Synapse, accompanied by photos of Bornheim in his lab at UC, Bornheim confronting with Geoffrey Gray at the ICRS meeting; and Hambert of the National Institutes of Health, who had established that CBD has neuroprotectant properties. I If one can find those pix in my “files,” I’ll post them. I’m kicking myself for operating with the mentality of a leafleter, not thinking beyond getting a good graphic or two for use in a black-and-white tabloid. I could have been a collecter.

F.G.

The following piece ran in the July 1999 issue of Synapse, accompanied by photos of Bornheim in his lab at UC, Bornheim confronting with Geoffrey Gray at the ICRS meeting; and Hambert of the National Institutes of Health, who had established that CBD has neuroprotectant properties. I If one can find those pix in my “files,” I’ll post them. I’m kicking myself for operating with the mentality of a leafleter, not thinking beyond getting a good graphic or two for use in a black-and-white tabloid. I could have been a collecter.

F.G.
fi’s CBI antagonist completely prevented self-administration of both agonists, sug-
gestng that cannabinoi reinforcing ef-
facts are specifi mediately through CB 1 receptors. Pretreatment with naloxone
(an opioid antagonist) blocked the desire
for cannabinoi drugs, and the CBI an-
tagont SR 141716 A blocked morphine
self-admin-istration. These results point to
“mutual regu-lation between endogenous
‘ C B I S ’ o p i d Systems and Cannabinoids in the Neu-
robiological control of reward.”

• Mechoulam and colleagues reported
fi nding high concentrations of 2-AG in
mammalian milk, suggesting that can-
na binoi might play a role in maternal-
off-spring bonding, as well as in appetite
stimulation.

• The cannabinoi receptor is coupled
through the cell membrane to a G-protein,
which transduces signals inside the cell. Howlett
identified a peptide fragment on
the CBI receptor, 14 amino acids long, that
activates the signal transduction pathway
inside the cell.

• Michelle Glass of the National Institute
on Deafness and Other Communication
Disorders determined that different con-
formations of the CBI receptor —induced
by the various agonists — can be distin-
guished by different G-proteins within
the cell. “It is possible,” Glass concluded,
“that by understanding the abilities of
the receptors to couple to different G-proteins,
and the ability of differen agonists to di-
rect this coupling, ligands may be devel-
oped that enable specific signal transduc-
tion pathways to be selectively targeted.”

• Vincenzo Di Marzo, who previously had
found that anandamide and 2-AG inhibit
breast cancer cell proliferation in vitro by
acting on CB 1 receptors, reported that the endocannabinoi inhibit proliferation
of prostate cancer cells by the same mecha-
nism. They also inhibit the proliferation
of cancer cells induced by nerve growth fac-
tor. Di Marzo concluded, “These fi ndings
suggest that novel anti-tumor drugs may
be developed from these endogenous com-
pounds.”

• CBD has shown potential as an anticon-
vulsant in animals and an antiepileptic in
humans. Its antioxidant and neuroprotect-
tive properties were described at the 1998
ICRS meeting by Aidan Hampson of the
National Institute of Mental Health, who
determined that rats treated with CBD
suffer milder damage when strokes are in-
duced. This year Hampson examined the
effect of CBD on enzymes that play a role
in inflammation. (Inflamed nerve sheaths
apparently play a role in stroke.) He found
that CBD selectively inhibits lipoxygen-
ases —some but not all of the subtypes
— which make inflammatory mediators
called leukotrienes.

Cannabinoids’ Wide Impact
Bornheim describes the annual ICRS
meeting as “a much more open, family
of thing compared to other confer-
ces. You have a mixture of hard basic
scientists, behavioral scientists, drug-abuse
scientists, plus a few marijuana advocates
who attend as well. Everybody sort of
tolerates each other; there’s very little ill
feeling —as long as there’s science there.”
Bornheim says that the past two ICRS con-
ferences have left him with the impression
that “cannabinoids are neuromodulators—
they have some specifi effects, but mainly
they work by dampening the levels or ac-
tivity of other systems. The NMDA recep-
tor, adrenalin release, the GABA receptor,
dopamine, the opioid system, pituitary
hormone, prolactin, serotonin—virtually
every system in the brain is impacted by
the cannabinoids.”

The fact that cannabinoids affect so many
systems makes them more diffi ci to study
and to develop therapeuti drugs. “The
FDA doesn’t approve of polypharmacy in
general,” he observes. “To get a drug com-
bination through the FDA is very di cult.
And here you’re talking about something
with hundreds of different compounds and
you have to prove that every one of them is
really safe. If a drug company came up and
said ‘We’re making this therapeutic with
100 different compounds and it’s effec-
tive,’ the FDA would say, ‘Let’s see toxic-
ity data on every single one.’ ”

“It gets down to the basic diff erence be-
tween Western medicine and Eastern medi-
cine. Eastern medicine uses herbal extracts
with hundreds of different compounds
and they believe that the combination has
value. Western medicine says, ‘If it works,
there’s probably one component that’s do-
ing the job and everything else is compli-
cating the issue. Let’s fi nd that ingredient.
Let’s make it 100 times more active with
chemical substitutes, and then bombarding
the body and knocking out the problem.”

“I’m not saying which one is right; that’s
how the two philosophies go. Marijuanaclearly falls into the category of a holistic
medicine; which isn’t to say that you can’t
develop Western-style drugs from it. The
advantage of the Western approach is its
potential for selectivity—you can deliver
to a single site.”

In the 1970s more than 100 differen cann-
na binoi metabolites were characterized in
different animals. Their activity was deter-
mined by microinjection into the spine or
directly into the brain ventricles, followed
by measurement for analgesia or body tem-
perat ure. Only 7-hydroxy-THC was found
to be highly active. It is several-fold more
psychoactive than THC itself, says Born-
heim, who has found that brain levels of
7-hydroxy-THC are increased more than
10-fold after CBD pre-treatment. Inter-
est in cannabinoi metabolites dwindled,
Bornheim says, after only one proved to be
active. Today only his lab and one in Japan
are dedicated to research in this area. If and
when cannabinoi drugs go into clinical
trials, however, interest may be renewed.

Captions:
Bornheim in his lab, measuring brain lev-
els of drugs by HPLC.

Bornheim conferred with Geoffrey Guy
(right) after presenting his paper at the
International Cannabinoi Research Soci-
ety meeting in Acapulco June 21. Guy has
been licensed by the UK Home Office to
produce cannabis plant extracts for use in
clinical trials.

Aidan Hampson of NIH has established
that CBD has neuroprotectant properties.