The Great Pot Experiment

Legalization keeps rolling ahead. But because of years of government roadblocks on research, we don’t know nearly enough about the dangers of marijuana—or the benefits

BY BRUCE BARCOTT AND MICHAEL SCHERER

Brave new world
A legal escape in Colorado for Gustim Tubbs, 24, and Savannah Kay, 23, remains a neurological mystery that science is just now untangling

Photographs by Danielle Levitt for TIME
Though they look normal, their lives are anything but, and not just because of the pricey real estate they call home on the 30th floor of a research building near Mount Sinai Hospital. For skeptics of the movement to legalize marijuana, the rodents are canaries in the drug policy coal mine. For defenders of legalization, they are curiosities. But no one doubts that something is happening in the creatures’ titty little brains.

In one experiment, Hurd’s rats spent their adolescence getting high, on regular doses of tetrahydrocannabinol (THC), the psychoactive compound in marijuana. In the past, scientists have found that rats exposed to THC in their youth will show changes in their brain in adulthood. But scientists and others point out that a shift to fund the real science of pot still has a long way to go. The legacy of the war on drugs haunts the medical establishment, and federal rules still put onerous restrictions on the labs around the country that seek to work with marijuana, which remains classified among the most dangerous and least valuable drugs. “We can do studies on cocaine and morphine without a problem, because they are Schedule II,” explains Fair Vassoler, a researcher at Tufte University who has replicated Hurd’s rat experiment with synthetic pot. “But marijuana is Schedule I.”

Hurd’s rats also showed differences in the neocortex of the ones with drug-damaged parents. Even the grandkids have begun to show behavioral differences in how they seek out rewards. “This data tell us we are passing on more than things that happen during our lifetimes to our kids and grandkids,” Hurd explains, though it remains unclear how those changes manifest in humans. “I wasn’t expecting these results, and it’s fascinating.”

Welcome to the encouraging, troubling and strangely divided frontier of marijuana science. The most common illicit drug on the planet and one of the fastest growing industries in America, pot remains—surprisingly—something of a medical mystery, thanks in part to decades of obstruction and misinformation by the federal government. Potentially ground breaking studies on the drug’s healing powers are being done to find treatments for conditions like epilepsy, posttraumatic stress disorder (PTSD), Alzheimer’s disease, Parkinson’s disease, sickle-cell disease and multiple sclerosis. But there are also discoveries about the drug’s impact on recreational users.

The effects are generally less severe than of those to alcohol and alcohol, which together cause more than 560,000 American deaths annually. Unlike boozes, marijuana isn’t a neurotoxin, and unlike cigarettes, it has an uncertain connection to lung cancer. Unlike heroin, pot brings almost no risk of sudden death without a secondary factor like a car crash. But science has also found clear indications that in addition to short-term effects on cognition, pot can change developing brains, possibly affecting mental abilities and disorders, especially if exposure is fairly far too long. The same drug that seems relatively harmless in moderation for adults appears to be riskier if used in excess. In restricted settings, those brains are still developing. “It has a whole host of effects on learning and cognition that other drugs don’t,” says Todd Gilman, a Harvard Medical School researcher who has been studying the brains of human offspring, as well as those of rats, she also found differences in the neurons of the 10th floor of a research building near the Upper East Side.

That all may change soon. On Capitol Hill, a left-right coalition of Senators Kirsten Gillibrand of New York, Rand Paul of Kentucky and Cory Booker of New Jer- sey introduced a bill in March to federally legalize medical marijuana in states that have already approved it. “For far too long,” said Paul, a Republican candidate for Presi- dent, “the government has enforced unnec- essary prohibition without regard for the ability of the medical community to deter- mine the medicinal value of marijuana.”

Yasmin Hurd raises rats on the Upper East Side of Manhattan that will blow your mind.

When she analyzed the brains of the rats, she also found differences in the neu- ral circuitry of the ones with drug using parents. Even the grandkids have begun to show behavioral differences in how they seek out rewards. “This data tell us we are passing on more than things that happen during our lifetimes to our kids and grandkids,” Hurd explains, though it remains unclear how those changes manifest in humans. “I wasn’t expecting these results, and it’s fascinating.”

Beyond Reeker Madness

That relatively measured tone is a far cry from the shrill warnings of Harry J. Anslinger, the first commissioner of the Bureau of Narcotics, who in the 1930s set the standard for America’s fraught debate over marijuana with wild exaggerations. “How many murders, suicides, robberies, criminal assaults, holdups, burglaries and deeds of maniacal insanity it causes each year, especially among the young, can only be conjectured,” he wrote as part of a campaign to terrify the country. As recently as the 1970s, President Richard Nixon talked about the drug as a weapon of the nation’s enemies. “That’s why the com- munists and the left翅膀 were pushing the stuff,” he was recorded saying in pri- vate. “They’re trying to destroy us.”

The official line today is better ground- ed in data and research. And the new focus of researchers is interest in how marijuana, more than those faced by scientists studying other Schedule I drugs, like heroin and LSD. Pot studies must pass intensive review by the U.S. Public Health Service, a process that has delayed and thwarted much research for many years. Scientists have had to times a catch 22 for scientists seeking to understand the drug. “The government’s research restrictions are so severe that it’s difficult to find and show the medical benefit,” says neurobiologist R. Douglas Paul, a Republican candidate for Presi- dent, “the government has enforced unnec- essary prohibition without regard for the ability of the medical community to deter- mine the medicinal value of marijuana.”

The Cannabinoid System

Harm researchers and neuroscientists agree on at least one thing. Marijuana’s positive and negative effects both spring from the same source: the brain’s endocannabi- nobinoid system. First discovered in the late 1990s, it is a complex neural system that researchers are only beginning to fully comprehend.

A little brain Science: 101

One of the most interesting things about the brain is that other cells in the brain through electrochemical processes. Neurons talk to each other through chemical messengers known as neurotransmitters—including dopamine, serotonin, glutamate and com- pounds called endocannabinoids—which in turn send instructions to your body about what to do. Researchers now know the body pro- duces endocannabinoids, which activate cannabinoid receptors known as endocannabinoid receptors. Interestingly, one plant on earth produces a similar compound that hits those same endocannabinoid receptors, marijuana-derived cannabinoids like THC and cannabidiol (CBD). Mice endocannabinoids, which impact feelings of hunger and pleasure. Cannabinoid receptors have been linked to many conditions where they play a key role in regulating the actions of other neurotransmitters. “The more we investigate the hidden recesses of the brain, the more it seems that practically every neuron either releases endocannabinoids or can sense them using cannabinoid receptors,” explains Gregory Verdeman, a neuroscientist and endocannabinoid researcher at Florida’s Eckerd College. Neurotransmitters carry brain communication through synapses. “But too much synaptic excitation is poisonous—it damages cells,” says

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Endocannabinoids are a mechanism for putting on the brakes when that toxic level of excitation is approached. Cannabinoids like CBD may be thought of as neuroprotectors—that is, brain protectors. In fact, the NIH actually owns a patent (No. 6,699,357) on cannabinoids as neuroprotectors, based on the work of researcher Aiden Hampson and his mentor, Nobel Prize–winning neuroscientist Julius Axelrod. They found that CBD showed particular promise in limiting neurological damage in patients with Alzheimer’s disease and Parkinson’s disease and in those who have suffered a stroke or head trauma.

Endocannabinoids also play a role in the regulation of pain, mood, appetite, memory and even the life and death of individual cells. Curiously, cannabinoid receptors aren’t densely packed in the medulla (within the brain stem), which controls breathing and the cardiovascular system. That’s why a heroin overdose can be fatal—the drug shuts down the respiratory control center—but a marijuana overdose generally can’t. PTSD researchers are keen to crack the cannabinoid code because the compounds appear to play a role in extinguishing unpleasant memories. “Part of what happens with PTSD is that the brain’s stress buffers have been blown out by trauma,” says Gerdeman. “Endocannabinoids within the amygdala—the brain region important for emotional learning and memory—act as a key mechanism for what we call memory extinction.”

But what accounts for the potentially healing effects of pot in some can cause harm in others? That’s because endocannabinoids appear to play a critical role in the development of the adolescent brain. If the brain were a house, the childhood years would be spent pouring the foundation and framing up the walls. Adolescence is when the wiring and plumbing get finished. Neural networks are refined and strengthened through pruning. The strong synapses, axons and dendrites are preserved, the weak culled.

Researchers now believe the cannabinoid system plays a critical role in this neural fine tuning. This is where the worries of the government’s research restrictions are so severe that it’s difficult to find and show the medical benefit.” —R. DOUGLAS FIELDS, NATIONAL INSTITUTES OF HEALTH

The Healing Possibilities

While American research on the potential harms from marijuana is booming, the U.S. continues to lag in funding investigations into the possible benefits. In the late 1990s, the U.S. and British governments commissioned separate studies of medical marijuana. The U.K. study was spurred by multiple-sclerosis patients’ using pot to calm spasticity. The U.S. study, done by the Institute of Medicine, was in response to California’s 1996 legalization of medical marijuana.

Both studies reached a similar conclusion: medical pot wasn’t a hippie’s delusion. The research showed that the stuff held real therapeutic potential for specific conditions, including epilepsy, chronic pain and glaucoma. The British responded by treating marijuana as a plant with biotech prospects. U.K. officials licensed GW Pharmaceuticals, a startup lab in Salisbury, England, to grow and develop cannabinoid drugs, some of which U.S. scientists like Hurd use in their research.

The Americans, meanwhile, failed down the war on drugs. Barry McCaffrey, Bill Clinton’s drug czar, was outraged at the Institute of Medicine’s results. “I think what the IOM report said is that smoked marijuana is harmful, particularly for those with chronic conditions,” he said—pretty much the opposite of the government’s research restrictions are so severe that it’s difficult to find and show the medical benefit.”

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report’s conclusions. Nonetheless, he and then Attorney General Janet Reno vowed to prosecute medical marijuana patients and doctors who prescribed the drug. Shortly thereafter, the U.S. Department of Health and Human Services adopted even tougher strictures against the study of marijuana as a medicine.

The federal antipot policies resulted in a strange kind of scientific trade deficit. The U.S. leads the world in studies of marijuana’s harm, but we’re net importers of data dealing with its healing potential. THC discoverer Raphael Mechoulam runs the world’s leading cannabinoid lab at the Hebrew University of Jerusalem. Spanish biologist Manuel Guzmán is doing cutting-edge work on the potential of cannabinoids to retard the growth of glioblastoma, one of the deadliest forms of brain cancer. Canada’s health agency may soon approve the world’s first clinical trial to test medical marijuana on military and police veterans with PTSD.

There are signs of change at home, though. This year, the Colorado department of public health awarded $9 million in grants for medical marijuana research, funded with tax revenue from state-licensed pot stores. They will be among the first U.S. clinical trials to look into the effectiveness of marijuana for childhood epilepsy, irritable bowel disease, cancer pain, PTSD and Parkinson’s disease. Dr. Kelly Knupp, a pediatric epilepsy specialist at Children’s Hospital in Denver, will track children using high CBD marijuana strains to calm seizures. “Some of these children can have 100 to 200 seizures a day,” Knupp says. “We’re hoping we can measure seizure frequency to see if there’s any improvement” among kids trying the cannabinoid medicine.

This Is a Rat on Drugs

Back at Hurd’s upper east side lab, the rats have begun to show the way. In a separate experiment, she gave heroin addicted rats doses of CBD and found that it decreased their willingness to work hard for more heroin, suggesting that parts of marijuana could help human drug addicts stay clean. She is now testing that hypothesis by giving CBD tablets, made in England, to recovering human addicts in New York City.

She is also continuing to study the behavior of rats whose only exposure to marijuana’s active ingredients came through the DNA passed on to them from their parents or grandparents. That research suggests that THC may have epigenetic effects, which have been found in other drugs like cocaine and heroin, changing the way genes express themselves in the brains of offspring. This doesn’t necessarily mean that parents who smoked weed in high school have damaged their kids, because those changes may be overrun by other behaviors. The science is too new to know for sure. “It’s not a given that this is going to happen,” Hurd explains of her rats. “They tell us the potential.”

That word—potential—still qualifies much of what is known about pot, but it won’t be that way for long. The science of pot is likely to expand in the coming years, and it could boom if federal restrictions are lifted. What the government once dismissed as a communist plot that prompted murderous rages has turned out to be a window into the very workings of the human mind. In the years to come, researchers may yet find genetic markers that predispose people to pot-induced psychotic reactions, map out the specific ways in which THC changes the brain and find new medicines for some of the most intractable illnesses. Until then, the great marijuana experiment will continue in a country where 1 in 10 adults—and 35% of high school seniors—admit to conducting their own, mostly recreational, research.