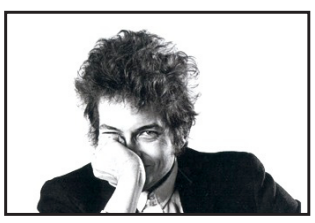
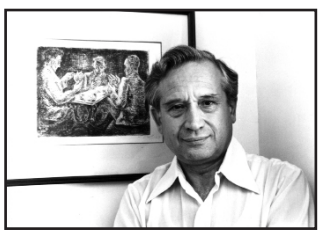
Introducing a special section from *Smoke Signals,* the new "social history of marijuana" by Martin A. Lee

• The Riddle of THC

On August 28, 1964, the day Bob Dylan lit up and handed the Beatles their first joint in a New York City hotel room, Dr. Raphael Mechoulam was working intently in his laboratory at the Hebrew University in Jerusalem. The young Israeli chemist and his research partner, Yechiel Gaoni, would soon become the first scientists to fully isolate and synthesize delta-9-tetrahydrocannabinol, or THC, marijuana's principal psychoactive component.





Mechoulam's groundbreaking research was subsidized by the U.S. National Institutes for Health (NIH), which had suddenly become desirous of more objective information about the herb. As the use of marijuana soared among middle class youth, officialdom started to get anxious, especially when the sons and daughters of prominent politicians were caught smoking it.

Queried by members of Congress as to whether pot caused brain damage, the NIH scurried to gather basic scientific data. But hard science was difficult to come by in large part due to the stubborn refusal of the Federal Bureau of Narcotics to sanction laboratory research. For a long time, the illegality of cannabis acted as a deterrent to research in the United States.

From a scientific perspective, the riddle of THC was not easy to unravel. The small number of researchers who studied cannabis over the years found the herb difficult to work with because many of its 421 distinct compounds are "lipophilic" (soluble in fat but not in water), which means they can't be separated and scrutinized without sophisticated equipment. Scientists would eventually ascertain that at least 100 of these lipophilic compounds —known as "cannabinoids"— are unique to the marijuana plant. In addition to the cannabinoids, a term coined by Mechoulam, marijuana contains various alkaloids, flavonoids and terpenoids (essential aromatic oils).

The isolation and synthesis of THC would prove to be a highly significant event in the history of psychopharmacology. Mechoulam, then 34, announced his discovery in a letter to the editor of the Journal of the American Chemical Society on July 20, 1965. Although he didn't realize it at the time, Mechoulam had lit a slow-burning fuse that would detonate a revolution in medical science.

• The Brain and Marijuana

When American researchers at Johns Hopkins University identified receptor sites in the brain capable of binding with opiates in 1973, some scientists expected that the discovery of receptor sites for marijuana would soon follow. But these were difficult to pin down. Fifteen years would elapse before a government-funded study at the St. Louis University School of Medicine determined that the mammalian brain has receptor sites —specialized protein molecules embedded in cell membranes— that respond pharmacologically to compounds in marijuana resin. Every cell membrane has lots of receptors for many types of messenger molecules, which influence the activity of the cell.

Initially identified by Professor Allyn Howlett and her graduate student William Devane, cannabinoid receptors turned out to be far more abundant in the brain than any other G-protein-coupled receptors. Tagged radioactively, a potent THC analog synthesized by Pfizer ("CP55,940") enabled researchers to begin mapping the locations of cannabinoid receptors in the brain.

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These receptors were found to be concentrated in regions responsible for mental and physiological processes that are affected by marijuana —the hippocampus (memory), cerebral cortex (higher cognition), cerebellum (motor coordination) basal ganglia (movement), hypothalamus (appetite), the amygdala (emotions), and elsewhere. There are few cannabinoid receptors in the brain stem, the region that controls breathing and heartbeat —which is why no one has ever suffered a fatal overdose of marijuana.

On July 18, 1990, at a meeting of the National Academy of Science's Institute of Medicine, Lisa Matsuda announced that she and her colleagues at the National Institute of Mental Health (NIMH) had achieved a major breakthrough —they pinpointed the exact DNA sequence that encodes a THC-sensitive receptor in the rat's brain. People have the same receptor, which consists of 472 amino acids strung together in a crumpled chain that squiggles back and forth across the cell membrane seven times. Cannabinoid receptors function as subtle sensing devices, tiny vibrating scanners perpetually primed to pick up biochemical cues that flow through fluids surrounding each cell. Matsuda also disclosed that she had successfully cloned the marijuana receptor.

The cloning of the cannabis receptor was crucial. It opened the door for scientists to sculpt molecules —new drugs-that "fit" these receptors somewhat like keys in a slot. Some keys ("agonists") turned the receptor on; others ("antagonists") turned it off. In addition to synthesizing cannabinoid receptor agonists and antagonists, scientists experimented with genetically engineered "knockout" mice that lacked this receptor. When administered to knockout mice, the THC had nowhere to bind and hence could not trigger any activity. This was further proof that THC works by activating cannabinoid receptors in the brain and central nervous system. Finally, after fifty centuries of medicinal usage, the scientific basis of cannabis therapeutics was coming into focus.

Researchers soon identified a second type of cannabinoid receptor, dubbed "CB-2," which is prevalent throughout the peripheral nervous system and the immune system. CB-2 receptors are also present in the gut, spleen, liver, heart, kidneys, bones, blood vessels, lymph cells, endocrine glands, and reproductive organs. THC stimulates the CB-2 receptor, but this does not result in the psychoactive high that pot is famous for (because CB-2 receptors are not concentrated in the brain); THC binding to CB-1, the central nervous system receptor, causes the high. The CB-1 receptor mediates psychoactivity. CB-2 regulates immune response. Marijuana is such a versatile substance because it acts everywhere, not just in the brain.

Just as the study of opium resulted in the discovery of endorphins, the brain's own morphinelike substance, so, too, marijuana research would lead to the discovery of a natural, internal THC-like compound, our "inner cannabis," so to speak. In 1992, Raphael Mechoulam, in collaboration with NIMH research fellow William Devane and Dr. Lumír Hanus, found a novel neurotransmitter, a naturally occurring endogenous (meaning "made internally") cannabinoid. This "endocannabinoid" attaches to the same mammalian brain cell receptors as THC. Mechoulam decided to call it "anandamide," deriving from the Sanskrit word for bliss. In 1995, his group discovered a second major endocannabinoid molecule, "2-AG" (2-arachidonoylglycerol), which binds to both CB-1 and CB-2 receptors.

By tracing the metabolic pathways of THC, scientists had stumbled upon a hitherto unknown molecular signaling system that plays a crucial role in regulating a broad range of biological processes. This molecular signaling system modulates how we experience pain, stress, hunger, sleep, our circadian rhythms, our blood pressure, body temperature, bone density, fertility, intestinal fortitude, mood, metabolism, memory retention, and more.

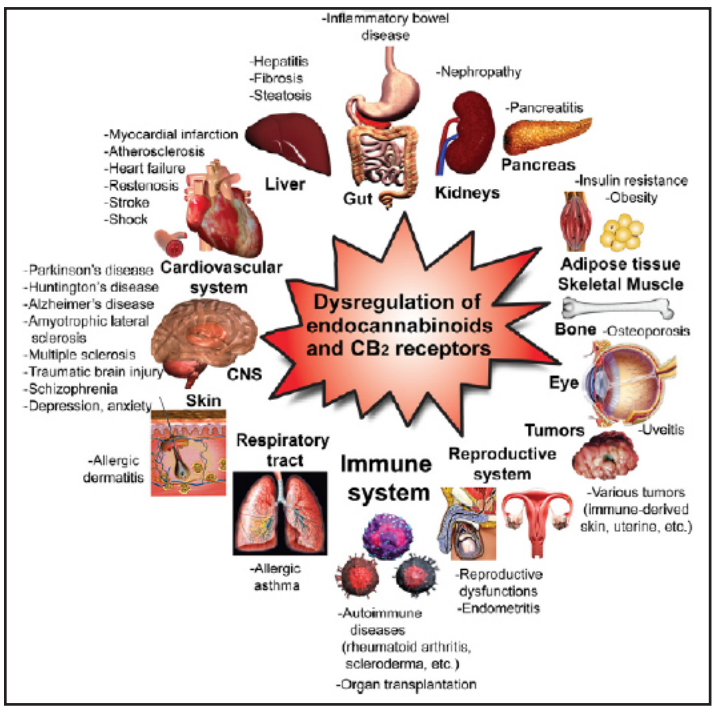
Scientists call it "the endocannabinoid system" —so named after the plant that led to its discovery. The name suggests that the plant came first, but in fact, as Dr. John McPartland explained, this ancient internal signal system started evolving more than 500 million years ago (long before cannabis appeared), when the most complex life-form was sponges. Endocannabinoids and their receptors are present in fish, reptiles, earthworms, leeches, amphibians, birds, and mammals —every animal except insects. Its long evolutionary history indicates that the endocannabinoid system must serve a very important and basic purpose in animal physiology.

Drug-company investigators paid close attention to cutting-edge developments in cannabinoid research, which few people outside the scientific community were privy to. Endocannabinoids and their receptors emerged as a hot topic among scientists who shared their findings in highly technical peer-reviewed journals and at annual conclaves hosted by the International Cannabinoid Research Society (ICRS). Advances in the burgeoning field of cannabinoid studies would pave the way for new treatment strategies for various pathological conditions-cancer, diabetes, neuropathic pain, arthritis, osteoporosis, obesity, Alzheimer's, multiple sclerosis, and several odd diseases of unknown etiology that seemed to have as their common denominator an inflammatory or autoimmune dysfunction.

The discovery of the endocannabinoid system has breathtaking implications for nearly every area of medicine, including reproductive biology. Dr. Mauro Maccarrone at the University of Teramo, Italy, describes the endocannabinoid system as the "guardian angel" or "gatekeeper" of mammalian reproduction. Endocannabinoid signaling figures decisively throughout the reproductive process —from spermatogenesis to fertilization, ovuductal transport of the zygote, embryo implantation, and fetal development. Cannabinoid receptors proliferate in the placenta and facilitate neurochemical "cross-talk" between the embryo and the mother. A misfiring of the endocannabinoid system could result in serious problems, including ectopic pregnancy and miscarriage. Appropriate levels of endocannabinoids in maternal milk are critically important for the initiation of suckling in newborns. Infant colic has been attributed to a dearth of endocannabinoids.

Fride observed that knockout mice missing CB receptors resemble babies who suffer from "failure to thrive" syndrome.

Israeli scientist Ester Fride observed that knockout mice missing CB receptors resemble babies who suffer from "failure to thrive" syndrome. (Mice lacking CB receptors don't suckle and they die prematurely.) This is one of many enigmatic conditions that may arise because of a dysfunctional endocannabinoid system. Individuals have different congenital endocannabinoid levels and sensitivities. University of Washington neurologist Ethan Russo postulates that "clinical endocannabinoid deficiency" underlies migraines, fibromyalgia, irritable bowel disease, and a cluster of other degenerative conditions, which may respond favorably to cannabinoid therapies.



Pathological conditions involving dysregulation of endocannabinoid-CB2 signaling were depicted in a paper by P. Pacher and R. Mechoulam, "Is lipid signaling through cannabinoid 2 receptors part of a protective system?" in *Progress in Lipid Research*, February 2011.

For Big Pharma, cannabinoid research became a tale of

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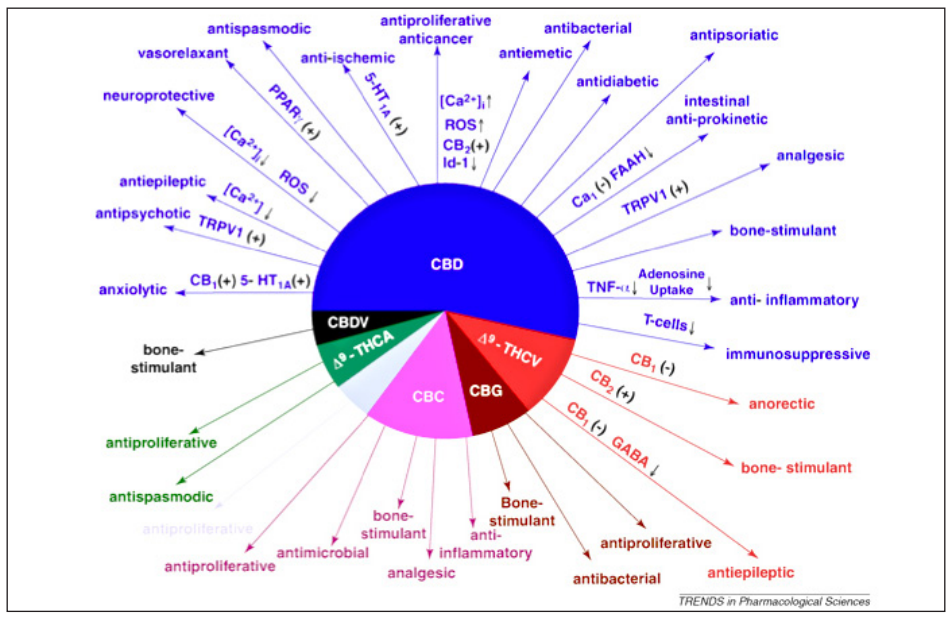

Medical effects of non-psychoactive cannabinoids and proposed mechanisms of action were diagrammed for a review article in *Trends in Pharmacological Sciences* by Angelo Izzo of the University of Naples and colleagues. (+) signifies direct action, (-) indirect.

knockout mice and men. Using genetically engineered rodents that lacked CB receptors, researchers were able to prove that cannabinoid compounds can alter disease progression and attenuate experimentally induced symptoms. An "animal model" of osteoporosis, for example, was created in normal mice and in knockout mice without cannabinoid receptors. When a synthetic cannabinoid drug was given to both groups of osteoporotic mice, bone damage was mitigated in the normal mice but had no effect on rodents sans CB receptors —which means that cannabinoid receptors are instrumental in regulating bone density.

Other experiments would establish that CB receptor signaling modulates pain and analgesia, inflammation, appetite, gastrointestinal motility, neuroprotection and neurodegeneration, along with the ebb and flow of immune cells, hormones, and other mood-altering neurotransmitters such as serotonin, dopamine, and glutamate. When tickled by THC or its endogenous cousins, cannabinoid receptors trigger a cascade of biochemical changes on a cellular level that put the brakes on excessive physiological activity.

The human immune system, an amazing physiological wonder, kicks on like a furnace when a fever is required to fry a virus or bacterial invader. And when the job is done, endocannabinoid signaling turns down the flame, cools the fever, and restores homeostasis. (Cannabinoids-endo, herbal, and synthetic-are anti-inflammatory; they literally cool the body.) But if the feedback loop misfires, if the pilot light burns too high, if the immune system over- reacts to chronic stress or mistakes one's body for a foreign object, then the stage is set for an autoimmune disease or an inflammatory disorder to develop.

Retrograde signaling serves as an inhibitory feedback mechanism that tells other neurotransmitters to cool it when they are firing too fast.

Endocannabinoids are the only neurotransmitters known to engage in "retrograde signaling," a unique form of intracellular communication that inhibits immune response, reduces inflammation, relaxes musculature, lowers blood pressure, dilates bronchial passages, increases cerebral blood flow (a rush of thoughts!), and normalizes overstimulated nerves. Retrograde signaling serves as an inhibitory feedback mechanism that tells other neurotransmitters to cool it when they are firing too fast.

A German research team would later demonstrate that CB-2 receptor activation restrains the formation of bone reabsorbing cells, known as osteoclasts, by down-regulating osteoclast precursors, thus tipping the balance in favor of osteoblasts, cells that facilitate bone formation.

Prior to the discovery of the endocannabinoid system, retrograde signaling was known to occur only during the embryonic development of the brain and nervous system. Endocannabinoids choreograph "a broad array of developmental processes in the embryonic brain," explains Dr. John McPartland, including neural stem cell proliferation and differentiation, a process guided by extracellular cues conveyed via CB receptors. Scientists would learn that cannabinoid receptor signaling also regulates adult neurogenesis (brain cell growth) and stem cell migration.

High endocannabinoid levels in the brain are triggered by strokes and other pathological events —attesting to the neuroprotective function of the endocannabinoid signaling. A major function of the endocannabinoid system —and therefore a significant effect of the cannabinoids in marijuana— is neuroprotective in nature: protecting brain cells from too much excitation. The endocannabinoid system, according to Mechoulam, is part of the body's "general protective network, working in conjunction with the immune system and vari- ous other physiological systems." His discoveries posed a direct challenge to scientific orthodoxy by revealing that the brain has a natural repair kit, an in-built mechanism of protection and regeneration, which can mend damaged nerves and brain cells.

Ironically, the U.S. government's unending search for marijuana's harmful properties yielded astonishing scientific insights that validated the herb's therapeutic utility. By stimulating CB-1 and CB-2 receptor signaling, marijuana functions as a substitute "retrograde messenger" that mimics the way our bodies try to maintain balance. Cannabis is a unique herbal medicine that taps into how our bodies work naturally. Thanks to this plant, scientists have been able to decipher the primordial language that nerve and brain cells use to communicate. From womb to tomb, across countless generations, the endo- cannabinoid system guides and protects.

But a big disconnect existed between the world of science and the general public. Aside from certain segments of the scientific community, few people knew about the endocannabinoid system. Doctors, journalists, public officials —hardly anyone was clued in to the latest scientific research that went a long way toward explaining why marijuana is such a versatile remedy and why it is, by far, the most sought-after illicit substance on the planet.

• The Anti-Cancer Potential of Cannabinoids

Peer-reviewed scientific studies in several countries show THC and other compounds found only in marijuana are effective not only for cancer symptom management (pain, nausea, loss of appetite, fatigue, and so on), but they confer a direct antitumoral effect as well.

Animal experiments conducted by Manuel Guzmán at Madrid's Complutense University in the late 1990s revealed that a synthetic cannabinoid injected directly into a malignant brain tumor could eradicate it. Reported in *Nature Medicine*, this remarkable finding prompted additional studies in Spain and elsewhere that confirmed the anticancer properties of marijuana-derived compounds.

Guzmán's team administered pure THC via a catheter into the tumors of nine hospitalized patients with glioblastoma (an aggressive form of brain cancer) who had failed to respond to standard therapies. This was the first clinical trial assessing the antitumoral action of cannabinoids on human beings, and the results, published in the *British Journal of Cancer,* were very promising. THC treatment was associated with significantly reduced tumor cell proliferation in all test subjects.

No Big Pharma chemotherapy drugs could induce apoptosis (cell death) in cancer cells without trashing the whole body.

Guzmán and his colleagues found that THC and its synthetic emulators selectively killed tumor cells while leaving healthy cells unscathed. No Big Pharma chemotherapy drugs could induce apoptosis (cell death) in cancer cells without trashing the whole body. Up to 90 percent of advanced cancer patients suffer cognitive dysfunction from "chemo brain," a common side effect of corporate cancer meds that indiscriminately destroy brain matter, whereas cannabinoids are free-radical scavengers that protect brain tissue and stimulate brain cell growth.

There is mounting evidence that cannabinoids may "represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis [the formation of new blood vessels] and the metastatic spreading of cancer cells," according to the scientific journal *Mini-Reviews in Medicinal Chemistry*. Studies from scientists around the world have documented the anticancer properties of cannabinoid compounds for various malignancies, including (but not limited to):

Prostate cancer. Researchers at the University of Wisconsin found that the administration of the synthetic cannabinoid WIN-55,212–2, a CB-1 and CB-2 agonist, inhibited prostate cancer cell growth and also induced apoptosis.

Colon cancer. British researchers demonstrated that THC triggers cell death in tumors of the colon, the second leading cause of cancer deaths in the United States.

Pancreatic cancer. Spanish and French scientists determined that cannabinoids selectively increased apoptosis in pancreatic cell lines and reduced the growth of tumor cells in animals, while ignoring normal cells.

Skin carcinoma. Spanish researchers noted that the administration of synthetic cannabinoids "induced a considerable growth inhibition of malignant tumors" on the skin of mice.

Breast cancer. Scientists at the California Pacific Medical Center in San Francisco found that THC and other plant cannabinoids inhibited human breast cancer cell proliferation and metastasis and shrank breast cancer tumors. 1.3 million women worldwide are diagnosed yearly with breast cancer and a half million succumb to the disease.

Cervical cancer. German researchers at the University of Rostock reported that THC and a synthetic cannabinoid suppressed the invasion of human cervical carcinoma into surrounding tissues by stimulating the body's production of TIMP-1, a substance that helps healthy cells resist cancer.

Leukemia. Investigators at St. George's University and Bartholomew's Hospital in London found that THC acts synergistically with conventional antileukemia therapies to enhance the effectiveness of anti-cancer agents in vitro (in a test tube or petri dish). Scientists had previously shown that THC and cannabidiol were both potent inducers of apoptosis in leukemic cell lines.

Stomach cancer. According to Korean researchers at Catholic University in Seoul, WIN-55,212–2, a synthetic cannabinoid, reduced proliferation of stomach cancer cells.

Cancer of the bile duct. The administration of THC inhibits bile-duct cancer cell proliferation, migration, and invasion and induces biliary cancer cell apoptosis, according to experiments conducted at Rangsit University in Patum Thani, Thailand.

Lymphoma, Hodgkin's, Kaposi's sarcoma. Researchers at the University of South Florida ascertained that THC thwarts the activation and replication of the gamma herpes virus. This virus increases a person's chances of developing cancers such as Hodgkin's, non-Hodgkin's lymphoma, and Kaposi's sarcoma.

Liver cancer. Italian scientists at the University of Palermo found that a synthetic cannabinoid caused programmed cell death in liver cancer.

Lung cancer. Harvard University scientists reported that THC cuts tumor growth in common lung cancer in half and "significantly reduces the ability of the cancer to spread." Lung cancer is the number one cancer killer in the world. More Americans die of lung cancer each year than any other type of cancer.

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Manuel Guzmán, the Spanish scientist who showed that direct injection of THC into an aggressive cancer of the brain could slow its growth, in a still from *What if Cannabis Cured Cancer?* The documentary by Len Richmond, released as a DVD in 2010, helped publicize the anti-cancer properties of cannabinoids. *What if...* was entered in 21 international film festivals and it won first prize in four. Subtitled versions have been produced in 12 languages. California clinicians interviewed by Richmond for the film continue to get requests for advice from cancer patients and their loved ones.